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Research Article

Kidney Function Estimated From Cystatin C, But Not Creatinine, Is Related to Objective Tests of Physical Performance in Community-Dwelling Older Adults

Mark Canney,[1,2] Donal J. Sexton,[1,2] Matthew DL. O'Connell,[1] Rose Anne Kenny,[1] Mark A. Little,[2] and Conall M. O'Seaghdha[3]

[1]The Irish Longitudinal Study on Ageing, Department of Medical Gerontology, Trinity College Dublin, Ireland. [2]Trinity Health Kidney Centre, Trinity Centre for Health Sciences, Tallaght Hospital, Dublin, Ireland. [3]Department of Renal Medicine, Beaumont Hospital, Dublin, Ireland.

Address correspondence to Mark Canney, MB BCh BAO, The Irish Longitudinal Study on Ageing, Department of Medical Gerontology, Lincoln Gate, Trinity College Dublin, Ireland. E-mail: mcanney@tcd.ie

Decision Editor: Stephen Kritchevsky, PhD

Abstract

Background: The burden of chronic kidney disease is highest among older adults but the significance of a diminished level of kidney function in this heterogeneous population is poorly understood. We sought to examine the relationship between estimated glomerular filtration rate (eGFR) and objective physical performance in older adults.

Methods: Cross-sectional analysis of 4,562 participants from The Irish Longitudinal Study on Ageing, a national cohort of community-dwelling adults aged ≥50 years. We used multivariable linear or quantile regression to model the association between categories of cystatin C (eGFR$_{cys}$) or creatinine eGFR (eGFR$_{cr}$) and the following outcomes: gait speed, timed-up-and-go (TUG) and grip strength. Relationships were further explored using natural eGFR splines. We examined effect modification by age in the relationship between eGFR and gait speed.

Results: Mean (*SD*) age was 61.8 (8.3) years, 53.6% were female and median (IQR) eGFR$_{cys}$ was 82 (70–94) mL/min/1.73m^2. In multivariable-adjusted models, participants in the lowest eGFR$_{cys}$ category (< 45 mL/min/1.73m^2) had 3.32 cm/s (95% confidence interval [95%CI] 0.02–6.62) slower mean gait speed, 1.32 kg (95%CI 0.20–2.44) lower mean grip strength, and 0.31 seconds (95% CI –0.04 to 0.65) longer median TUG versus the reference group (eGFR$_{cys}$ ≥ 90 mL/min/1.73m^2). The relationship between eGFR$_{cys}$ and outcomes appeared linear but varied by age. The association between eGFR$_{cr}$ and outcomes tended towards a U-shape.

Conclusions: Cystatin C eGFR was linearly related to poorer physical performance beyond middle age among community-dwelling adults. The non-linear relationships observed with eGFR$_{cr}$ underscore the limitations of creatinine as a predictor of frailty outcomes in older individuals.

Keywords: Chronic kidney disease—Population study—Gait speed—Grip strength—Timed-up-and-go

Chronic kidney disease (CKD) increases the risk of cardiovascular and all-cause mortality independent of traditional risk factors such as hypertension (1) and diabetes (2). The risk-based paradigm of CKD classification (3) has come under scrutiny due to a high burden of CKD among older individuals despite a comparatively low incidence of end stage kidney disease (4). The majority of older adults with CKD have relatively modest reductions in estimated glomerular filtration rate (eGFR), and would not be expected to experience symptoms attributable solely to kidney disease. It is in this heterogeneous population that there is a pressing need to better understand the clinical phenotype of CKD. Changing the outcome measure in the older CKD population from a "hard" outcome such as mortality to a more proximal, person-centred outcome such as frailty could improve our understanding of CKD as a disease entity.

Studies of frailty in kidney disease to date have tended to adopt a phenotypic definition of frailty to identify robust, pre-frail and frail individuals (5). The frailty phenotype, a combination of self-report and objectively measured variables, has demonstrated an independent and graded association with CKD and has been shown to predict all-cause mortality in the CKD population (6,7). There has, however, been considerable heterogeneity among prior studies with respect to the definition of frailty (8). The original frailty criteria have not

been consistently applied across different cohorts ([9]). There are potential limitations associated with the use of self-reported variables in the context of perceived physical ability ([10]). Recent studies have instead focused their attention on objective measures of physical performance in specific populations such as older hospitalized patients ([11]), individuals with coronary artery disease ([10]), and CKD patients recruited from out-patient clinics ([12]). There is a paucity of data regarding the relationship between objective tests of physical performance and kidney function in the general population of older adults. Most studies to date have used creatinine to calculate eGFR. Creatinine is known to display U-shaped relationships with clinical outcomes due to confounding by muscle mass, an issue that is particularly relevant in the context of ageing and frailty. Cystatin C has emerged as a potentially preferable filtration marker in older people as it appears to be less influenced by muscle mass ([13]) or dietary protein intake ([14]).

