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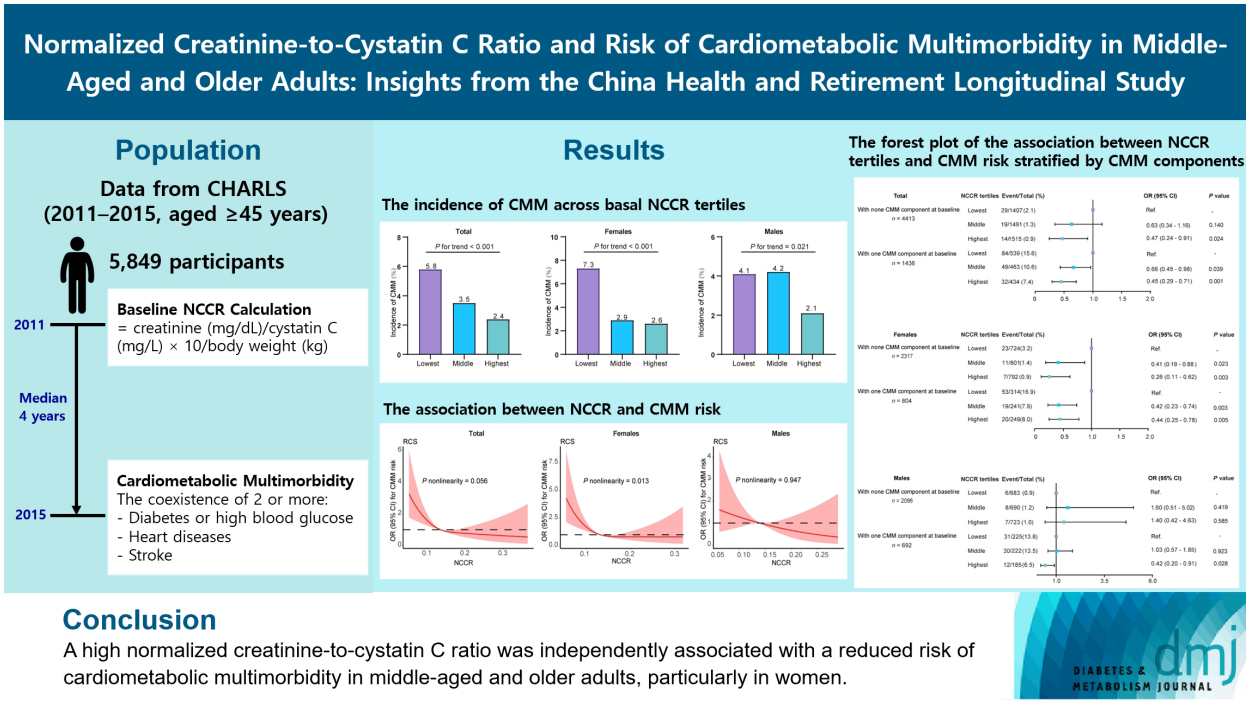

Highlights

- **This study explores the predictive role of NCCR on CMM in middle-aged and older adults.**
- **High NCCR levels were associated with a reduced risk of CMM in this population.**
- **NCCR was inversely associated with CMM in woman with none or one basal CMM component.**
- **This relationship remained significant among men with one basal CMM component.**
- **Non-obese individuals with high NCCR levels had the lowest CMM risk in men and women.**

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Normalized Creatinine-to-Cystatin C Ratio and Risk of Cardiometabolic Multimorbidity in Middle-Aged and Older Adults: Insights from the China Health and Retirement Longitudinal Study

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Background: Normalized creatinine-to-cystatin C ratio (NCCR) was reported to approximate relative skeletal muscle mass and diabetes risk. However, the association between NCCR and cardiometabolic multimorbidity (CMM) remains elusive. This study aimed to explore their relationship in a large-scale prospective cohort.
Methods: This study included 5,849 middle-age and older participants from the China Health and Retirement Longitudinal Study (CHARLS) enrolled between 2011 and 2012. The baseline NCCR was determined as creatinine (mg/dL)/cystatin C (mg/L)×10/body mass (kg). CMM was defined as the simultaneous occurrence of two or more of the following conditions: heart disease, stroke, and type 2 diabetes mellitus. Logistic regression analysis and Cox regression analysis were employed to estimate the relationship between NCCR and CMM. The joint effect of body mass index and NCCR on the risk of CMM were further analyzed.
Results: During a median 4-year follow-up, 227 (3.9%) participants developed CMM. The risk of CMM was significantly decreased with per standard deviation increase of NCCR (odds ratio, 0.72; 95% confidence interval, 0.62 to 0.85) after adjustment for confounders ($P<0.001$). Further sex-specific analysis found significant negative associations between NCCR and CMM in female either without or with one CMM component at baseline, which was attenuated in males but remained statistically significant among those with one basal CMM component. Notably, non-obese individuals with high NCCR levels had the lowest CMM risk compared to obese counterparts with low NCCR levels in both genders.
Conclusion: High NCCR was independently associated with reduced risk of CMM in middle-aged and older adults in China, particularly females.

