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Research Article

Diagnostic Power of Serum Creatinine/Cystatin C Ratio for Identifying Low MRI-Muscle Volume and Low Grip Strength: Data From 9 731 to 149 707 UK Biobank Older Adults

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Abstract

Background: Biomarkers for sarcopenia are lacking. We examined the diagnostic power of serum creatinine to cystatin C ratio for identifying low magnetic resonance imaging-muscle volume and low grip strength in a large observational study of UK Biobank older adults.

Methods: Serum creatinine and cystatin C were measured via immunoassays (Beckman Coulter AU5800 and Siemens Advia 1800, respectively) and grip strength by hydraulic hand dynamometer at baseline visit (2008–2010). magnetic resonance imaging-thigh fat-free muscle volume and DXA-derived appendicular lean mass were measured at imaging visit (2014–2018). Extreme outliers were removed, and covariates (demographic, lifestyle, and clinical factors, as well as time elapsed between baseline-imaging visit) were adjusted for in statistical models.

Results: 12 873 older adults (mean age: 63.5 ± 2.7 years, 44.2% women) were included for fat-free muscle volume and appendicular lean mass/body mass index; 149 707 older adults (mean age: 64.0 ± 2.9 years, 50.5% women) for grip strength. Despite significant associations ($p < .05$), in fully adjusted models, creatinine to cystatin C showed poor to acceptable diagnostic power for identifying low fat-free muscle volume when using cutpoints of 20th percentile (area under the curve: 0.577 men; 0.622 women) and *T* scores of −2 (area under the curve: 0.596 men; 0.659 women) and −2.5 (area under the curve: 0.609 men; 0.722 women). In fully adjusted model, creatinine to cystatin C showed poor diagnostic power (area under the curves: <0.70) for identifying low appendicular lean mass/body mass index or low grip strength, irrespective of the cutpoint used.

Conclusions: Creatinine to cystatin C may not be a suitable biomarker for identifying low muscle volume or low strength in older adults. This finding, drawn from a large sample size and the use of advanced medical imaging, marks an important contribution to the sarcopenia field.

Keywords: Biomarkers, Medical Imaging, Sarcopenia, Skeletal Muscle

In the European Consensus Revision, sarcopenia is described as a progressive and generalized skeletal muscle disorder that may present as low muscle mass, strength, and/or function (1). These age-related changes in the structure and function of skeletal muscle may be accelerated by poor lifestyle (ie, physical inactivity, low nutritional status) and/or disease-related (immunological changes with acute/chronic diseases) factors (2,3). Socioeconomic consequences of this muscle disorder are profound, with older adults at high risk of poor health-related quality of life (4), falls (5), and fractures (5).

Since sarcopenia was first described as the "age-related loss of lean body mass" by Dr Irwin Rosenberg in 1989, there has been a progressive increase in research efforts to understand the pathophysiology of this disorder in addition to optimal

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diagnostic and prognostic markers. In terms of the latter, identifying a blood biomarker that holds high diagnostic capacity for low muscle mass has proven elusive. One biomarker in the muscle field that has gathered attention is the ratio of serum creatinine to cystatin C (Cr:Cyc), as recently highlighted in the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis, and Musculoskeletal Diseases working report relating to biochemical markers on sarcopenia treatment (6).

Creatinine and cystatin C are both commonly used in the assessment of kidney disease (7). Around 98% of creatine is stored in skeletal muscle, and following metabolism, its product creatinine is filtered by the kidneys and excreted in urine. Both muscle metabolism and kidney function can influence serum creatinine levels in a bidirectional manner, making it difficult to interpret this standalone biomarker (8). The nephrology field has sought to counteract this limitation by developing reference equations including Cystatin C, a protein found in similar quantities in human tissues and also filtered by the kidneys (6,8).

Emerging studies have looked at the relationship between Cr:Cyc and metrics of lean mass or muscle mass in older adults. Moderate associations were found between Cr:Cyc and CT-muscle cross-sectional area in one retrospective study of 226 ICU patients (9). Another study (10) showed poor sensitivity and specificity of Cr:Cyc for identifying low appendicular muscle mass/height^2 in 371 community-dwelling older adults, although this study used bioelectrical impedance analysis to estimate appendicular lean mass, which is not the gold standard of measuring muscle mass (11,12). Contrary to these findings, a cross-sectional study showed positive relationships between Cr:Cyc and appendicular lean mass (by bioelectrical impedance analysis) in 908 community-dwelling older adults in Japan (13). A very recent study (14) showed positive associations between Cr:Cyc and DXA-appendicular lean mass (adjusted for height squared or body mass index [BMI]) obtained 5 years later in 1 118 community-dwelling older women. Neither of these studies directly examined the diagnostic capability of Cr:Cyc for identifying low lean mass using an Receiver Operating Characteristic (ROC) analysis or related tests.

