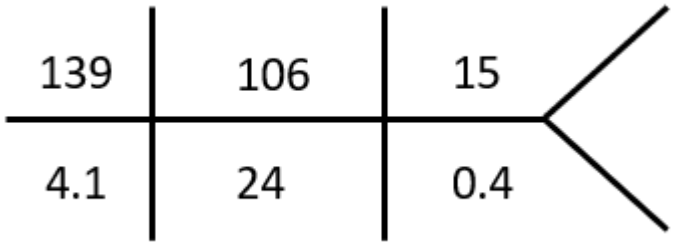
What's the difference? Clinical information beyond kidney function in the difference between eGFR by cystatin C vs. creatinine

GERIATRICS GRAND ROUNDS 11/02/2021

O. ALISON POTOK, MD

Gertrude

70 year old White female with PMHx HTN and COPD, presenting for COPD flare. She weighs 41 kg.



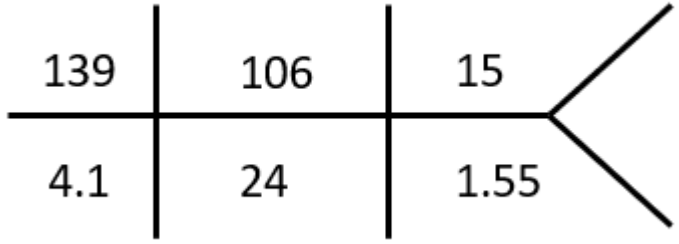
Are you concerned ?

What test(s) do you order ?

Would you place referral to nephrology ? Why ?

Edgar

65 year old African American male, personal trainer, weighs 95 kg. He presents with shoulder injury after lifting heavy weights



UA shows SG 1.015, pH 6.5, no prot, no glucose, no leukocyte est, no nitrite, no ketone, 0-2 WBC, 0-2 RBC

UACR is 0.006 mg/g

Are you concerned ?

What test(s) do you order ?

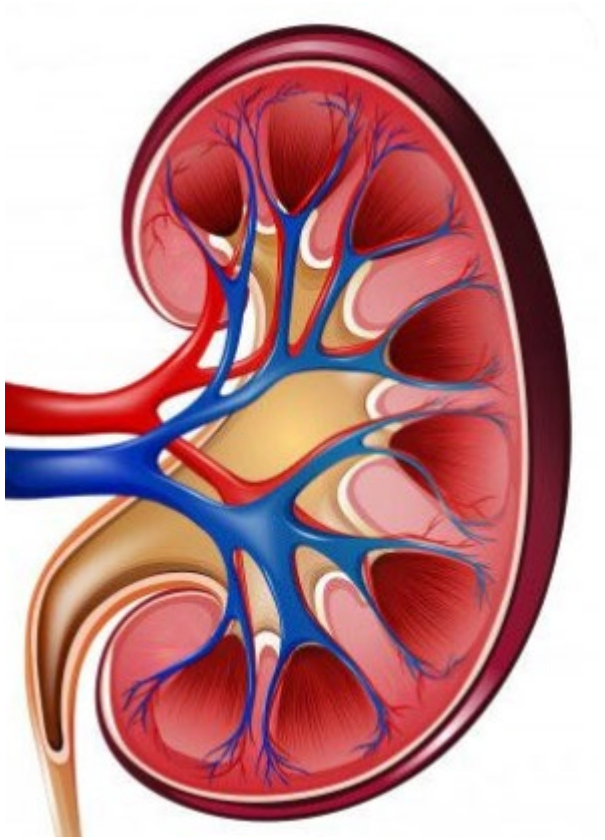
Would you place referral to nephrology ? Why ?

Background

Kidney function is assessed by calculating an estimated Glomerular Filtration Rate **eGFR**, usually based on serum **creatinine (ratio of creat production to serum level)**

Creatinine is a product of muscle metabolism and its serum **concentration** may be **influenced** by age, gender, ethnicity, muscle mass, malnutrition, diet, physical activity,...

Creatinine is used as a marker of kidney function as it is freely filtered, it is not (or minimally) reabsorbed, and it is secreted by the tubules



Singh et al. NDT 2007; Shlipak et al. AJKD 2013

Background

Cystatin C is an alternative marker of kidney function, and **better predictor** of ESRD, death risk from all causes, cardiovascular events and heart failure

Cystatin C is secreted by all the nucleated cells in the body, not only by muscle.

It is metabolized by the kidneys, so not present in the urine.

Rule et al. JASN 2011; Stevens et al. KI 2009

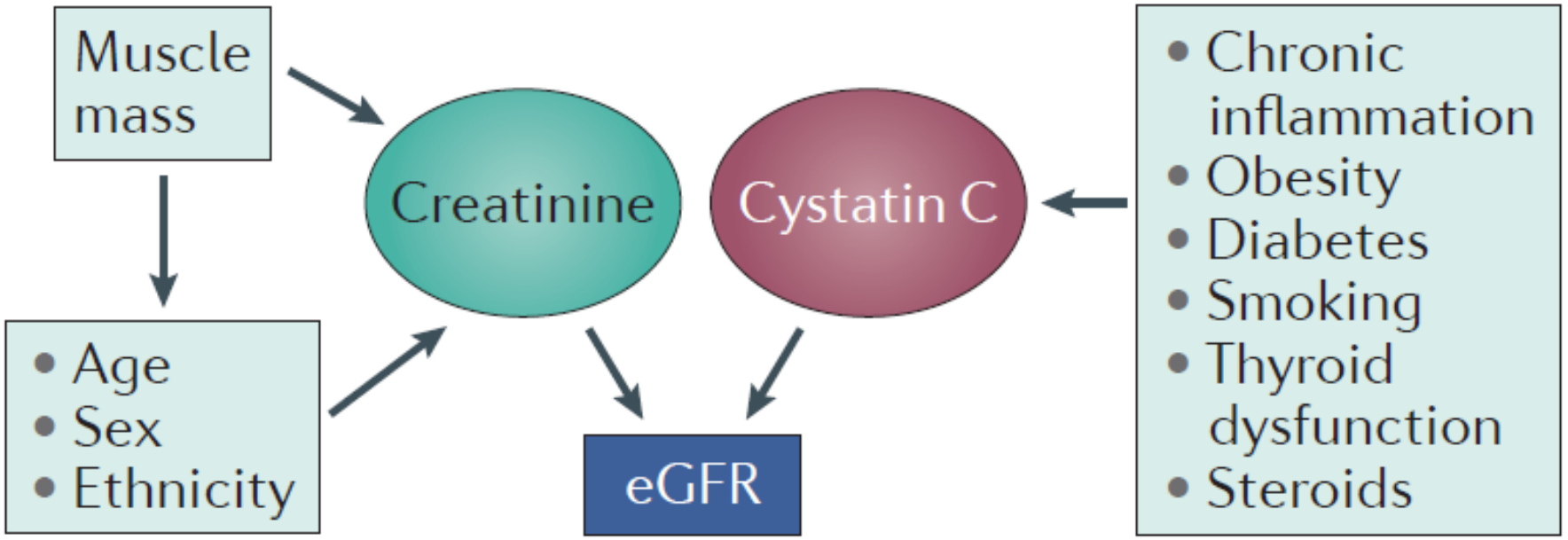


Figure 1 | **Non-GFR determinants that affect estimated GFR.**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Estimating Glomerular Filtration Rate from Serum Creatinine and Cystatin C

Lesley A. Inker, M.D., Christopher H. Schmid, Ph.D., Hocine Tighiouart, M.S., John H. Eckfeldt, M.D., Ph.D., Harold I. Feldman, M.D., Tom Greene, Ph.D., John W. Kusek, Ph.D., Jane Manzi, Ph.D., Frederick Van Lente, Ph.D., Yaping Lucy Zhang, M.S., Josef Coresh, M.D., Ph.D., and Andrew S. Levey, M.D., for the CKD-EPI Investigators*

From Tufts Medical Center, Boston (L.A.I., C.H.S., H.T., Y.L.Z., A.S.L.); the University of Minnesota, Minneapolis (J.H.E.); the University of Pennsylvania School of Medicine, Philadelphia (H.I.F.); the University of Utah, Salt Lake City (T.G.); National Institutes of Health, Bethesda, MD (J.W.K.); Johns Hopkins University, Baltimore (J.M., J.C.); and Cleveland Clinic Foundation, Cleveland (F.V.L.). Address reprint requests to Dr. Inker at the Division of Nephrology, Tufts Medical Center, 800 Washington St., Box 391, Boston, MA 02111, or at linker@tuftsmedicalcenter.org.