Keywords: Creatinine; Cystatin C; Multimorbidity; Obesity; Prospective studies

INTRODUCTION

Cardiometabolic multimorbidity (CMM), defined as simultaneously suffering from more than one of cardiometabolic diseases: heart disease, stroke and type 2 diabetes mellitus (T2DM), is rapidly rising in prevalence with population aging and a serious threat to public health [1-5]. Cumulative evidence indicated that CMM was associated with not only life expectancy reduction but also mental problems to suffering populations [4,6,7]. Despite the fact that individuals with CMM endure a

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more profound burden of health consequences than those with a solitary cardiometabolic disorder, reliable biomarkers for predicting CMM remain elusive.

Skeletal muscle, as the main consumer of glucose, plays a pivotal role in determining systemic insulin sensitivity [8,9]. Loss of skeletal muscle mass and low muscle function, collectively termed as sarcopenia, have been implicated in adverse health outcomes such as depression, nonalcoholic fatty liver disease (NAFLD), diabetes, and cardiovascular disease (CVD) among middle-age and older individuals [8-13]. However, the widely recognized tools for measuring skeletal muscle mass, including dual-energy X-ray absorptiometry (DEXA), computed tomography (CT) and magnetic resonance imaging, are expensive and inapplicable for large-scale epidemiological surveys.

Serum creatinine and cystatin C are common markers for evaluating renal function in clinical practice. Recently, the ratio of creatinine-to-cystatin C (CCR) has been validated as a reliable surrogate index for estimating muscle mass [14,15]. Plenty of studies have validated the use of CCR as a reliable surrogate index for muscle mass, demonstrating its correlation with muscle mass measurements obtained through gold standard methods like CT and DEXA across various populations, including older adults, cancer patients, and critically ill individuals [15-20]. Moreover, a growing body of research suggests that CCR may have prognostic value, with decreased CCR levels being associated with increased risk of cardiovascular or all-cause mortality in some studies [10,16,21], although inconsistent results were observed in some other studies [22-24].

Despite the prevalent use of height-adjusted skeletal muscle mass in defining sarcopenia, plenty of studies have indicated that weight-adjusted skeletal muscle mass (measured by DEXA or CT) was more associated with insulin resistance index, such as homeostasis model assessment of insulin resistance, as well as related diseases such as T2DM, metabolic syndrome (MS), NALFD, and CVD [8,9,11,25-28]. Furthermore, a prior investigation has elucidated that normalized creatinine-to-cystatin C ratio (NCCR), defined as weight-adjusted CCR, exhibited a more robust association with weight-adjusted muscle mass assessed by bioelectrical impedance analysis (BIA) compared to non-normalized counterpart [29]. Notably, a prospective study has also highlighted an adverse relationship between NCCR and diabetes risk, with a mediating effect of 93.1% attributed to the insulin resistance index metabolic score for insulin resistance (METSIR) [30]. Whereas, whether NCCR is associated with the risk of CMM remains unknown. Consequently, we aimed to decipher the association between NCCR and long-term CMM risks among middle-age and older population based on a prospective cohort study from the China Health and Retirement Longitudinal Study (CHARLS).

METHODS

Study population

The CHARLS is an ongoing nationally prospective study with participants randomly and representatively selected from 150 county-level units from 28 provinces in China [31]. The baseline survey carried out between 2011 and 2012 included 17,708 participants, with all participants followed up every 2 years. This study used the data from 2021 to 2015 for analysis. Those younger than 45 years or without age information (n=777), without blood samples information (n=99), missing baseline NCCR values (n=9,689), with abnormal anthropometric indicators (n=48), with baseline estimated glomerular filtration rate (eGFR) ≤30 mL/min/1.73 m^2 (n=22), missing diagnostic information of diabetes, stroke, and heart disease at recruitment (n=57), with baseline prevalent CMM (n=302), lost to follow-up (n=767), and missing diagnostic information of diabetes, stroke, and heart disease during follow-up (n=98) were excluded. Finally, a total of 5,849 participants were enrolled in this analysis (Supplementary Fig. 1). The protocol was approved by the Ethical Review Committee of Peking University (approval number: IRB00001052-11,015). All participants provided informed consent.

Covariate variables

Information on age, gender, residence (rural and urban), marital status (married and others including never married, separated, divorced and widowed), educational level (less than lower secondary education, upper secondary & vocational training and tertiary education), history of smoking (current smoker and non-current smoker) or drinking (ever drinking and never drinking), history of chronic diseases (T2DM, heart disease, stroke, hypertension, dyslipidemia, and kidney disease) were collected using standardized questionnaires [13]. Height (cm), body weight (kg), waist circumstance (WC, cm), and blood pressure were measured using standard methods as previously described [30]. Handgrip strength (HGS) was determined using a handgrip dynamometer (YuejianTM WL-1000 dynamometer, Nantong Yuejian Physical Measurement Instrument Co. Ltd., Nantong, China) twice, and the average data for

the dominant hand were chosen for the analysis.

