

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), m ²	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.

^aThe 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.

^cOffice 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				
<i>Effect of independent variables on mean GFR</i>				
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
<i>Effect of independent variables on the standard deviation of GFR</i>				
Variable	β	95% confidence interval		P-value
Unhealthy 50-year-old female (intercept)	12.40	10.53	to 14.61	<0.001
<i>Percent change associated with each independent variable</i>				
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				
<i>Effect of independent variables on mean GFR</i>				
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
<i>Effect of independent variables on the standard deviation of GFR</i>				
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 m². 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.

^bBest 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.

<i>Effect of independent variables on mean GFR</i>			
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
<i>Effect of independent variables on the standard deviation of GFR</i>			
Variable	β	95% confidence interval	P-value
Unhealthy 50-year-old female (intercept)	12.98	11.68 to 14.44	<0.001
<i>Percent change associated with each independent variable</i>			
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 m². 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 m²) 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

^aEstimates 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				
<i>Effect of independent variables on mean eGFR</i>				
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
<i>Effect of independent variables on the standard deviation of eGFR</i>				
Variable	β	95% confidence interval		P-value
Unhealthy 50-year-old female (intercept)	10.28	7.45	to 14.20	<0.001
<i>Percent change associated with each independent variable</i>				
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				
<i>Effect of independent variables on mean eGFR</i>				
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
<i>Effect of independent variables on the standard deviation of eGFR</i>				
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 m².

^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.

^bBest 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.

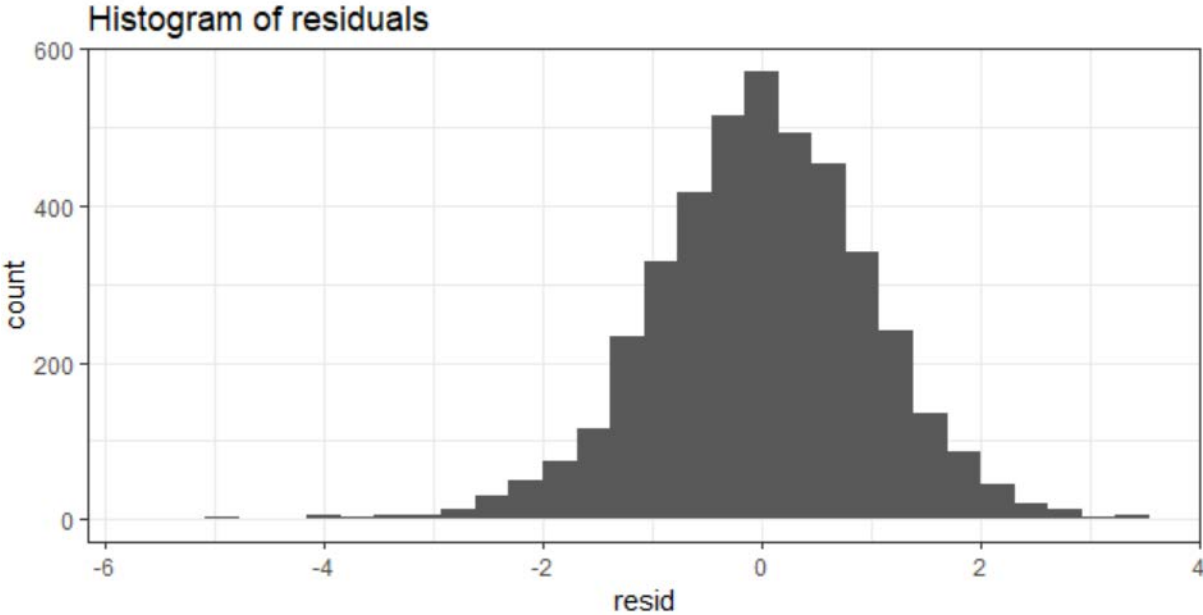


Figure S2.

