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ORIGINAL ARTICLE

Higher albumin:creatinine ratio and lower estimated glomerular filtration rate are potential risk factors for decline of physical performance in the elderly: the Cardiovascular Health Study

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ABSTRACT

Introduction. Mildly reduced renal function and elevated urine protein levels are each prospectively associated with hip fracture risk in older adults. Here we determine whether these markers are associated with reduced appendicular muscle performance.

Methods. We prospectively examined the associations of urine albumin:creatinine ratio (ACR) and reduced estimated glomerular filtration rate (eGFR) with longitudinal changes in grip strength and gait speed >2 years in 2317 older community-dwelling men and women (median age 77 years). The median ACR was 9.8 [interquartile range (IQR) 5.40–21.50] mg/g creatinine and the median eGFR was 71.6 (IQR 59.1–83.56) mL/min/1.73 m^2. Models were adjusted for demographic factors, clinical history and biochemical measures in four candidate pathways: diabetes, oxidative stress, inflammation and fibrosis.

Results. In demographic- and covariate-adjusted models, a 2-fold higher baseline urine ACR was associated with longitudinal changes of −0.17 kg [95% confidence interval (CI) −0.29 to −0.06) in grip strength and −1.10 cm/s (95% CI −1.67 to −0.53) gait speed per year. Corresponding estimates for a 10 mL/min/1.73 m^2 lower baseline eGFR were −0.13 kg (95% CI −0.23 to −0.04) and −0.89 cm/s (95% CI −1.37 to −0.40), respectively. The associations of a 2-fold higher baseline ACR and a 10 mL/min/1.73 m^2 lower baseline eGFR using cystatin C with grip strength and gait speed were equivalent to ∼1.2–1.9 additional years of age. Adjustment for covariates in candidate pathways did not attenuate these estimates.

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Conclusions. In older adults, higher ACR and lower eGFR are potential risk factors for a decline of physical performance >2 years.

Keywords: albuminuria, appendicular muscle mass, gait speed, grip strength, physical performance

INTRODUCTION

Epidemiological studies demonstrate that end-stage renal disease and advanced chronic kidney disease (CKD) are associated with frailty [1, 2], a constellation of symptoms and signs that includes involuntary weight loss, exhaustion, low physical activity and performance deficits in muscle strength and gait speed [3]. Frailty is associated with a poor prognosis [4]. This phenotype predicts incident falls, worsening mobility or activities of daily living, disability, hospitalization and death [3]. Moreover, the rates of decline in gait speed and grip strength influence the risk of disability and mortality [5, 6]. Lesser degrees of renal disease [estimated glomerular filtration rate (eGFR) <60 and <45 mL/min/1.73 m^2, respectively] are also associated with graded declines in physical performance and with prefrailty, a precursor of frailty [7–9].

From these data, it may be extrapolated that the association of renal disease with physical decline may occur early in the process of renal decline, when eGFR is ≥60 mL/min/1.73 m^2. Little is known about the progression of objectively measured performance deficits at this stage of renal disease and whether urinary protein excretion and impaired renal filtration have differential effects on physical performance. This issue is of special importance among the elderly in whom the age-related decline in filtration rate accelerates and in whom the prevalence rates of albuminuria (~35% by ages 70–75 years) and CKD (eGFR <60 mL/min/1.73 m^2; 17% at ages 60–79 years) are high [10, 11].

We have previously shown that albuminuria—adjusted for eGFR, falling and frailty—is associated with reduced hip and total body bone mineral density and with increased hip fracture risk [12]. We have also shown that mildly reduced eGFR, adjusted for a history of falling, physical activity and gait speed are associated with hip fracture risk [13]. Since appendicular bone and muscle share common arterial supplies, risk factors for impairment (e.g. advancing age, oxidative stress, inflammation, insulin resistance and fat infiltration) and common function (ambulation), it follows that early markers of renal disease may also be associated with low peripheral muscle quality.

Although the causes of physical dysfunction are manifold, a few appear to be relevant to renal disease. In particular, diabetes [14], inflammation [15] and oxidative stress [16] have been implicated as mediators of aging and muscle dysfunction in kidney disease. For example, carboxymethyl-lysine (CML) (a marker of oxidative stress) predicts hip fracture, coronary heart disease, stroke and disability risks [17–19]. Moreover, with increasing recognition of fibrosis as a common final pathway in CKD [20], it too appears to be a plausible candidate mechanism to link early renal impairment with physical dysfunction.