The aims of this study were to examine the association between eGFR and objective physical outcomes across the eGFR range in community-dwelling older adults, investigate whether this relationship varies by age, and compare the relative ability of cystatin C or creatinine to predict physical performance.

Methods

Study Population

This was a cross-sectional analysis from wave 1 of The Irish Longitudinal Study on Ageing (TILDA), a nationally representative cohort of Irish adults aged ≥ 50 years resident in the community. The study design has been described elsewhere ([15],[16]). A total of 8,175 participants (62% response rate) took part in wave 1 (June 2009–June 2011). Participants completed a computer assisted personal interview in their homes and were subsequently invited to have a comprehensive health assessment either at a health centre or in their home. Details of the health assessment have been described previously ([17]). In the primary analysis we included participants who completed a health centre assessment with complete data for kidney function and all three outcomes (*N* = 4,562, Supplementary Figure 1). In a secondary analysis we included participants who performed the timed-up-and-go (TUG) and grip strength tests during either a centre- or home-based assessment (*N* = 5,206). In keeping with the original frailty construct from the Cardiovascular Health Study, we excluded participants with Parkinson Disease or stroke, or a mini-mental state examination score < 18 ([5]). All participants provided written informed consent. Ethical approval for TILDA was granted by the Research Ethics Committee of Trinity College Dublin and all experimental procedures adhered to the Declaration of Helsinki.

Outcome Variables

Gait speed was measured using the GAITRite portable electronic walkway system (CIR Systems Inc, Havertown, PA). Participants were instructed to walk at their usual pace along the 4.88 m walkway. They started walking 2.5 m before the walkway and finished walking 2 m after the walkway to allow for acceleration and deceleration respectively. The average gait speed from two walks was recorded in centimetres per second (cm/s). For the TUG test participants were asked to stand from a seated position, walk 3 m at their usual pace, turn around, walk back to the chair and sit down. The time taken from the command "Go" to when the participant was sitting with their back resting against the chair was recorded in seconds. In the health centre the chair had armrests and was 46 cm

high. Walking aids were permitted and the test was performed once. Grip strength was measured twice from the dominant hand using a hydraulic hand dynamometer (Baseline, Fabrication Enterprises Inc., White Plains, NY). The maximum reading of force was recorded in kilograms (kg).

Predictor Variables

Cystatin C eGFR (eGFR$_{cys}$) and creatinine eGFR (eGFR$_{cr}$) were categorized as follows (mL/min/1.73m^2): ≥90 (reference); 75–89; 60–74; 45–59; <45. These categories are in keeping with Kidney Disease Improving Global Outcomes guidelines for staging of eGFR. Due to small numbers of participants with eGFR < 30 mL/min/1.73m^2, we created a single category for all participants with eGFR < 45 mL/min/1.73m^2. The CKD Epidemiology Collaboration equations were used to calculate eGFR from either cystatin C alone ([18]) or creatinine alone ([19]).

Covariates

Participant characteristics included age, sex, smoking history (current/former/never) and self-reported physician-diagnosed conditions. Medication use was recorded during the interview and cross-checked with medication labels. All medications were coded according to the World Health Organisation Anatomical Therapeutic Chemical Classification ([20]). Low (LDL) and high density lipoprotein (HDL) were measured from participants' blood prior to freezing of the samples. We defined the presence of diabetes as a self-reported physician's diagnosis and/or receiving insulin or oral hypoglycaemic medication. We defined the presence of hypertension as a self-reported physician's diagnosis and/or receiving antihypertensive medications. We defined the presence of cardiovascular disease as the number (0, 1, 2 or more) of the following self-reported physician-diagnosed conditions: angina, myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft, heart failure, or transient ischaemic attack. Height and waist circumference were measured at the health assessment. Comorbidity variables included polypharmacy (regular use of ≥5 medications excluding supplements) and number (0, 1, 2 or more) of the following self-reported physician-diagnosed chronic health conditions: chronic lung disease, asthma, arthritis, osteoporosis, malignancy, stomach ulcers, varicose ulcers, cirrhosis or severe liver damage.