*Additional investigators in the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) are listed in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2012;367:20-9.

ABSTRACT

BACKGROUND

Estimates of glomerular filtration rate (GFR) that are based on serum creatinine are routinely used; however, they are imprecise, potentially leading to the overdiagnosis of chronic kidney disease. Cystatin C is an alternative filtration marker for estimating GFR.

METHODS

Using cross-sectional analyses, we developed estimating equations based on cystatin C alone and in combination with creatinine in diverse populations totaling 5352 participants from 13 studies. These equations were then validated in 1119 participants from 5 different studies in which GFR had been measured. Cystatin and creatinine assays were traceable to primary reference materials.

RESULTS

Mean measured GFRs were 68 and 70 ml per minute per 1.73 m^2 of body-surface area in the development and validation data sets, respectively. In the validation data set, the creatinine–cystatin C equation performed better than equations that used creatinine or cystatin C alone. Bias was similar among the three equations, with a

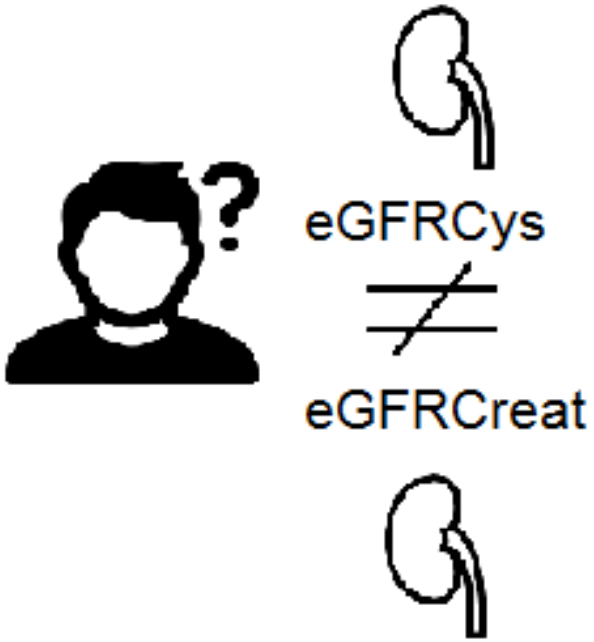
Inker et al. NEJM 2012

Table 2. Creatinine Equation (CKD-EPI 2009), Cystatin C Equation (CKD-EPI 2012), and Creatinine–Cystatin C Equation (CKD-EPI 2012) for Estimating GFR, Expressed for Specified Sex, Serum Creatinine Level, and Serum Cystatin C Level.*

Basis of Equation and Sex	Serum Creatinine†	Serum Cystatin C	Equation for Estimating GFR
	mg/dl	*mg/liter*	
CKD-EPI creatinine equation‡			
Female	≤0.7		$144\times(\text{Scr}/0.7)^{-0.329}\times0.993^{\text{Age}}$ [× 1.159 if black]
Female	>0.7		$144\times(\text{Scr}/0.7)^{-1.209}\times0.993^{\text{Age}}$ [× 1.159 if black]
Male	≤0.9		$141\times(\text{Scr}/0.9)^{-0.411}\times0.993^{\text{Age}}$ [× 1.159 if black]
Male	>0.9		$141\times(\text{Scr}/0.9)^{-1.209}\times0.993^{\text{Age}}$ [× 1.159 if black]
CKD-EPI cystatin C equation§			
Female or male		≤0.8	$133\times(\text{Scys}/0.8)^{-0.499}\times0.996^{\text{Age}}$ [× 0.932 if female]
Female or male		>0.8	$133\times(\text{Scys}/0.8)^{-1.328}\times0.996^{\text{Age}}$ [× 0.932 if female]
CKD-EPI creatinine–cystatin C equation¶			
Female	≤0.7	≤0.8	$130\times(\text{Scr}/0.7)^{-0.248}\times(\text{Scys}/0.8)^{-0.375}\times0.995^{\text{Age}}$ [× 1.08 if black]
		>0.8	$130\times(\text{Scr}/0.7)^{-0.248}\times(\text{Scys}/0.8)^{-0.711}\times0.995^{\text{Age}}$ [× 1.08 if black]
Female	>0.7	≤0.8	$130\times(\text{Scr}/0.7)^{-0.601}\times(\text{Scys}/0.8)^{-0.375}\times0.995^{\text{Age}}$ [× 1.08 if black]
		>0.8	$130\times(\text{Scr}/0.7)^{-0.601}\times(\text{Scys}/0.8)^{-0.711}\times0.995^{\text{Age}}$ [× 1.08 if black]
Male	≤0.9	≤0.8	$135\times(\text{Scr}/0.9)^{-0.207}\times(\text{Scys}/0.8)^{-0.375}\times0.995^{\text{Age}}$ [× 1.08 if black]
		>0.8	$135\times(\text{Scr}/0.9)^{-0.207}\times(\text{Scys}/0.8)^{-0.711}\times0.995^{\text{Age}}$ [× 1.08 if black]
Male	>0.9	≤0.8	$135\times(\text{Scr}/0.9)^{-0.601}\times(\text{Scys}/0.8)^{-0.375}\times0.995^{\text{Age}}$ [× 1.08 if black]
		>0.8	$135\times(\text{Scr}/0.9)^{-0.601}\times(\text{Scys}/0.8)^{-0.711}\times0.995^{\text{Age}}$ [× 1.08 if black]

Inker et al. NEJM 2012

Background



Background

Low serum Creat

Because low muscle mass

Artificially high eGFR by Creat

Normal-low kidney fx by CysC

High serum creat

Because high muscle mass

Artificially low eGFR by creat

But normal-high eGFR by CsyC

Background

Low serum Creat

Because low muscle mass

Artificially high eGFR by Creat

Normal-low kidney fx by CysC

High serum creat

Because high muscle mass

Artificially low eGFR by creat

But normal-high eGFR by CsyC

Is the difference in eGFR by CystatinC vs. by Creatinine (eGFRDiff) associated with frailty ?

To answer this question, we looked at 3 cohorts

Cardiovascular Health Study

CHS population:

- Adults ≥ 65 years old
- Community dwellers, independent for ADLs
- Able to provide consent, no proxy

Exclusion criteria:

- wheelchair-bound at baseline
- hospice treatment
- radiation therapy or chemotherapy for cancer

Predictor: eGFRDiff = $eGFR_{Cys}$ – $eGFR_{Cr}$ using values at baseline, CKD-EPI equations.