To our knowledge, no prospective study has evaluated the comparable associations of both eGFR and albuminuria with risk of physical function decline in a population-based cohort of elders. To elucidate the independent associations of mild impairments in eGFR and albuminuria with prospective muscle strength and gait speed, and the roles of candidate pathways in these associations, we prospectively studied participants from the Cardiovascular Health Study (CHS), an intensively phenotyped cohort of older Americans.

MATERIALS AND METHODS

CHS is an ongoing longitudinal study of adults ≥65 years of age in four US communities drawn from Medicare lists [21]. In 1989–90, 5201 participants were recruited, followed by an additional 687 African Americans in 1992–93. All participants gave informed consent upon study entry. Institutional review board approval was received at all clinical sites. From 1989–90 to 1998–99, participants were seen in clinic annually and had annual telephone contact between clinic visits.

Of the 5888 original and African American participants, 3826 (~65%) were seen in 1996–97, the baseline year for this study. At that time, 3051 had grip strength testing, 3144 had gait speed measurement, 2828 had urine testing and 3115 had cystatin measured. Two years later, in 1998–99, during a follow-up examination, 2888 had grip strength and 2889 had gait speed remeasured. A total of 2317 participants had complete baseline and follow-up muscle function assessment and baseline urine and renal testing (See Figure, Appendix).

Kidney function testing

In 1996–97, the baseline year for the current analysis, participants underwent spot urine testing in the fasting state for albumin and creatinine levels. Urine albumin was measured soon after collection on the Array 360 CE Protein Analyzer (Beckman Instruments, Fullerton, CA, USA) and urine creatinine on the Ektachem 700 Analyzer (Eastman Kodak, Rochester, NY, USA). Urinary albumin excretion was estimated as the urinary albumin:creatinine ratio (ACR) in milligrams of albumin per gram of creatinine. This method, based on a spot urine, yields results comparable to those from a 24-h urine collection [22]. At the same visit, participants underwent fasting phlebotomy. Cystatin levels were measured using an immunonephelometric assay [23]. We have reported that cystatin C is a stronger predictor of the risk of death and cardiovascular events in elderly persons than is creatinine [23]. We estimated the eGFR using cystatin C (eGFRcys) using the Chronic Kidney Disease Epidemiology Collaboration equations for cystatin.

Tests of muscle performance

Two tests of muscle function were performed in 1996–97 [24]: grip strength and gait speed. For grip strength, forearm muscle strength was measured by a hand-held Jamar A dynamometer, which recorded the force in kilograms of three maximal attempts with the subject's dominant and nondominant hands. The best of three attempts in the dominant hand was used. For gait speed, the time (to 0.1 s) required for a participant to walk a 15-foot course at his or her usual pace after starting from a standstill. Values were converted into centimeter per second analytically.

These two tests were repeated at a follow-up visit 2 years later (1998–99) {median follow-up 2.0 years [interquartile range (IQR) 1.95–2.03]}.

Covariates

Information was collected from the baseline year on demographics (sex, age, race), smoking status, medical history, seated blood pressure and technician-measured height, weight and waist circumference. Coronary heart disease was centrally adjudicated, as previously described [25]. Diabetes and impaired fasting glucose were defined using American Diabetes Association cut points and the use of hypoglycemic medication.

To examine candidate pathways, we used three measurements taken from the 1996–97 visit and performed at the CHS central laboratory [26]. High-sensitivity C-reactive protein (CRP) levels were measured with an assay developed in the CHS central laboratory [27]. Plasma levels of CML (an advanced glycation end product) were used as a measure of oxidative stress [17]. Procollagen type III N-terminal pro-peptide (PIIINP) was evaluated as a measure of systemic fibrosis [28].

Statistical methods

Baseline characteristics of the study cohort are presented by the presence or absence of albuminuria (≥30 mg albumin/g creatinine). To evaluate whether the ACR was prospectively associated with muscle strength and function during follow-up, we examined all participants with evaluable urine and blood samples and completed serial grip strength and gait speed tests. Because of a long right skew, ACR was $\log_2$ transformed and winsorized at the 95th percentile (i.e. values above this threshold were set to the 95th percentile). The associations of $\log_2$ ACR and eGFRcys with grip strength and gait speed change were examined through incrementally adjusted linear regression models. In all cases, the dependent variable was the performance measure in 1998–99, with adjustment for baseline values as recommended [29]. These models included Model 1 adjusted for age, gender and race; Model 2 additionally adjusted for height, waist circumference, current smoking, current use of alcohol, glycemic status, systolic blood pressure, prevalent cardiovascular disease, current hypertension medications and CRP; and Model 3 additionally adjusted for markers of two potential mediators, CML and PIIINP levels. We tested for linearity in the relationships of $\log_2$ ACR and eGFRcys with both outcomes using generalized additive models, with no meaningful departures from linearity.