Laboratory Data

At wave 1 a venous blood sample (25 mL) was collected from each consenting participant. Samples were transported to a central laboratory in temperature-controlled shipping boxes where they were centrifuged, aliquoted into cryovials and stored at –80°C. Cystatin C and creatinine were measured simultaneously from frozen plasma. Cystatin C was measured using a second generation particle enhanced immunoturbidimetric assay (Roche Tina-quant) on a Roche Cobas 701 analyzer. This assay has a measuring range of 0.4–6.8 mg/L and is traceable to the European reference standard material (ERM-DA471/IFCC) for cystatin C ([21]). Creatinine was measured using an enzymatic method traceable to isotope-dilution mass spectrometry.

Statistical Analysis

Continuous variables are presented as mean (standard deviation [*SD*]) and median (interquartile range [IQR]) for parametric and non-parametric distributions respectively. Categorical variables are presented as count (percent). The relationships between eGFR

categories and the outcomes gait speed and grip strength were assessed by multivariable linear regression. As TUG demonstrated a prominent right skew, we used quantile regression to investigate the relationship between eGFR categories and TUG time. Model 1 was adjusted for age, age-squared, sex, height, and waist circumference. Model 2 was adjusted for model 1 covariates plus cardiovascular disease, diabetes, hypertension, smoking, LDL, HDL, polypharmacy, and chronic health conditions.

To further examine the relationship between eGFR and each outcome in the health centre cohort, we modelled natural splines of eGFR in the multivariable adjusted models. We generated restricted cubic splines of continuous eGFR by placing five knots at equally spaced intervals (5th, 27.5th, 50th, 72.5th, and 95th centiles) along the distribution of eGFR. In an exploratory analysis, we investigated whether the relationship between eGFR and gait speed varied by age, by interacting continuous age with continuous eGFR, both expressed as quadratic terms. Interactions are presented graphically using the *marginsplot* command in Stata. We modelled the associations between $eGFR_{cys}$ and each outcome within age strata (50–64, 65–74, ≥75 years). Stratum-specific models were adjusted for age, sex, height, and waist circumference.

Missing data were assumed to be missing at random, and only complete cases were analysed. All analyses were performed using Stata version 14 (StataCorp, College Station, TX).

Results

Characteristics of the Health Centre Sample

A total of 4,562 participants had complete data for kidney function and all outcomes, and were included in the primary analysis.

Participant characteristics are detailed in Table 1. Mean (*SD*) age of the cohort was 61.8 (8.3) years, 53.6% were female and median (IQR) $eGFR_{cys}$ was 82 (70–94) mL/min/1.73m². Compared to participants with preserved kidney function ($eGFR_{cys}$ ≥ 90 mL/min/1.73m²), participants in the lowest $eGFR_{cys}$ category (< 45 mL/min/1.73m²) were older (73.7 vs 57.2 years) and tended to have a greater burden of cardiovascular and non-cardiovascular conditions. Compared to the final study population, participants excluded because of missing data for either a physical performance outcome (*n* = 97) or $eGFR_{cys}$ (*n* = 282) tended to be slightly older, were more likely female and had a higher prevalence of diabetes and non-cardiovascular comorbidity (Supplementary Table 1).

Association Between eGFR and Physical Outcomes

The association between categories of $eGFR_{cys}$ and each outcome is provided in Table 2. There was a trend for poorer performance across each test with decreasing $eGFR_{cys}$. In multivariable-adjusted models (Model 2), participants in the lowest $eGFR_{cys}$ category had, on average, 3.32 cm/s (95% confidence interval [95%CI] 0.02–6.62) slower gait speed compared to the reference group. They also demonstrated longer median TUG time (0.31 seconds [95% CI –0.04 to 0.65]) and lower mean grip strength (–1.32 kg [95% CI –0.20 to –2.44]). The relationship between cubic splines of $eGFR_{cys}$ and each outcome is illustrated in Figure 1. For gait speed and TUG time, the threshold for poorer performance was below an $eGFR_{cys}$ of approximately 80 mL/min/1.73m², beyond which the relationship was linear. The relationship between $eGFR_{cys}$ and grip strength was broadly linear across the $eGFR_{cys}$ range.