As seen by the earlier studies, there is some inconsistency in findings, which may partly be explained by differences in study designs, sample sizes, and most importantly, techniques used to evaluate muscle mass or lean mass. In regard to medical imaging techniques for quantifying muscle size, none of the previously mentioned studies have used accurate assessments of muscle volume by magnetic resonance imaging (MRI) (11).

Thus, we sought to advance knowledge on this topic by examining the diagnostic power of Cr:Cyc for identifying low MRI-muscle volume obtained 4 years later in a very large population of older men and women in the UK Biobank. In this cohort, lower MRI-muscle volume has been shown to be strongly associated with lower grip strength, a lower frequency of stair climbing, and a slow walking pace in 9 615 men and women when using a cross-sectional analysis (15). Consequently, we also included DXA-derived lean mass and grip strength as outcomes, as these muscle metrics are frequently used in the sarcopenia field (11).

Method

Study Design

This analysis was based on participants from the UK Biobank study. This study made use of the UK Biobank resource, application ID 92647. The Northwest Multicenter Research Ethics Committee in the United Kingdom approved the study, and prior to the start of the investigation, written informed consent was obtained (REC reference: 11/NW/03/820). The recruitment process and measurements used to collect data for this study can be found on the UK Biobank website: https://www.ukbiobank.ac.uk. Figure 1 shows the study design for the primary outcome of interest.

Participants

UK Biobank participants who remained active and attended the first imaging visit were included (2014–2019). Participants younger than 60 years were excluded as well as those with missing or extreme creatinine or cystatin C obtained in 2006–2010 (considered extreme if greater than Q3 + 1.5 × (Q3–Q1) or less than Q1 – 1.5 × (Q3–Q1), where Q1 and Q3 represent the first and third quartiles). We used Tukey's method to define outliers (16). Additionally, participants lacking MRI-muscle volume and DXA-lean mass, or any covariate data were excluded. The resulting cohort, termed the imaging cohort, consisted of 12 873 samples (Supplementary Figure 1). For specific outcomes, the sample sizes were 9 731 for fat-free muscle volume (FFMV), 10 260 for BMI-adjusted appendicular lean mass (ALM), and 10 484 for height-adjusted ALM. Participants attending baseline visits underwent similar inclusion and exclusion criteria for the outcome of grip strength at baseline (n = 149 707), forming the baseline cohort (Supplementary Figure 2).

Exposure: Creatinine to Cystatin C Ratio

Serum cystatin C levels were measured using a latex-enhanced immuno-turbidimetric assay conducted by Siemens (Erlangen, Germany) on the Siemens Advia 1800. Serum creatinine levels were assessed with an enzyme-based assay conducted by Beckman Coulter (High Wycombe, United Kingdom) on the Beckman Coulter AU5800. The coefficient of variation for both cystatin C and creatinine was controlled at 3% or less, as determined by internal quality control samples with known high, medium, and low concentrations. For technical details and quality control information, please refer to the reports from the UK Biobank: https://biobank.ctsu.ox.ac.uk/showcase/refer.cgi?id=5636.

Outcomes: MRI-Muscle Volume, DXA-Lean Mass & Grip Strength

MRI scans to quantify total thigh FFMV were conducted using a Siemens Aera 1.5 T scanner (Syngo MR D13) (Siemens, Erlangen, Germany) and AMRA Researcher (AMRA

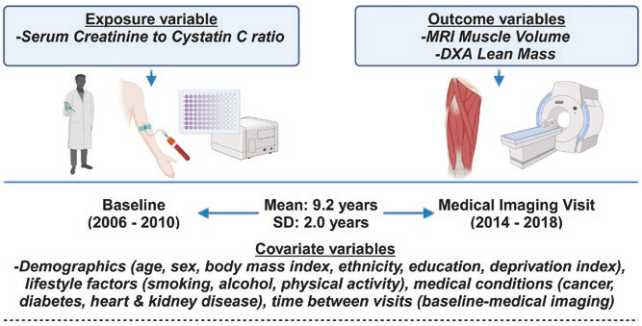

Figure 1. Shows the study design for the primary sample of interest.