Several sensitivity analyses were performed to gain further insights into the relationship of renal impairment and functional decline. (i) To explore changes in outcomes of 'clinical importance', we further examined the effect of ACR and eGFRcys on end points deemed clinically significant but conservative from prior studies of aging—a decline of at least 0.5 kg grip strength [30] or a decline of ≥30 cm/s [31] gait speed. Logistic regression models were adjusted as above. (ii) To put our findings into clinical context, we estimated the number of years of aging equivalent to the changes in the β coefficient for grip strength and gait speed. (iii) To test whether our findings were relevant to advanced older age or not, we categorized our analyses by the median age of the cohort (77 years). (iv) Finally, we examined whether the use of angiotensin-converting enzyme inhibitors (ACEis) or angiotensin II receptor blockers (ARBs) (which can lower ACR levels) modified the associations of ACR and CKD with functional decline.

Analyses were done using R (R Foundation for Statistical Computing, Vienna, Austria) [32].

RESULTS

A summary of baseline variables appears in Supplementary data, Table S1. The median eGFR was 71.6 (IQR 59.51–83.56) mL/min/1.73 m^2 and the median ACR was 9.8 (IQR 5.4–21.5) mg/g creatinine.

Baseline characteristics of participants characterized by the presence or absence of ALB are shown in Table 1. Participants with ALB were older and more likely male and to have hypertension, diabetes and to smoke, but less heavily. They had higher CRP, CML and PIIINP levels.

Primary analyses of grip strength

The mean difference in grip strength during the 2-year follow-up was −2.00 kg [95% confidence interval (CI) −2.17 to −1.83; $P < 0.001$] and the median change was −2.00 kg (IQR −4.67–0.67). Linear regression models of grip strength and gait speed change using ACR (per 2-fold higher level) and eGFRcys (per 10 mL/min/1.73 m^2/year lower level) are shown in Table 2.

After adjustment for age, sex and race, a 2-fold higher ACR was associated with a 0.23 kg decline in grip strength, while a 10 mL/min/1.73 m^2/year lower eGFRcys was associated with a 0.1 kg decrease per year. Further adjustments (Model 2), including glycemic status and CRP level, modestly attenuated the association of ACR with grip strength, but results remained statistically significant. These adjustments did not impact the association of lower eGFRcys on grip strength. Further adjustment for CML and PIIINP had no appreciable effect on either estimate. CML (per ng/mL) was associated with a −0.001 kg (95% CI −0.002–0.0; $P = 0.051$) change in grip strength (Model 3); per standard deviation of CML (225 ng/mL) grip strength was reduced 0.179 kg (−0.359–0.001; $P = 0.051$) and gait speed by 0.934 cm/s (−1.834 to −0.035; $P = 0.042$).

The regression coefficient for 1 year of aging was −0.16 kg of grip strength. Hence a doubling of baseline ACR was equivalent to −0.23/−0.16 = ∼1.4 years of aging, while a 10 mL/1.73 m^2/min/year lower eGFR was equivalent to 1.2 years of aging (−0.12/−0.10).

When analyses were repeated using the dichotomous variable ALB (i.e. ≥30 mg albumin/g creatinine), similar associations were observed (Supplementary data, Table S2).

Primary analyses of gait speed

The mean and standard deviation change of gait speed during 2-year follow-up was −6.1 cm/s (95% CI −7.0 to −5.1; $P < 0.001$) and the median decline was 1.0 cm/s (95% CI −22.6–0.3). A 2-fold higher baseline ACR was associated with a significant decline in gait speed of 1.39 cm/s (equivalent to a decline of ∼420 cm over 5 min) after adjustment for age, sex and race (Table 2). A 10 mL/min/1.73 m^2 lower baseline eGFRcys was associated with a 1.15 cm/s (equivalent to a decline of ∼340 cm over 5 min) slower gait speed. Further adjustments (Model 2), including glucose status and CRP level, attenuated these associations, but they remained statistically significant. Adjustment for CML and PIIINP had no effect on the models. CML (per ng/mL) was associated with a −0.004 cm/s (95% CI −0.008–0.0; $P = 0.042$) change in gait speed (Model 3).

