Low creatinine to cystatin C ratio is associated with lower muscle volumes and poorer gait speeds in the longitudinal Integrated Women's Health Program cohort

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Abstract

Objective: Little is known about the longitudinal associations between creatinine-cystatin C ratios (CCR) with muscle volume and function during the menopausal transition. We investigated the longitudinal relationship of baseline CCR, with muscle volumes measured by magnetic resonance imaging (MRI), and objectively measured muscle strength and physical performance after 6.6-year follow-up.

Methods: Participants from the Integrated Women's Health Programme (IWHP) cohort (n = 891, baseline mean age 56.2 ± 6.0) who attended both baseline and follow-up visits underwent objectively measured muscle strength and physical performance assessments and MRI. Creatinine to cystatin C ratio was calculated as (creatinine [mg/dL] / cystatin C [mg/L]) and low CCR were those in the lowest tertile (CCR < 8.16). Multivariable regression analyses were used to determine the associations of baseline CCR with muscle volumes and function 6.6 years later.

Results: Baseline low CCR was associated with lower MRI-measured muscle volumes and poorer physical function 6.6 years later. Compared to high CCR group, mean fat-free thigh muscle volume of the low CCR group was 0.350 L lower (95% CI, 0.183-0.518) after adjustment for covariates. Similarly, the low CCR group was associated with 0.029 m/s slower (95% CI, 0.006-0.053) slower mean usual gait and 0.049 m/s slower (95% CI, 0.020-0.078) mean narrow gait speeds. CCR was not associated with handgrip strength and repeated chair stands and one-leg stand tests.

Conclusion: Low CCR at baseline was associated with lower fat-free muscle volumes and poorer gait speeds 6.6 years later. The potential of CCR as a predictive biomarker for adverse events related to sarcopenia in midlife women merits further investigation.

Key Words: Creatinine, Cystatin C, Midlife women, Physical function, Sarcopenia, Skeletal muscle.

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Muscle mass and function decline in women after the menopause.[1,2] Poor muscle function as indicated by weak hand grip strength and low physical performance are associated with multiple adverse outcomes including hypertension,[3,4] diabetes,[5-7] frailty, falls, and mortality.[8] Besides muscle function, muscle mass is considered an important variable for health and its measurement is an integral part of current criteria for sarcopenia.[9-11] Muscle mass or volumes can be accurately measured with 3D-imaging modalities such as computed tomography scan and magnetic resonance imaging (MRI).[12] However, these methods require highly trained staff, expensive equipment, and calculations of muscle mass require arduous manual delineation of different muscle groups for each anatomical site.[12,13]

Most epidemiological and clinical studies rely on bioimpedance analysis or dual-energy x-ray absorptiometry of appendicular lean mass as proxies for total skeletal muscle mass.[9,10] However, muscle mass determined by bioimpedance analysis or dual-energy x-ray absorptiometry of appendicular lean mass tend to be inconsistently related to muscle-related clinical outcomes including diabetes, hypertension, and osteoporosis.[11,14,15] Objectively measured physical function assessments, such as handgrip strength and the Short Physical Performance Battery, correlate better with health outcomes[11,13] but are time-consuming, and require trained personnel. Thus, there is a need for a simple and practical method that can concomitantly measure total skeletal muscle mass and function.

The serum creatinine to serum cystatin C ratio (CCR) is a novel marker of skeletal muscle mass, and associations with physical function and health outcomes have been reported in cross-sectional studies.[16-18] Creatinine is generated by skeletal muscles as a degradation product of creatine-phosphate, an essential molecule which provides the energy transfer mechanism for muscle contraction.[19] Serum creatinine level is proportionate to creatine pool size in the body, which in turn is a measure of the total muscle mass. However serum creatinine levels rise with compromised renal function, limiting the use of absolute creatinine levels for estimation of total skeletal muscle mass.[20] Cystatin C, excreted by all nucleated cells, is freely filtered by the kidneys, and is unaffected by skeletal muscle mass.[21] Together, the serum creatinine (derived predominantly from muscles) to cystatin C (ubiquitously expressed) ratio has been proposed as a biomarker of total skeletal muscle mass and function that is independent of renal

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function.[17] Moreover, as serum creatinine and cystatin C are routinely measured as part of clinical care, CCR is readily available, and accessible.