Medical AB, Linköping, Sweden) image analysis software (17). The FFMV was defined as the total volume of all voxels with a fat fraction <50% (considered "viable muscle tissue") in the left and right anterior and posterior thighs (15,18). A dual-energy X-ray absorptiometry machine (GE-Lunar iDXA, Madison, WI) was used to quantify appendicular lean mass (sum of lean mass from arms and legs). Daily quality control was carried out for both MRI and DXA scans; see: https://biobank.ndph.ox.ac.uk/showcase/label.cgi?id=100003. Grip strength was measured using a Jamar J00105 hydraulic hand dynamometer with participants sitting upright in a chair and forearms resting on armrests (elbows bent at a 90-degree angle). Participants exerted their maximal force during a 3 second effort on the right and left sides. Verbal encouragement was provided. The maximal force from either side was used in the analysis.

To assess the discriminative power of Cr:Cyc, we dichotomized baseline grip strength and 3 imaging outcomes (FFMV, ALM/BMI, and ALM/Height^2) using sex-specific cutpoints set at 2 or 2.5 standard deviations (*SD*s) below an age-and-sex-specific mean, that is, *T* score −2 or −2.5, in a reference population based on previous studies using grip strength (19), FFMV (20), ALM/Height^2 (1), and ALM/BMI (21). Sensitivity analyses were conducted using sex-specific 20th percentiles in the data.

Baseline Covariates

Covariates were preselected based on the potential association with the exposure (Cr:Cyc) (7,22) or outcomes related to musculoskeletal health (2,14,23). Baseline covariates included self-reported demographics, that is, chronological age in years at recruitment, sex (Men or Women), ethnicity (categorized as White, Black, Asian, or Other), and educational qualification (college or university degree, A levels/AS levels or equivalent, O levels/GCSEs or equivalent, CSEs or equivalent, NVQ/HND/HNC or equivalent, other professional qualifications, eg, nursing, teaching, or none of the above). Additionally, socioeconomic status was assessed by an area-based material deprivation index, the Townsend deprivation index, where higher values indicate higher levels of material deprivation. Physiological or lifestyle factors were also considered, such as BMI, smoking status (never, current, or previous), alcohol intake frequency (from never to daily or almost daily), and physical activity group based on the short International Physical Activity Questionnaire (IPAQ) (24). Other covariates included the disease states of myocardial infarction, stroke, heart failure, cancer, chronic kidney disease, and diabetes, as well as the time difference between baseline and first imaging visits for imaging outcomes only. Disease states were determined using the first occurrence data derived by UK Biobank, which included multisource data (primary care data, hospital inpatient data, death register records, and self-reported medical conditions) based on 3-character ICD-10 codes to find the first diagnoses. We also calculated eGFR (based on the 2021 CKD-EPI creatinine–cystatin C equation (7)) and used it as a potential covariate. A list of data fields, including ICD-10 codes and ICD-9 codes if used for the disease covariates, and their field IDs for data extraction is provided in Supplementary Table 1.

Statistical Methods

A descriptive analysis was conducted to summarize variables using proper statistics in the baseline and imaging cohorts,

