GFR in Healthy Ageing: An Individual Participant Data Meta-Analysis of Iohexol Clearance in European Population-based Cohorts

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Significance Statement

Population mean GFR is lower in older age, but it is unknown whether healthy ageing is associated with preserved rather than lower GFR in some people. In this paper, the authors defined persons without major chronic disease and risk factors for chronic kidney disease as healthy and studied the cross-sectional association of being healthy with iohexol clearance in three European population-based cohorts. The mean and the 97.5th percentile of the GFR distribution were higher in healthy than in unhealthy old persons, but lower than in healthy middle-aged people. The GFR-age association was more negative in women than in men. These results suggest that although being healthy is associated with higher GFR in old age, healthy ageing is probably not associated with preserved GFR.

Abstract

Background

The prevalence of low glomerular filtration rate (GFR) is higher at older age. Although previous studies have indicated that some persons age without loss of GFR, it is unknown whether healthy ageing is associated with preserved rather than lower GFR. We investigated the cross-sectional association between measured GFR, age and health in persons aged between 50 and 97 years in the general population.

Methods

This study is a meta-analysis of 4209 iohexol clearance measurements in 2885 Europeans in a collaboration between the Berlin Initiative Study, the Age, Gene/Environment Susceptibility - Kidney Study and the Renal Iohexol Clearance Survey. We defined a healthy person as someone without major chronic disease and risk factors for chronic kidney disease and all others as unhealthy. We used a generalized additive model to study the GFR distribution by age according to health status.

Results

There were 935 (22%) GFR measurements in healthy and 3274 (78%) in unhealthy persons. The mean (95% confidence interval) GFR in healthy vs. unhealthy men was lower at older age by -0.72 (-0.96 to -0.48) vs. -1.03 (-1.25 to -0.80), and for women by -0.92 (-1.14 to -0.70) vs. -1.22 (-1.43 to -1.02) mL/min/1.73 m^2/year. For healthy and unhealthy persons of both sexes, both the 97.5^{th} and 2.5^{th} GFR percentile exhibited a negative linear association with age.

Conclusion

Healthy ageing is associated with a higher mean GFR than unhealthy ageing, but both the mean and 97.5 percentiles of the GFR distribution are lower in old healthy persons than in

middle-aged healthy persons. This suggests that healthy ageing is not associated with preserved GFR in old age.

Introduction

The Global Burden of Disease Study has found that ageing was responsible for 43% of the increased loss of disability-adjusted life-years caused by chronic kidney disease (CKD) between 1990 and 2016.[1] Improved survival for the oldest age groups combined with an almost exponential increase in CKD prevalence with age indicate that this trend will probably continue.[2]

Because of the age-related reduction in population mean GFR, there is an ongoing debate about whether the CKD definition should be changed to incorporate age-varying GFR thresholds.[3, 4] However, it is not known whether lower mean GFR in older people is caused by natural senescence or by diseases associated with lower GFR in the elderly. Some longitudinal studies have found a preserved or improved rather than lower GFR in a significant proportion of ageing persons.[5] Although this suggests that good health may prevent age-related GFR decline, studies of kidney biopsies from living kidney donors demonstrate that a reduction in the number of nephrons occurs from a young age even in the absence of disease.[6]

Our current knowledge about ageing and GFR in the general population mainly comes from cross-sectional studies performed decades ago, which have been summarized in a detailed review by Delanaye et al.[7] Few, if any, of these studies were population-based, and the number of participants older than 65 years was very small.[7] Because the prevalence of chronic disease is higher at older age, we have little knowledge about the effects of natural ageing vs. disease on GFR in the last decades of life. Although there are some large population-based studies based on GFR estimated from serum creatinine, [8-15] this approach is problematic in older people because of confounding by sarcopenia and other non-GFR related factors.[16-20]

We performed a meta-analysis of individual participant data from four population-based studies in three European cohorts where GFR had been measured using plasma iohexol

clearance in persons aged between 50 and 97 years. Our aims were to study the association of GFR with age in healthy persons and predict reference intervals for GFR in healthy ageing across the studied age range. As it would not be possible to perform a population-based study with a high number of truly healthy individuals in the oldest age-groups, we designed the study to use a generalized additive regression model to adjust for the association of comorbidity and risk factors with GFR and to predict the distribution of GFR in hypothetically healthy persons.

Methods

Study population

This cross-sectional investigation was a collaboration between population-based studies in Europe that measured GFR using exogenous filtration markers. Information about eligible studies was obtained from the European Kidney Function Consortium and from a search of literature databases. Three eligible cohorts were identified: The Renal Iohexol Clearance Survey in Tromsø 6 (RENIS-T6) (n=1632),[21] the Berlin Initiative Study (BIS) (n=610)[22] and the Age, Gene/Environment Susceptibility (AGES) - Kidney Study (n=819) (Figure 1).[23] The RENIS cohort included a repeated GFR measurement in the RENIS Follow-up Study (RENIS-FU) after a mean follow-up of 5.6 years (n=1329).[24] The examinations in RENIS-T6 and RENIS-FU were both included in the present investigation.

The RENIS cohort included participants between 50 and 63 years of age at baseline from the sixth wave of a series of population surveys in the municipality of Tromsø in Northern Norway.[21] The response rate in the sixth Tromsø Study was 74% for persons eligible for RENIS.[25] BIS recruited persons from the German healthcare fund ‘‘Allgemeine Ortskrankenkasse Nordost’’ in Berlin. The response rate for the total BIS cohort was 8.1%. AGES-Kidney is a substudy of the AGES-II-Reykjavik Study, which was a follow-up of the population-based Reykjavik Study in Iceland.[23] The response rate in the AGES-II-Reykjavik Study was 71% [26] and for those eligible for AGES-Kidney 65%.[23]

The inclusion criteria for the three cohorts were similar, except that AGES-Kidney excluded individuals receiving active cancer treatment, and BIS excluded persons that required nursing care during daytime and nighttime. RENIS excluded persons with self-reported diabetes, cardiovascular disease or kidney disease at baseline in RENIS-T6, but diabetes diagnosed by HbA1c ≥ 6.5% (≥ 48 mmol/mol) at baseline and incident cases during follow-up were

included.[21 22 23] Persons receiving renal replacement therapy were excluded from all three cohorts.

The people invited to AGES-Kidney and RENIS were random samples of the general population, and those invited to BIS a random sample from the ‘‘Allgemeine Ortskrankenkasse Nordost’’, which provides insurance coverage to almost 50% of persons older than 70 years in Berlin.[22] Although participation was voluntary, the three cohorts of examined persons were all representative of their source populations. The RENIS cohort has been found similar to all eligible patients in the sixth Tromsø Study with respect to key variables.[27] The mean estimated GFR, calculated using the MDRD equation, was 89.3 vs. 90.6 ml/min/1.73 m^2 for women, and 93.1 vs. 93.2 ml/min/1.73 m^2 for men in RENIS and the Tromsø Study, respectively.

The prevalence of the most important chronic diseases in BIS was similar to that of all persons older than 70 years in the “Allgemeine Ortskrankenkasse Nordost”.[28] Also, the prevalence of diabetes,[29] myocardial infarction,[30] angina pectoris,[30] stroke[31] and cancer[32] were of similar order of magnitude as in other German studies of chronic diseases in older adults.

The participants in AGES-Kidney were younger, had lower systolic blood pressure, and were less likely to be current smokers or have cardiovascular disease or diabetes than participants in AGES-II-Reykjavik who were not included.[23] The mean estimated GFR was 65.7 vs. 64.1 mL/min/1.73 m^2 among those who participated and those who did not.[23] More detailed information about the cohorts can be found in previous publications.[21-24]

Technically unsuccessful measurements were excluded from the investigations (RENIS-T6, n=5; RENIS-FU, n=5; AGES-Kidney n=14; BIS n=40) (Figure 1).[21, 23, 24, 33]

This study was approved by the ethical review boards of the three respective investigations. The study adhered to the Declaration of Helsinki. All the subjects provided informed written consent.

Data

Data on morbidity, smoking habits and medication use were obtained through questionnaires in all three cohorts. The use of individual classes of antihypertensive medications was registered in the following dichotomous variables: beta blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, calcium-channel blockers, loop diuretics, thiazide diuretics, mineralocorticoid receptor antagonists, other diuretics and other antihypertensive drugs, including alpha blockers. The use of lipid-lowering medications, antidiabetic drugs and cardiac glycosides (digoxin/digitoxin) was also registered. Smokers were categorized as current, previous or never.

Definitions

Diabetes was defined as either self-reported diabetes, use of anti-diabetic medication or HbA1c ≥ 6.5% (≥ 48 mmol/mol).

Details about urinary creatinine and albumin measurements in all three cohorts have been given previously.[23, 28, 34] The urinary albumin-to-creatinine ratio (ACR) was classified in the categories <10 mg/g, ≥ 10 and < 30 mg/g, and ≥ 30 mg/g, corresponding to the categories optimal, high normal and high/very high/nephrotic.[35]

In RENIS and AGES-Kidney, blood pressure (BP) was measured as described previously,[23, 36] and in BIS, according to the ESC/ESH recommendations.[37] Subjects with an office systolic BP ≥ 140 mm Hg, diastolic BP ≥ 90 mm Hg, or those who were on antihypertensive medications were categorized as having hypertension according to the ESC/ESH guidelines.[37]

GFR measurements

GFR was measured as plasma iohexol clearance in all three cohorts. Multiple-sample protocols were used in AGES-Kidney and BIS, and a single-sample protocol in RENIS. Details of the GFR measurement methods, including an investigation of agreement between the multiple- and single-sample protocols, have been previously reported.[38] Substantial

agreement between the methods was found. Iohexol concentration was measured with high-performance liquid chromatography in all three cohorts.[38] The iohexol assays of the three studies were calibrated by reanalyzing thawed samples in the laboratory of the Department of Medical Biochemistry, University Hospital of North Norway (UNN), Tromsø, Norway. The results of the calibration have been reported previously.[38] No calibration was found to be necessary for the BIS and RENIS samples, but the following equation was used to calibrate the AGES-Kidney results to the UNN laboratory: $\log(\text{iohexol}_{UNN})=-0.091+1.025 \times \log(\text{iohexol}_{AGES})$.[38] This calibration resulted in a mean difference in GFR of only 0.87 mL/min from the original results.