The associations between $eGFR_{cr}$ categories and each outcome are described in Table 3. In multivariable-adjusted models

Table 1. Characteristics of the Health Centre Assessment Sample (*N* = 4,562) According to Category of Cystatin C Estimated Glomerular Filtration Rate (eGFR, mL/min/1.73m²)

	Cystatin C eGFR Category				
	≥ 90	75–89	60–74	45–59	<45
	(*n* = 1,524)	(*n* = 1,486)	(*n* = 1,027)	(*n* = 379)	(*n* = 146)
Age	57.2 (6.1)	60.9 (6.7)	65.0 (8.2)	69.9 (8.2)	73.7 (8.2)
Female sex	790 (51.8)	792 (53.3)	555 (54.0)	235 (62.0)	75 (51.4)
Height (cm)	167.2 (8.9)	166.6 (9.2)	165.9 (9.2)	163.7 (9.0)	163.6 (8.6)
Smoking					
Current	167 (11.0)	224 (15.1)	198 (19.3)	71 (18.7)	13 (8.9)
Former	618 (40.6)	578 (38.9)	382 (37.2)	153 (40.4)	70 (48.0)
Never	739 (48.5)	684 (46.0)	447 (43.5)	155 (40.9)	63 (43.2)
Waist (cm)	91.9 (13.0)	94.0 (12.9)	97.5 (13.9)	99.2 (14.2)	101.0 (15.8)
Hypertension	433 (28.4)	488 (32.8)	495 (48.2)	246 (64.9)	119 (81.5)
Diabetes	72 (4.7)	73 (4.9)	70 (6.8)	44 (11.6)	27 (18.5)
CV conditions					
0	1,458 (95.7)	1386 (93.3)	908 (88.4)	317 (83.6)	100 (68.5)
1	53 (3.5)	78 (5.3)	86 (8.4)	49 (12.9)	27 (18.5)
2 or more	13 (0.9)	22 (1.5)	33 (3.2)	13 (3.4)	19 (13.0)
LDL (mmol/L)	3.02 (0.92)	3.03 (0.92)	2.87 (0.96)	2.68 (0.95)	2.49 (0.89)
HDL (mmol/L)	1.62 (0.45)	1.57 (0.42)	1.51 (0.43)	1.45 (0.41)	1.39 (0.44)
Comorbidities					
0	921 (60.4)	791 (53.2)	496 (48.3)	143 (37.7)	50 (34.3)
1	447 (29.3)	513 (34.5)	356 (34.7)	156 (41.2)	59 (40.4)
2 or more	156 (10.2)	182 (12.3)	175 (17.0)	80 (21.1)	37 (25.3)
Polypharmacy	97 (6.4)	146 (9.9)	187 (18.3)	115 (30.8)	73 (50.7)

Note: Numbers expressed as mean (*SD*) or count (percent). Data missing for height (*n* = 1), waist circumference (*n* = 6), LDL/HDL (*n* = 9) and polypharmacy (*n* = 21). CV = cardiovascular; HDL = high density lipoprotein; LDL = low density lipoprotein; TUG = timed up and go.

Table 2. Relationship Between Categories of Cystatin C Estimated Glomerular Filtration Rate (eGFR, mL/min/1.73m^2) and Physical Performance Tests in Health Centre Assessment Sample

eGFR	Model 1	p	Model 2	p
	Gait Speed (cm/s)			
≥90	Reference		Reference	
75–89	0.14 (–1.15 to 1.44)	.83	0.63 (–0.65 to 1.90)	.34
60–74	–1.76 (–3.28 to –0.23)	.02	–0.48 (–2.0 to 1.04)	.54
45–59	–6.40 (–8.62 to –4.17)	<.001	–3.83 (–6.06 to –1.59)	.001
<45	–7.21 (–10.49 to –3.93)	<.001	–3.32 (–6.62 to –0.02)	.05
p trend[a]	<.001		.006	
	Timed Up and Go (s)			
≥90	Reference		Reference	
75–89	–0.02 (–0.15 to 0.11)	.74	–0.07 (–0.20 to 0.06)	.30
60–74	0.12 (–0.04 to 0.27)	.13	0.07 (–0.09 to 0.23)	.38
45–59	0.56 (0.34 to 0.77)	<.001	0.26 (0.03 to 0.49)	.03
<45	0.61 (0.29 to 0.94)	<.001	0.31 (–0.04 to 0.65)	.08
p trend[a]	<.001		.02	
	Grip Strength (kg)			
≥90	Reference		Reference	
75–89	–0.31 (–0.74 to 0.12)	.16	–0.28 (–0.72 to 0.15)	.20
60–74	–0.40 (–0.91 to 0.10)	.12	–0.38 (–0.89 to 0.14)	.15
45–59	–0.62 (–1.36 to 0.12)	.10	–0.53 (–1.29 to 0.23)	.17
<45	–1.44 (–2.53 to –0.35)	.01	–1.32 (–2.44 to –0.20)	.02
p trend[a]	.01		.03	

Note: Model 1 (*n* = 4,555)—adjusted for age, age-squared, sex, height, and waist circumference. Model 2 (*n* = 4,525)—adjusted for model 1 covariates plus cardiovascular disease, diabetes, hypertension, smoking, low and high density lipoprotein, polypharmacy, and chronic health conditions.

