Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods 1

The UK Biobank invited participation by post from adults (target age 40-69 years) who were registered with the National Health Service between 2006 and 2010, and who lived within reasonable travelling distance of an assessment centre in the United Kingdom. The response rate to invitation was 5.5%[1].

The procedure of biochemical sampling for UK Biobank has been described previously[2–4]. Single baseline samples of blood serum and spot urine were collected from each participant and analysed at a central laboratory. Serum and urine creatinine were measured using an enzymatic (creatinase), IDMS-traceable, method on Beckman Coulter AU5400 instrument (coefficient of variation (CV) <2.8% over 3 levels of control)[5]. Serum cystatin C was measured by latex enhanced immunoturbidimetric method on a Siemens ADVIA 1800 instrument (CV <1.4% over 2 levels of control)[5]. Urine microalbumin was measured by immunoturbidimetric method using reagents and calibrators sourced from Randox Bioscience UK (CV <2.1% over 2 levels of control)[6].

eMethods 2

UK Biobank algorithm for determination of kidney failure outcome

As follow-up biochemical data were not routinely available, kidney failure was defined from hospital admission data according to a pre-specified algorithm, using ICD10 and OPCS4 codes to identify participants who required maintenance kidney replacement therapy (KRT)[7]. Participants with a kidney transplant or undergoing peritoneal dialysis were assumed to be receiving maintenance KRT for kidney failure. For participants who received haemodialysis, this was assumed to be indicative of kidney failure only if there was an associated indicator of CKD stage 5 prior to KRT, or within 365 days of KRT[7].

eMethods 3

Method of ascertainment of area under receiving operating curve (AUROC) for incremental discrimination of eGFRcr and eGFRcys for CVD and mortality.

Within older (age 65-73 years; n=76,629) and younger (age <65 years; n=351,773) age groups, participants were divided into training (80%) and test (20%) datasets. Logistic regression models were generated in the training datasets for both older and younger age groups for fatal/non-fatal cardiovascular disease (CVD) and all-cause mortality as follows:

- CVD risk factors: age, sex, smoking status, systolic and diastolic blood pressure, total, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, history of diabetes or hypertension, use of blood pressure or cholesterol-lowering medications
- CVD risk factors + eGFRcr
- CVD risk factors + eGFRcys

In the test datasets, predictions of the likelihood of CVD and mortality were generated using the predict() function. Predicted values in training and test datasets were compared using AUROC (Supplementary eTable 8) and plotted in receiver operating curves (Supplementary eFigure 5).

eReferences

1. Batty GD, Gale CR, Kivimäki M, Deary IJ, Bell S: Comparison of risk factor associations in UK Biobank against representative, general population based studies with conventional response rates: prospective cohort study and individual participant meta-analysis. *BMJ* 368: m131, 2020
2. Elliott P, Peakman TC: The UK Biobank sample handling and storage protocol for the collection, processing and archiving of human blood and urine. *Int. J. Epidemiol.* 37: 234–244, 2008
3. UK Biobank: UK Biobank Showcase. Blood Sample Collection, Processing and Transport. [Internet]. 2011 [cited 2019 Apr 17]
4. UK Biobank: UK Biobank showcase. Biospeciments manual: Collection of biological samples, processing and storage. [Internet]. 2011 [cited 2019 Apr 17]
5. UK Biobank's Enhancements Working Group: UK Biobank biomarker panel [Internet]. 1–4, 2014 [cited 2019 May 9]
6. UK Biobank: UK Biobank Showcase. Details of assays and quality control information for the urinary biomarker data. v1.0.
7. Bush K, Nolan J, Zhang Q, Herrington W, Sudlow C: Definitions of End Stage Renal Disease for UK Biobank Phase 1 Outcomes Adjudication Documentation prepared by : On behalf of UK Biobank Outcome Adjudication Group Definitions of End Stage Renal Disease , UK Biobank phase 1 outcomes adjudication. 2017

eTable 1

Baseline characteristics of participants by CKD status in older (age 65-73 years) and younger (age <65 years) participants: concordance testing between eGFRcr and eGFRcr-cys