GFR was indexed to 1.73 m^2 body surface area. Body surface area was estimated using the equation developed by Dubois and Dubois.[39]

Serum creatinine was analyzed using the same isotope dilution mass spectrometry-traceable enzymatic assay (CREA Plus, Roche Diagnostics, Mannheim, Germany) in all three cohorts.[33, 36, 40] Estimated GFR was calculated from serum creatinine (eGFRcrea) using the Chronic Kidney Disease Epidemiology Collaboration equation.[41]

Statistical methods

Characteristics of the study participants were provided at the time of the GFR measurements, i.e. characteristics for the RENIS cohort was reported for both the baseline (RENIS-T6) and the follow-up (RENIS-FU) examination. Quantile regression was used for testing the unadjusted difference in median GFR across health status categories.

"Health status" was defined as a dichotomous variable where a healthy person was defined as a person with no history of myocardial infarction, angina pectoris, coronary revascularization procedures, stroke, cancer, diabetes, hypertension, current smoking, or use of lipid-lowering medication or cardiac glycosides; body mass index (BMI) <30 kg/m^2 and ACR < 30 mg/g. Because information about heart failure was not available in BIS and RENIS, it was not

included in the definition. However, most persons with heart failure caused by coronary heart disease would have been classified as unhealthy and medications commonly used for heart failure such as angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, beta-blockers, loop diuretics and mineralocorticoid receptor blockers were classified as antihypertensive drugs that would also have caused a participant to be categorized as unhealthy. Additionally, we included cardiac glycosides as another indicator of heart failure.

This investigation was designed as a meta-analysis with individual participant data using a one-stage statistical analysis.[42] The associations between GFR indexed for body surface area and age, sex, health status and cohort membership were explored in generalized additive regression models for location, scale and shape (GAMLSS) using the gamV procedure from the mgcViz-package in R.[43, 44] GAMLSS is a new regression method suitable for modeling the age-dependent distribution of variables. A detailed explanation of the method can be found in the Supplemental Material. In brief, the mean and standard deviation (SD) of the GFR distribution are modeled as separate functions of the independent variables in the same regression model. These functions may be linear or non-linear. In addition to investigating the association of the independent variables with the mean of the GFR distribution as in ordinary regression methods, GAMLSS makes it possible to investigate their association with the SD of the distribution. This means that the association of any percentile of the GFR distribution across age can be studied instead of focusing only on the mean, similar to quantile regression.

We analyzed the associations between GFR indexed for body surface area as the dependent variable and age, sex and health status as independent variables. We adjusted for the correlation between the first (RENIS-T6) and second (RENIS-FU) GFR measurement for the same individual in the RENIS cohort by including a random intercept for each participant in all models. Adjustment for cohort effects were made by including random coefficients for cohort membership and for the interaction between cohort membership and other independent variables. We assumed the same cohort effects for both rounds (RENIS-T6 and RENIS-FU)

of RENIS. The variance-covariance structure of the random effects was assumed to be independent in all models. The GFR-age association was defined as the difference in mean GFR per one year older age and is represented by the coefficient for the age-variable in the regression model. A negative GFR-age association signifies a lower population mean GFR by older age. The regression coefficient for the interaction between age and health status represents the association between health status and the GFR-age association.

The Akaike Information Criterion (AIC) was used to compare the fit of different regression models.[45] This criterion scores the models for fit to the data, but penalizes the score for the number of independent variables and complexity of the model. A lower AIC indicates a better fit.

We first analyzed both the mean and the SD of the GFR distribution as functions of the main effects of age, sex and the health status variable. We also included the interaction between age and health status and a random sex-specific effect for cohort membership to adjust for possible differences in GFR distribution between the cohorts.

In this model, statistically significant main effects of all the independent variables and the age-health status interaction were found for the mean of GFR ($p<0.05$). The cohort random effect was statistically significant for men, but not for women. This means that there is variation in the GFR level between the cohorts for men, but not for women. For the SD of GFR, there was no main effect of sex and no sex-specific cohort random effect ($p \geq 0.05$). Accordingly, in the SD part of the model, the sex-specific cohort random effect was removed and a common cohort random effect for both sexes ($p<0.05$) was retained. The AIC for this model was 33380.43.

To investigate the possibility of different associations between age and GFR distributions across the cohorts, we included random effects for the interaction between age and cohort in the functions for both the mean and the SD of GFR. The effect was statistically significant for

the mean, but not for the SD. This means that the GFR-age associations may differ between the cohorts, and adding this effect to the function for the mean of the model improved the fit (AIC=33306.61).

Next, we tested interactions between age and sex, and health status and sex, for both the mean and SD in this model. Only the interaction between age and sex for the mean was statistically significant (p=0.005). This interaction also improved the fit (AIC=33302.43) and was included in the model.

Possible non-linear effects of age were tested by adding smooth terms for the interaction between age and health status, and age and sex in separate models. This was done for both the mean and SD of GFR, but model fit was no better for these models than for the model without non-linear terms (AIC=33302.98 for the interaction between age and health status; AIC=33304.35 for age and sex). In a separate model, we also tested the effect of the three-way interaction between age, sex and health status on the GFR mean, which was not statistically significant (p=0.34).

The final model was used to predict and plot the 2.5th, median and 97.5th percentiles for the GFR distribution for individuals aged 50 to 95 years.[46] We predicted the percentiles separately for men and women by health status. The random cohort effects in the model were set at zero in these predictions, which means that the predictions represent an average between the three cohorts.

We used R version 3.5.1 (2018-07-02) (https://www.r-project.org/). Statistical significance was set at $p<0.05$.

Results

The combined RENIS, BIS and AGES-Kidney cohorts comprise 4326 GFR measurements in 3002 persons. Of these, 4209 (97%) observations in 2885 persons had complete datasets without missing data (Table S1) (Figure 1). Observations with missing data were omitted from the study population because multiple imputation methods for generalized additive regression models are not available.

Baseline characteristics of the study population are shown in Table 1. RENIS-T6 and RENIS-FU combined covered the age range 50 to 70 years, and the age ranges for BIS and AGES-Kidney were 70 to 97, and 74 to 93 years, respectively. The differences between the cohorts shown in Table 1 reflect the variation in age and in inclusion criteria. AGES-Kidney and BIS are similar, except for higher prevalence of diabetes and ACR>=30 mg/g in BIS than in AGES-Kidney. The number of persons with BMI < 20 kg/m^2 was 26 (1.6 %) in RENIS-T6, 31 (2.3 %) in RENIS-FU, 4 (0.7 %) in BIS and 15 (2.1 %) in AGES-Kidney.

A total of 513 (32%), 360 (27%), 18 (3%), and 44 (6%) participants were categorized as healthy in RENIS-T6, RENIS-FU, BIS and AGES-Kidney, respectively (Table 2). Baseline characteristics according to health status are shown in Table S2. A scatterplot of all the GFR measurements vs. age according to health status is presented in Figure 2.

Table 2 shows the observed median, the 2.5th and 97.5 percentiles for GFR according to the health status variable for each of the cohorts. In BIS and AGES-Kidney, there was a statistically significant higher GFR for healthy vs. unhealthy persons ($P<0.05$), but not in RENIS-T6 or RENIS-FU.

Using GAMLSS regression, we analyzed the mean and the SD of the GFR distribution as functions of age, sex, cohort and the health status variable (Table 3 and Table S3). The intercept of the model corresponds to the GFR-estimate for an unhealthy 50-year-old woman (Table 3). Being healthy was associated with a slightly lower mean GFR of 3.25 mL/min/1.73

m^2 at age 50 years, but with a markedly higher GFR-age association of 0.30 mL/min/1.73 m^2 per year, as represented by the coefficient for the interaction between age and health status in Table 3 ($p<0.001$). Consequently, GFR was higher for healthy than for unhealthy people at all ages above 61 years (Figure 3). The GFR-age association was less negative for men than for women, being respectively -0.72 (95% CI -0.96 to -0.48) vs. -0.92 (95% CI -1.14 to -0.70) mL/min/1.73 m^2 per year for healthy, and -1.03 (95% CI -1.25 to -0.80) vs. -1.22 (95% CI -1.43 to -1.02) mL/min/1.73 m^2 per year for unhealthy persons ($p=0.005$ for the interaction between sex and the GFR-age association). The difference in GFR-age association between men and women was also observed when we stratified by age younger or older than 70 years (Figure S2), and by cohort, although this was not statistically significant (0.12, 0.12 and 0.16 mL/min/1.73 m^2 per year in RENIS, AGES-Kidney and BIS, respectively).

There was no statistically significant association between the SD of the GFR distribution and older age (Table 3). This means that although mean GFR was lower at higher age, the variation in GFR at any given age for a given health status was more or less the same. However, healthy persons had a 19 % lower SD of their GFR distribution than the unhealthy ($p<0.001$), indicating that GFR varies less in healthy than in the unhealthy persons (Table 3).

The random effects in the model demonstrate that there were differences between the cohorts with regard to the association between GFR and male sex, in the GFR-age association across age and in the SD of the GFR distribution ($p<0.05$) (Table S3). Because we had only three different cohorts, which may be considered few for the estimation of random effects, we replaced the random cohort effects with fixed effects and reanalyzed the model. The point estimates of the fixed effects model were very similar to the random effects model (Table S4).

We repeated the analyses of the model shown in Table 3 with non-indexed GFR, measured in mL/min, as the dependent variable and height and weight added as independent variables. The effect of being healthy on the GFR-age association was very similar to that in the primary

analysis (0.32 (95% CI 0.20 to 0.45) vs. 0.30 (95% CI 0.18 to 0.43) mL/min/1.73 m^2 per year; Table 3).

Results of stratified analyses according to sex and age using the final model can be found in Supplemental Figure S2. The GFR-age association for healthy persons was consistently lower than zero in all the subgroups ($p<0.05$). The confidence interval for healthy persons over 70 years of age was wide due to the small sample size in this category.