Although CCR has been reported to be associated with health outcomes such as diabetes,[22] malnutrition, and mortality[23] in cross-sectional studies, longitudinal associations of CCR with muscle mass and physical function are few and have only been studied in older adults.[23,24] Compared to premenopausal women, postmenopausal women had accelerated loss of muscle mass and strength, suggesting a potential negative effect of estrogen decline on skeletal muscle,[2,25] necessitating studies in midlife women.

As such, the aim of the study is to examine associations of baseline serum CCR, and its relationship with MRI-measured muscle mass and objectively measured physical function after 6.6 years of follow-up in a population of community dwelling midlife women. If a longitudinal relationship with muscle mass and function is identified, CCR may be a useful unitary biomarker of women who are at risk for sarcopenia and attendant adverse health outcomes.

METHODS

Study Design

The Integrated Women's Health Program (IWHP) is a prospective longitudinal cohort examining critical health issues faced by midlife Singaporean women. Midlife women aged 45-69 years, were first recruited in 2014-2016 from well-women clinics at the National University Hospital, Singapore. Exclusion criteria included potentially life-threatening diseases, pregnancy, or low literacy. Out of 2,191 eligible participants, 1,201 women were enrolled at baseline. Details of the study cohort had been previously published.[26] From 2021 to 2023, 891 (74.2%) of the IWHP participants were recontacted and invited to participate in a follow-up study. Both baseline and follow-up studies were approved by the Domain Specific Review Board of the National Healthcare Group, Singapore (reference numbers: 2014/00356 and 2020/00201). All participants gave written informed consent.

Outcomes: muscle volumes, strength, and physical performance after 6.6 years

At the follow-up visit, participants underwent muscle volume measurements with magnetic resonance imaging (MRI), in a Siemens Biograph mMR 3 T MRI scanner (Siemens Healthineers, Erlangen Germany). Total lean tissue volume (TLTV) from thoracic vertebrae 9 to the lower end of the thigh muscles, fat-free thigh muscle volume ($FFMV_{THIGH}$), and fat-free spinae erector muscle volume ($FFMV_{SE}$) were measured utilizing a 6-minute 2-point Dixon Vibe protocol. Semiautomated analysis of the images was measured using AMRA Researcher (AMRA Medical AB, Linköping, Sweden). The protocol has been described elsewhere.[27] Muscle volumes were expressed as liters (L).

Muscle strength was measured using handgrip strength and physical performance was assessed using the 5-time repeated chair stand test, one-leg stand test, usual gait speed, and narrow gait speed, by trained study coordinators. Handgrip strength was assessed using a hand-held dynamometer (Jamar, Bolingbrook, IL). Two measurements were conducted in each hand, and the highest reading of the four was analyzed. For the chair stand test, participants were asked to rise five times from the chair without support, and the time taken was recorded. In the one-leg stand test, participants were instructed to stand on one leg for up to 30 seconds. Usual gait speed was assessed by a 6-m walk at usual pace. Narrow gait speed was repeated on the same course, but participants were asked to walk within a path width of 20 cm.

Exposure: Creatinine-cystatin C ratio at baseline

Fasting blood was drawn at baseline, processed within 6 hours, and stored at −80°C. Creatinine and cystatin C were measured at the National University Hospital (NUH) Referral Laboratory, accredited by the Joint Commission International. Baseline creatinine and cystatin C levels were measured using Alinity C Creatinine (Enzymatic) Reagent kit (Abbott Laboratories, Chicago, IL) and Quantikine ELISA Human Cystatin C Immunoassay (R&D Systems, Minneapolis, MN) respectively. Creatinine to cystatin C ratio (CCR) was calculated as [creatinine(mg/dL) / cystatin C (mg/L)].[17]

Parameters collected at baseline

Sociodemographic characteristics collected at baseline visit included age, ethnicity (Chinese/Malay/Indian), education level (no formal education or primary education/secondary or preuniversity education/University education), monthly household income (<SGD 3,000/SGD 3000-6,999/≥SGD 7,000), marital status (not married/married), current employment status (unemployed/employed), current smoking status (yes/no), and alcohol consumption status (yes/no). Menopausal status (premenopausal/perimenopausal/postmenopausal) was determined based on menstrual pattern, history of hysterectomy, or bilateral oophorectomy.[26] Women were classified as premenopausal if they had menstruated in the past 3 months; perimenopausal if there were changes in menstrual frequency or 3 to 11 months of amenorrhea; postmenopausal if they reported amenorrhea for at least 12 consecutive months or surgical menopause.[28] Use of systemic hormone therapy (HT) and statins was obtained from a medical inventory.