	Older participants (65-73 years)				Younger participants (< 65 years)			
Baseline characteristics	**Neither**	**Cr only**	**Cys C only**	**Both**	**Neither**	**Cr only**	**Cys C only**	**Both**
N	73,571	795	1,042	1,221	348,498	1,274	1,003	998
Age (years): median [IQR]	67 [66, 68]	67 [66, 68]	67 [66, 69]	67 [66, 69]	55 [48, 60]	60 [55, 62]	61 [57, 63]	61 [58, 63]
Male sex: n(%)	34858 (47.4)	290 (36.5)	445 (42.7)	529 (43.3)	153974 (44.2)	391 (30.7)	362 (36.1)	380 (38.1)
Smoking status: n(%)								
Never	37160 (50.5)	431 (54.2)	459 (44.0)	557 (45.6)	197523 (56.7)	756 (59.3)	467 (46.6)	505 (50.6)
Previous	30989 (42.1)	327 (41.1)	428 (41.1)	555 (45.5)	111805 (32.1)	447 (35.1)	333 (33.2)	382 (38.3)
Current	5008 (6.8)	31 (3.9)	148 (14.2)	102 (8.4)	37998 (10.9)	69 (5.4)	193 (19.2)	106 (10.6)
Unknown	414 (0.6)	6 (0.8)	7 (0.7)	7 (0.6)	1172 (0.3)	2 (0.2)	10 (1.0)	5 (0.5)
eGFRcr (ml/min/1.73m^2): median [IQR]	92 [81, 96]	57 [55, 58]	65 [62, 70]	5 [50.9 57]	99 [89, 105]	57 [54, 58]	66 [62, 71]	54 [50, 57]
eGFRcys (ml/min/1.73m^2): median [IQR]	78.8 [69.7, 88.7]	68.6 [63.2, 75.7]	46.9 [43.1, 50.2]	48.9 [43.2, 53.9]	92.8 [81.5, 103.1]	75.8 [66.5, 87.4]	46.8 [42.8, 50.3]	49.6 [43.0, 55.4]
eGFRcr-cys (ml/min/1.73m^2): median [IQR]	88 [79, 96]	65 [62, 69]	57 [54, 58]	52 [48, 56]	99 [89, 107]	68 [63, 74]	56 [54, 58]	52 [48, 56]
uACR category:								
<10mg/g	63,505 (86.3)	694 (87.3)	812 (77.9)	953 (78.1)	316,590 (90.8)	1,151 (90.3)	773 (77.1)	763 (76.5)
10-29mg/g	10,066 (13.7)	101 (12.7)	230 (22.1)	268 (21.9)	31,908 (9.2)	123 (9.7)	230 (22.9)	235 (23.5)
Systolic blood pressure (mmHg)	147.7 (19.5)	144.4 (19.7)	146.5 (19.7)	143.6 (19.2)	137.3 (18.8)	139.0 (19.7)	140.6 (19.3)	139.3 (19.7)
Diastolic blood pressure (mmHg)	82.2 (10.4)	80.6 (10.3)	81.2 (10.6)	80.2 (11.4)	82.1 (10.6)	81.6 (10.8)	82.6 (11.2)	81.1 (11.1)
Total cholesterol (mmol/L)	5.7 (1.2)	5.7 (1.2)	5.3 (1.3)	5.3 (1.2)	5.7 (1.1)	5.8 (1.2)	5.3 (1.2)	5.4 (1.3)
HDL cholesterol (mmol/L)	1.5 (0.4)	1.5 (0.4)	1.3 (0.4)	1.3 (0.4)	1.5 (0.4)	1.5 (0.4)	1.3 (0.4)	1.3 (0.4)
LDL cholesterol (mmol/L)	3.6 (0.9)	3.5 (0.9)	3.3 (1.0)	3.3 (1.0)	3.6 (0.8)	3.6 (0.9)	3.3 (0.9)	3.4 (1.0)
Diabetes: n(%)	4690 (6.4)	53 (6.7)	160 (15.4)	168 (13.8)	12561 (3.6)	54 (4.2)	175 (17.4)	167 (16.7)
Hypertension: n(%)	24829 (33.7)	302 (38.0)	591 (56.7)	722 (59.1)	73462 (21.1)	384 (30.1)	523 (52.1)	565 (56.6)
Cholesterol-lowering medications: n(%)	20118 (27.3)	271 (34.1)	435 (41.7)	561 (45.9)	38621 (11.1)	237 (18.6)	355 (35.4)	403 (40.4)
Blood pressure medications: (%)	10789 (14.7)	110 (13.8)	285 (27.4)	326 (26.7)	29979 (8.6)	159 (12.5)	249 (24.8)	265 (26.6)

Summary of baseline demographic and clinical characteristics by CKD status in older participants (65-73 years) and younger participants (<65 years). CKD status was defined as: "No CKD": eGFRcr ≥60 and eGFRcys ≥60 (reference group), "eGFRcr G3": eGFRcr <60 and eGFRcys ≥60, "eGFRcys G3": eGFRcr ≥60 and eGFRcys <60, "Both G3": eGFRcr <60 and eGFRcys <60. All eGFR units are in mL/min/1.73m^2. eGFRcr: estimated glomerular filtration rate based on serum creatinine; eGFRcys: estimated glomerular filtration rate based on serum cystatin C; eGFRcr-cys: estimated glomerular filtration rate based on serum creatinine and cystatin C; HDL: high density lipoprotein; LDL: low density lipoprotein.

eTable 2

Cross-sectional associations of 5-year age increments with kidney function as estimated by eGFRcr, eGFRcys and eGFRcr-cys