[a]*p* value for linear trend across ordered categorical variable.

(Model 2), eGFR$_{cr}$ was not associated with poorer performance in any test. For some outcomes, the direction of the relationship was opposite to that of eGFR$_{cys}$. For example, participants with eGFR$_{cr}$ of 45–59 mL/min/1.73m^2 had, on average, 1.36 (95% CI 0.62–2.11) kg *higher* grip strength than those with eGFR$_{cr}$ ≥ 90 mL/min/1.73m^2. The relationships between cubic splines of eGFR$_{cr}$ and the outcomes gait speed and TUG tended towards a U-shape or inverse U-shape (Figure 2).

Figure 3 provides a graphical illustration of the differential relationship between eGFR and gait speed for a participant aged 55, 65, or 75 years. There was little evidence of an association between eGFR$_{cys}$ and gait speed at age 55 years. The linear relationship between eGFR$_{cys}$ and gait speed became evident at the latter two ages. The relationship between eGFR$_{cr}$ and gait speed became progressively inverse U-shaped with age. Supplementary Table 2 reports age stratum-specific estimates for the association between continuous eGFR$_{cys}$ and each outcome. These slope estimates indicate comparatively worse performance in gait speed and TUG with advancing age per unit decrease in eGFR$_{cys}$. The relationship between eGFR$_{cys}$ and grip strength did not vary as much by age. Box plots illustrating the distribution of eGFR$_{cys}$ across age categories are provided in Supplementary Figures 2 and 3. It should be acknowledged that the interaction between age and eGFR may have been limited by reduced sample sizes at the extremes of age and eGFR.
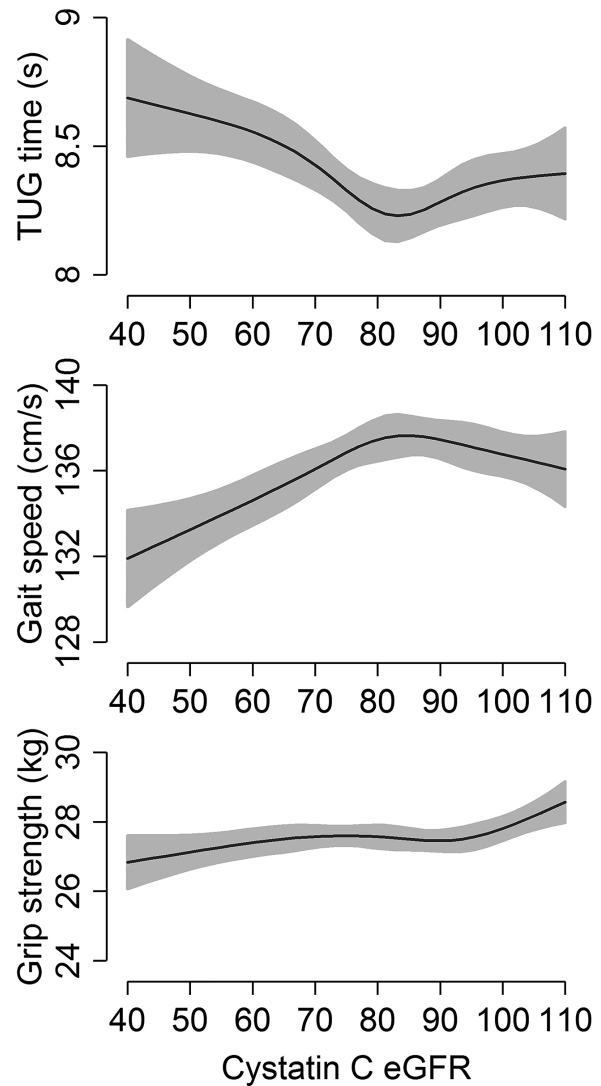
Figure 1. Multivariable adjusted relationship between physical performance tests and cubic splines of cystatin C estimated glomerular filtration rate (eGFR, mL/min/1.73m^2). Models adjusted for age, age-squared, sex, height, waist circumference, cardiovascular disease, diabetes, hypertension, smoking, low and high density lipoprotein, polypharmacy and chronic health conditions. TUG = timed up and go.