Visceral adipose tissue (VAT) was measured using dual-energy x-ray absorptiometry (DXA) (Hologic Discovery Wi, Apex software version 4.5, Marlborough, MA). Daily calibration of the DXA machine was performed using the Hologic hip and whole-body models. Height and body weight were recorded twice and once, respectively by trained study coordinators using SECA769 Electronic Measuring Station (SECA GmbH & Co. KG, Hamburg, Germany). BMI was calculated by the formula: [body weight (kg)] / [height (m)].[2]

High-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF- α) inflammatory markers were measured using ELISA assay kits (DRG International, Inc., Springfield Township, NJ), chemiluminescence immunoassays (ADVIA Centaur Analyzer, Siemens Healthineers, Erlangen, Germany) and Colorimetric assay kits (Beckman Coulter, Inc., Brea, CA) respectively at the NUH Referral Laboratory, and were presented as continuous variables.

Statistical Analyses

Baseline CCR was categorized into tertiles. Prior research suggested that the distinctions between second and third

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tertiles in this study may not yield significant differences in outcomes.[24,29] As such, the second and third tertiles were subsequently combined into a single category (high CCR), while the first tertile was maintained as a separate category (low CCR) in current analyses. The low CCR group had CCR < 8.16 while high CCR group had CCR ≥ 8.16. This is consistent with a previous report indicated CCR < 8.0 as a cutoff for weak muscle strength.[29] Independent samples *t* test or Mann-Whitney *U* test and Pearson's chi-square tests were used to assess crude associations of CCR groups with baseline continuous and categorical variables, respectively. Univariate analysis was also performed between baseline CCR groups and muscle mass, strength, and physical performance at follow-up. Continuous variables are summarized as mean ± standard deviation (SD) for normally distributed variables and median (interquartile range [IQR]) for nonnormally distributed variables, and categorical variables as frequencies and percentages (%).

Linear regression was performed to evaluate associations of baseline CCR groups with MRI-derived $FFMV_{THIGH}$, $FFMV_{SE}$, and TLTV. Model 1 was adjusted for sociodemographic factors of age, ethnicity, education level, and menopausal status, smoking, alcohol status, VAT, HT usage, and statins usage. Model 2 was further adjusted for inflammatory markers. VAT was substituted for BMI as a more specific measure of central obesity.[30] Linear regression was also used to assess associations of baseline CCR groups with individual muscle strength and physical performance test. Physical performance at baseline was also adjusted for in Model 1. Results were presented as mean/adjusted mean differences with corresponding 95% confidence interval. All analyses were performed using SPSS 29.0 (SPSS Inc., Chicago, IL). All statistical tests were two-sided, and significance was set at 0.05.

RESULTS

Participant characteristics at baseline

Of the 1,201 participants recruited at baseline, five individuals had missing CCR data (Fig. 1). Of the remaining 1,196 participants, 891 participants returned for the follow-up visit (74.2%). The 310 participants excluded from analyses were more likely to be of lower education, unemployed, have higher levels of TNF-α, and slower narrow gait speed (Supplemental Table 1, http://links.lww.com/MENO/B354). Muscle strength and physical performance were analyzed in the 891 participants with muscle function data on follow-up. The mean follow-up time was 6.6 ± 0.5 years. Of these, 498 participants had MRI measurements of sufficient quality for analyses of muscle volumes. Reasons for exclusion from MRI muscle volumes analyses include 265 who refused MRI scans, 126 women where MRI scans were not performed because of possible safety or image quality issues and two women were deceased before their MRI scans (Fig. 1).

Table 1 shows the baseline characteristics of study participants who attended both baseline and follow-up visits. Participants were categorized into low (CCR < 8.16), or high (CCR ≥ 8.16) groups according to CCR measured at the baseline visit. At baseline, participants in low CCR group were more likely to be older, of Malay ethnicity, have lower education levels, be postmenopausal, were smokers, and were on statins. Low CCR was associated with higher VAT and BMI. Levels of all inflammatory markers, hs-CRP, IL-6, and TNF-α, were also higher in participants in low CCR group. Participants with low CCR manifested weaker muscle strength and poorer physical performance, namely, weaker handgrip strength, shorter one-leg stand times, and slower gait speeds at baseline.