=> “Higher is better”

Cardiovascular Health Study

Primary outcome: Fried frailty score at baseline

- Unintentional weight loss,
- Weakness (grip strength),
- Fatigue (questionnaire),
- Physical activity (days walked in prior 2 weeks),
- Slowness (Gait speed)

Cardiovascular Health Study

Primary outcome: Fried frailty score at baseline

- Unintentional weight loss,
- Weakness (grip strength),
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- Slowness (Gait speed)

0 => not frail
1 or 2 => pre-frail
≥ 3 => frail

Cardiovascular Health Study

Primary outcome: Fried frailty score at baseline

- Unintentional weight loss,
- Weakness (grip strength),
- Fatigue (questionnaire),
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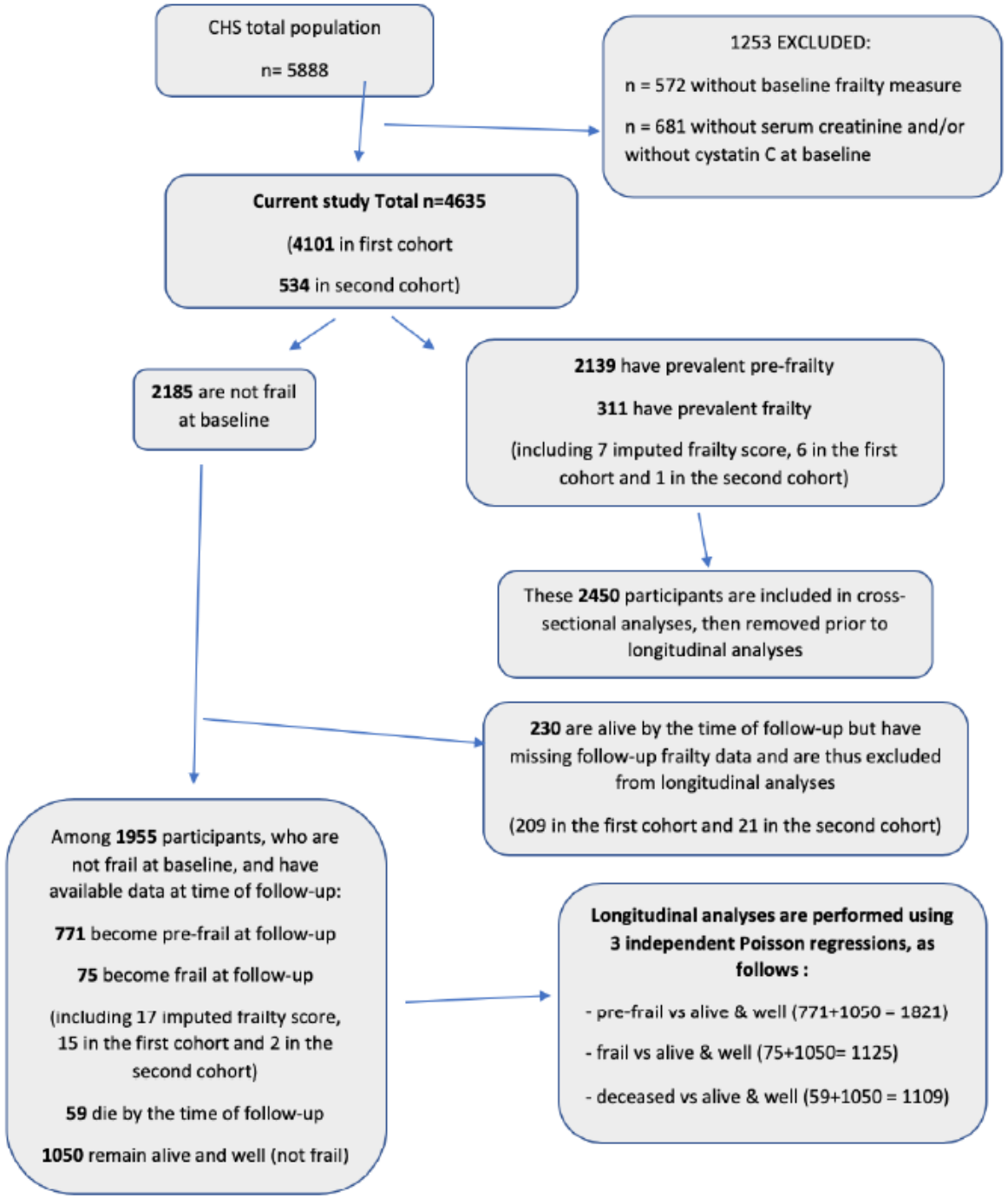
- Slowness (Gait speed)

0 => not frail
1 or 2 => pre-frail
≥ 3 => frail

Incident frailty evaluated at year 5 (among those without frailty at baseline). All-cause mortality examined as competing risk.


CHS total population
n= 5888
1253 EXCLUDED:
n = 572 without baseline frailty measure
n = 681 without serum creatinine and/or without cystatin C at baseline
Current study Total n=4635
(4101 in first cohort
534 in second cohort)
2185 are not frail at baseline
2139 have prevalent pre-frailty
311 have prevalent frailty
(including 7 imputed frailty score, 6 in the first cohort and 1 in the second cohort)
These 2450 participants are included in cross-sectional analyses, then removed prior to longitudinal analyses
230 are alive by the time of follow-up but have missing follow-up frailty data and are thus excluded from longitudinal analyses
(209 in the first cohort and 21 in the second cohort)
Among 1955 participants, who are not frail at baseline, and have available data at time of follow-up:
771 become pre-frail at follow-up
75 become frail at follow-up
(including 17 imputed frailty score, 15 in the first cohort and 2 in the second cohort)
59 die by the time of follow-up
1050 remain alive and well (not frail)
Longitudinal analyses are performed using 3 independent Poisson regressions, as follows :
- pre-frail vs alive & well (771+1050 – 1821)
- frail vs alive & well (75+1050= 1125)
- deceased vs alive & well (59+1050 = 1109)

S1. Baseline Characteristics of CHS participants by eGFRDiff ($eGFR_{Cys}$ - $eGFR_{Cr}$)

	Negative eGFRDiff group	Reference group	Positive eGFRDiff group	TOTAL	
	eGFRDiff < -15	-15 ≤ eGFRDiff < + 15	eGFRDiff ≥ +15		
N (%)	740 (16)	3362 (73)	533 (11)	4635	
mean eGFRDiff, mL/min/1.73m^2	-23 (8)	-0.1 (8)	22 (6)	-1 (14)	
range eGFRDiff	-68 to -15	-15 to 15	15 to 71	-68 to 71	
Baseline age, years (SD)	72 (5)	73 (6)	71 (4)	72 (5)	<0.0001
male n (%)	146 (20)	1366 (41)	284 (53)	1796 (39)	<0.0001
Non African-American n (%)	616 (83)	2863 (85)	432 (81)	3911 (84)	0.03
Diabetes Mellitus n (%)	154 (21)	495 (15)	60 (11)	709 (15)	<0.0001
Frequent fallers n (%)	30 (4)	83 (2)	8 (2)	121 (3)	0.01
Gait speed, m/s (SD)	0.80 (0.21)	0.87 (0.21)	0.95 (0.21)	0.87 (0.21)	<0.0001
15 feet walking time, s (SD)	6.3 (2.9)	5.6 (2.0)	5.1 (1.6)	5.7 (2.2)	<0.0001
Not frail n (%)	255 (34)	1607 (48)	323 (61)	2185 (47)	
pre-frail n (%)	407 (55)	1541 (46)	191 (36)	2139 (46)	<0.0001
frail n (%)	78 (11)	214 (6)	19 (3)	311 (7)	
Mortality over 3 to 4 years of follow-up	59 (8)	193 (6)	12 (2)	264 (6)	<0.0001

BMI= Body Mass Index, Creat = serum creatinine, Cys = serum cystatin C, f/u = follow-up, Participants with gait speed: total n = 4573 (n= 726; 3317; 530 in negative, reference, and positive eGFRDiff group respectively.