Table 1. Participant Characteristics of the Imaging or Baseline Cohort

	Imaging (*n* = 12 873)	Baseline (*n* = 149 707)
Predictor of interest		
Creatinine to cystatin C ratio (Cr/Cys)	0.92 ± 0.15	0.88 ± 0.15
Creatinine (mg/dL)	0.83 ± 0.15	0.82 ± 0.15
Cystatin C (mg/L)	0.91 ± 0.11	0.94 ± 0.13
Baseline covariates		
Age at baseline (years)	63.48 ± 2.73	64.04 ± 2.84
Time between 2 visits (years)	9.2 ± 2.04	
BMI (kg/m^2)	26.62 ± 3.87	27.34 ± 4.34
Sex (=women)	5 686 (44.17%)	75 633 (50.52%)
Ethnicity		
White	12 658 (98.33%)	145 791 (97.38%)
Black	27 (0.21%)	974 (0.65%)
Asian	27 (0.21%)	974 (0.65%)
Other	86 (0.67%)	1 100 (0.73%)
Education		
College or University degree	1 383 (10.74%)	14 103 (9.42%)
A levels/AS levels or equivalent	5 580 (43.35%)	43 240 (28.88%)
O levels/GCSEs or equivalent	211 (1.64%)	3 272 (2.19%)
CSEs or equivalent	870 (6.76%)	11 008 (7.35%)
NVQ/HND/HNC or equivalent	2 562 (19.90%)	31 865 (21.28%)
Other prof. qualifications	891 (6.92%)	10 608 (7.09%)
None of the above	1 376 (10.69%)	35 611 (23.79%)
Townsend deprivation index	−2.13 ± 2.58	−1.67 ± 2.89
Smoking status		
Never	6 916 (53.72%)	75 042 (50.13%)
Previous	5 353 (41.58%)	63 123 (42.16%)
Current	604 (4.69%)	11 542 (7.71%)
IPAQ		
High	5 427 (42.16%)	62 019 (41.43%)
Moderate	5 481 (42.58%)	62 983 (42.07%)
Low	1 965 (15.26%)	24 705 (16.50%)
Alcohol		
Never	571 (4.44%)	11 548 (7.71%)
Special occasions only	948 (7.36%)	16 451 (10.99%)
1–3 times a month	1 142 (8.87%)	14 342 (9.58%)
Once or twice a week	2 840 (22.06%)	35 281 (23.57%)
3 or 4 times a week	3 584 (27.84%)	34 568 (23.09%)
Daily or almost daily	3 788 (29.43%)	37 517 (25.06%)
Disease diagnosis		
Myocardial infarction (=yes)	545 (4.23%)	9 211 (6.15%)
Stroke (=yes)	187 (1.45%)	3 106 (2.07%)
Heart failure (=yes)	33 (0.26%)	986 (0.66%)
Cancer (=yes)	716 (5.56%)	11 721 (7.83%)
Chronic kidney disease (=yes)	134 (1.04%)	1 910 (1.28%)
Diabetes (=yes)	552 (4.29%)	9 660 (6.45%)

Notes: BMI = body mass index; IPAQ = International Physical Activity Questionnaire.

separately (Table 1). The outcomes of interest were further summarized for each individual quantile group of Cr:Cyc. Four quantile groups were compared for each outcome using a Kruskal–Wallis test (Table 2).

The nonlinearity of the relationship between Cr:Cyc and each continuous outcome was visualized by sex and for the overall sample by means and their confidence intervals for individual quartile groups of Cr:Cyc (Supplementary Figure 3), and it was formally tested by a chi-square test comparing the goodness of fit between a cubic spline linear regression model with the knots at the 25th, 50th, and 75th percentiles of Cr:Cyc and a linear regression model. Given that most nonlinearity test results were statistically significant, except for ALM/Height^2 in women, the cubic spline linear regression models were used for subsequent association analyses to link Cr:Cyc with continuous outcomes.

The association between Cr:Cyc and an outcome was tested by a chi-square test comparing the goodness of fit between the cubic spline linear regression model and its reduced model without the nonlinear function of Cr:Cyc. Additionally, a bootstrap method was implemented to repeatedly simulate individual data from the observed data with replacement to create 1 000 replicates of the data to fit the same association model. The fitted values were collected across replicates to calculate the mean predicted values for individual quartile groups of Cr:Cyc and their 95% confidence intervals. Both unadjusted and adjusted models were fitted, adjusting for baseline covariates for all outcomes (age, sex, BMI, ethnicity, education, Townsend deprivation index, smoking status, alcohol intake frequency, IPAQ activity group, myocardial infarction, stroke, heart failure, cancer, chronic kidney disease, and diabetes), and time difference between baseline and imaging visits additionally for imaging outcomes.

The discriminative power of Cr:Cyc for a dichotomized outcome was evaluated in a cubic spline logistic regression model, with the knots at the 25th, 50th, and 75th percentiles of Cr:Cyc. The results were presented with a ROC curve including the area under the curve (AUC). Sensitivity analyses were performed in sex-specific groups and/or using different outcome cutpoints. Additionally, we reported the ROCs and AUCs of covariates-adjusted Cr:Cys (Cr:Cys after regressing out the effects of covariates using a linear regression model). Given some studies (25) have used the biomarker difference (creatinine minus cystatin C) instead of the ratio (creatinine/cystatin C) in predicting muscle-outcomes, we repeated the analysis using the biomarker difference to see if this influenced results. All AUCs were interpreted as acceptable (0.7–0.8), excellent (0.8–0.9), or outstanding (>0.9) following recommendations in clinical research (26). All hypothesis tests were 2-sided. *p*-Values below 5% were deemed to be statistically significant. The statistical analyses were performed in R version 4.2.2, using the packages including "spline," "pROC," and "boot."