Baseline CCR associated with MRI muscle volumes measured 6.6 years later

In *univariate analyses,* low CCR at baseline was associated with lower MRI muscle volumes measured after 6.6 years (Table 2A). All MRI-measured muscle volumes ($FFMV_{THIGH}$, $FFMV_{SE}$, and TLTV) were lower in participants with low CCR measured at the baseline visit.

In *multivariable linear regression analysis*, low CCR at baseline was associated with lower muscle mass volumes ($FFMV_{THIGH}$, $FFMV_{SE}$, and TLTV) on longitudinal follow-up (Table 3). Compared with the high CCR group, the mean

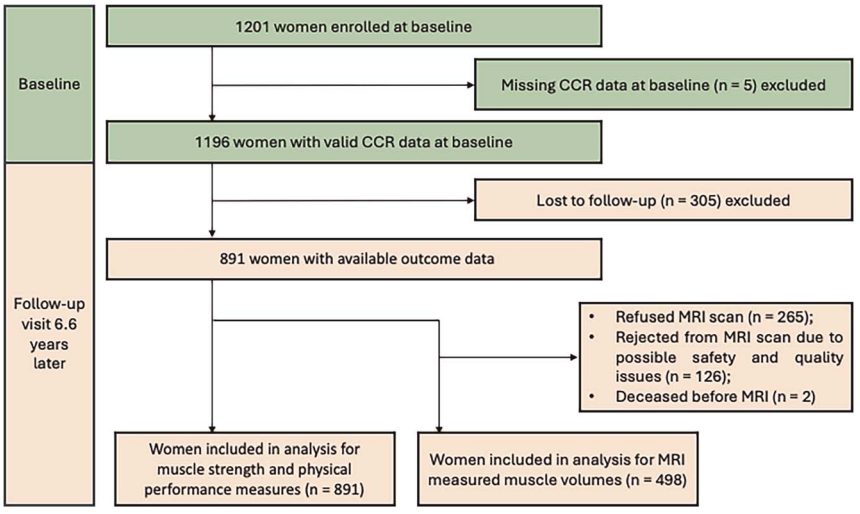

FIG. 1. Study design and flowchart at baseline (green) and on longitudinal follow-up 6.6 years later (beige) boxes. Participants rejected from MRI scan due to safety and quality issues include presence of implants or other medical devices (n = 64), claustrophobia (n = 57), and inability to lie flat on the MRI table (n = 5). CCR, creatinine-cystatin C ratio; MRI, magnetic resonance imaging.

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TABLE 1. Baseline characteristics of study participants according to CCR levels measured at baseline