Secondary Analysis

A total of 5,206 participants completed the TUG and grip strength tests at either a centre- (*n* = 4,603) or home-based (*N* = 603) assessment. Supplementary Table 3 compares their characteristics to those who did not partake in any form of health assessment (*n* = 2,229). Compared to those with no assessment, the centre assessment cohort tended to be younger with less cardiovascular risk factors and polypharmacy. In contrast, the home assessment sample tended to be older with a greater degree of cardiovascular and non-cardiovascular comorbidity. The pattern of association between eGFR$_{cys}$ categories and physical performance was similar to that in the primary analysis (Supplementary Table 4). In fully adjusted models, participants with eGFR$_{cys}$ < 45 mL/min/1.73m^2 had evidence of longer median TUG time (0.73s [95% CI 0.42–1.03]) and lower mean grip strength (–1.21kg [95% CI –0.29 to –2.14]) compared to the reference group.

Table 3. Relationship Between Categories of Creatinine Estimated Glomerular Filtration Rate (eGFR, mL/min/1.73m²) and Physical Performance Tests in Health Centre Assessment Sample

| eGFR	Model 1	p	Model 2	p
	Gait Speed (cm/s)			
≥90	Reference		Reference	
75–89	1.86 (0.58 to 3.14)	.004	1.68 (0.42 to 2.94)	.009
60–74	2.69 (1.18 to 4.21)	<.001	2.53 (1.04 to 4.02)	.001
45–59	0.86 (−1.36 to 3.08)	.45	1.55 (−0.65 to 3.75)	.17
<45	−4.87 (−8.60 to −1.14)	.01	−2.26 (−5.98 to 1.46)	.23
p trend[a]	.37		.08	
	Timed Up and Go (s)			
≥90	Reference		Reference	
75–89	−0.03 (−0.16 to 0.09)	.63	−0.02 (−0.15 to 0.11)	.78
60–74	−0.10 (−0.25 to 0.05)	.18	−0.13 (−0.28 to 0.03)	.11
45–59	−0.004 (−0.22 to 0.21)	.97	−0.11 (−0.34 to 0.12)	.36
<45	0.51 (0.15 to 0.88)	.006	0.32 (−0.07 to 0.71)	.11
p trend[a]	.85		.28	
	Grip Strength (kg)			
≥90	Reference		Reference	
75–89	0.78 (0.36 to 1.21)	<.001	0.73 (0.31 to 1.16)	.001
60–74	0.91 (0.41 to 1.41)	<.001	0.85 (0.34 to 1.35)	.001
45–59	1.35 (0.62 to 2.09)	<.001	1.36 (0.62 to 2.11)	<.001
< 45	0.98 (−0.26 to 2.21)	.12	1.03 (−0.23 to 2.29)	.11
p trend[a]	<.001		<.001	

Note: Model 1 (*n* = 4,554)—adjusted for age, age-squared, sex, height, and waist circumference. Model 2 (*n* = 4,525)—adjusted for model 1 covariates plus cardiovascular disease, diabetes, hypertension, smoking, low and high density lipoprotein, polypharmacy, chronic health conditions.

[a]*p* value for linear trend across ordered categorical variable.

Discussion

In this large cohort of community-dwelling older adults, reductions in kidney function were associated with poorer performance in objective tests of physical function. This relationship was stronger when GFR was estimated from cystatin C compared to creatinine, the latter tending towards a U- or inverse U-shape. Cystatin C eGFR was linearly related to slower gait speed and longer TUG below an eGFR$_{cys}$ of approximately 80 mL/min/1.73m². The association between eGFR$_{cys}$ and gait speed varied by age. Our findings suggest that eGFR$_{cys}$ is a predictor of poorer physical performance in older adults, but the potential contribution of a diminished level of kidney function to poorer physical outcomes may only be encountered in the oldest old.