Table 1. Association of $eGFR_{Diff}$ With Prevalent Frailty

	$eGFR_{Diff}$ (per 1-SD greater)	$eGFR_{Diff}$ Group		
		Negative (<−15)	Reference (−15 to +15)	Positive (≥15)
Prevalent Prefrailty				
Sample size		740	3,362	533
No. of events	2,139	407	1,541	191
OR (95% CI)				
Unadjusted	0.71 (0.66-0.76)	1.66 (1.40-1.98)	1.00 (reference)	0.62 (0.51-0.75)
Model 1	0.70 (0.65-0.76)	1.72 (1.43-2.06)	1.00 (reference)	0.65 (0.54-0.80)
Model 2	0.73 (0.68-0.79)	1.59 (1.32-1.91)	1.00 (reference)	0.70 (0.57-0.86)
Prevalent Frailty				
No. of events	311	78	214	19
OR (95% CI)				
Unadjusted	0.53 (0.46-0.60)	2.30 (1.72-3.07)	1.00 (reference)	0.44 (0.27-0.72)
Model 1	0.50 (0.43-0.58)	2.61 (1.88-3.62)	1.00 (reference)	0.56 (0.34-0.93)
Model 2	0.51 (0.43-0.60)	2.38 (1.70-3.33)	1.00 (reference)	0.56 (0.33-0.95)

Note: Model 1adjusted for age (per 5 years), sex, race, C-reactive protein level, serum albumin level, and $eGFR_{cr}$ category. Model 2 adjusted for model 1 plus hypertension, diabetes, using blood pressure medications at baseline, high-density lipoprotein cholesterol level, total cholesterol level, smoking, and prevalent coronary heart disease. Abbreviations: CI, confidence interval; OR, odds ratio; SD, standard deviation (here, 15 mL/min/1.73 m^2).

Table 2. Association of Baseline $eGFR_{Diff}$ With Incident Frailty and Mortality at Follow-up Time Point

	$eGFR_{Diff}$ (per 1-SD greater)	$eGFR_{Diff}$ Group		
		Negative (<−15)	Reference (−15 to +15)	Positive (≥15)
Prefrailty Outcome				
Sample size	1,821	181	1,355	285
No. of events	771	85	586	100
IR (95% CI)				
Unadjusted	0.82 (0.76-0.89)	1.16 (0.93-1.46)	1.00 (reference)	0.68 (0.55-0.84)
Fully adjusted	0.89 (0.81-0.97)	1.06 (0.83-1.35)	1.00 (reference)	0.81 (0.65-1.01)
Frailty Outcome				
Sample size	1,125	123	809	193
No. of events	75	27	40	8
IR (95% CI)				
Unadjusted	0.48 (0.38-0.61)	5.32 (3.27-8.68)	1.00 (reference)	0.76 (0.36-1.63)
Fully adjusted	0.45 (0.34-0.61)	6.97 (3.89-12.49)	1.00 (reference)	0.88 (0.40-1.94)

Table 2. Association of Baseline $eGFR_{Diff}$ With Incident Frailty and Mortality at Follow-up Time Point

		$eGFR_{Diff}$ Group		
	$eGFR_{Diff}$ (per 1-SD greater)	Negative (<−15)	Reference (−15 to +15)	Positive (≥15)
Mortality Outcome				
Sample size	1,109	111	807	191
No. of events	59	15	38	6
IR (95% CI)				
Unadjusted	0.66 (0.50-0.88)	3.20 (1.76-5.82)	1.00 (reference)	0.60 (0.25-1.42)
Fully adjusted	0.52 (0.37-0.74)	6.57 (3.27-13.19)	1.00 (reference)	0.59 (0.24-1.44)

Note: Associations stratified by $eGFR_{cr}$ and $eGFR_{cys}$ are provided in Table S2.
Abbreviations: IR, incidence rate; see Table 1 for other abbreviation expansions and description of the fully adjusted model (model 2).

SPRINT

"A Randomized Trial of Intensive versus Standard Blood-Pressure Control"

SPRINT population:

- Adults ≥ 50 years old
- SBP ≥130 mm Hg
- at least 1 additional CVD risk factor (including: clinical cardiovascular event other than a stroke, chronic kidney disease defined by eGFR of 20 to 59 mL/min/1.73m2, Framingham risk score ≥15%)

Exclusion criteria: history of diabetes, polycystic kidney disease, stroke.

Randomized to intensive BP control (SBP <120 mmHg) vs standard (SBP < 140 mmHg)

SPRINT

Intensive BP control led to lower rates of cardiovascular events, heart failure and mortality, including among people with chronic kidney disease.

Similar findings in sub-population of ≥75 years old.

When stratified by baseline frailty status, higher event rates noted with increasing frailty in both groups

SPRINT

Exposure: **eGFRDiff = eGFRCys – eGFRCr** at baseline

Frailty Index (35 items) in SPRINT

- Questionnaires: self-rated general health, does your health limit you in certain activities, pain, depression, energy, sleep, self-care, smoking…
- PMHx: heart attack, cancer, heart failure, angina, afib
- Labs: cholesterol, Na, K, Glucose, BUN
- BMI
- SBP and DBP, orthostatic hypotension
- MoCA, logical memory delayed recall, digit symbol test
- Gait speed (only in ≥ 75 yo)

=> Score between 0 and 1 with higher scores meaning more frail

Frailty defined as Score > 0.21

SPRINT

Table 2. Association of $eGFR_{Diff}$ With Frailty at Baseline

	$eGFR_{Diff}$ (per 1-SD greater)	$eGFR_{Diff}$ Group		
		Negative (<–15)	Reference (–15 to +15)	Positive (≥15)
Sample size	2,125	379	1,573	173
OR (95% CI)				
Unadjusted	0.75 (0.71-0.79)	1.28 (1.11-1.46)	1.00 (reference)	0.50 (0.42-0.60)
Adjusted for $eGFR_{cr}$ CKD stage	0.72 (0.68-0.76)	1.63 (1.41-1.89)	1.00 (reference)	0.59 (0.49-0.70)
Fully adjusted[a]	0.76 (0.71-0.81)	1.41 (1.21-1.65)	1.00 (reference)	0.61 (0.50-0.73)

Note: Frailty defined as frailty index score > 0.21.

Abbreviations and definitions: CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; $eGFR_{cr}$, glomerular filtration rate estimated using serum creatinine level; $eGFR_{cys}$, glomerular filtration rate estimated using cystatin C level; $eGFR_{Diff}$, $eGFR_{cys} - eGFR_{cr}$ (in mL/min/1.73 m^2); OR, odds ratio; SD, standard deviation (here, 15 mL/min/1.73 m^2).

[a]Adjusted for age, sex, race, randomization arm, urinary albumin-creatinine ratio, history of cardiovascular disease, systolic blood pressure, number of baseline blood pressure medications, high-density lipoprotein cholesterol level, total cholesterol level, smoking status, and $eGFR_{cr}$ CKD stage.