The predicted median and 95% reference intervals for GFR in a healthy person based on the final GAMLSS model (Table 3) have been plotted against age for men and women in Figure 3. The group defined as unhealthy is shown in gray for comparison. In healthy persons, the 60 ml/min/1.73 m^2 threshold intersects the 2.5th percentile at age 67.1 years for women and 70.8 years for men (Figure 3). Table 4 presents predicted median GFR values and 95% reference ranges for five-year intervals in healthy men and women. Predicted 10th, 25th, 75th and 90th percentiles of the GFR distribution can be found in Table S5.

The final GAMLSS-model in Table 3 was reanalyzed using eGFRcrea as the dependent variable instead of iohexol clearance (Table S6). The predicted median and 95% reference interval for eGFRcrea in a healthy person are compared to iohexol-clearance in Figure 4. Contrary to iohexol clearance, there was no sex-difference in the eGFRcrea-age association. Also, the SD of the eGFRcrea distribution demonstrated an increase with both age and female sex which was not seen with iohexol clearance. However, the eGFRcrea-age association was still negative for the 97.5th percentiles in both sexes (Figure 4).

Discussion

We found a negative linear association between population mean GFR and older age, even in persons defined as healthy by a set of very stringent criteria. The point estimate for the GFR-age association in healthy persons was -0.72 and -0.92 mL/min/1.73 m^2 per year in men and women, respectively. Previous cross-sectional estimates of the GFR-age association have varied widely,[47-55] probably because of differences between the study populations. In potential living kidney donors, point estimates between -0.5 and -0.9 mL/min/1.73 m^2/year have been found.[51-53, 56-58]

If adjustment for health status had eliminated the GFR-age association, this would have supported the hypothesis that poor health fully accounts for the finding of lower mean GFR in old age.[5] It is noteworthy that the SD of GFR did not increase with age in healthy persons as would be expected if a subset of this group had unrecognized kidney disease while others aged with preserved GFR. If even a minority of exceptionally healthy individuals aged with preserved rather than lower GFR, one would expect no or only a weak age association for the 97.5th percentile of the GFR distribution. Although the absence of these findings in the present study does not refute the hypothesis, it suggests that age or other factors may contribute to the association. A similar finding regarding the 95th percentile was observed in a study of potential living kidney donors by Chakkera et al.[59] The results are also consistent with histologic findings in biopsies from living kidney donors, which indicate that nephron number is lower at older age even in apparently healthy persons, although the study by Denic et al. only included persons younger than 75 years and may not be representative of older healthy people in the general population.[6]

The observation of a high proportion of persons with non-declining GFR in some longitudinal studies may be explained by a failure to use statistical methods that take measurement error into account.[8, 10, 12, 60-62] This will overestimate the variability of the rate at which GFR

declines and the proportion of persons with non-declining GFR. Also, none of these studies used precise methods to measure GFR,[8-15, 60-66] and, except for one small Swedish study,[67] they were not population-based.[60, 61, 63-66] The Baltimore Longitudinal Study of Aging is often referred to as having found that one-third of a group of healthy persons experienced no decline in GFR. However, the study may have been biased by the use of creatinine clearance for assessing GFR and the inclusion of patients with diabetes in the healthy group.[60]

Being unhealthy was associated with a slightly higher GFR in the regression model (Table 3), which indicates that mean GFR for unhealthy persons was higher than for healthy persons among the youngest participants (Figure 3). One explanation for this paradoxical finding may be the glomerular hyperfiltration associated with obesity, smoking, elevated blood pressure and other risk factors. [68-73] Previous longitudinal results from the RENIS cohort and Pima-Indians in the U.S. have indicated that hyperfiltration is independently associated with a more rapid decline in GFR.[74]

The GFR-age association was less negative in men than in women (Table 3). This finding was consistent across all three cohorts and in models adjusting for differences in health status between the sexes. Previous population-based studies,[9, 12] small studies using measured GFR [51, 52, 54, 75-77] and studies of persons with established CKD [62, 78-81] have yielded mixed results about sex differences in GFR-age associations, but most of them did not fully adjust for comorbidity and risk factors. Our findings may partly explain the higher prevalence of CKD in women than in men, but do not explain why more men than women initiate renal replacement therapy.[82] However, the findings should be interpreted with caution because of the lack of longitudinal data.

Statistically significant random effects demonstrated differences in mean GFR for men and in GFR-age associations across the three cohorts (Table S3). Selection bias relative to the source populations in the RENIS and AGES-Kidney cohorts seems unlikely because these cohorts

had high participation rates and estimated GFR similar to those who did not participate. [23, 25, 26] The participation rate in BIS was lower, but comparisons with the source population indicate that the cohort was representative.[28] The most probable explanation for the heterogeneity may be unmeasured confounders. Unmeasured morbidity, risk factors and medications are the most likely possibilities, but differences in genetic, epigenetic or environmental factors cannot be excluded, as e.g. the dietary intake of protein. There are also other indications of geographical variations in kidney disease within Europe. One study of CKD prevalence found that Norway had the lowest and North-Eastern Germany the highest prevalence,[83] and that these differences could not be explained by variations in hypertension, diabetes or obesity.

One method for defining reference intervals for physiologic or biochemical parameters is to take the 95th interpercentile range of their distribution in a population of healthy persons. For age-dependent parameters, it is almost impossible to find cohorts of sufficient size for the oldest age groups, which include very few truly healthy individuals. [7] Accordingly, most previous studies of reference intervals for GFR have included few individuals older than 70 years and have made no distinction between healthy subjects and others.[53, 84-86] By contrast, we used a statistical model to estimate the effects of disease and risk factors and to predict percentiles of GFR in healthy persons between age 50 and 95 years. Because we adjusted for the heterogeneity between the cohorts, the predictions represent an average of the observations in three different geographic regions.

A comparison between classification of low GFR based on the 2.5th percentile for healthy persons in the present study and the currently accepted criterion for CKD stage 3 to 5 (GFR < 60 mL/min/1.73 m^2) shows that the criterion underestimates the prevalence of low GFR in women younger than 67.1 years and in men younger than 70.8 years and overestimates the prevalences at higher ages (Figure 3). However, this is the result of applying a low percentile and a rather strict definition of “healthy” to assess the effect of age on GFR under optimal

physiologic conditions. In addition to reference intervals for GFR in healthy persons, an optimal classification system for CKD should be based on the risk of adverse outcomes at different levels of GFR. Further research of GFR as a risk factor in old age is needed.[87]

In clinical practice, eGFRcrea is the most commonly used method for assessing GFR. Similar to iohexol clearance, both the median and 97.5th percentile of eGFRcrea had negative associations with age (Figure 4). However, there were several differences between eGFRcrea and iohexol clearance when modeling their relationship with age (Table S6). A study of potential kidney donors also found differences between the 95th percentiles of eGFRcrea and measured GFR.[59] This indicates that measured GFR should be used for establishing reference intervals for GFR.

The principal strength of this study is that we used measured instead of estimated GFR and that the cohorts are population-based. To our knowledge, the three cohorts included in the study are the only ones in Europe with these characteristics. The number of included persons far exceeds that of previous studies using measured GFR, especially in the oldest age groups. Although the low number of healthy persons in the highest age groups may have limited the power of statistical tests for the interaction between age, health status and other variables, it seems unlikely that we have failed to include a significant number of very old healthy persons with preserved GFR that would have changed our conclusion.

A consensus about an operational definition of “healthy” does not exist. Although it could have been made more stringent, we believe that the definition used in this investigation is very conservative and excludes most common conditions that affect GFR. One exception is that the definition does not explicitly include heart failure because this information was not available in BIS and RENIS. However, we believe that the inclusion of other cardiovascular disease and medications as indicators of heart failure ensured that very few of these patients were misclassified as healthy (see Methods). Another possible limitation of the definition is

that it does not explicitly exclude persons with specific types of kidney disease, or persons with CKD based on kidney damage other than albuminuria as ascertained by kidney imaging or urine sediment examination. However, the criteria excluding persons with albuminuria and hypertension will probably also exclude most of these persons. Therefore, we assume that this limitation had only a small impact on our estimates.

The heterogeneity between the three cohorts is a reason for caution in applying the results to other populations. We cannot exclude a survivor bias in the estimates of the GFR distribution, especially in the older age groups. However, this would support rather than weaken our conclusion of a lower GFR in older healthy persons. Due to the cross-sectional design of our study, the GFR-age associations apply at the population level, whereas the rates of change at the individual level could not be estimated. In principle, GFR-age associations observed over time in follow-up of individuals may differ from those observed across cohorts of individuals at different ages.[88] However, even allowing for great variation and possible non-linear individual GFR trajectories, the finding that the 2.5th percentile in healthy 50 year old persons is similar to the 97.5th percentile in healthy 95 year old (Figure 3) suggests that ageing with preserved GFR across this age span must be very uncommon. Although difficult to perform, longitudinal studies of GFR decline would be of value to confirm these findings at the individual level. Another limitation was the difference between the cohorts regarding inclusion of subjects and available data on morbidity and risk factors. Statistical methods have been used to adjust for these differences.

We conclude that there is a negative linear GFR-age association in healthy people aged between 50 and 95 years, and an even more negative association for people with chronic diseases and CKD risk factors. Although it can only conclusively be demonstrated in longitudinal studies with repeated GFR measurements in the same individuals, this finding suggests that healthy ageing is not associated with preserved GFR in old age.