The regression coefficient for a 10 mL/min/1.73 m^2/year lower eGFRcys was −0.74 cm/s. Hence a doubling of baseline ACR (−1.39) was equivalent to ∼1.9 extra years of age; a 10-unit lower baseline eGFRcys (−1.15/−0.75) was equivalent to ∼1.5 extra years of age (1.15/0.75).

Table 1. Baseline characteristics of the CHS cohort from 1996 to 1997 categorized by albuminuria (≥30 mg/g creatinine) status

Characteristics	Total	No albuminuria	Albuminuria	P-value
Sample, *n*	2317	1903	414	
Male, *n* (%)	950 (41.0)	751 (39.4)	199 (48.1)	<0.01
Age (years), *n*	77.6 ± 4.4	77.4 ± 4.4	78.4 ± 4.9	<0.01
Black race, *n* (%)	362 (15.6)	299 (15.7)	63 (15.2)	0.86
Education ≥12 grades, *n* (%)	1141 (49.4)	945 (49.8)	196 (47.6)	0.44
Height (m)	1.64 ± 0.09	1.64 ± 0.09	1.64 ± 0.1	0.8
Waist (cm)	97.3 ± 12.74	97.39 ± 12.66	96.88 ± 13.14	0.47
BMI (kg/m^2)	27.01 ± 4.52	27.06 ± 4.51	26.78 ± 4.55	0.26
BMI <18, *n*	30 (1.3)	23 (1.1)	9 (2.2)	
BMI 18–24.9, *n*	766 (33.2)	617 (32.6)	149 (36.1)	
BMI 25–29.9, *n*	1016 (44)	856 (45.2)	160 (38.7)	
BMI >30, *n*	496 (21.5)	401 (21.2)	95 (23)	
Smoking status, *n* (%)	*n* = 2280	*n* = 1873	*n* = 407	0.05
Current	171 (7.5)	135 (7.2)	36 (8.8)	
Former	991 (43.5)	798 (42.6)	193 (47.4)	
Never	1118 (49)	940 (50.2)	178 (43.7)	
Alcohol, *n* (%)	*n* = 2309	*n* = 189	*n* = 413	0.78
None	1291 (55.9)	1054 (55.6)	237 (57.4)	
1–7 drinks/week	771 (33.4)	639 (33.7)	132 (32.0)	
>7 drinks/week	247 (10.7)	203 (10.7)	44 (10.7)	
Glucose status, *n* (%)	*n* = 2308	*n* = 189	*n* = 412	<0.01
Normal	1800 (78)	1542 (81.3)	258 (62.6)	
Impaired fasting glucose	163 (7.1)	125 (6.6)	38 (9.2)	
Diabetes	345 (14.9)	229 (12.1)	116 (28.2)	
Hypertension, *n* (%)	1465 (63.4)	1132 (59.6)	333 (80.6)	<0.01
Hypertension medications	1349 (58.2)	1042 (54.8)	307 (74.2)	<0.01
Prevalent CHD, *n* (%)	532 (23)	394 (20.7)	138 (33.3)	<0.01
eGFR mean (mL/min/1.73 m^2)	71.65 ± 19.0	73.54 ± 18.2	62.9 ± 20.0	<0.01
eGFR <60 mL/min/1.73 m^2, *n* (%)	586 (25.3)	408 (21.4)	178 (43)	<0.01
CRP >3 mg/L, *n* (%)	982 (42.7)	782 (41.4)	200 (48.5)	<0.01
CML (ng/mL)	620.6 ± 212.7	611.8 ± 196.6	661.1 ± 271.5	<0.01
PIIINP (ng/mL)	4.8 ± 1.7	4.7 ± 1.6	5.2 ± 2.3	<0.01
Daily physical activity (kcal), median (IQR)	787.5 (270–1695)	795 (280–1704)	682.5 (245–1665)	0.55
Baseline gait speed (cm/s)	900 ± 200	900 ± 200	900 ± 300	<0.01
Baseline grip (kg)	28.0 ± 9.8	28.0 ± 9.9	28.0 ± 9.6	0.95

Values presented as mean ± standard deviation unless stated otherwise.
All participants had complete baseline (1996–97) and follow-up (1998–99) muscle functional assessment and baseline urine and renal testing (1996–97).