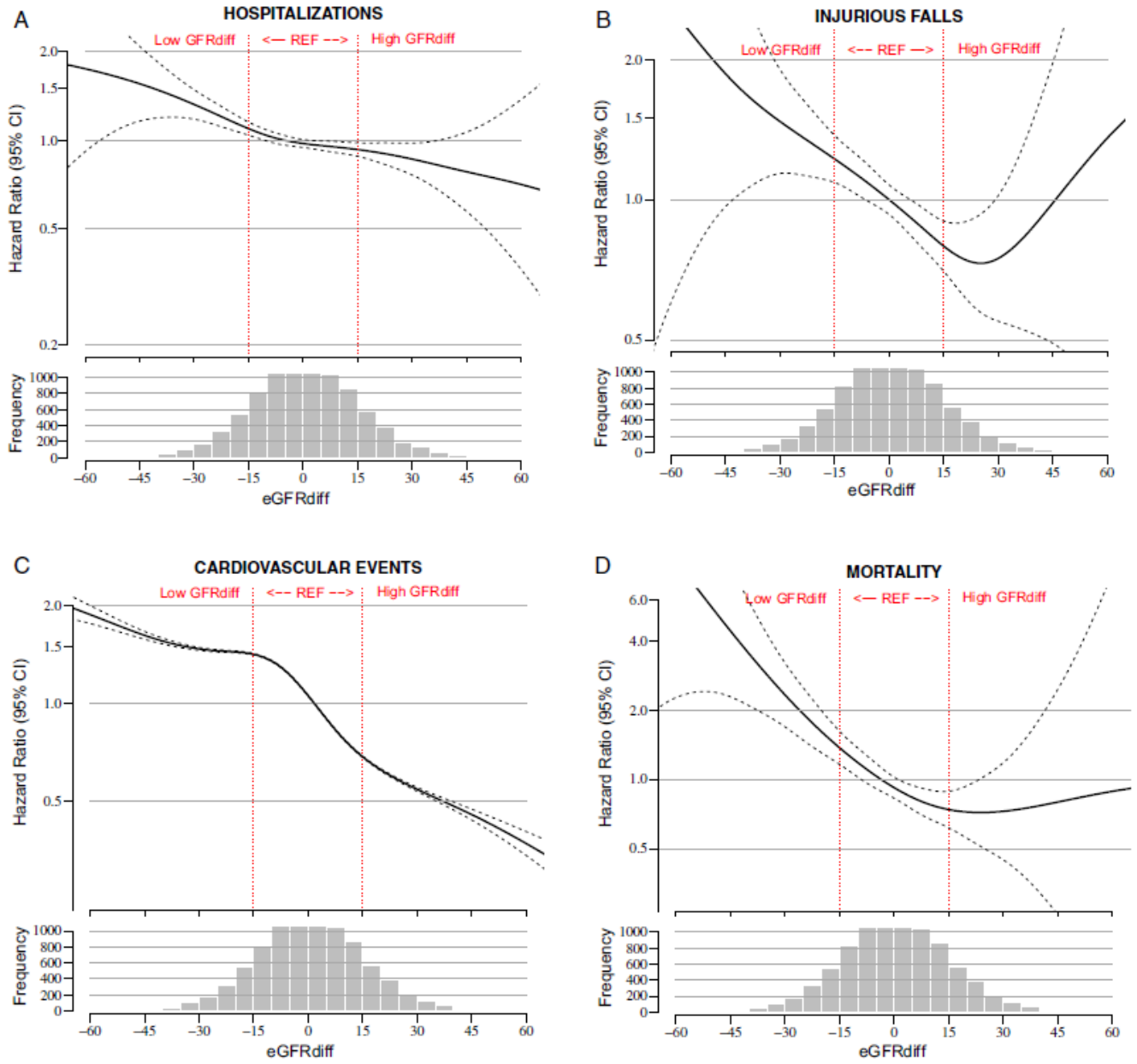
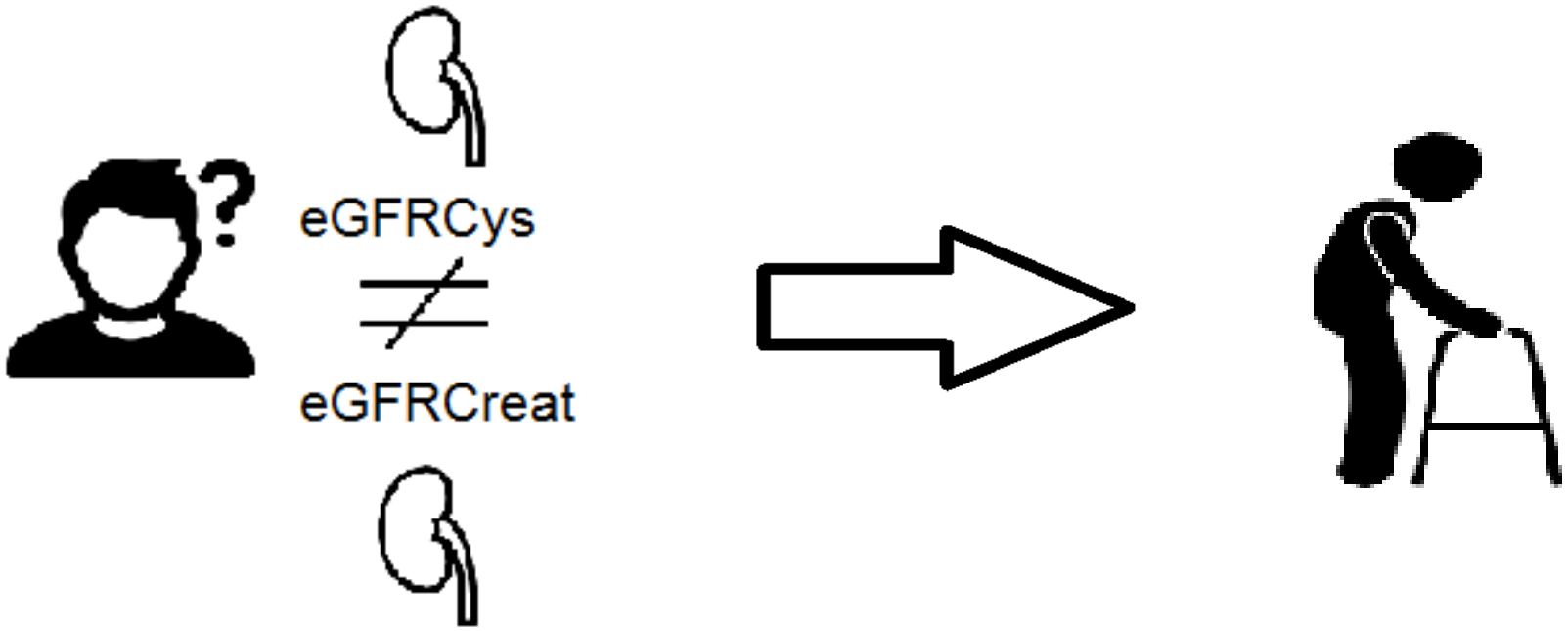
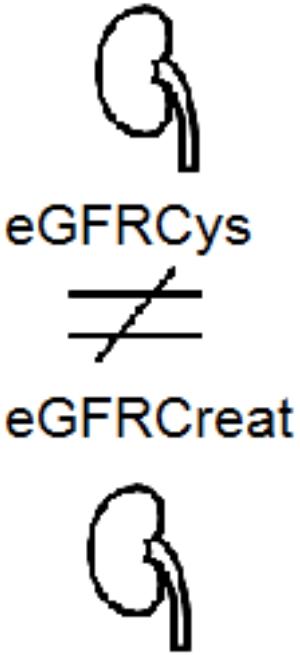
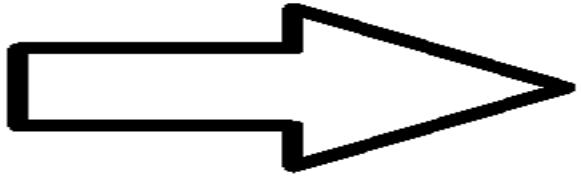