Baseline characteristics	Baseline CCR			*P*
	Overall	Low CCR (CCR < 8.16)	High CCR (CCR ≥ 8.16)	
No. participants	891	290	601	
Age, yr	56.16 ± 6.01	56.83 ± 5.98	55.84 ± 6.01	0.021
Ethnicity				0.003
Chinese	722 (83.8)	220 (30.5)	502 (69.5)	
Malay	50 (5.8)	26 (52.0)	24 (48.0)	
Indian	90 (10.4)	35 (38.9)	55 (61.1)	
Education				0.006
No formal/primary	105 (11.9)	43 (41.0)	62 (59.0)	
Secondary and preuniversity	579 (65.9)	198 (34.2)	381 (65.8)	
University	195 (22.2)	47 (24.1)	148 (75.9)	
Monthly household income				0.074
<$3,000	209 (26.8)	78 (37.3)	131 (62.7)	
$3,000–$6,999	350 (44.9)	117 (33.4)	233 (66.6)	
≥$7,000	221 (28.3)	60 (27.1)	161 (72.9)	
Marital status				0.660
Not married	167 (18.8)	57 (34.1)	110 (65.9)	
Married	720 (81.2)	233 (32.4)	487 (67.6)	
Employment status				0.210
Unemployed	272 (30.8)	97 (35.7)	175 (64.3)	
Employed	612 (69.2)	192 (31.4)	420 (68.6)	
Menopausal status				0.004
Premenopausal	121 (13.6)	26 (21.5)	95 (78.5)	
Perimenopausal	136 (15.3)	38 (27.9)	98 (72.1)	
Postmenopausal	634 (71.2)	226 (35.6)	408 (64.4)	
Smoking				0.023
No	870 (98.3)	281 (32.3)	589 (67.7)	
Yes	15 (1.7)	9 (60.0)	6 (40.0)	
Alcohol drinking				0.213
No	826 (93.3)	275 (33.3)	551 (66.7)	
Yes	59 (6.7)	15 (25.4)	44 (74.6)	
Systemic hormone therapy				0.372
No	839 (94.2)	276 (32.9)	563 (67.1)	
Yes	52 (5.8)	14 (26.9)	38 (73.1)	
Statins				0.018
No	662 (74.3)	201 (30.4)	461 (69.6)	
Yes	229 (25.7)	89 (38.9)	140 (61.1)	
VAT	115.30 ± 51.89	128.05 ± 56.83	109.15 ± 48.18	<0.001
BMI	24.10 ± 4.36	24.92 ± 4.74	23.71 ± 4.11	<0.001
hs-CRP (mg/L)	1.20 (0.60–2.53)	1.50 (0.80–3.15)	1.10 (0.50–2.30)	<0.001
IL-6 (pg/mL)	2.00 (1.41–2.90)	2.10 (1.41–3.25)	1.41 (1.41–2.75)	0.002
TNF-α (pg/mL)	6.30 (4.98–7.80)	6.80 (5.50–8.30)	6.00 (4.80–7.50)	<0.001
Handgrip strength (kg)	19.75 ± 6.44	18.47 ± 6.51	20.37 ± 6.32	<0.001
Repeated chair stands (s)	11.52 ± 3.84	11.69 ± 4.50	11.44 ± 3.48	0.417
One-leg stand (s)	26.13 ± 8.27	24.55 ± 9.63	26.88 ± 7.43	<0.001
Usual gait speed (m/s)	1.19 ± 0.20	1.17 ± 0.20	1.20 ± 0.19	0.026
Narrow gait speed (m/s)	1.19 ± 0.23	1.16 ± 0.23	1.21 ± 0.23	0.006

Mean ± SD are presented for parametric continuous variables and median (IQR) are presented for nonparametric continuous variables, while n (%) are presented for categorical variables.

Continuous variables were analyzed using either the independent samples *t* test or Mann-Whitney *U* test for parametric and nonparametric data respectively. Categorical variables were analyzed using Pearson's chi-square test.

BMI, body mass index; CCR, creatinine-cystatin C ratio; hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin 6; TNF-α, tumor necrosis factor alpha; VAT, visceral adipose tissue.

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TABLE 2. Univariate analysis of the longitudinal association between CCR tertiles at baseline, with (A) MRI muscle volume indices and (B) muscle strength and physical performance measured at follow-up after a mean of 6.6 years

	Baseline CCR			
A) MRI—Muscle volume indices at follow-up visit	**Overall**	**Low CCR (CCR < 8.16)**	**High CCR (CCR ≥ 8.16)**	***P***
No. participants	498	156	342	
Total thigh and spinae erector muscle volume, $FFMV_{TOTAL}$ (L)	6.99 ± 0.99	6.71 ± 0.95	7.11 ± 0.98	<0.001
Thigh fat-free muscle volume, $FFMV_{THIGH}$ (L)	6.55 ± 0.93	6.28 ± 0.90	6.67 ± 0.93	<0.001
Spinae erector fat-free muscle volume, $FFMV_{SE}$ (L)	0.43 ± 0.08	0.42 ± 0.08	0.44 ± 0.08	0.005
Total lean tissue volume, TLTV (L)	14.53 ± 1.88	14.23 ± 1.88	14.66 ± 1.86	0.019
B) Objectively measured muscle strength and physical performance at follow-up visit	**Baseline CCR**			
	Overall	**Low CCR (CCR < 8.16)**	**High CCR (CCR ≥ 8.16)**	***P***
No. participants	891	290	601	
Handgrip strength (kg)	20.16 ± 4.85	19.70 ± 4.40	20.39 ± 5.05	0.039
Repeated chair stands (s)	13.31 ± 3.88	13.55 ± 4.06	13.20 ± 3.79	0.207
One-leg stand (s)	23.53 ± 9.64	21.44 ± 10.51	24.54 ± 9.03	<0.001
Usual gait speed (m/s)	1.11 ± 0.19	1.07 ± 0.18	1.13 ± 0.19	<0.001
Narrow gait speed (m/s)	1.07 ± 0.24	1.01 ± 0.24	1.10 ± 0.23	<0.001

Mean ± SD are presented for normally distributed continuous variables.