Results

Population Characteristics

Table 1 shows the participant characteristics of the imaging and baseline cohorts. A total of 12 873 older adults (mean age: 63.5 ± 2.7 years, 44.2% women) were included in the imaging cohort for MRI/DXA outcomes (FFMV, ALM/

Table 2. Fully Adjusted Associations (Predicted Values and Their 95% Confidence Intervals) for Outcomes Across Quartile Groups of Cr:Cyc

	Group	Q1	Q2	Q3	Q4	Non-Linearity *p*-Value	Association *p*-Value
Grip strength	All	24.291 (24.217, 24.368)	28.952 (28.861, 29.052)	34.101 (33.992, 34.194)	38.278 (38.185, 38.38)	<1e−323	2.38E−37
	Women	21.958 (21.881, 22.031)	23.059 (23, 23.122)	23.744 (23.68, 23.809)	24.528 (24.449, 24.604)	<1e−323	6.44E−43
	Men	37.555 (37.445, 37.671)	39.421 (39.336, 39.504)	40.361 (40.269, 40.447)	41.299 (41.194, 41.413)	<1e−323	6.74E−50
FFMV	All	8.255 (8.185, 8.319)	9.519 (9.418, 9.618)	10.657 (10.574, 10.745)	11.386 (11.312, 11.466)	1.73E−80	3.58E−13
	Women	7.592 (7.528, 7.656)	7.765 (7.714, 7.811)	7.857 (7.805, 7.906)	8.01 (7.952, 8.069)	4.46E−49	9.19E−09
	Men	11.345 (11.269, 11.421)	11.606 (11.542, 11.671)	11.757 (11.692, 11.829)	11.893 (11.815, 11.974)	8.08E−39	2.99E−09
ALM/BMI	All	0.678 (0.673, 0.682)	0.778 (0.771, 0.784)	0.852 (0.847, 0.858)	0.906 (0.901, 0.911)	2.36E−37	0.002
	Women	0.628 (0.623, 0.633)	0.652 (0.648, 0.656)	0.666 (0.662, 0.67)	0.681 (0.676, 0.687)	1.05E−21	0.007
	Men	0.891 (0.885, 0.897)	0.915 (0.911, 0.92)	0.926 (0.921, 0.93)	0.94 (0.935, 0.945)	2.84E−18	0.002
ALM/Height^2	All	6.587 (6.550, 6.628)	7.017 (6.972, 7.063)	7.399 (7.361, 7.438)	7.719 (7.684, 7.758)	2.03E−76	3.75E−05
	Women	6.364 (6.312, 6.416)	6.346 (6.307, 6.391)	6.342 (6.298, 6.378)	6.339 (6.303, 6.381)	6.38E−29	5.39E−04
	Men	7.758 (7.713, 7.806)	7.806 (7.766, 7.841)	7.851 (7.816, 7.896)	7.933 (7.888, 7.972)	6.53E−47	2.42E−04

Notes: ALM = appendicular lean mass; BMI = body mass index; Cr:Cyc = creatinine to cystatin C; FFMV = fat-free muscle volume; IPAQ = International Physical Activity Questionnaire.

BMI & ALM/Height^2), and 149 707 older adults (mean age: 64.0 ± 2.9 years, 50.5% women) in the baseline cohort for grip strength outcome.

When using a *T* score of –2 as the cutpoint, the prevalence of low FFMV in our population was 4.7% (200) in women and 7.8% (426) in men. Supplementary Table 2 shows the full prevalence of low FFMV, low ALM/BMI, low ALM/height^2, and low grip strength using age- and sex-specific normative values (20th percentile and *T* scores of –2*SD* and –2.5*SD*s).

Associations Between Cr:Cys and Outcomes

Lower Cr:Cys was significantly associated with lower grip strength, FFMV, ALM/BMI, and ALM/Height^2 overall and by sex after adjusting for covariates ($p < .05$), except for ALM/Height^2 in men and in women (Table 2). The corresponding unadjusted analysis showed similar results (absolute differences ≤0.091, data not shown).

Sensitivity analysis showed negligible effect of interchanging CKD (from linked health records) with eGFR as a covariate on the association between Cr:Cys and outcomes in fully adjusted models (data not shown). We also refitted models by excluding non-White participants for the same outcomes (data not shown). Again, associations were not materially altered in fully adjusted models.