Author contributions

B.O.E., R.P., N.E., T.M., O.S.I. and E.S. designed the study. B.O.E., R.P., N.E., T.M., M.vdG., V.G., O.S.I., L.A.I., A.S.L. and E.S. organized the GFR measurements and collected the data. B.O.E. analyzed the data, made the figures and drafted the paper. B.O.E., R.P., N.E., T.M.., M.vdG., V.G., O.S.I., L.A.I., T.G.J., A.S.L., M.D.S., H.T. and E.S. interpreted the data and revised the paper. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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Table 1. Characteristics of the population-based cohorts

	RENIS-T6[a]	RENIS-FU[a]	BIS	AGES-Kidney
Number of participants, n (%)	1622 (100.0)	1324 (100.0)	547 (100.0)	716 (100.0)
Age (SD), years	58.1 (3.8)	63.6 (4.0)	78.4 (6.2)	80.3 (4.1)
Male sex, n (%)	797 (49.1)	657 (49.6)	311 (56.9)	317 (44.3)
Body weight (SD), kg	79.7 (14.4)	79.4 (14.3)	77.3 (14.0)	77.1 (14.1)
Height (SD), cm	170.6 (8.7)	170.6 (8.7)	166.2 (8.5)	167.7 (9.4)
Body mass index (SD), kg/m^2	27.3 (4.0)	27.2 (4.1)	27.9 (4.3)	27.4 (4.3)
Body surface area (SD), m2	1.9 (0.2)	1.9 (0.2)	1.9 (0.2)	1.9 (0.2)
Cardiovascular disease				
Myocardial infarction, n (%)	1 (0.1)	18 (1.4)	83 (15.2)	89 (12.4)
Myocardial revascularization, n (%)	5 (0.3)	26 (2.0)	93 (17.0)	113 (15.8)
Angina pectoris, n (%)	2 (0.1)	12 (0.9)	56 (10.2)	60 (8.4)
Stroke, n (%)	3 (0.2)	24 (1.8)	42 (7.7)	53 (7.4)
Diabetes, n (%)	19 (1.2)	42 (3.2)	136 (24.9)	81 (11.3)
Cancer, n (%)	76 (4.7)	120 (9.1)	123 (22.5)	134 (18.7)
Hypertension[b], n (%)	692 (42.7)	693 (52.3)	503 (92.0)	623 (87.0)
Systolic blood pressure (SD), mmHg	129.7 (17.6)	130.7 (17.0)	144.9 (21.5)	142.3 (20.3)
Diastolic blood pressure (SD), mmHg	83.4 (9.8)	81.9 (9.3)	82.3 (13.0)	69.6 (10.7)
Antihypertensive medication, n (%)	298 (18.4)	420 (31.7)	425 (77.7)	524 (73.2)
Digoxin or digitoxin, n (%)	1 (0.1)	6 (0.5)	18 (3.3)	24 (3.4)
Lipid lowering medication, n (%)	106 (6.5)	232 (17.5)	202 (36.9)	287 (40.1)
Anti-diabetic medication, n (%)	0 (0.0)	11 (0.8)	99 (18.1)	44 (6.1)
Smoking				
Never, n (%)	503 (31.0)	432 (32.6)	263 (48.1)	295 (41.2)
Current, n (%)	344 (21.2)	177 (13.4)	32 (5.9)	42 (5.9)
Previous, n (%)	775 (47.8)	715 (54.0)	252 (46.1)	379 (52.9)
Absolute GFR (SD), mL/min	104.0 (20.1)	98.5 (19.8)	64.8 (19.2)	66.7 (19.4)
Body surface area-indexed GFR (SD), mL/min/ 1.73m^2	94.0 (14.4)	89.1 (14.5)	60.5 (16.3)	61.9 (16.6)
CKDEPI estimate of GFR based on creatinine (SD), mL/min/ 1.73m^3	94.9 (9.5)	88.2 (10.5)	68.8 (17.1)	65.5 (17.1)
Urinary albumin-to-creatinine ratio ≥ 30.0 mg/g, n (%)	24 (1.5)	26 (2.0)	126 (23.0)	110 (15.4)
Urinary albumin-to-creatinine ratio ≥ 300.0 mg/g, n (%)	1 (0.1)	2 (0.2)	19 (3.5)	15 (2.1)

Data are shown as mean (standard deviation) or n (percent).

Abbreviations: RENIS-T6, Renal Iohexol Clearance in Tromsø 6;RENIS-FU, the Renal Iohexol-clearance Survey Follow-up Study; BIS, Berlin Initiative Study; AGES-Kidney, Age, Gene/Environment Susceptibility - Kidney Study; GFR, glomerular filtration rate; SD, standard deviation; CKDEPI, Chronic Kidney Disease Epidemiology Collaboration.

[a]RENIS-T6 and RENIS-FU are the baseline and follow-up examinations of the RENIS cohort.

[b]Office systolic blood pressure ≥ 140 mm Hg, office diastolic blood pressure ≥ 90 mm Hg, or the use of antihypertensive medications.

Table 2. GFR (mL/min/1.73m^2) according to health status of participants in the population-based cohorts.

	Number of participants		Median		2.5th percentile		97.5th percentile	
	Unhealthy	Healthy[a]	Unhealthy	Healthy	Unhealthy	Healthy	Unhealthy	Healthy
RENIS-T6[b]	1109	513	94.2	93.1	65.6	63.0	123.1	118.9
RENIS-FU[b]	964	360	89.2	90.1	57.5	66.5	117.5	115.3
BIS	529	18	60.4	69.8[c]	29.7	44.2	88.7	96.2
AGES-Kidney	672	44	62.5	72.4[c]	26.2	42.4	90.5	98.4
Total	3274	935	82.6	90.8	34.0	59.7	117.8	118.0

Abbreviations: RENIS-T6, Renal Iohexol Clearance in Tromsø 6;RENIS-FU, the Renal Iohexol-clearance Survey Follow-up Study; BIS, Berlin Initiative Study; AGES-Kidney, Age, Gene/Environment Susceptibility - Kidney Study; GFR, glomerular filtration rate .

[a]"Healthy" defined as no cardiovascular disease, cancer, diabetes, hypertension, smoking, lipid-lowering medication or digoxin, as well as body mass index <30 kg m^{-2} and urinary albumin-to-creatinine ratio < 30 mg g^{-1}.

[b]RENIS-T6 and RENIS-FU are the baseline and follow-up examinations of the same cohort.

c P<0.05 for difference between "unhealthy" and "healthy" category in the BIS and AGES-Kidney cohorts.

Table 3. General additive mixed model analysis of GFR mean and standard deviation in three population-based cohorts. Fixed effects of health status, age and sex.

Effect of independent variables on mean GFR

Variable	β	95% confidence interval	P-value
Unhealthy 50-year-old female (intercept)	98.91	97.43 to 100.39	<0.001
Age, per year	-1.22	-1.43 to -1.02	<0.001
Healthy (yes/no)[a]	-3.25	-4.86 to -1.63	<0.001
Male sex	-0.82	-8.54 to 6.90	0.84
Interaction between age and being healthy[a]	0.30	0.18 to 0.43	<0.001
Interaction between age and male sex	0.20	0.06 to 0.34	0.005

Effect of independent variables on the standard deviation of GFR

Variable	β	95% confidence interval	P-value
Unhealthy 50-year-old female (intercept)	12.40	10.53 to 14.61	<0.001
Percent change associated with each independent variable			
Age, per year	-0.1 %	-0.6 % to 0.3 %	0.52
Healthy (yes/no)[a]	-18.6 %	-23.9 % to -13.0 %	<0.001
Male sex	1.4 %	-3.5 % to 6.6 %	0.59

Abbreviations: RENIS, Renal Iohexol Clearance Survey; BIS, Berlin Initiative Study; AGES-Kidney, Age, Gene/Environment Susceptibility - Kidney Study; GFR, glomerular filtration rate.

GFR measured in mL/min/1.73 m^2. Model adjusted for random cohort effects and for random intercepts for each participant, see supplementary Table S3 for random effect results.

[a] "Healthy" defined as no cardiovascular disease, cancer, diabetes, hypertension, smoking, lipid-lowering medication or digoxin, as well as body mass index <30 kg m^{-2} and urinary albumin-to-creatinine ratio < 30 mg/g.

Table 4. Predicted percentiles of GFR (mL/min/1.73 m^2) for healthy women and men according to age group[a].

Age group (years)	Women				Men			
	Number of GFR measurements	Median	2.5th percentile	97.5th percentile	Number of GFR measurements	Median	2.5th percentile	97.5th percentile
50 to 54	226	93.4	73.7	113.1	217	93.0	73.1	113.0
55 to 59	405	88.8	69.2	108.3	423	89.4	69.6	109.3
60 to 64	566	84.2	64.7	103.6	521	85.8	66.1	105.5
65 to 69	296	79.6	60.3	98.9	293	82.2	62.7	101.8
70 to 74	129	75.0	55.8	94.1	102	78.6	59.2	98.0
75 to 79	253	70.4	51.4	89.4	225	75.0	55.7	94.3
80 to 84	164	65.8	46.9	84.7	188	71.4	52.2	90.6
85 to 89	68	61.2	42.4	79.9	79	67.8	48.8	86.8
>=90	20	56.6	38.0	75.2	34	64.2	45.3	83.1

[a] Estimates corresponding to Figure 3.