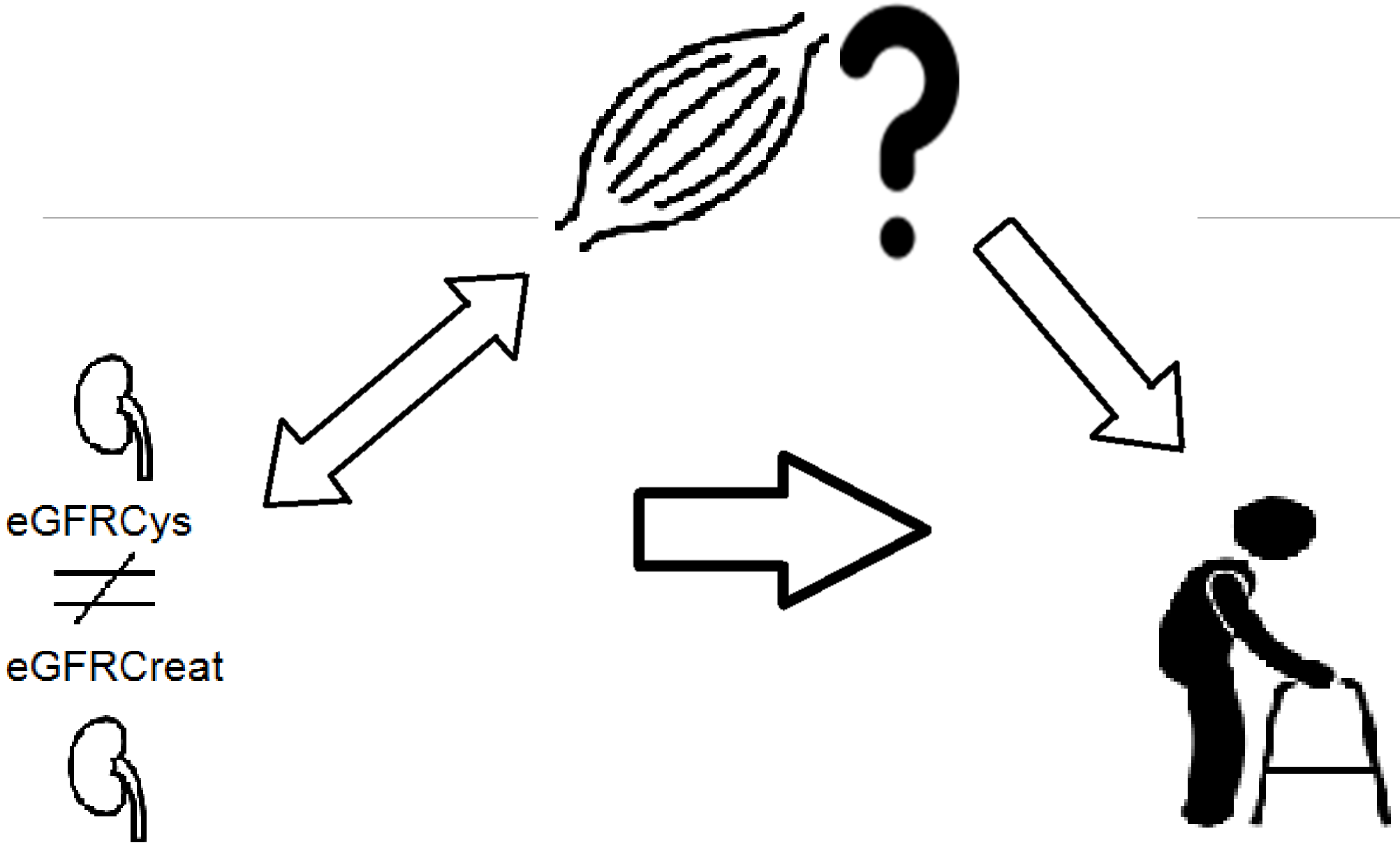
Figure 2. Adjusted spline curves of the association of the difference in estimated glomerular filtration rate ($eGFR_{Diff}$; GFR estimated using cystatin C level [$eGFR_{cys}$] − GFR estimated using creatinine level [$eGFR_{cr}$]) with injurious falls, hospitalizations, cardiovascular events, and mortality. Abbreviations: CI, confidence interval; REF, reference.


eGFRCys
≠
eGFRCreat

SPRINT, CHS






eGFRCys
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eGFRCreat

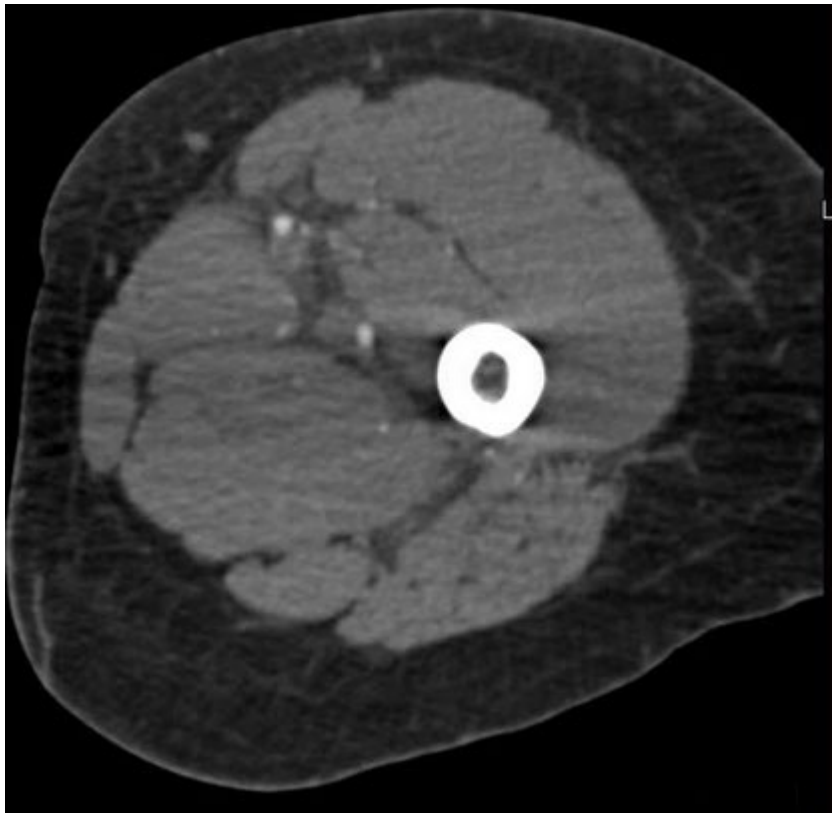
Health, Aging and Body Composition study

Well-functioning older adults aged 70 to 79 years

Independent for ADLs,

No difficulty walking or climbing stairs

Limited to those with measures of cystatin C, serum creatinine, CT imaging at baseline (n=2970)



Health Aging, Body Composition study

Frailty: HABC Physical Performance Battery (HABCPPB continuous 0-4)

- usual walk
- narrow walk
- chair stand
- standing balance

Higher score = better performance

Table 1. Baseline characteristics by eGFRDiff (=$eGFR_{Cys}$ – $eGFR_{Cr}$) groups in well-functioning community-living elders

	Negative eGFRDiff ≤ -10 mL/min/1.73m^2	Reference -10 < eGFRDiff ≤ +10mL/min/1.73m^2	Positive eGFRDiff > 10 mL/min/1.73m^2	TOTAL
Participants	446	1565	959	2970
mean eGFRDiff (SD), mL/min/1.73m^2	-17 (7)	0.6 (5)	20 (8)	4 (14)
range eGFRDiff mL/min/1.73m^2	-47 to -10	-10 to 10	10 to 77	-47 to 77
mean age (SD), years	74 (3)	74 (3)	73 (3)	74 (3)
men N(%)	226 (51)	787 (50)	425 (44)	1438 (48)
White N(%)	258 (58)	931 (59)	555 (58)	1744 (59)
Hypertension N(%)	241 (55)	820 (53)	448 (47)	1509 (51)
Diabetes Mellitus N(%)	85 (19)	244 (16)	108 (11)	437 (15)
mean BMI (SD) kg/m^2	28 (5)	28 (5)	27 (4)	27 (5)
median CRP [IQR] mg/dL	1.98 [1.15; 3.64]	1.79 [1.03; 3.31]	1.45 [0.90; 2.62]	1.67 [0.99; 3.13]
FRAILTY MEASURES				
Poor functional status N(%)	163 (38)	373 (25)	175 (19)	711 (25)
HABCPPB score mean (SD)	2.0 (0.6)	2.2 (0.5)	2.3 (0.5)	2.2 (0.5)
Fallers in past 12 months n(%)	108 (24)	328 (21)	181 (19)	617 (21)
Average grip strength (SD) kg	27.9 (10.0)	30.0 (10.0)	30.7 (10.3)	29.9 (10.1)
6 meter gait speed (SD) m/s	1.12 (0.24)	1.17 (0.23)	1.22 (0.23)	1.18 (0.24)