Frailty has been shown to predict adverse outcomes among patients receiving dialysis (22). This unique population has a complex set of comorbidities and exhibits a markedly higher prevalence of frailty compared to age-matched peers in the general population (23). Similarly, individuals with referred CKD tend to have substantial reductions in eGFR and, as such, might be expected to have complications from their CKD. For example, in a study of 385 patients referred to a CKD clinic, the mean eGFR of the sample was 41 mL/min/1.73m² (12). Performance in tests of lower extremity function was reduced in these patients compared to healthy controls, and poor physical performance was an independent predictor
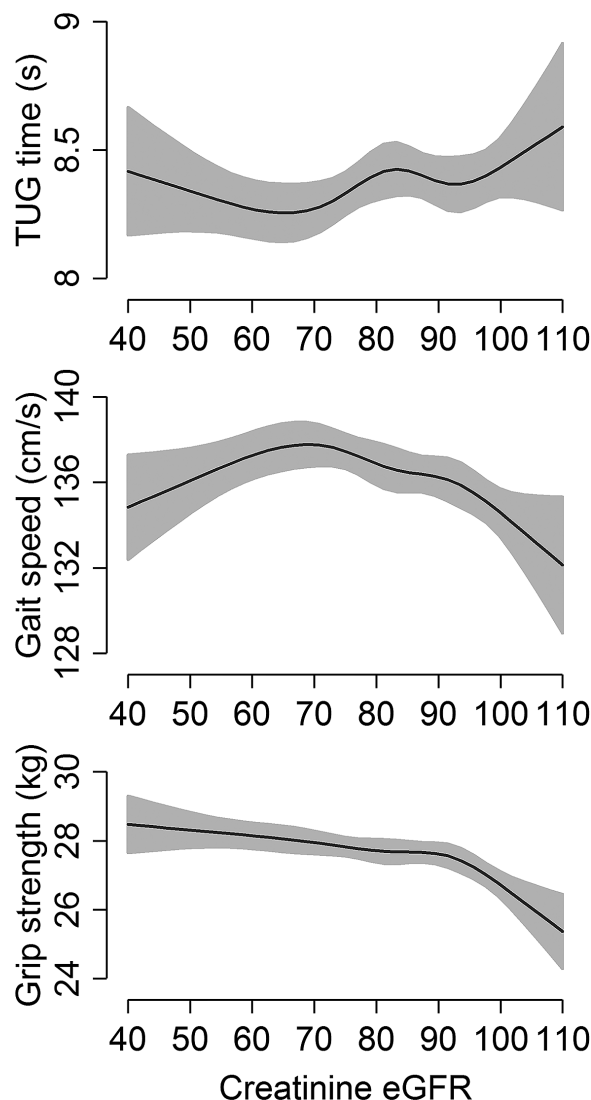
Figure 2. Multivariable adjusted relationship between physical performance tests and cubic splines of creatinine estimated glomerular filtration rate (eGFR, mL/min/1.73m²). Models adjusted for age, age-squared, sex, height, waist circumference, cardiovascular disease, diabetes, hypertension, smoking, low and high density lipoprotein, polypharmacy and chronic health conditions. TUG = timed up and go.

of mortality. Given the steep age gradient in CKD prevalence in the general population (24), along with anticipated rapid growth in the older population, the bulk of CKD will be encountered in the community rather than the minority referred to a nephrology clinic. Our study expands existing knowledge by demonstrating declines in standardised tests of physical performance with diminishing eGFR in a large sample of older community-dwelling adults across a broad range of eGFR.

Similar to other studies, we found that cystatin C out-performed creatinine as a predictor of physical function or frailty. In a sub-sample of 1,226 participants aged >60 years from the Framingham Offspring Study, CKD defined by eGFR$_{cys}$ < 60 mL/min/1.73m² (but not eGFR$_{cr}$ < 60 mL/min/1.73m²) was associated with higher odds of self-reported incident mobility disability (25). An analysis of Cardiovascular Health Study participants demonstrated a graded association between eGFR$_{cys}$ and prevalent and incident frailty
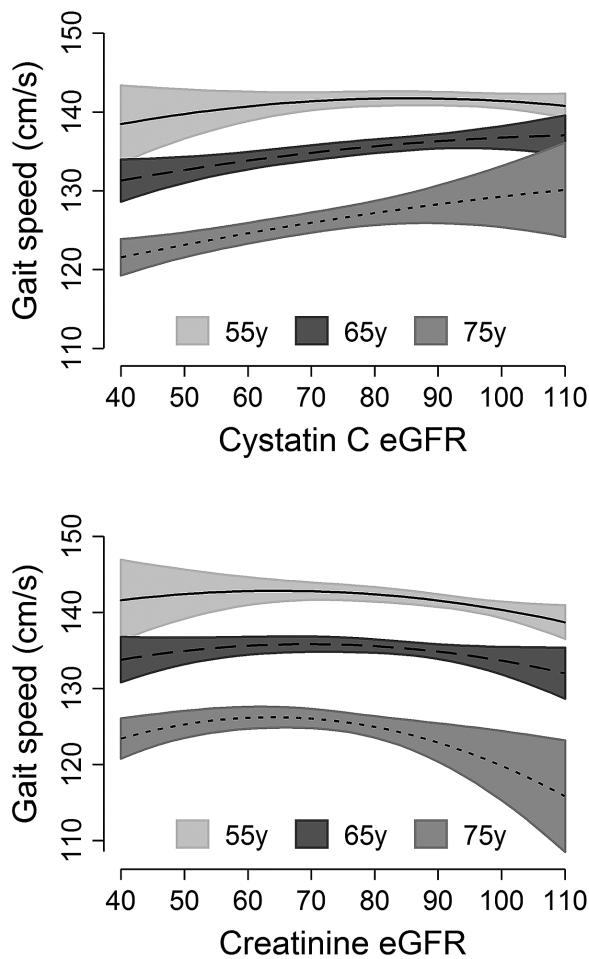
Figure 3. Predicted marginal mean gait speed for a participant aged 55 (solid line), 65 (dashed line) and 75 years (dotted line) across the range of estimated glomerular filtration rate (eGFR, mL/min/1.73m²) from cystatin C or creatinine. Models adjusted for sex, height, waist circumference, cardiovascular disease, diabetes, hypertension, smoking, low and high density lipoprotein, polypharmacy and chronic health conditions.