Age bracket (years)		eGFRcr (mL/min/1.73m^2)		eGFRcys (mL/min/1.73m^2)		eGFRcr-cys (mL/min/1.73m^2)	
	N	Median	IQR	Median	IQR	Median	IQR
<45 (Intercept)	46,170	109	98; 113	105	95; 111	108	100;115
45-50	58,409	-4	-4; -3	-4	-4; -4	-3	-3; -3
50-55	66,692	-7	-7; -7	-10	-10; -8	-8	-8; -7
55-60	78,242	-10	-10; -10	-16	-17; -12	-12	-13; -11
60-65	102,260	-14	-14; -13	-21	-21; -17	-16	-17; -15
65-70	74,766	-18	-18; -16	-27	-26; -23	-21	-22; -19
70-73	1,863	-20	-20; -18	-31	-29; -27	-24	-25; -23

Quantile regression to estimate median (IQR) change in eGFR with increasing age across age brackets.

eTable 3

Cross-sectional associations of 5-year age increments with kidney function as estimated by $eGFRcr_{2009}$, eGFRcys and $eGFRcr\text{-}cys_{2009}$

Age bracket (years)		$eGFRcr_{2009}$ (mL/min/1.73m^2)		eGFRcys (mL/min/1.73m^2)		$eGFRcr\text{-}cys_{2009}$ (mL/min/1.73m^2)	
	N	Median	IQR	Median	IQR	Median	IQR
<45 (Intercept)	46,170	105	98; 110	105	95; 111	104	96;111
45-50	58,409	-4	-4; -4	-4	-4; -4	-3	-4; -4
50-55	66,692	-8	-7; -8	-10	-10; -8	-9	-9; -8
55-60	78,242	-11	-11; -11	-16	-17; -12	-13	-13; -12
60-65	102,260	-15	-15; -15	-21	-21; -17	-17	-18; -16
65-70	74,766	-19	-19; -18	-27	-26; -23	-22	-22; -21
70-73	1,863	-22	-22; -20	-31	-29; -27	-25	-26; -24

Quantile regression to estimate median (IQR) change in eGFR with increasing age across age brackets.

eTable 4

Concordance of eGFRcr and eGFRcys in older and younger participants

Older (65-73 years)

		eGFRcys <60	eGFRcys ≥60	
eGFRcr	**<60**	1,279 1.7%	737 1.0%	2,016
	≥60	6,278 8.2%	68,335 89.2%	74,613
		7,557	69,072	76,629

Younger (<65 years)

		eGFRcys <60	eGFRcys ≥60	
eGFRcr	**<60**	978 0.3%	1,294 0.4%	2,272
	≥60	6,887 2.0%	342,614 97.4%	349,501
		7,865	343,908	351,773

Concordance tables of eGFRcr and eGFRcys in older (65-73 years) and younger (<65 years) participants. eGFRcr: estimated glomerular filtration rate based on serum creatinine; eGFRcys: estimated glomerular filtration rate based on serum cystatin C. eGFR measurements are in mL/min/1.73m^2.

eTable 5

Concordance between $eGFRcr_{2009}$ and eGFRcys in older and younger participants

Older (65-73 years)

		eGFRcys <60	eGFRcys ≥60	
$eGFRcr_{2009}$	<60	1,871	1,468	3,339
		2.4%	1.9%	
	≥60	5,686	67,604	73,290
		7.4%	88.2%	
		7,557	69,072	76,629

Younger (<65 years)

		eGFRcys <60	eGFRcys ≥60	
	<60	1,415	2,302	3,717
		0.4%	0.7%	
	≥60	6,450	341,606	348,056
		1.8%	97.1%	
		7,865	343,908	351,773

Concordance tables of $eGFRcr_{2009}$ and eGFRccys in older (65-73 years) and younger (<65 years) participants. $eGFRcr_{2009}$: estimated glomerular filtration rate based on serum creatinine from CKD-EPI 2009, including race coefficients; eGFRcys: estimated glomerular filtration rate based on cystatin C. eGFR measurements are in $mL/min/1.73m^2$.

eTable 6

Concordance between eGFRcr and eGFRcr-cys in older and younger participants

Older (65-73 years)

		eGFRcr-cys <60	eGFRcr-cys ≥60	
eGFRcr	<60	1,221 2%	1,042 1%	2,263
	≥60	795 1%	73,571 96%	74,366
		2,016	74,613	76,629

Younger (<65 years)

		eGFRcr-cys <60	eGFRcr-cys ≥60	
eGFRcr	<60	998 <1%	1,274 <1%	2,272
	≥60	1,003 <1%	348,498 99%	349,501
		2,001	349,772	351,773

Concordance tables of eGFRcr and eGFRcr-cys in older (65-73 years) and younger (<65 years) participants. eGFRcr: estimated glomerular filtration rate based on serum creatinine; eGFRcr-cys: estimated glomerular filtration rate based on serum creatinine and cystatin C. eGFR measurements are in mL/min/1.73m^2.