When analyses were repeated using ALB, similar associations were observed (Supplementary data, Table S2).

Sensitivity analyses

The Model 2–adjusted odds ratios for clinically significant declines were 1.09 (95% CI 1.02–1.7; P = 0.02) for a doubling in ACR and 1.06 (95% CI 1.01–1.13; P = 0.04) for a 10 mL/min/1.73 m^2/year decrease in eGFRcys.

When analyses were categorized by age (above or below the cohort median) (Supplementary data, Table S3), the associations with both outcomes tended to be of similar strength for ACR. Although they tended to be weaker for eGFRcys in participants above the median age, tests of interaction with age were not significant (P > 0.2).

Finally, among participants using an ACEi/ARB, gait speed was not significantly decreased with a doubling of ACR [Model 2: $\log_2$ ACR 0.2 cm/s (95% CI −0.93–1.33; P = 0.73)]. In contrast, participants not taking these medications demonstrated a significant decline in gait speed [Model 2: −1.52 cm/s (95% CI −2.21 to −0.94; P < 0.001)] ($P_{interaction} = 0.01$). We observed no significant interactions between grip strength decline or the impact of a 10 mL/min/1.73 m^2 lower eGFR in participants treated or not treated with an ACEi/ARB.

DISCUSSION

In this study of older adults with mostly mild renal dysfunction, higher baseline ACR and lower baseline eGFRcys were each prospectively associated with statistically significant lower grip strength and walking speed 2 years later. These relationships were independent of each other and were not appreciably altered by concomitant derangements in glycemia, oxidative stress, fibrosis or inflammation. The changes are apt to have meaningful consequences, particularly because we examined the effects of modest changes in both excess urine protein and eGFR. The associations of a higher baseline ACR with grip and gait change were approximately equivalent to an additional 1.4 and 1.9 years of age; the corresponding associations of 10 mL/min/1.73 m^2/year lower baseline eGFRcys approximated 1.2 and 1.5 additional years of age. When we formally examined the likelihood of previously defined clinical thresholds in grip strength or gait speed, both measures of kidney function were associated with risk, highlighting their potential role in loss of function among elders. Finally, our exploratory results suggest

Table 2. Change in grip strength in kilograms and change in gait speed in centimeters/second at follow-up

Measure of muscle function	β	SE (95% CI)	P-value
Grip			
Model 1			
Log_2 ACR	−0.23	0.05 (−0.33 to −0.12)	<0.001
eGFRcys10	−0.10	0.05 (−0.20 to −0.01)	0.03
Model 2			
Log_2 ACR	−0.17	0.06 (−0.29 to −0.06)	0.003
eGFRcys10	−0.13	0.05 (−0.23 to −0.04)	0.007
Model 3			
Log_2 ACR	−0.16	0.06 (−0.28 to −0.05)	0.006
eGFRcys10	−0.12	0.05 (−0.22 to −0.02)	0.02
Gait			
Model 1			
Log_2 ACR	−1.39	0.27 (−1.91 to −0.87)	<0.001
eGFRcys10	−1.15	0.23 (−1.60 to −0.69)	<0.001
Model 2			
Log_2 ACR	−1.10	0.29 (−1.67 to −0.53)	<0.001
eGFRcys10	−0.89	0.25 (−1.37 to −0.40)	<0.001
Model 3			
Log_2 ACR	−1.06	0.30 (−1.64 to −0.48)	<0.001
eGFRcys10	−0.74	0.26 (−1.24 to −0.23)	0.005

Each model shows two coefficients: per doubling of ACR (log_2 ACR) and 10 mL/min/1.73 m^2 lower eGFR (eGFRcys10). Models (M) are adjusted as follows: M1: grip or gait speed at baseline, age, sex, race, clinic; M2: M1 + height, waist circumference, current smoking, current alcohol, log(CRP), glucose status (normal, impaired fasting glucose, diabetes mellitus), systolic blood pressure, prevalent CVD, hypertension medications; M3: M2 + CML and PIIINP levels.

(but do not prove) that the use of an ACEi and ARB may attenuate the impact of ACR on gait speed decline.