which, like our study, became evident below an eGFR$_{cys}$ of 75 mL/min/1.73m² ([26]). A study from the Health ABC cohort documented U-shaped relationships between eGFR$_{cr}$ and a number of objective tests of physical function ([27]). Compared to the Health ABC cohort, our study population was more population-representative and had a broader range of age. In addition, we have provided a more granular comparison of creatinine and cystatin C, with both biomarkers expressed as eGFR using standardised equations.

We found that the relationship between eGFR$_{cr}$ and gait speed became progressively U-shaped with age. Creatinine eGFR was linearly related to grip strength but in the opposite direction to eGFR$_{cys}$. These findings mirror the risk relationships of creatinine with mortality, and emphasize the limitations of using creatinine as a predictor of outcomes in older individuals. For outcomes such as frailty, which are linked to muscle quality and function, cystatin C is likely to be a superior biomarker to creatinine. It must also be acknowledged that cystatin C has been shown to have "non-GFR" determinants such as inflammation, smoking, and obesity, which could also contribute to frailty and poorer physical performance ([28–30]). There is emerging evidence that cystatin C may be a biomarker of unsuccessful ageing. For example, in a study of older men, cystatin C

was associated in a graded fashion with increased risks of frailty and mortality ([31]). Conversely, in a study of older women, the lowest quartile of cystatin C was an independent predictor of preserved mobility 10 years later ([32]).

The linear relationship we observed between eGFR$_{cys}$ and gait speed only became evident after middle-age. Older adults have by far the highest prevalence of undifferentiated CKD ([24]). The development of frailty in this age demographic is of paramount concern as it can lead to loss of independence and an increased rate of complications such as falls and disability. The independent association between eGFR and physical performance suggests that a reduction in eGFR is not a benign entity in this sub-population of older individuals. The threshold for poorer performance was consistent with studies of endpoints such as cardiovascular events and mortality ([33]). Future studies should examine whether physical performance tests could provide a means of better risk-stratifying the heterogeneous population of older adults with diminished eGFR. In the clinical setting, objective and easily standardized tests of frailty could offer a practical advantage over frailty constructs, the latter more time-consuming to obtain and variably applied across studies, thereby limiting comparability of findings in the literature.

Our findings should be interpreted in the context of potential limitations. The cross-sectional design limits our ability to infer causality in the relationship between kidney function and physical outcomes. There may have been residual measured or unmeasured confounding in this relationship. The observations regarding a modifying effect of age should be interpreted in the context of their exploratory nature. Kidney function was measured at a single time point and urinary protein was not measured in the participants. The TILDA sample is virtually all Caucasians and excluded individuals in institutionalised care, limiting the generalizability of our findings. These limitations are balanced by several strengths. We measured physical performance using objective standardized tests in a large sample of community-dwelling older adults encompassing a broad range of age and eGFR. The TILDA dataset is comprehensive, facilitating a robust appraisal of potential confounders. Creatinine and cystatin C were measured simultaneously using standardized assays, and the participants' blood samples were taken on the same day as their health assessment.

In conclusion, we report a relationship between reductions in kidney function defined by cystatin C and objective markers of physical performance in a large national cohort of community-dwelling older adults. The association between creatinine eGFR and physical performance was non-linear, underscoring the limitations of creatinine as a predictor of clinical outcomes in this population. Further studies in similarly representative populations are warranted to ascertain the potential value of incorporating physical performance tests into the clinical and risk assessment of CKD in an ageing population.

Supplementary Material

Supplementary data is available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

Funding

Acknowledgments

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