Interchanging the biomarker ratio for the biomarker difference resulted in significant associations with outcomes but smaller effect sizes or smaller mean differences between quartile groups (Supplementary Table 4).

Diagnostic Power of Cr:Cys for Outcomes

The sex-specific models showed better AUCs than a model using all samples across outcomes, irrespective of covariates (Figures 2 and 3 fully adjusted; Supplementary Figures 4–6 unadjusted). For sex-specific models, pushing the threshold to the extreme improved the AUC but it came with greater uncertainty due to a small number of cases, as reflected in the 95% confidence interval (Figures 2 and 3 fully adjusted; Supplementary Figures 4–6 unadjusted). The AUC was generally low regardless of outcomes, cutpoints, and subgroups. In the fully adjusted models, Cr:Cyc showed poor to acceptable diagnostic power for identifying low FFMV in older adults when using cutpoints of the 20th percentile (AUC: 0.577 vs 0.589 using age only in men; 0.622 vs 0.531 using age only in women) and T scores of –2 (AUC: 0.596 vs 0.59 using age only in men; 0.659 vs 0.543 using age only in women) and –2.5 (AUC: 0.609 vs 0.593 using age only in men; 0.722 vs 0.561 using age only in women). In the fully adjusted model, Cr:Cyc showed poor diagnostic power (AUCs: <0.70) for identifying low ALM/BMI or low grip strength, irrespective of the cutpoint used.

Interchanging the biomarker ratio for the biomarker difference resulted in negligible differences in diagnostic power, with overlapped 95% confidence intervals of AUC (Supplementary Figures 7–10).

Discussion

We sought to examine the diagnostic power of Cr:Cyc for identifying low MRI-muscle volume measured 4 years later