eTable 7

Cox proportional hazards of fatal/non-fatal cardiovascular disease and all-cause mortality: concordance testing between eGFRcr and eGFRcys

Older (65-73 years): 76,629 participants						
CKD status	**Fatal/non-fatal CVD**			**All-cause mortality**		
	N events	**HR (95% CI)**	**P**	**N events**	**HR (95% CI)**	**P**
No CKD (n=68,335)	4,288	1 (Ref)		7,700	1 (Ref)	
eGFRcr G3 (n=737)	47	1.11 (0.83-1.47)	0.496	85	1.11 (0.89-1.37)	0.350
eGFRcys G3 (n=6,728)	703	1.64 (1.51-1.78)	<0.001	1,284	1.69 (1.59-1.80)	<0.001
Both G3 (n= 1,279)	167	1.93 (1.65-2.26)	<0.001	266	1.71 (1.51-1.93)	<0.001
Younger (< 65 years): 351,773 participants						
CKD status	**Fatal/non-fatal CVD**			**All-cause mortality**		
	N events	**HR (95% CI)**	**P**	**N events**	**HR (95% CI)**	**P**
No CKD (n=342,614)	8,661	1 (Ref)		13,565	1 (Ref)	
eGFRcr G3 (n= 1,294)	40	1.11 (0.81-1.51)	0.530	65	1.05 (0.82-1.34)	0.704
eGFRcys G3 (n=6,887)	559	1.86 (1.70-2.03)	<0.001	1,001	2.12 (1.98-2.26)	<0.001
Both G3 (n=978)	68	1.61 (1.27-2.05)	<0.001	145	2.13 (1.80-2.51)	<0.001

Cox proportional hazards models for fatal/non-fatal cardiovascular disease (the first of myocardial infarction, stroke or cardiovascular death) and all-cause mortality presented as hazard ratio (HR) with 95% confidence intervals. All models were adjusted for atherosclerotic risk factors (age, sex, smoking status, systolic and diastolic blood pressure, total, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, history of diabetes or hypertension, and use of blood pressure or cholesterol-lowering medications) and albuminuria. Results are displayed for older participants (65-73 years; top) and younger participants (<65 years; bottom), with concordance testing between eGFRcr and eGFRcys. CKD status was defined as: "No CKD": eGFRcr $\geq$60 and eGFRcys $\geq$60 (reference group), "eGFRcr G3": eGFRcr <60 and eGFRcys $\geq$60, "eGFRcys G3": eGFRcr $\geq$60 and eGFRcys <60, "Both G3": eGFRcr <60 and eGFRcys <60. All eGFR units are in mL/min/1.73m^2.

eTable 8

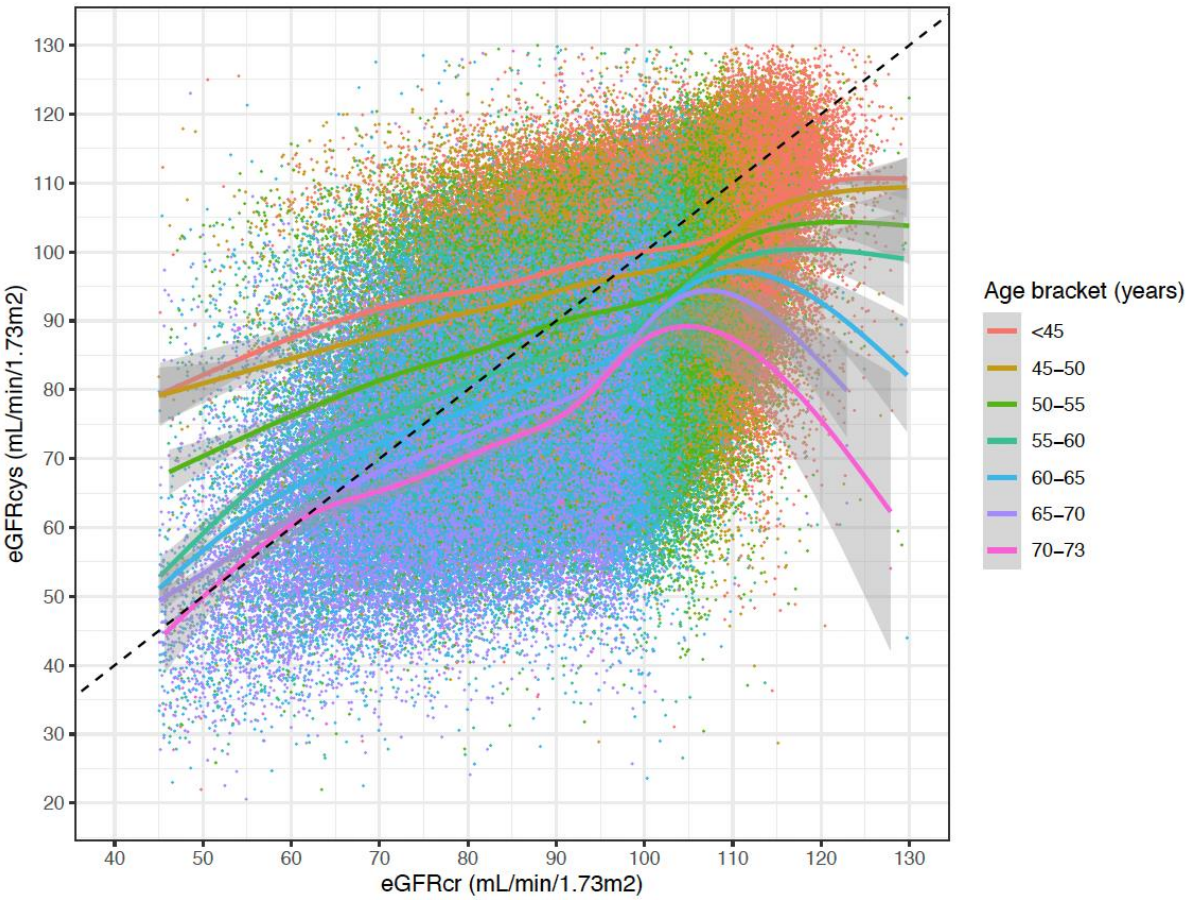
Cox proportional hazards of fatal/non-fatal cardiovascular disease and all-cause mortality: concordance testing between $eGFRcr_{2009}$ and eGFRcys