It may be argued that a 2-year follow-up period is too short for meaningful conclusions regarding the prospective associations of early kidney dysfunction with physical performance. With a median age of ∼77 years in the cohort, 2 years of follow-up constitutes a significant percentage of remaining life expectancy. Longer-term findings are likely to be seriously influenced by the competing risks of attrition and death.

Three prior cross-sectional studies are consistent with our prospective findings. In the I-Lan Longitudinal Aging Study from Taiwan [33] (mean age 63 ± 9 years), the prevalence of prefrailty/frailty and the components of weakness and slowness of gait increased across quartiles of ACR <30 mg/g creatinine. There were no differences across quartiles of eGFR. In the Systolic Blood Pressure Intervention Trial hypertension cohort [31] (mean age 79.8 years), mean gait speed was significantly higher in participants with an ACR (milligram/gram creatinine) <30 versus those ≥30–299 and ≥300. Finally, a prior CHS study [34] reported that a high burden of multiple microvascular disorders (brain white matter, retinal vascular disease and albuminuria) was more strongly associated with functional decline than eGFR levels.

How ALB is mechanistically related to lower muscle function is uncertain. Our current findings were present at a stage of renal disease that is usually not related to metabolic complications (e.g. acidosis, hyperphosphatemia) that can affect muscle function [35]. Likewise, while ALB is related to inflammation factors and oxidative stress [36], we adjusted our findings for these processes and our results were largely unaffected even though we have previously reported that higher CML levels in CHS—our marker of oxidative stress—are associated with incident disability and prevalent frailty [19]. It is therefore likely that alternate mechanisms are present. Several explanations are possible. First, we have shown that ALB is related to cognitive impairment [37]. Prospective studies show that slow gait speed and grip strength are associated with cognitive decline [38]. Second, ALB is related to impairments in other microvascular beds (e.g. skin and heart [39, 40]) and to generalized endothelial dysfunction [41], suggesting that ALB is a marker of a systemic disorder that could affect the microcirculation of muscle. Third, there is a bidirectional association of ALB with sarcopenia and muscle weakness. Kidney disease leads to decreased muscle mass [42] but sarcopenia can also predate the development of ALB [43].

Strengths of this study include a large number of participants in whom kidney function and physical performance were measured systematically and in multiple complementary ways. We included many covariates, some of which are plausible intermediates in the causal pathway between renal and muscle disease yet have rarely been measured in cohort studies. We used cystatin C levels to estimate GFR, which is more accurate than creatinine for assessing renal function in older adults [44]. Our study has limitations. First, urine testing was conducted only once; urine albumin levels vary, which may have biased estimates to the null because of potential misclassification of the ACR predictor. However, a single urine albumin specimen is a reliable means of predicting the geometric mean of multiple measures of ALB [45]. Second, the present cohort was exclusively elderly. Therefore we cannot extrapolate our results to younger people, although declines in physical performance are less common in such populations. Third, the markers of inflammation, oxidative stress and fibrosis that we adjusted for were not comprehensive markers of their associated processes, so these processes may still play a role in the association of renal disease and functional decline. Finally, life expectancy has improved over the past 20 years since the time of urine testing done in this study, such that participants reaching extreme old age now may receive different medical care than did participants in 1999; whether this would mitigate the adverse effect of albuminuria or reduced kidney function is unknown.

In conclusion, early impairments of ACR and eGFR are each independently and prospectively associated with a decline in muscle strength and function in older adults. Adjustment for hyperglycemia, fibrosis, inflammation and oxidative stress do not materially attenuate these results. The current findings suggest an early onset of aging-related functional decline in peripheral muscle in association with processes associated with early renal disease. These findings also suggest that small changes in ACR and eGFR may serve as biomarkers for the frailty syndrome and for the multiple processes that lead to biological aging. Further studies are needed to explore this hypothesis.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

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AUTHORS' CONTRIBUTIONS

J.I.B. provided the research idea. P.B., J.I.B. and K.J.M. provided the study design. J.A.R., J.A.C., J.H.I. and K.J.M. were responsible for data acquisition. P.B., J.I.B., H.A.F., J.A.R., J.A.C., J.H.I. and K.J.M. were responsible for data analysis and interpretation. P.B. provided statistical analysis. Each author contributed important intellectual content during manuscript writing and accepts accountability for the overall work.

CONFLICT OF INTEREST STATEMENT

None declared.

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Appendix