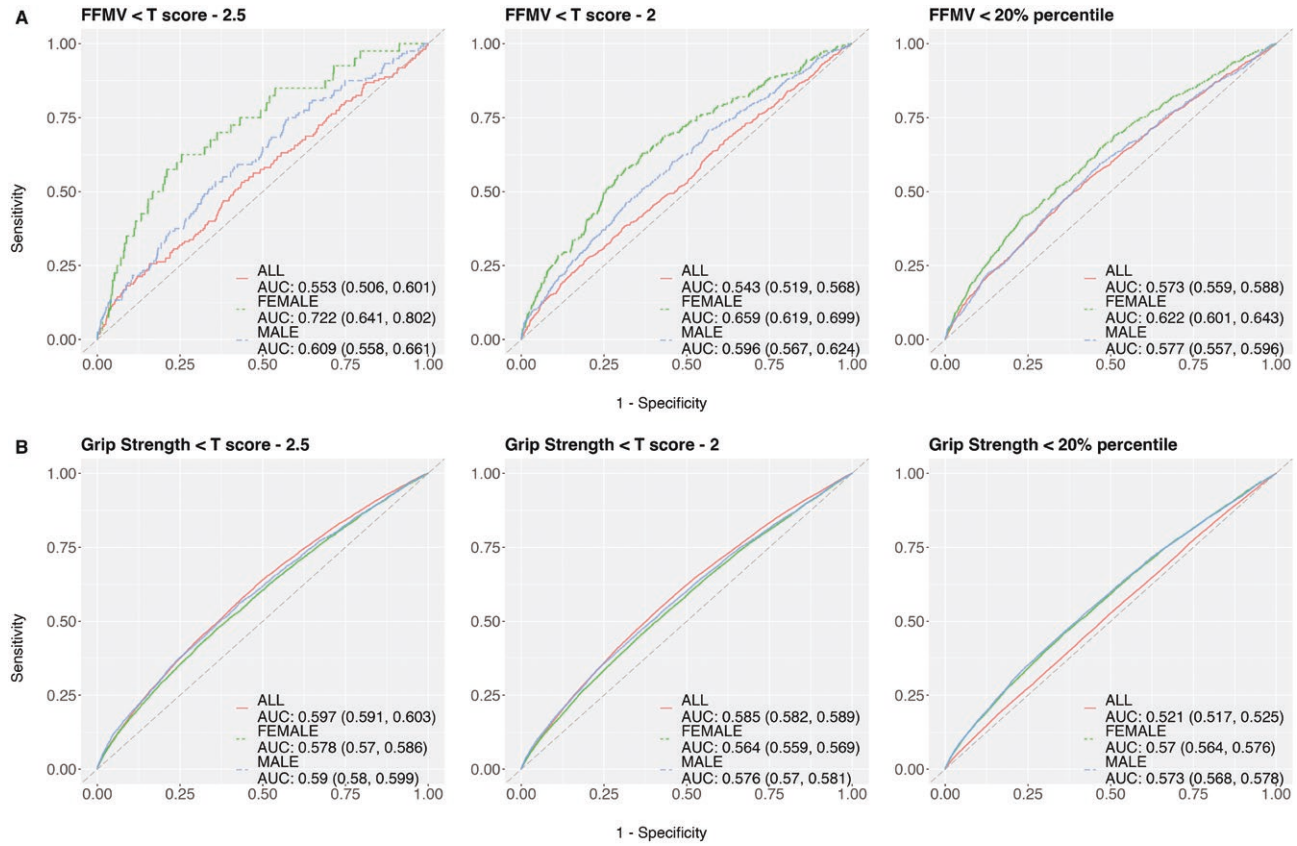

Figure 2. Receiver operator characteristic curves shows the diagnostic power of Cr:Cyc for identifying low FFMV (**A**) and low grip strength (**B**) using different cutpoints. Models are fully adjusted for covariates. *Notes*: Cr:Cyc = creatinine to cystatin C; FFMV = fat-free muscle volume.

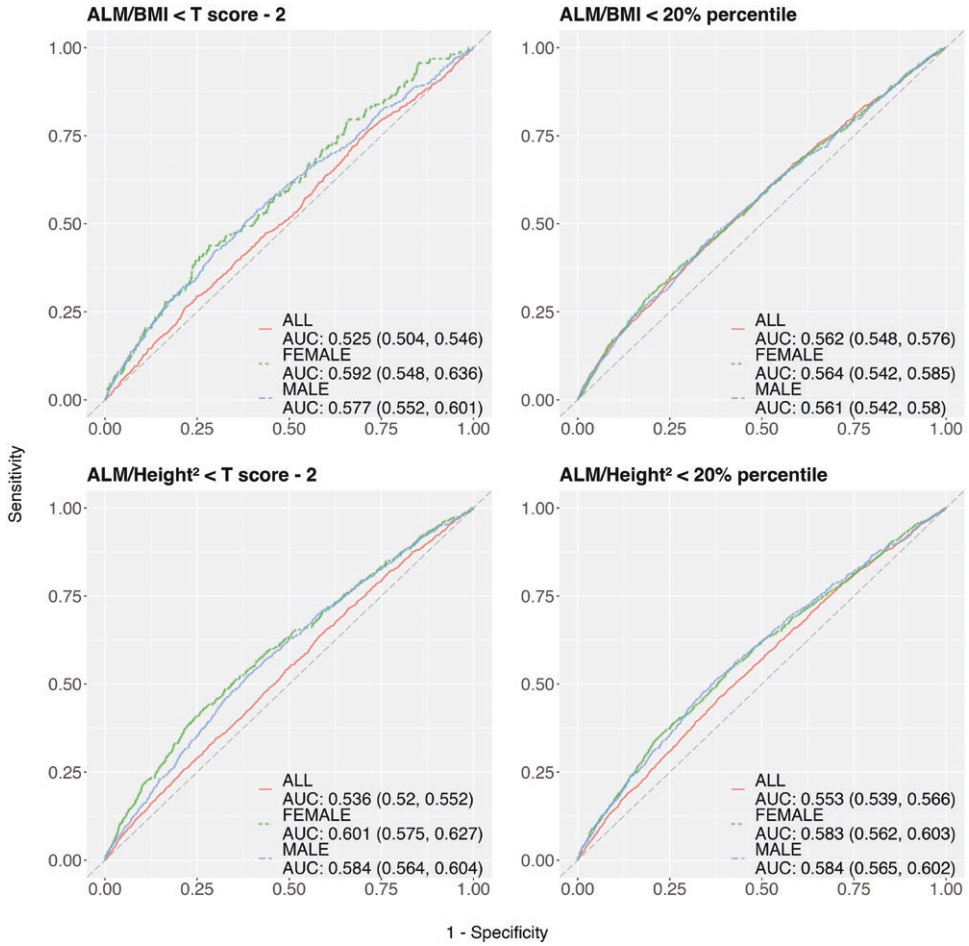

Figure 3. Receiver operator characteristic curves shows the diagnostic power of Cr:Cyc for identifying low ALM/BMI or ALM/Height^2 using different cutpoints. Models are fully adjusted for covariates. *Notes*: ALM = appendicular lean mass; BMI = body mass index; Cr:Cyc = creatinine to cystatin C.