Older (65-73 years): 76,629 participants						
CKD status	**Fatal/non-fatal CVD**			**All-cause mortality**		
	N events	**HR (95% CI)**	**P**	**N events**	**HR (95% CI)**	**P**

Neither (n=67,604)	4,239	1 (Ref)		7,617	1 (Ref)	
Creat (n=1,468)	96	1.08 (0.88-1.32)	0.460	168	1.05 (0.90-1.22)	0.555
Cys C (n=5,686)	629	1.62 (1.49-1.77)	<0.001	1,172	1.70 (1.60-1.81)	<0.001
Both (n=1,871)	241	1.91 (1.67-2.18)	<0.001	378	1.67 (1.51-1.86)	<0.001
Younger (< 65 years): 351,773 participants						
CKD status	**Fatal/non-fatal CVD**			**All-cause mortality**		
	N events	**HR (95% CI)**	**P**	**N events**	**HR (95% CI)**	**P**
Neither (n=341,606)	8,626	1 (Ref)		13,515	1 (Ref)	
Creat (n=2,302)	75	1.11 (0.89-1.40)	0.347	115	1.00 (0.83-1.20)	0.977
Cys C (6,450)	523	1.87 (1.70-2.04)	<0.001	946	2.15 (2.00-2.30)	<0.001
Both (n=1,415)	104	1.67 (1.37-2.02)	<0.001	200	1.99 (1.73-2.29)	<0.001