Figure 1

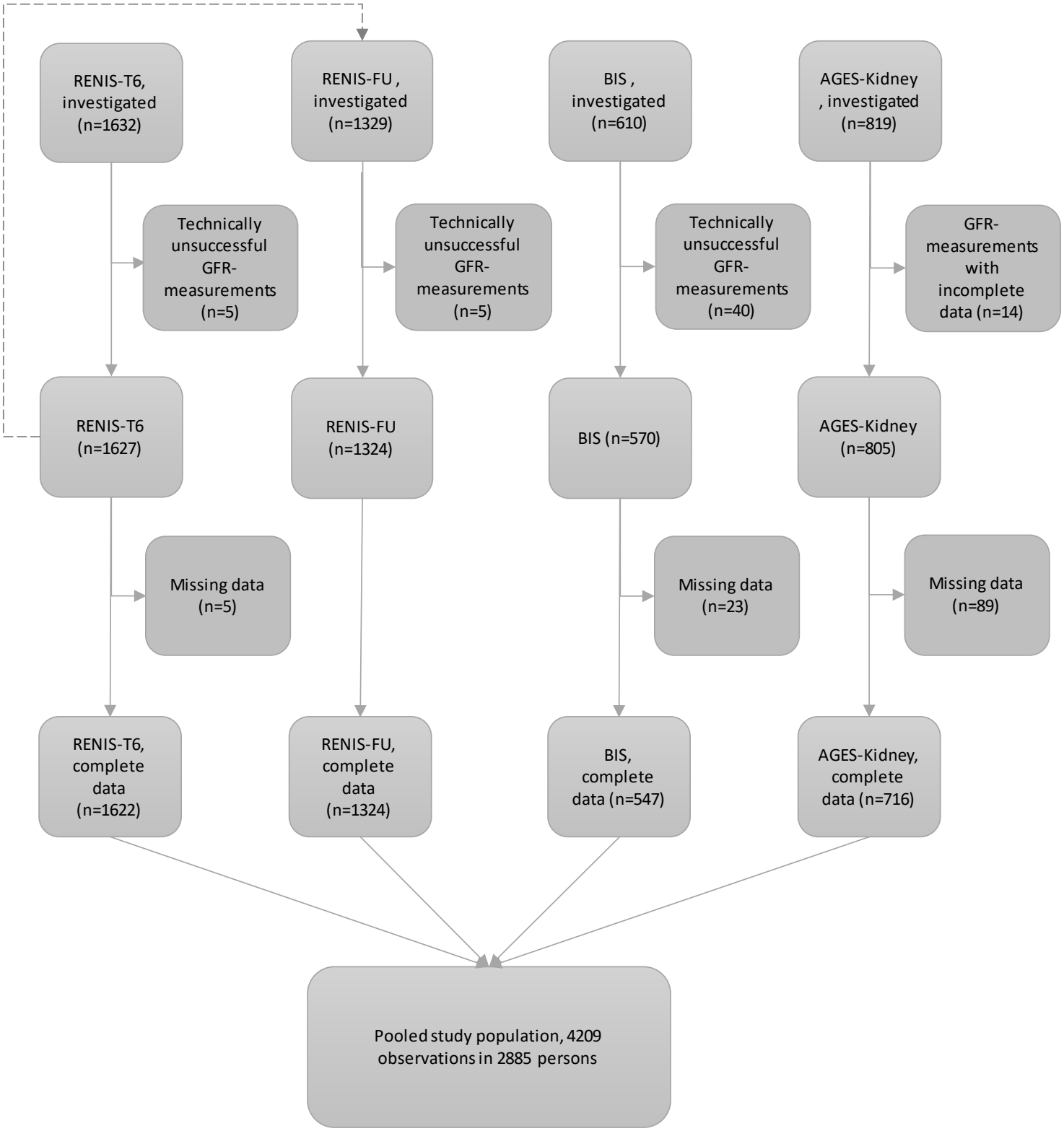
RENIS-T6, investigated (n=1632)
RENIS-FU , investigated (n=1329)
BIS , investigated (n=610)
AGES-Kidney , investigated (n=819)
Technically unsuccessful GFR-measurements (n=5)
Technically unsuccessful GFR-measurements (n=5)
Technically unsuccessful GFR-measurements (n=40)
GFR-measurements with incomplete data (n=14)
RENIS-T6 (n=1627)
RENIS-FU (n=1324)
BIS (n=570)
AGES-Kidney (n=805)
Missing data (n=5)
Missing data (n=23)
Missing data (n=89)
RENIS-T6, complete data (n=1622)
RENIS-FU, complete data (n=1324)
BIS, complete data (n=547)
AGES-Kidney, complete data (n=716)
Pooled study population, 4209 observations in 2885 persons

Figure 2

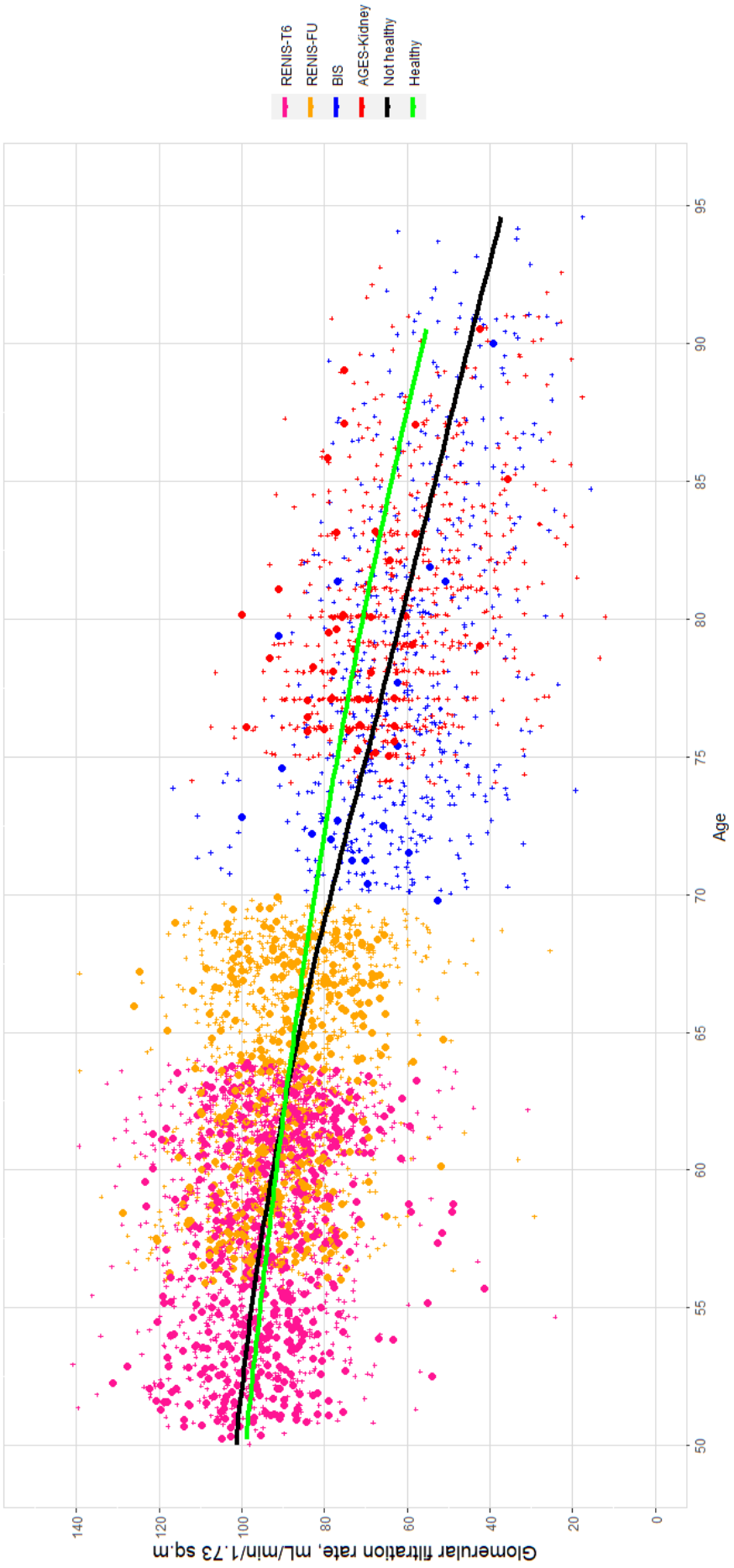
RENIS-T6
RENIS-FU
BIS
AGES-Kidney
Not healthy
Healthy
Glomerular filtration rate, mL/min/1.73 sq.m
Age
140
120
100
80
60
40
20
0
50
55
60
65
70
75
80
85
90
95

Figure 3

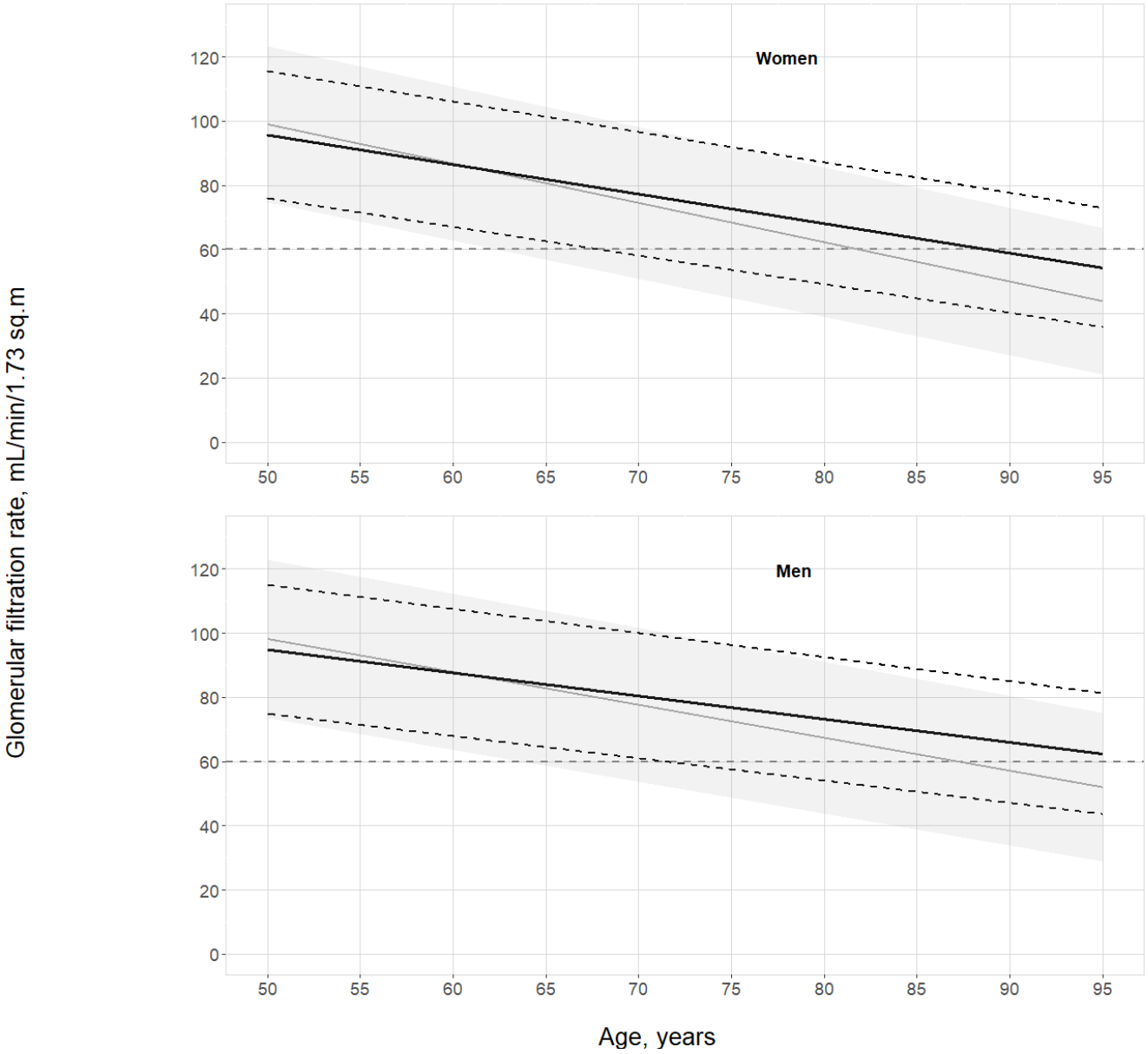
Women
Men
120
100
80
60
40
20
0
50
55
60
65
70
75
80
85
90
95
Glomerular filtration rate, mL/min/1.73 sq.m
Age, years