Continuous variables were analyzed using the independent samples *t* test for parametric data.

CCR, creatinine-cystatin C ratio; $FFMV_{SE}$, fat-free muscle volume–spinae erector; $FFMV_{THIGH}$, fat-free muscle volume–thigh; $FFMV_{TOTAL}$, fat-free muscle volume - total;MRI, magnetic resonance imaging; TLTV, total lean tissue volume.

$FFMV_{THIGH}$ of the low CCR group was 0.350 L lower (95% CI, 0.183-0.518) after adjustment for age, ethnicity, education level, menopausal status, smoking, alcohol consumption, VAT, HT usage, statins usage, and inflammatory markers (Table 3). Similarly, the mean $FFMV_{SE}$ and the mean TLTV for low CCR group were 0.022 L lower (95% CI, 0.008-0.037), and 0.424 L lower (95% CI, 0.096-0.753), respectively, compared to the high CCR group after adjustment.

Sensitivity analysis showed that the association between low CCR groups and lower $FFMV_{THIGH}$, $FFMV_{SE}$ and TLTV remained significant after adjusting for BMI instead of VAT in fully adjusted models (Supplemental Table 2, http://links.lww.com/MENO/B354).

Baseline CCR associated with objectively measured muscle function 6.6 years later

In univariate analyses, low CCR at baseline was associated with lower muscle strength and poorer physical performance measured after 6.6 years (Table 2B). Handgrip strength was weaker, one-leg stand times were shorter, and both usual and narrow walking speeds were slower in the low CCR group.

In *multivariable linear regression analyses*, low CCR at baseline was associated with slower usual and narrow walking speeds (Table 4). Compared to the high CCR group, the usual gait speed of the low CCR group was slower by 0.029 m/s (95% CI, 0.006-0.053) after adjustment for age, ethnicity, education level, menopausal status, smoking, alcohol consumption, baseline usual gait speed, VAT, HT usage, statins usage and inflammatory markers in the final model. Similarly, the mean narrow gait walking speed for low CCR group was 0.049 m/s slower (95% CI, 0.020-0.078). Associations between the CCR groups with handgrip strength and one-leg stand tests were attenuated after adjustment in Model 1. CCR was not associated with the repeated chair stands test in the unadjusted model.

Associations between baseline CCR groups and gait speed at follow-up remained significant after adjusting for

TABLE 3. Linear regression analysis of the longitudinal association between CCR tertiles at baseline and MRI muscle mass indices measured at follow-up after a mean of 6.6 years (N = 498)

	$FFMV_{THIGH}$			$FFMV_{SE}$			TLTV		
CCR groups	**Unadjusted**	**Model 1**	**Model 2**	**Unadjusted**	**Model 1**	**Model 2**	**Unadjusted**	**Model 1**	**Model 2**
Low CCR (n = 156) CCR < 8.16	−0.394 (−0.568, −0.220)	−0.375 (−0.540, −0.210)	−0.350 (−0.518, −0.183)	−0.022 (−0.037, −0.007)	−0.025 (−0.039, −0.010)	−0.022 (−0.037, −0.008)	−0.426 (−0.781, −0.071)	−0.470 (−0.794, −0.146)	−0.424 (−0.753, −0.096)
High CCR (n = 342) CCR ≥ 8.16		Reference			Reference			Reference	

Data are presented as mean differences and 95% confidence intervals.

Model 1: Adjusted for age, ethnicity, education level, menopausal status, smoking, alcohol consumption, VAT, use of hormone therapy and use of statins.

Model 2: Adjusted for covariates in Model 1 + inflammatory markers (hs-CRP, IL-6, and TNF-α).

CCR, creatinine-cystatin C ratio; $FFMV_{SE}$, fat-free muscle volume–spinae erector; $FFMV_{THIGH}$, fat-free muscle volume–thigh; hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin-6 (IL-6); TLTV, total lean tissue volume; TNF-α, tumor necrosis factor alpha; VAT, visceral adipose tissue.