in a large observational study of UK Biobank adults. Findings showed that Cr:Cyc was associated with FFMV (and most muscle metrics, including ALM/BMI and grip strength) in the fully adjusted analyses. However, this biomarker offered poor to acceptable (at best) diagnostic power for identifying low FFMV in older men and women. Findings were poor when interchanging FFMV for ALM/BMI or grip strength. This finding was not materially altered by the inclusion of relevant covariates. Together, our findings suggest that Cr:Cyc may not be a suitable biomarker for identifying low muscle volume or low grip strength in older adults.

Previous studies have investigated the association between Cr:Cyc and muscle metrics in the context of aging and acute/chronic diseases. Similar to our findings, positive associations have been observed between Cr:Cyc and CT-muscle area in ICU patients (9) as well as between this biomarker and ALM/BMI or grip strength in various studies, including older community-dwelling Australian women (14) and Japanese men (13). While these studies did not include an AUC-ROC discriminatory analysis, one such study (10) found that Cr:Cyc offered poor sensitivity and specificity for identifying low appendicular muscle mass/height^2 in 371 community-dwelling older adults. Our study corroborates these findings and makes an important contribution to this research topic by including an accurate measure of muscle volume via MRI (11). We also included a full complement of adjustments for demographics, lifestyle factors, and chronic diseases in men and women. Our sample size is at least 10-fold greater than previous studies on this topic, and we were able to evaluate the diagnostic performance of Cr:Cyc across important sex-specific muscle-outcomes relevant to the field of sarcopenia. We did not utilize a specific sarcopenia definition as the field is currently evolving and transitioning into a unified global definition (27). Nevertheless, our cutpoints were derived from population-specific normative values for MRI-muscle, DXA-lean mass, and grip strength, which have been outlined in previous sarcopenia definitions (1,21).

Despite the overall poor diagnostic power of Cr:Cyc for our muscle-outcomes, it was noteworthy that pushing the cutpoint to the extreme improved the AUC, but it came with greater uncertainty due to a small number of cases, as reflected in the wider 95% confidence interval. A greater number of the "oldest-old" (eg, aged 70 or 80+) where low muscle volume (20), low ALM/BMI (28) or low grip strength (19) are more prevalent may have provided more insights in answering our research question. We will consider revisiting this research question in future years when the UK Biobank participants have aged and attended repeated MRI imaging visits that will allow analysis over a much longer follow-up. Until then (or further data that proves otherwise), we do not recommend Cr:Cyc as a suitable biomarker for identifying low muscle volume or low grip strength in community-dwelling older adults.

Our study is not without its limitations. We acknowledge that all observational studies are open to residual

confounding, and we cannot determine cause-and-effect from such study designs as the one presented here. Nonetheless, we removed outliers and adjusted for demographics, lifestyle factors, and disease classifications (as well as adjustment for time differences between measures) in statistical models to reduce the influence of residual confounding. Despite the adjustment for time difference, our results may be affected by the fact that Cr:Cys (and covariates) were measured years prior to the imaging outcomes (mean difference: 9.2 ± 2.0 years; Figure 1). It is plausible that the diagnostic ability may be improved for outcomes in the short-term. As mentioned, including repeat measures of our biomarkers and outcomes would have strengthened the ability to answer the research question. Identifying the relationship between Cr:Cyc and whole-body D3Cr muscle mass (measured by stable isotopes) (29) may also prove fruitful, especially considering this measure has been consistently associated with poor health outcomes (30). We, and others, should consider these factors in future analysis on this research topic. Finally, although Cr:Cyc was not found to be a suitable biomarker in this study, the approach taken to account for heterogeneity in muscle volume and grip strength and target Cr:Cyc as a potential diagnostic marker for low values of these muscle-related outcomes represents an important application of the emerging field of precision gerontology (31,32).

To conclude, we found that Cr:Cyc was consistent associated with FFMV and other important muscle metrics such as ALM/BMI and grip strength. However, our findings suggest that Cr:Cyc may not be a suitable biomarker for identifying the risk of low muscle volume or low grip strength in older adults. This finding, drawn from a large sample size and the use of advanced medical imaging, marks an important contribution to the sarcopenia field.

Supplementary Material

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

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Conflict of Interest

None.

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