Table 1. Baseline characteristics by eGFRDiff (=$eGFR_{Cys}$ – $eGFR_{Cr}$) groups in well-functioning community-living elders

	Negative eGFRDiff ≤ -10 mL/min/1.73m²	Reference -10 < eGFRDiff ≤ +10mL/min/1.73m²	Positive eGFRDiff > 10 mL/min/1.73m²	TOTAL
Participants	446	1565	959	2970
mean eGFRDiff (SD), mL/min/1.73m²	-17 (7)	0.6 (5)	20 (8)	4 (14)
range eGFRDiff mL/min/1.73m²	-47 to -10	-10 to 10	10 to 77	-47 to 77
CT SCAN				
Abdominal muscle area (SD) cm²	69 (20)	71 (19)	70 (19)	70 (19)
Total thigh muscle area (SD) cm²	214 (52)	224 (55)	225 (57)	223 (56)
Quadriceps muscle area (SD) cm²	99 (26)	103 (26)	104 (27)	103 (26)
Thigh fat area (SD) cm²	194 (113)	177 (99)	169 (86)	177 (98)
Total body fat mass (SD) kg	28.9 (10.1)	27.0 (8.6)	25.3 (7.6)	26.7 (8.6)
Limb fat mass (SD) kg	13.7 (5.3)	12.8 (4.5)	12.2 (4.0)	12.7 (4.5)
DXA SCAN				
Total Fat Free Mass FFM (SD) kg	48.9 (10.2)	49.2 (10.3)	48.4 (10.5)	48.9 (10.4)
Appendicular lean mass/height² (SD) kg/m²	7.19 (1.24)	7.23 (1.28)	7.16 (1.32)	7.20 (1.29)

Table 2. Association between eGFRDiff (=$eGFR_{Cys}$ – $eGFR_{Cr}$) and thigh muscle area (cm^2) on CT scan.

	Model 1		Model 2	
Exposure	β (95% CI)	p value	β (95% CI)	p value
eGFRDiff (per SD= 14 increment)	4.5 (3.2; 5.7)	<0.0001	7.3 (6.3; 8.3)	<0.0001
Negative eGFDiffGroup ($\leq$ -10 mL/min/1.73m^2)	-10.2 (-14.0; -6.4)	<0.0001	-13.9 (-16.9; -11.0)	<0.0001
Reference eGFRDiffGroup (-10 < eGFRDiff $\leq$ +10mL/min/1.73m^2)	0 (ref)		0 (ref)	
Positive eGFRDiffGroup (> 10 mL/min/1.73m^2)	4.5 (1.6; 7.4)	<0.01	8.3 (6.0; 10.6)	<0.0001

Model 1 = adjusted for age, gender, race,
Model 2 = model 1 + education, BMI, serum albumin, CRP, smoking, hypertension, diabetes, chronic kidney disease category by $eGFR_{Cr}$, study site

Table 3. Association of eGFRDiff (=$eGFR_{Cys}$ – $eGFR_{Cr}$) group and poor functional status (lowest quartile HABCPPB score, i.e. score < 1.89)

	Negative eGFDiff Group (≤ -10 mL/min/1.73m^2)		Reference group	Positive eGFDiff Group (> 10 mL/min/1.73m^2)	
	OR (95% CI)	p value	OR	OR (95% CI)	p value
Cases/N	163/446		373/1565	175/959	
Model 1	1.99 (1.54; 2.56)	<0.0001	1	0.72 (0.58; 0.90)	<0.0001
+ thigh muscle area on CT	1.78 (1.37; 2.31)	<0.0001	1	0.79 (0.63; 0.99)	<0.0001
+ thigh fat area on CT	1.97 (1.53; 2.55)	<0.0001	1	0.73 (0.59; 0.91)	<0.0001
+ Appendicular lean mass on DXA scan	1.97 (1.53; 2.55)	<0.0001	1	0.73 (0.58; 0.90)	<0.0001
+ Limb fat mass on CT	1.94 (1.50; 2.51)	<0.0001	1	0.74 (0.59; 0.92)	<0.0001
+ Fat free mass on DXA scan	1.96 (1.51; 2.55)	<0.0001	1	0.71 (0.57; 0.89)	<0.0001
+ abdominal muscle area on CT	2.05 (1.58; 2.66)	<0.0001	1	0.72 (0.58; 0.91)	<0.0001
+ total thigh muscle area + thigh fat area + Appendicular lean mass + Limb fat mass	1.68 (1.29; 2.19) 	<0.0001	1	0.80 (0.64; 1.00) 	<0.0001

Model 1 = adjusted for age, gender, race, education, BMI, serum albumin, CRP, smoking, hypertension, diabetes, chronic kidney disease category by $eGFR_{Cr}$, study site

Table 4. Association of eGFRDiff (=$eGFR_{Cys}$ – $eGFR_{Cr}$) and poor functional status (Lowest quartile of HABCPPB score, i.e. ≤ 1.89)

	eGFRDiff (per SD= 14 increment)	
	OR (95% CI)	p value
Cases/N: 711/2970		
Model 1	0.70 (0.63; 0.77)	<0.0001
+ thigh muscle area on CT	0.75 (0.67; 0.83)	<0.0001
+ thigh fat area on CT	0.70 (0.63; 0.77)	<0.0001
+ Appendicular lean mass on DXA scan	0.70 (0.63; 0.78)	<0.0001
+ Limb fat mass on CT	0.71 (0.64; 0.78)	<0.0001
+ Fat free mass on DXA scan	0.69 (0.62; 0.77)	<0.0001
+ abdominal muscle area on CT	0.69 (0.62; 0.76)	<0.0001
+ total thigh muscle area + thigh fat area + Appendicular lean mass + Limb fat mass	0.77 (0.69; 0.85)	<0.0001

Model 1 = adjusted for age, gender, race, education, BMI, serum albumin, CRP, smoking, hypertension, diabetes, chronic kidney disease category by $eGFR_{Cr}$, study site

Take home points from HABC study

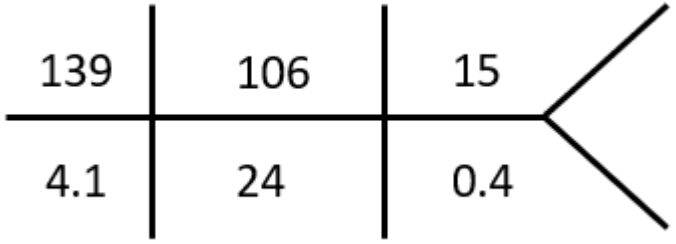
- Confirms previous findings that eGFRDiff is clinically relevant and strongly associated with poor functional performance in well-functioning community-living older adults.

- Lower eGFRDiff is also strongly associated with lower muscle quantity and muscle strength.

- Despite eGFRDiff being associated with lower muscle area, low muscle mass did not meaningfully attenuate the relationship of eGFRDiff with functional status.

Going back to our clinical cases…

70 year old White female with PMHx HTN and COPD, presenting for COPD flare. She weighs 41 kg.