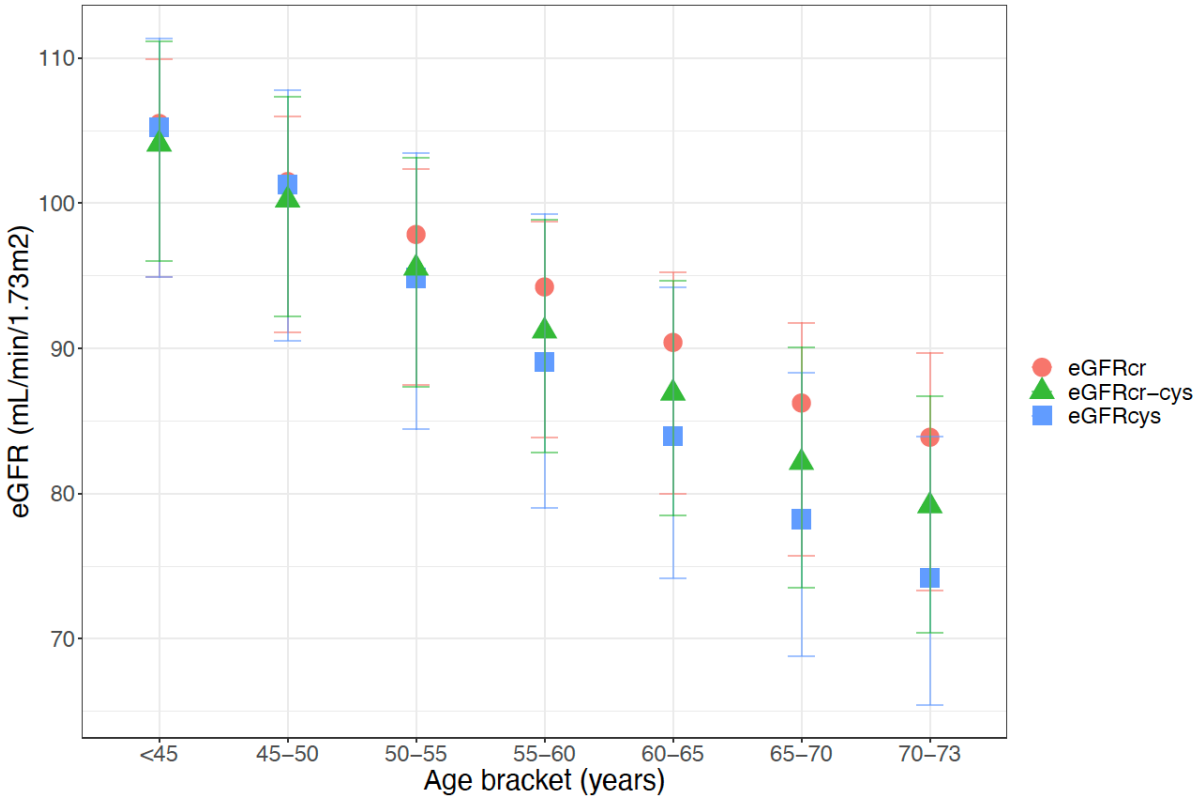
Cox proportional hazards models for fatal/non-fatal cardiovascular disease (the first of myocardial infarction, stroke or cardiovascular death) and all-cause mortality presented as hazard ratio (HR) with 95% confidence intervals. All models were adjusted for atherosclerotic risk factors (age, sex, smoking status, systolic and diastolic blood pressure, total, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, history of diabetes or hypertension, and use of blood pressure or cholesterol-lowering medications) and albuminuria. Results are displayed for older participants (65-73 years; top) and younger participants (<65 years; bottom), with concordance testing between $eGFRcr_{2009}$ and eGFRcys. CKD status was defined as: "No CKD": $eGFRcr_{2009} \geq 60$ and eGFRcys ≥ 60 (reference group), "eGFRcr G3": $eGFRcr_{2009} < 60$ and eGFRcys ≥ 60, "eGFRcys G3": $eGFRcr_{2009} \geq 60$ and eGFRcys <60, "Both G3": $eGFRcr_{2009} < 60$ and eGFRcys <60. All eGFR units are in mL/min/1.73m^2.

eFigure 1



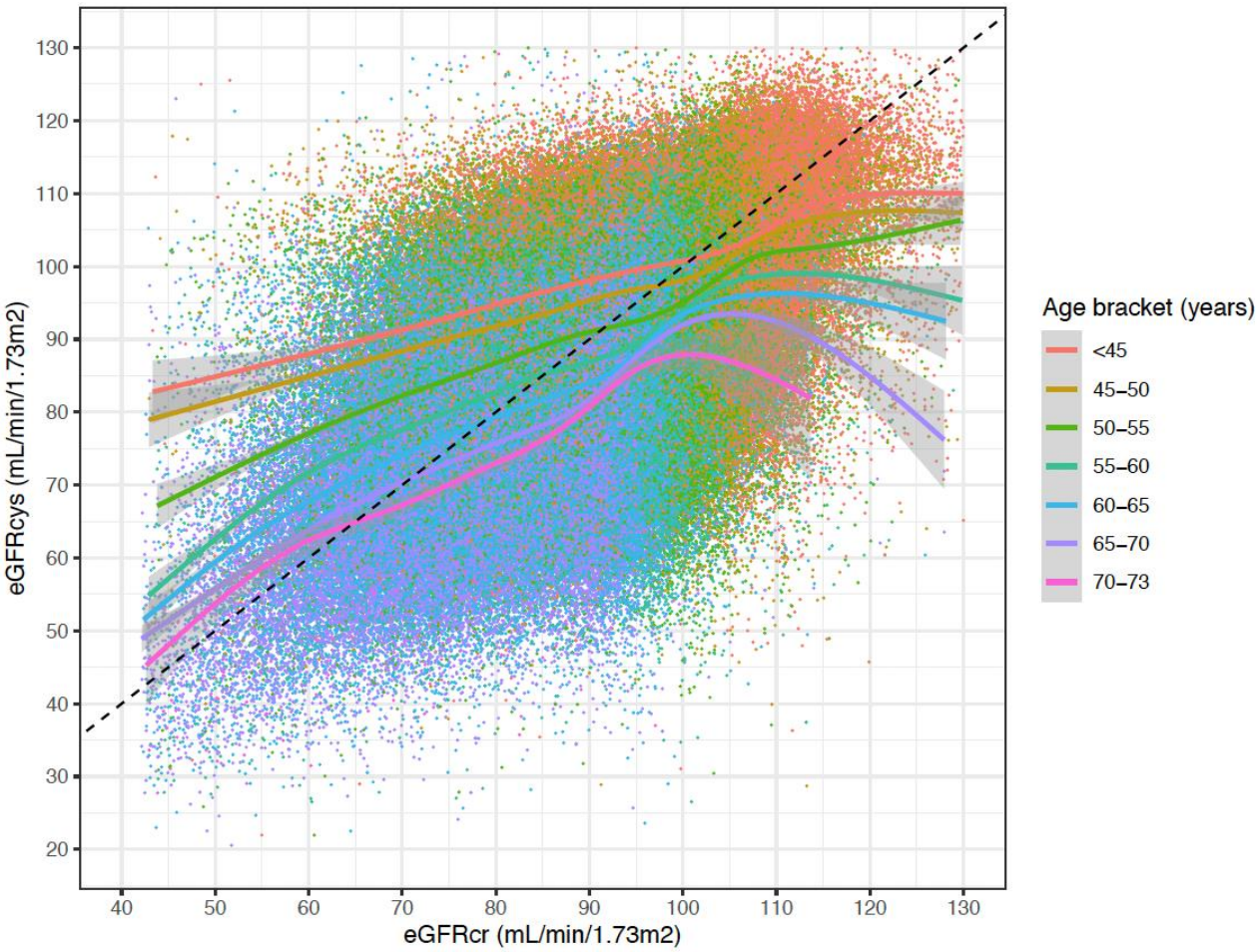
Scatter plot of eGFRcys against eGFRcr and locally-weighted linear regression (LOESS) trend lines plotted for each age bracket.