Figure 4

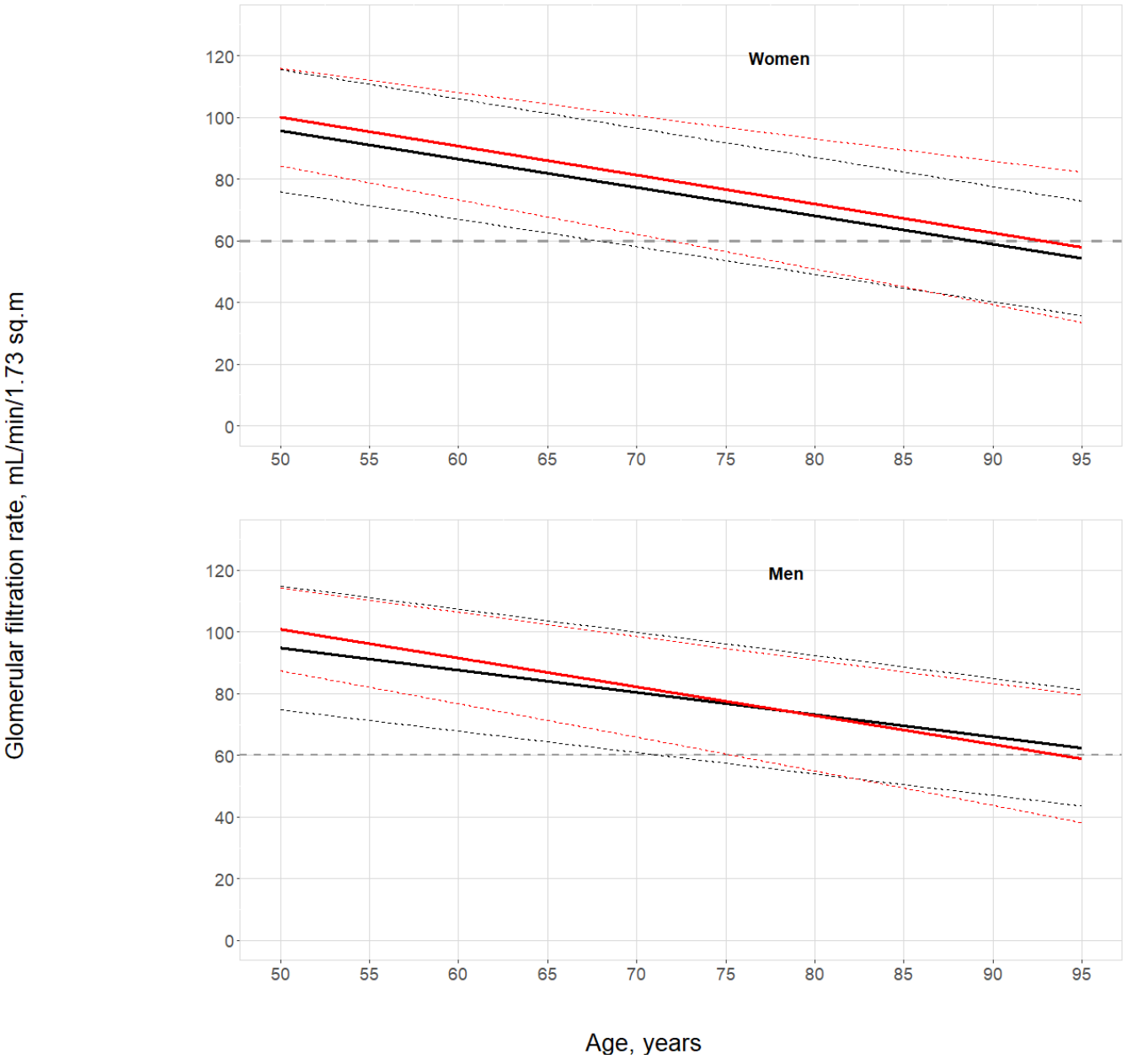
Women
Men
120
100
80
60
40
20
0
50
55
60
65
70
75
80
85
90
95
Glomerular filtration rate, mL/min/1.73 sq.m
Age, years

Figure Legends

Figure 1. Inclusion of participants from RENIS-T6 (Renal Iohexol Clearance Survey in Tromsø 6), RENIS-FU (RENIS Follow-up Study), BIS (Berlin Initiative Study) and AGES-Kidney (Age, Gene/Environment Susceptibility - Kidney Study) in the meta-analysis. The dashed arrow from RENIS-T6 to RENIS-FU indicates the repeated measurements of GFR in the RENIS cohort after a mean follow-up of 5.6 years.

Figure 2. Body surface area-indexed GFR measured as plasma iohexol-clearance and plotted against age in the RENIS, BIS and AGES-Kidney cohorts (n=4209). The marker colors indicate cohort membership. Filled circles indicate measurements in healthy persons and crosses in unhealthy persons. Measurements for both the baseline (RENIS-T6) and the follow-up examinations (RENIS-FU) of the same persons in the RENIS cohort are shown. The red and green curves represent unadjusted LOESS (locally estimated scatterplot smoothing) fits to measurements in unhealthy and healthy persons, respectively.

Figure 3. Predicted median (bold black line), 2.5^{th} and 97.5^{th} percentiles (dashed black lines) as a function of age for healthy women (upper panel) and men (lower panel). The predicted median (gray line) and 95% interpercentile intervals (dark grey band) are shown for persons classified as unhealthy for comparison. The grey dashed line indicates the 60 mL/min/1.73 m^2 level

Figure 4. Predicted medians (bold lines), 2.5^{th} and 97.5^{th} percentiles (dashed lines) of iohexol clearance (black) and eGFR based on creatinine (red) as functions of age for healthy women (upper panel) and men (lower panel). The grey dashed line indicates the 60 mL/min/1.73 m^2 level

Supplemental Material

GFR in Healthy Ageing: An Individual Participant Data Meta-Analysis of Iohexol Clearance in European Population-based Cohorts

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Supplemental Methods

The generalized additive regression model for location, scale and shape

In ordinary regression analyses, the distribution of the dependent variable is commonly assumed to be normal conditional on the independent variables. The mean of this distribution is estimated as a function of the independent variables, whereas its variance is assumed to be constant. However, in many real-life situations the variance may also be a function of the independent variables, and the distribution of the dependent variable may exhibit both skewness and kurtosis. In a generalized additive regression model for location, scale and shape (GAMLSS),[1, 2] the parameters describing all these properties of the distribution of the dependent variable (the variance, skewness and kurtosis) can be estimated as separate functions of the independent variables. These functions may be non-linear and are often modeled as splines of the independent variables.

The GAMLSS provides great flexibility in modeling population data, and percentiles of the conditional distribution of the dependent variable can be estimated to calculate reference intervals for e.g. age-dependent variables. The WHO has recommended this statistical method for establishing length and weight standards for children.[3]

Supplemental References

1. Rigby, RA, Stasinopoulos, DM: Generalized Additive Models for Location, Scale and Shape. *J R Stat Soc Ser C Appl Statist*, 54**:** 507-554, 2005.

2. Wood, SN: *Generalized Additive Models. An Introduction with R.*, Boca Raton, CRC Press, 2017.

3. World Health Organization: *WHO child growth standards: length/height for age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age, methods and development*, World Health Organization, 2006.

Tables

Table S1. Missing data in RENIS-T6, RENIS-FU, BIS and AGES-Kidney.

	RENIS-T6	RENIS-Follow Up	BIS	AGES-Kidney
Number of participants	1627	1324	570	805
Age (years)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Male sex	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Body weight (kg)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Height (cm)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Body mass index (kg/m^2)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Body surface area (m^2)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Urinary albumin-to-creatinine ratio (mg/g)	5 (0.3 %)	0 (0.0 %)	6 (1.1 %)	3 (0.4 %)
Smoking	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	54 (6.7 %)
Myocardial infarction	0 (0.0 %)	0 (0.0 %)	8 (1.4 %)	0 (0.0 %)
Myocardial revascularization	0 (0.0 %)	0 (0.0 %)	6 (1.1 %)	0 (0.0 %)
Angina pectoris	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Stroke	0 (0.0 %)	0 (0.0 %)	5 (0.9 %)	0 (0.0 %)
Diabetes	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Cancer	0 (0.0 %)	0 (0.0 %)	2 (0.4 %)	0 (0.0 %)
Systolic blood pressure (mmHg)	0 (0.0 %)	0 (0.0 %)	1 (0.2 %)	2 (0.2 %)
Diastolic blood pressure (mmHg)	0 (0.0 %)	0 (0.0 %)	1 (0.2 %)	2 (0.2 %)
Antihypertensive medication	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	31 (3.9 %)
Digoxin or digitoxin	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	31 (3.9 %)
Lipid lowering medication	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	31 (3.9 %)
Anti-diabetic medication	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	31 (3.9 %)
Absolute GFR (mL min^{-1})	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Participants without missing data	1622 (99.7 %)	1324 (100.0 %)	547 (96.0 %)	716 (88.9 %)

Data are shown as n(percent).