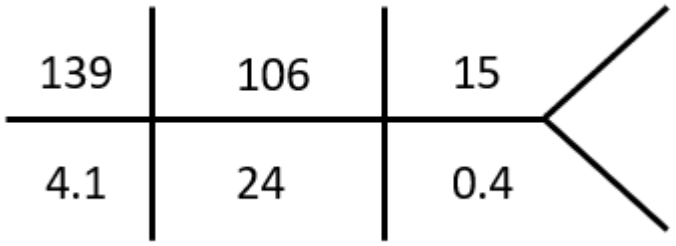
Are you concerned ?

What test(s) do you order ?

Would you place referral to nephrology ? Why ?

Gertrude

70 year old White female with PMHx HTN and COPD, presenting for COPD flare. She weighs 41 kg.



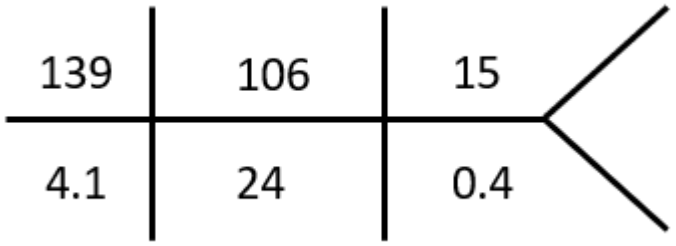
Are you concerned ? Yes eGFR-Cr = 106 mL/min

What test(s) do you order ?

Would you place referral to nephrology ? Why ?

Gertrude

70 year old White female with PMHx HTN and COPD, presenting for COPD flare. She weighs 41 kg.



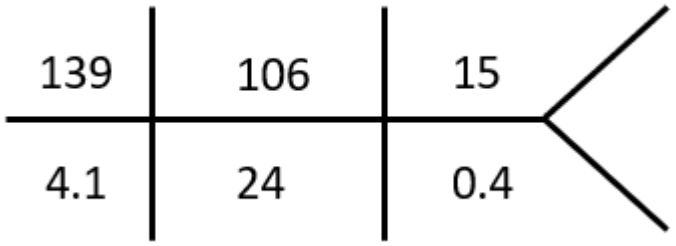
Are you concerned ? Yes eGFR-Cr = 106 mL/min

What test(s) do you order ? Cystatin C

Would you place referral to nephrology ? Why ?

Gertrude

70 year old White female with PMHx HTN and COPD, presenting for COPD flare. She weighs 41 kg.



Are you concerned ? Yes eGFR-Cr = 106 mL/min

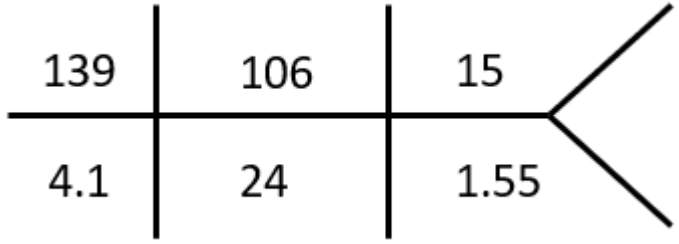
What test(s) do you order ? Cystatin C

Would you place referral to nephrology ? Why ? possibly, if the cystatin C shows low GFR

CysC is 1.5 mg/dL => eGFR is 41 mL/min

Edgar

65 year old African American male, personal trainer, weighs 95 kg. He presents with shoulder injury after lifting heavy weights



UA shows SG 1.015, pH 6.5, no prot, no glucose, no leukocyte est, no nitrite, no ketone, 0-2 WBC, 0-2 RBC

UACR is 0.006 mg/g

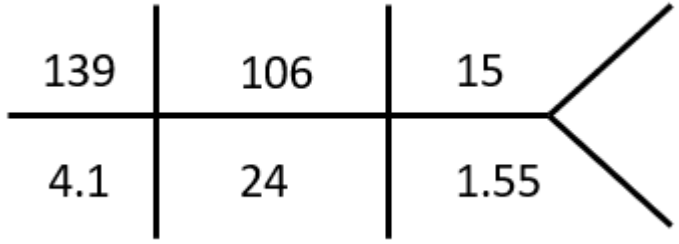
Are you concerned ?

What test(s) do you order ?

Would you place referral to nephrology ? Why ?

Edgar

65 year old African American male, personal trainer, weighs 95 kg. He presents with shoulder injury after lifting heavy weights



UA shows SG 1.015, pH 6.5, no prot, no glucose, no leukocyte est, no nitrite, no ketone, 0-2 WBC, 0-2 RBC

UACR is 0.006 mg/g

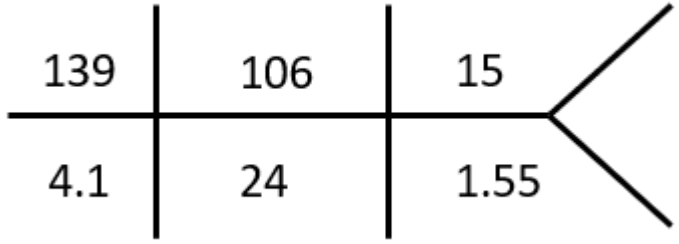
Are you concerned ? Maybe ? eGFR-Cr = 49 mL/min

What test(s) do you order ?

Would you place referral to nephrology ? Why ?

Edgar

65 year old African American male, personal trainer, weighs 95 kg. He presents with shoulder injury after lifting heavy weights



UA shows SG 1.015, pH 6.5, no prot, no glucose, no leukocyte est, no nitrite, no ketone, 0-2 WBC, 0-2 RBC

UACR is 0.006 mg/g

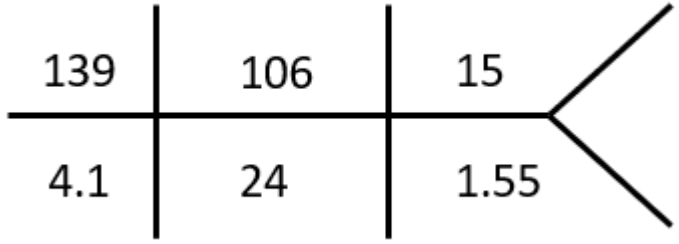
Are you concerned ? Maybe ? eGFR-Cr = 49 mL/min

What test(s) do you order ? Cystatin C !

Would you place referral to nephrology ? Why ?

Edgar

65 year old African American male, personal trainer, weighs 95 kg. He presents with shoulder injury after lifting heavy weights



UA shows SG 1.015, pH 6.5, no prot, no glucose, no leukocyte est, no nitrite, no ketone, 0-2 WBC, 0-2 RBC

UACR is 0.006 mg/g

Are you concerned ? Maybe ? eGFR-Cr = 49 mL/min

What test(s) do you order ? Cystatin C !

Would you place referral to nephrology ? Why ? depends on cysC results. Cystatin C it is 0.95 mg/dL

=> eGFR-Cys is 82 mL/min

Conclusions

- There is important clinical information embedded in the difference in eGFR by cystatin C and by creatinine
- A negative eGFRDiff (eGFRCr > eGFRCys) is associated with frailty and bad outcomes
- These associations are only partially explained by muscle quantity/quality
- Check cystatin C to confirm creatinine-based GFR in older adults

Thank you

CHS

- Michael G. Shlipak
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- Michelle C. Odden

Dena E. Rifkin
Joe H. Ix

Alison Moore

HABC

- Michael G. Shlipak
- Ronit Katz
- Nisha Bansal
- Stephen B. Kritchevsky

SPRINT

- Michael G. Shlipak
- Ronit Katz
- Amret T. Hawfield
- Michael V. Rocco
- Walter T. Ambrosius
- Monique E. Cho
- Nicholas M. Pajewski
- Anjay Rastogi

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