eFigure 2



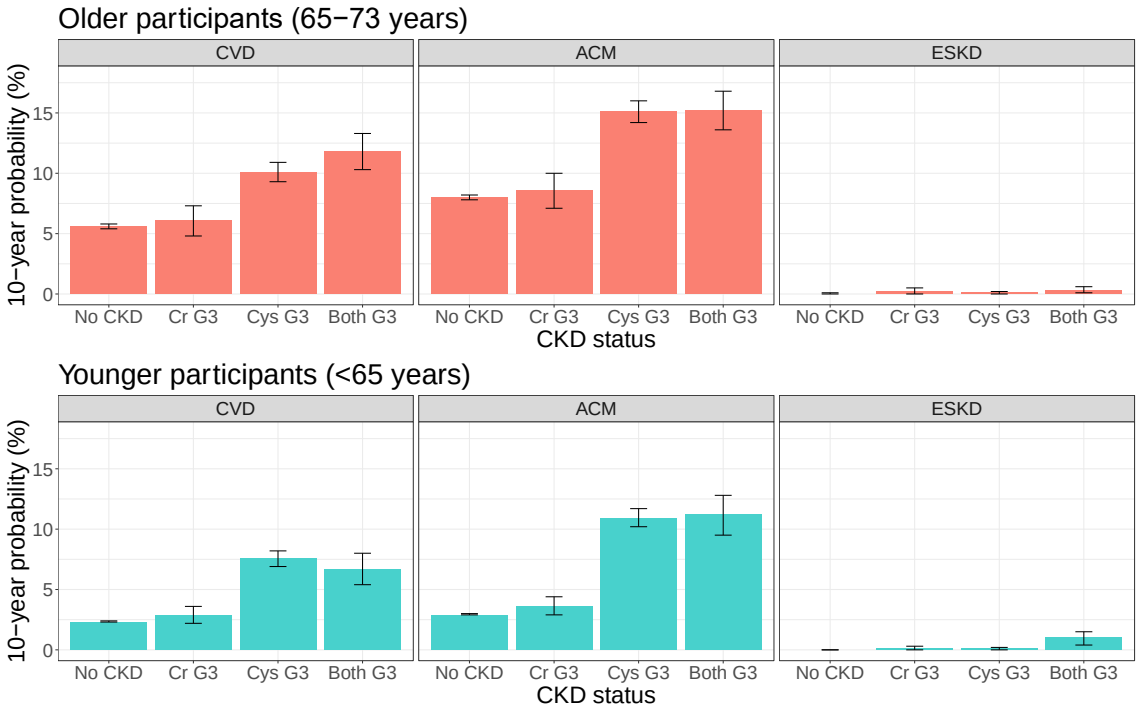
Plot of median (IQR) $eGFRcr_{2009}$, eGFRcys and $eGFRcr\text{-}cys_{2009}$ across 5-year age brackets.