Abbreviations: RENIS-T6, Renal Iohexol Clearance in Tromsø 6;RENIS-FU Study, the Renal Iohexol-clearance Survey Follow-up Study; BIS, Berlin Initiative Study; AGES-Kidney, Age, Gene/Environment Susceptibility - Kidney Study; GFR, glomerular filtration rate .

Table S2. Characteristics of the study population[a] according to health status

	Unhealthy	Healthy[b]
Number of observations, n (%)	3274 (100.0)	935 (100.0)
Age (SD), years	67.8 (10.2)	60.8 (6.6)
Male sex, n (%)	1673 (51.1)	409 (43.7)
Body weight (SD), kg	80.4 (14.8)	73.4 (10.8)
Height (SD), cm	169.3 (9.0)	170.3 (8.7)
Body mass index (SD), kg/m^2	28.0 (4.3)	25.2 (2.5)
Body surface area (SD), m2	1.9 (0.2)	1.8 (0.2)
Cardiovascular disease		
Myocardial infarction, n (%)	191 (5.9)	0 (0.0)
Myocardial revascularization, n (%)	237 (7.3)	0 (0.0)
Angina pectoris, n (%)	130 (4.0)	0 (0.0)
Stroke, n (%)	122 (3.8)	0 (0.0)
Diabetes, n (%)	278 (8.5)	0 (0.0)
Cancer, n (%)	453 (13.8)	0 (0.0)
Hypertension[b], n (%)	2511 (76.7)	0 (0.0)
Systolic blood pressure (SD), mmHg	138.1 (19.6)	120.2 (10.4)
Diastolic blood pressure (SD), mmHg	81.4 (12.2)	77.3 (7.4)
Antihypertensive medication, n (%)	1667 (50.9)	0 (0.0)
Digoxin or digitoxin, n (%)	49 (1.5)	0 (0.0)
Lipid lowering medication, n (%)	827 (25.3)	0 (0.0)
Anti-diabetic medication, n (%)	154 (4.7)	0 (0.0)
Smoking		
Never, n (%)	1109 (33.9)	384 (41.1)
Current, n (%)	595 (18.2)	0 (0.0)
Previous, n (%)	1570 (48.0)	551 (58.9)
Absolute GFR (SD), mL/min	89.1 (27.1)	96.9 (18.9)
Body surface indexed GFR (SD), mL/min/ $1.73m^2$	80.3 (21.6)	90.6 (14.4)
CKDEPI estimate of GFR based on creatinine (SD), mL/min/ $1.73m^3$	82.4 (18.2)	91.4 (10.6)
Urinary albumin-creatinine ratio ≥ 30.0 mg/g, n (%)	286 (8.7)	0 (0.0)
Urinary albumin-to-creatinine ratio ≥ 300.0 mg/g, n (%)	37 (1.1 %)	0 (0.0 %)

Data are shown as mean (standard deviation) or n (percent).

Abbreviation: GFR, glomerular filtration rate; SD, standard deviation; CKDEPI, Chronic Kidney Disease Epidemiology Collaboratio.

[a]The study population comprises both the baseline and follow-up examinations of the RENIS cohort (RENIS-T6 and RENIS-FU), which means that the standard deviations in the table should be interpreted with caution.

[b]"Healthy" defined as no cardiovascular disease, cancer, diabetes, hypertension, smoking, lipid-lowering medication or digoxin, as well as body mass index <30 kg m^{-2} and urinary albumin-to-creatinine ratio < 30 mg g^{-1}.

[c]Office systolic blood pressure ≥ 140 mm Hg, office diastolic blood pressure ≥ 90 mm Hg, or the use of antihypertensive medications.

Table S3. General additive mixed model analysis of GFR mean and standard deviation in three population-based cohorts. Fixed and random effects.

Fixed effects

Effect of independent variables on mean GFR

Variable	β	95% confidence interval	P-value
Unhealthy 50-year-old female (intercept)	98.91	97.43 to 100.39	<0.001
Age, per year	-1.22	-1.43 to -1.02	<0.001
Healthy (yes/no)[a]	-3.25	-4.86 to -1.63	<0.001
Male sex	-0.82	-8.54 to 6.90	0.84
Interaction between age and being healthy[a]	0.30	0.18 to 0.43	<0.001
Interaction between age and male sex	0.20	0.06 to 0.34	0.005

Effect of independent variables on the standard deviation of GFR

Variable	β	95% confidence interval	P-value
Unhealthy 50-year-old female (intercept)	12.40	10.53 to 14.61	<0.001
Percent change associated with each independent variable			
Age, per year	-0.1 %	-0.6 % to 0.3 %	0.52
Healthy (yes/no)[a]	-18.6 %	-23.9 % to -13.0 %	<0.001
Male sex	1.4 %	-3.5 % to 6.6 %	0.59

Random effects

Effect of independent variables on mean GFR

Variable	Estimate	95% confidence interval	P-value
Cohort effect for males			
RENIS[b]	6.59	-0.67 to 13.85	0.07
BIS[b]	-4.86	-12.05 to 2.34	0.19
AGES-Kidney[b]	-1.73	-8.95 to 5.48	0.64
Standard deviation of random effect	6.16	2.19 to 17.28	0.003
Interaction between cohort effect and age			
RENIS[b]	0.19	-0.01 to 0.39	0.06
BIS[b]	-0.13	-0.33 to 0.07	0.20
AGES-Kidney[b]	-0.06	-0.26 to 0.13	0.54
Standard deviation of random effect	0.17	0.06 to 0.47	0.03
Random intercept, standard deviation	5.09	4.80 to 5.39	<0.001

Effect of independent variables on the standard deviation of GFR

Variable	Estimate	95% confidence interval	P-value
Cohort effect, percent change associated with each independent variable			
RENIS[b]	-15 %	-26 % to -2.1 %	0.02
BIS[b]	5.0 %	-8.4 % to 20 %	0.48
AGES-Kidney[b]	12 %	-2 % to 28 %	0.11
Standard deviation of random effect	12 %	3.7 % to 41 %	<0.001

Abbreviations: RENIS, Renal Iohexol Clearance Survey; BIS, Berlin Initiative Study; AGES-Kidney, Age, Gene/Environment Susceptibility - Kidney Study; GFR, glomerular filtration rate.

GFR measured in mL/min/1.73 m^2. The fixed effect part of this table is identical to Table 3 in the main article.

[a]"Healthy" defined as no cardiovascular disease, cancer, diabetes, hypertension, smoking, lipid-lowering medication or digoxin, as well as body mass index <30 kg m^{-2} and urinary albumin-to-creatinine ratio < 30 mg/g.

[b]Best linear unbiased predictions of effects.

Table S4. General additive mixed model analysis of GFR mean and standard deviation in three population-based cohorts. Fixed cohort effects.

Effect of independent variables on mean GFR

Variable	β	95% confidence interval	P-value
Unhealthy 50-year-old female (intercept)	98.87	97.37 to 100.37	<0.001
Age, per year	-1.22	-1.30 to -1.14	<0.001
Healthy (yes/no)[a]	-3.22	-4.84 to -1.59	<0.001
Male sex	-0.96	-4.36 to 2.44	0.58
Interaction between age and being healthy[a]	0.30	0.18 to 0.42	<0.001
Interaction between age and male sex	0.20	0.06 to 0.34	0.004
Male in the RENIS cohort	6.69	4.60 to 8.78	<0.001
Male in the BIS cohort	-4.92	-6.77 to -3.08	<0.001
Male in the AGES-Kidney cohort	-1.77	-3.70 to 0.17	0.07
Age, per year, in the RENIS cohort	0.19	0.14 to 0.25	<0.001
Age, per year, in the BIS cohort	-0.13	-0.18 to -0.08	<0.001
Age, per year, in the AGES-Kidney cohort	-0.06	-0.11 to -0.02	0.006

Effect of independent variables on the standard deviation of GFR

Variable	β	95% confidence interval	P-value
Unhealthy 50-year-old female (intercept)	12.98	11.68 to 14.44	<0.001
Percent change associated with each independent variable			
Age, per year	-0.3 %	-0.8 % to 0.1 %	0.14
Healthy (yes/no)[a]	-18 %	-24 % to -13 %	<0.001
Male sex	1.5 %	-3.4 % to 6.7 %	0.56
RENIS cohort	-18 %	-23 % to -12 %	<0.001
BIS cohort	6 %	1 % to 12 %	0.02
AGES-Kidney cohort	14 %	8 % to 21 %	<0.001

Abbreviations: RENIS, Renal Iohexol Clearance Survey; BIS, Berlin Initiative Study; AGES-Kidney, Age, Gene/Environment Susceptibility - Kidney Study; GFR, glomerular filtration rate.

GFR measured in mL/min/1.73 m^2. This model is identical to the model in Table S3, but uses fixed instead of random cohort effects.

The standard deviation of the random intercept in this model was 5.09 (95% confidence interval 4.81 to 5.39).

[a] "Healthy" defined as no cardiovascular disease, cancer, diabetes, hypertension, smoking, lipid-lowering medication or digoxin, as well as body mass index <30 kg m^{-2} and urinary albumin-to-creatinine ratio < 30 mg/g.

Table S5. Predicted percentiles of GFR (mL/min/1.73 m^2) for healthy women and men according to age group[a].

Age group (years)	Women				Men			
	10th percentile	25th percentile	75th percentile	90th percentile	10th percentile	25th percentile	75th percentile	90th percentile
50 to 54	80.5	86.6	100.2	106.3	80.0	86.2	99.9	106.1
55 to 59	76.0	82.0	95.5	101.6	76.5	82.6	96.3	102.4
60 to 64	71.5	77.5	90.9	96.9	72.9	79.0	92.6	98.7
65 to 69	67.0	72.9	86.2	92.2	69.4	75.5	89.0	95.0
70 to 74	62.4	68.4	81.6	87.5	65.9	71.9	85.3	91.3
75 to 79	57.9	63.8	76.9	82.8	62.4	68.4	81.6	87.6
80 to 84	53.4	59.3	72.3	78.1	58.9	64.8	78.0	83.9
85 to 89	48.9	54.7	67.6	73.5	55.4	61.2	74.3	80.2
>=90	44.4	50.2	63.0	68.8	51.8	57.7	70.7	76.5

[a] Estimates based on the model in Table 3 in the main article.