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TABLE 4. Linear regression analysis of the longitudinal association between CCR tertiles at baseline and muscle strength and physical performance measured at follow-up after a mean of 6.6 yr

	Handgrip strength			Repeated chair stands			One-leg stand		
CCR groups	**Unadjusted**	**Model 1**	**Model 2**	**Unadjusted**	**Model 1**	**Model 2**	**Unadjusted**	**Model 1**	**Model 2**
Low CCR (n = 290) CCR < 8.16	−0.683 (−1.363, −0.002)	0.426 (−0.206, 1.058)	0.489 (−0.142, 1.120)	0.350 (−0.194, 0.894)	−0.162 (−0.709, 0.385)	−0.186 (−0.734, 0.363)	−3.100 (−4.437, −1.762)	−0.866 (−2.064, 0.331)	−0.736 (−1.933, 0.461)
High CCR (n = 601) CCR ≥ 8.16		Reference			Reference			Reference	

	Usual gait speed			Narrow gait speed		
CCR groups	**Unadjusted**	**Model 1**	**Model 2**	**Unadjusted**	**Model 1**	**Model 2**
Low CCR (n = 290) CCR < 8.16	−0.064 (−0.089, −0.038)	−0.031 (−0.054, −0.008)	−0.029 (−0.053, −0.006)	−0.093 (−0.126, −0.060)	−0.050 (−0.079, −0.021)	−0.049 (−0.078, −0.020)
High CCR (n = 601) CCR ≥ 8.16		Reference			Reference	

Data are presented as mean differences and 95% confidence intervals.

Model 1: Adjusted for age, ethnicity, education level, menopausal status, smoking, alcohol consumption, baseline physical performance, VAT, use of hormone therapy, and use of statins.

Model 2: Adjusted for covariates in Model 1 + inflammatory markers (hs-CRP, IL-6, and TNF-α).

CCR, creatinine-cystatin C ratio; hs-CRP, High-sensitivity C-reactive protein; IL-6, interleukin-6; VAT, visceral adipose tissue; TNF-α, tumor necrosis factor alpha.

BMI instead of VAT in fully adjusted models (Supplemental Table 3, http://links.lww.com/MENO/B354).

DISCUSSION

In this study, we report the finding that baseline lower serum CCR, reflecting lower muscle mass, was associated with lower MRI-measured muscle volumes and poorer physical function 6.6 years later. To the best of our knowledge, this is the first study to clarify the relationship between CCR with later muscle volumes and function in community-dwelling midlife women. Low CCR at baseline was associated with lower MRI-measured fat-free muscle volumes ($FFMV_{THIGH}$, $FFMV_{SE}$) and TLTV, independent of age, ethnicity, education level, menopausal status, smoking, alcohol consumption, VAT, HT usage, statins usage, and inflammatory markers. Most importantly, low CCR at baseline was associated with slower gait speeds in both the usual and narrow walk performance measured 6.6 years later in fully adjusted models. However, CCR was not associated with handgrip strength, repeated chair stands, and one-leg stand tests. These findings suggest that CCR may be a clinical marker to identify women who could be at risk for developing deficient muscle mass and physical performance.

Estrogen decline at menopause decreases muscle mass, strength, and physical performance.[31] In *animal studies,* ovariectomy results in a 10% decrease in strength that corresponded with an 18% decrease in fiber cross-sectional area and, in the absence of estrogen muscle, is more prone to injury and regrowth is limited.[32] In *human studies*, postmenopausal women experience a rapid decrease in muscle mass and strength and are more vulnerable to age-related frailty.[31] Women have an accelerated reduction of 0.6% in muscle mass per year after menopause.[33] Muscle area and grip strength were greater in estrogen replacement therapy users than in nonusers and estrogen replacement therapy can improve muscle protein synthesis following resistance training.[31] Our findings suggest that CCR may be a useful measurement to identify women during the menopausal transition with accelerated declines in muscle mass and physical performance and beyond, facilitating timely interventions to reduce risk of sarcopenia.[34]

The association between CCR with skeletal muscle mass, grip strength and gait speed has been postulated from cross-sectional studies in older adults. In a study of 677 community-dwelling older adults (mean age >70), individuals with lower CCR had lower muscle mass and reduced grip strength and gait speed.[35] Our study contributes knowledge from a longitudinal perspective, further elucidating the relationship between CCR and muscle mass and physical function within a cohort of younger community-dwelling midlife women. Similar to our findings, longitudinal associations in a group of 1,253 Japanese older adults (mean age at baseline >70), indicated that individuals with lower levels of CCR had greater annual declines in skeletal muscle mass index and maximum gait speeds.[24] Our results showed that lower levels of CCR were associated with not only lower levels of muscle volumes 6.6 years later but also slower usual and narrow gait speeds, independent physical performance at baseline. Walking speed assesses lower body muscle function and neuromuscular coordination, which is essential for frailty assessment and prevention of falls.[36,37]