eFigure 3



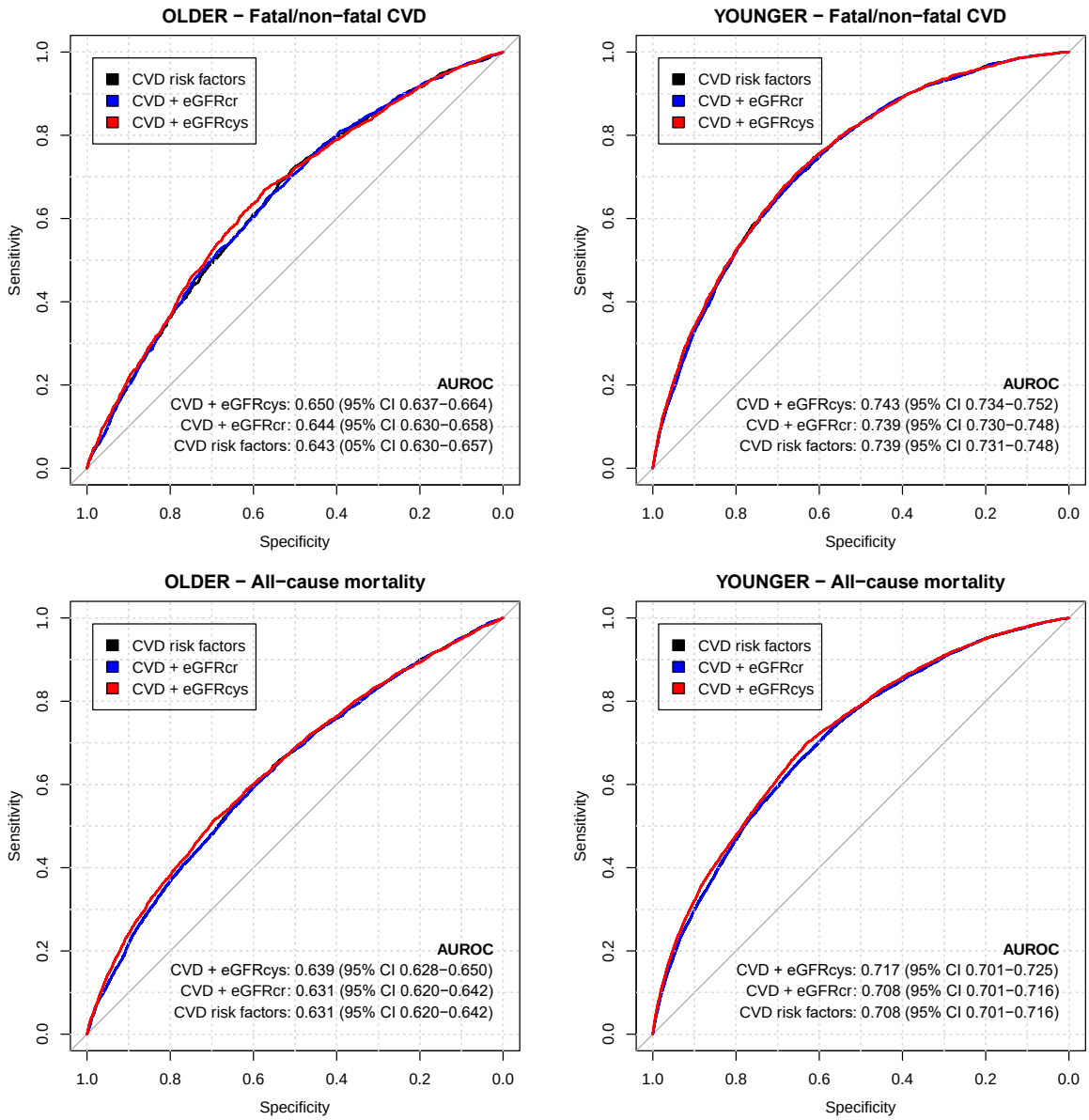
Scatter plot of eGFRcys against $eGFRcr_{2009}$ and locally-weighted linear regression (LOESS) trend lines plotted for each age bracket.

eFigure 4



Bar graphs showing the 10-year probability of outcomes of interest (and 95% confidence intervals) according to CKD status. CKD status was defined as: "No CKD": $eGFRcr_{2009} \geq 60$ and eGFRcys ≥ 60 (reference group), "eGFRcr G3": $eGFRcr_{2009} < 60$ and eGFRcys ≥ 60, "eGFRcys G3": $eGFRcr_{2009} \geq 60$ and eGFRcys < 60, "Both G3": $eGFRcr_{2009} < 60$ and eGFRcys < 60. All eGFR units are in mL/min/1.73m^2. CVD: Fatal/non-fatal cardiovascular disease. ACM: all-cause mortality. ESKD: end-stage kidney disease.

eFigure 5



Receiving operating curves for incremental discrimination of eGFRcr and eGFRcys for CVD and mortality. CVD risk factors: cardiovascular disease risk factors (age, sex, smoking status, systolic and diastolic blood pressure, total, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, history of diabetes or hypertension, and use of blood pressure or cholesterol-lowering medications). eGFRcr: estimated glomerular filtration rate based on serum creatinine. eGFRcys: estimated glomerular filtration rate based on cystatin C. AUROC: area under receiver operating curve.