Table S6. General additive mixed model analysis of creatinine-based eGFR mean and standard deviation in three population-based cohorts. Fixed and random effects.

Fixed effects

Effect of independent variables on mean eGFR

Variable	β	95% confidence interval	P-value
Unhealthy 50-year-old female (intercept)	101.92	100.91 to 102.92	<0.001
Age, per year	-1.13	-1.29 to -0.97	<0.001
Healthy (yes/no)[a]	-1.87	-3.02 to -0.71	0.002
Male sex	0.83	-0.22 to 1.87	0.12
Interaction between age and being healthy[a]	0.19	0.10 to 0.29	<0.001
Interaction between age and male sex	0.00	-0.07 to 0.08	0.905

Effect of independent variables on the standard deviation of eGFR

Variable	β	95% confidence interval	P-value
Unhealthy 50-year-old female (intercept)	10.28	7.45 to 14.20	<0.001
Percent change associated with each independent variable			
Age, per year	1.0 %	0.5 % to 1.4 %	<0.001
Healthy (yes/no)[a]	-21.5 %	-26.7 % to -15.9 %	<0.001
Male sex	-15.0 %	-19.3 % to -10.5 %	<0.001

Random effects

Effect of independent variables on mean eGFR

Variable	Estimate	95% confidence interval	P-value
Cohort effect for males			
RENIS[b]	0.00	-0.02 to 0.02	0.99
BIS[b]	0.00	-0.02 to 0.02	0.99
AGES-Kidney[b]	0.00	-0.02 to 0.02	1.00
Standard deviation of random effect	0.01	0.01 to 0.01	0.06
Interaction between cohort effect and age			
RENIS[b]	0.14	-0.01 to 0.29	0.07
BIS[b]	-0.05	-0.20 to 0.10	0.49
AGES-Kidney[b]	-0.09	-0.24 to 0.06	0.25
Standard deviation of random effect	0.13	0.05 to 0.35	<0.001
Random intercept, standard deviation	3.56	3.40 to 3.72	<0.001

Effect of independent variables on the standard deviation of eGFR

Variable	Estimate	95% confidence interval	P-value
Cohort effect, percent change associated with each independent variable			
RENIS[b]	-31 %	-50 % to -6.4 %	0.02
BIS[b]	22.0 %	-10.4 % to 66 %	0.21
AGES-Kidney[b]	20 %	-12 % to 63 %	0.26
Standard deviation of random effect	31 %	10.4 % to 108 %	<0.001

Abbreviations: RENIS, Renal Iohexol Clearance Survey; BIS, Berlin Initiative Study; AGES-Kidney, Age, Gene/Environment Susceptibility - Kidney Study; eGFR, estimated glomerular filtration rate.
eGFR measured in mL/min/1.73 m^2.
[a] "Healthy" defined as no cardiovascular disease, cancer, diabetes, hypertension, smoking, lipid-lowering medication or digoxin, as well as body mass index <30 kg m^{-2} and urinary albumin-to-creatinine ratio < 30 mg/g.
[b] Best linear unbiased predictions of effects.

Figure Legends

Figure S1. Histogram showing the residuals for the final GAMLSS model of GFR corresponding to Table 3 in the main article.

Figure S2. GFR-age association for the GAMLSS models, stratified according to age and sex.

Figures

Figure S1.

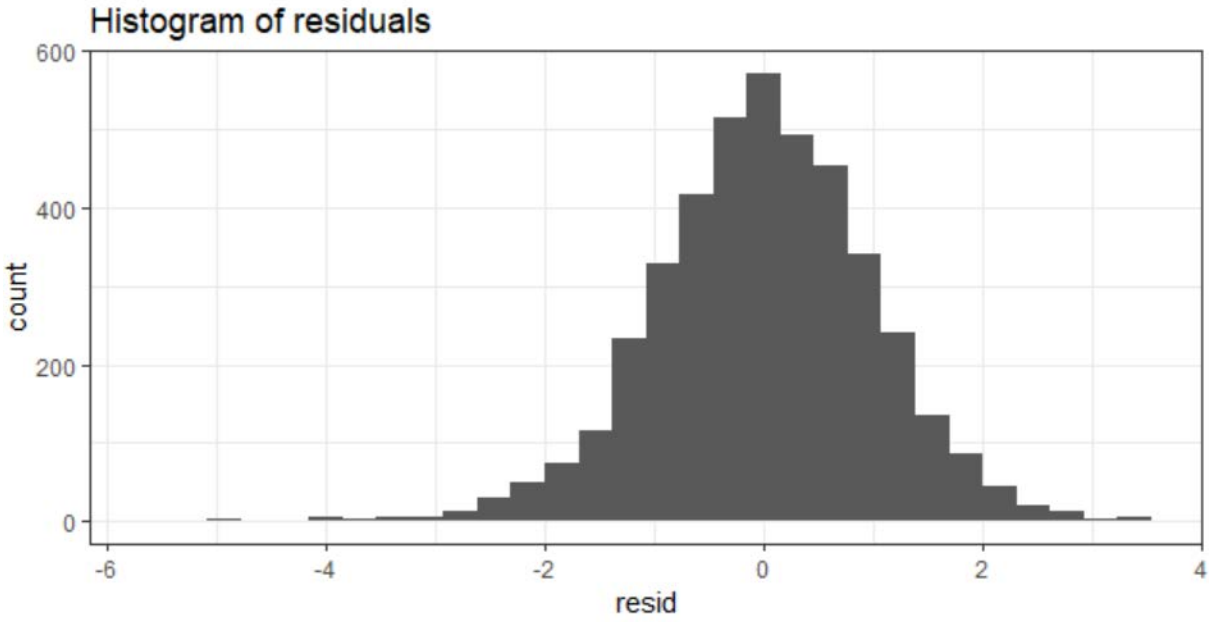
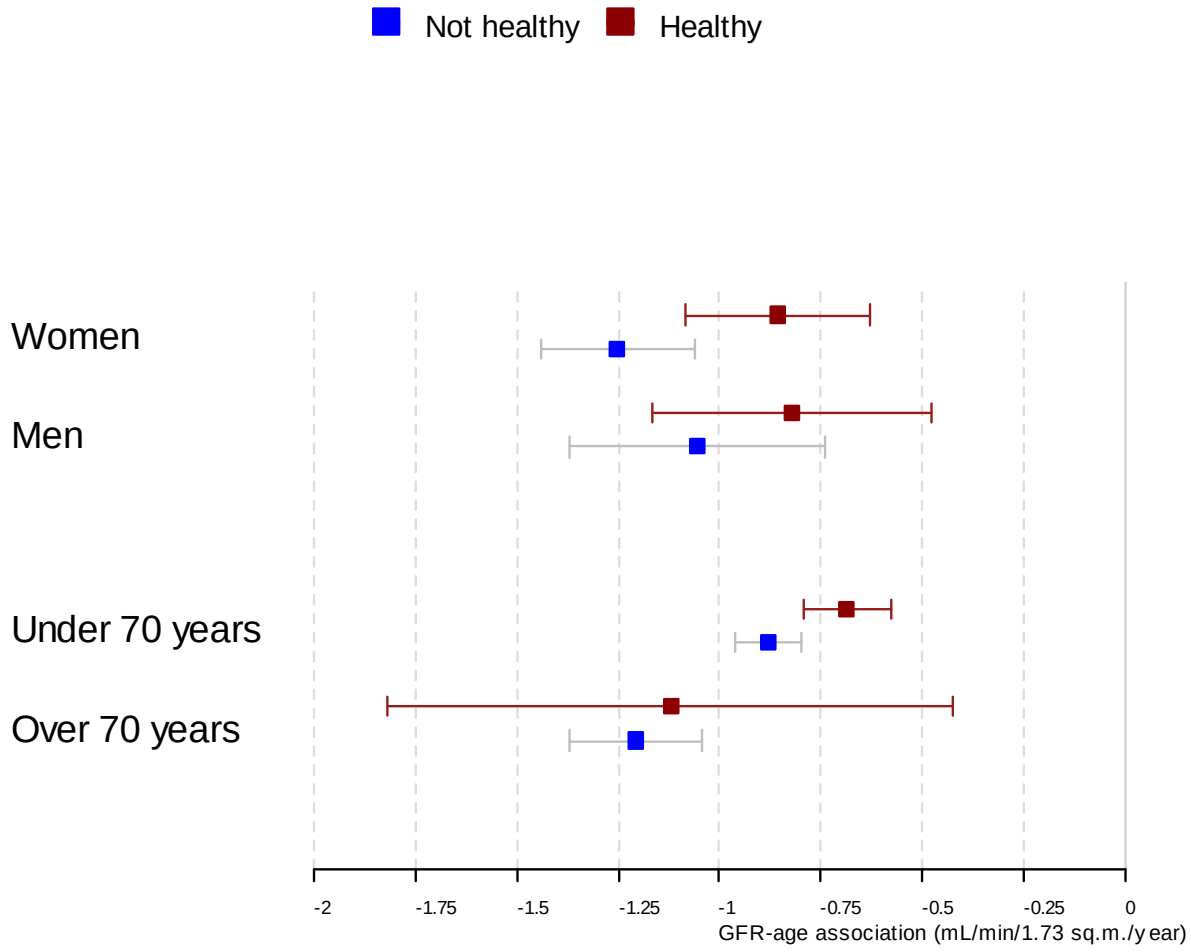


Figure S2.


Not healthy
Healthy
Women
Men
Under 70 years
Over 70 years
-2
-1.75
-1.5
-1.25
-1
-0.75
-0.5
-0.25
0
GFR-age association (mL/min/1.73 sq.m./year)