Our findings were consistent with the report that gait speed in Singaporean women starts to decline from the age of 50.[38] Gait speed was shown to predict adverse sarcopenic outcomes-disability, falls, and mortality,[39] and is the only physical performance test associated with an increased risk of hospitalization.[37] Early detection and management of the sarcopenia may significantly reduce the risk of morbidity and mortality related to sarcopenia.[40] Current diagnostic modalities, such as DXA and physical tests, may not timely detect the onset of the decline in sarcopenic parameters, and are not time- or cost-effective in the long run.[41] Our study showed that CCR, reflective of later reduction in muscle volumes and impairment in physical performance such as gait speeds, may

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serve as a biomarker for screening of preclinical sarcopenia. Serum creatinine and cystatin C levels are routinely measured in clinical settings, enhancing their clinical feasibility to detect patients who are at risk of sarcopenia.

In our study, the association between baseline CCR and muscle mass and physical performance decline 6.6 years later was independent of inflammatory biomarkers. Previous studies have hypothesized that the association between CCR and sarcopenia could be attributed to systemic inflammation.[35,42,43] Sarcopenia can occur secondary to systemic diseases, which can directly impact muscle metabolism, resulting in loss of muscle mass.[10,44] Furthermore, higher level of systemic inflammation was inversely associated with measures of kidney function.[45] Inflammatory cytokines such as IL-6 and TNF-α can impair renal blood flow and glomerular filtration rate (GFR), leading to renal dysfunction.[46] A reduction in cystatin C clearance by the kidneys would contribute to increased cystatin C levels in the blood and consequently, a reduction in the overall CCR. However, fully adjusted models showed that the relationship is independent of systemic inflammatory markers (hs-CRP, IL-6, and TNF-α), suggesting that the biological nature of CCR may possess predictive value on sarcopenic parameters, independent of inflammation.

The strength of our study was the use of MRI to directly estimate muscle volumes, rather than surrogate measures such as BIA or DXA, which captures total body lean mass rather than muscle mass directly.[12,14] In contrast, MRI can distinguish between muscle, fat and soft tissues with high accuracy and precision,[13] and potentially strengthening the link between muscle volumes and functional outcomes related to sarcopenia.[47] In addition, we used validated muscle strength and physical performance tests, allowing us to accurately understand the relationship of CCR with muscle strength and physical performance.

There are several limitations in our study. Dietary intake of protein-rich foods was not recorded, which could have influenced serum creatinine levels. Our study did not fully consider factors related to ectopic fat in muscle, which may affect muscle quality and function. Next, women who were unable to attend the follow-up visit could have been of poorer health status, thereby contributing to the lack of associations with other physical function measures. Additionally, we did not have measures of skeletal muscle volumes at the baseline visit, and the relationship between CCR and skeletal muscles volumes might have been driven by baseline differences. Furthermore, we cannot exclude the possibility that the use of multiple comparisons may have resulted in the correlation between CCR with narrow and usual gait speed but not handgrip strength, repeated chair stands and one-leg stand tests. Nevertheless, because gait speed assesses the coordinated performance of muscle groups in the whole body,[38,39] the lack of associations with the other tests may be related to the more isolated assessment of the other tests. Lastly, our analyses have categorized one-third of the participants into low CCR and the remaining two-thirds into high CCR groups. The prevalence of sarcopenia ranged from 27% to 32.2% in community-dwelling adults locally in Singapore,[48] while the global prevalence of sarcopenia ranged from 8% to 36% in individuals <60 years old.[49] This categorization reflects the local and global prevalence of sarcopenia and provides more clinically interpretable results between CCR and sarcopenic parameters.

CONCLUSIONS

In summary, we report that lower CCR at baseline was associated with lower muscle volumes, and poorer gait speeds at follow-up. Because both muscle volumes and poorer gait speed are constituents of current diagnostic criteria of sarcopenia, CCR may be a simple and reliable tool to help identify midlife women at risk of developing early sarcopenia and associated probability of adverse health outcomes. Future challenges include determination of threshold values in CCR that can reliably predict sarcopenia and the need for specific interventions designed to reduce declines in muscle mass and physical performance associated with the menopause transition.[34]

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