Laboratory parameters detection

Venous blood samples of enrolled participants were collected, transported and stored following standard procedures [13]. Serum fasting blood glucose, glycosylated hemoglobin (HbA1c), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglyceride (TG) were measured as previous described. Serum creatinine and cystatin C were measured using a rate-blanked and compensated Jaffe creatinine method and particle-enhanced turbimetric assay, respectively.

Definition of variables

NCCR=creatinine (mg/dL)/cystatin C (mg/L)×10/body mass (kg). The eGFR was calculated using combination of creatinine and cystatin C [32]. Body mass index (BMI) was calculated as previous described [33]. Participants were divided into non-obese and obese subgroups with a cutoff of BMI ≥25 kg/m^2 according to the World Health Organization recommended BMI classification criteria for Asians [34,35]. Lipid accumulation product and Visceral adiposity index (VAI) was calculated by genders as previously described [36]. T2DM was defined following the 2005 American Diabetes Association criteria: a HbA1c level ≥6.5%; a fasting plasma glucose level ≥7 mmol/L; a random blood glucose level ≥11.1 mmol/L, and/or self-reported diagnosis ("Have you been diagnosed with diabetes or hyperglycemia by a doctor?") or use of glucose-lowering drugs. The identification of participants with heart disease or stroke was mainly based on self-report at recruitment and follow-up surveys ("Have you been diagnosed by a doctor with heart disease, coronary artery disease, angina, congestive heart failure, or other heart problems?" and "Have you been diagnosed by a doctor as having a stroke?"). Hypertension was defined as a mean of systolic blood pressure (SBP) ≥140 mm Hg, a mean of diastolic blood pressure (DBP) ≥90 mm Hg, a history of hypertension ("Have you been diagnosed with hypertension by a doctor?"), or the use of anti-hypertensive agents. Dyslipidemia was defined as TC ≥240 mg/dL, LDL-C ≥160 mg/dL, HDL-C <40 mg/dL, TG ≥200 mg/dL, a history of dyslipidemia ("Have you been diagnosed with dyslipidemia by a doctor?"), and/or the use of lipid-lowering medications. Kidney disease was defined as self-reported diagnosis ("Have you been diagnosed with kidney disease by a doctor?") or use of related drugs. Participants who had suffered from two or more of the diseases (heart disease, stroke, diabetes, or high blood sugar) at the same time were defined as having CMM.

Statistical analysis

Given the disparity in the distribution of NCCR between genders, the participants were stratified into three groups according to the sex-specific NCCR tertiles (female: lowest tertile <0.1179, middle tertile ≥0.1179 and <0.1466, highest tertile ≥0.1466; male: lowest tertile <0.1254, middle tertile ≥0.1254 and <0.1518, highest tertile ≥0.1518). Baseline characteriskics were analyzed across the three groups. Continuous variables were expressed as mean±standard deviation (SD) or median (range) following normality detection by Shapiro-Wilk test. Categorical variables were expressed as number (proportion). Data difference between three groups were compared by one-way analysis of variance (ANOVA) or Kruskal–Wallis test or chi-square tests, respectively.

Multivariate logistic regression models were used to calculate the odds ratio (OR) and 95% confidence interval (CI) of incident CMM related to per SD increase or tertiles of NCCR in total participants or by genders. Model 1 was without adjustment; Model 2 was adjusted for age, gender, education, marital status, residence, smoking, and drinking; Model 3 was adjusted for model 2 plus VAI, baseline eGFR, hypertension, dyslipidemia, kidney disease, baseline stroke, heart disease, and diabetes; Model 4 was adjusted for model 3 plus HGS. To evaluate the dose-response association between NCCR and CMM, restricted cubic spline analysis was also carried out with adjustment for covariables in model 4. Additionally, low NCCR was defined as the lowest tertile and high NCCR was defined as the middle and highest tertiles. Subjects were further categorized into four subgroups: obese and low NCCR (OB+LNCCR), obese and high NCCR (OB+HNCCR), non-obese and low NCCR (NOB+LNCCR), non-obese and high NCCR (NOB+HNCCR). Joint effect of BMI and NCCR on the occurrence of CMM were then analyzed both in total participants or by genders. Furthermore, possible modifications of the relationship of NCCR with CMM were investigated through stratified analyses: examining the influence of various factors such as baseline CMM components, outcome CMM components, age, smoking status, drinking status, marital status, educational level, baseline hypertension, dyslipidemia, and kidney disease. These analyses aimed to identify subgroups within which the relationship between NCCR and CMM may be stronger or weaker.

In addition, Kaplan–Meier curves were employed to illustrate the cumulative incidence of CMM across different subgroups defined by sex-specific NCCR tertiles or joint subgroups of BMI and NCCR. The log-rank test was used to statistically compare the differences between the curves. To further quantify the relationship between NCCR tertiles or the joint BMI+NCCR subgroups and CMM risk, four Cox proportional hazards models were fitted, stratified by gender. These models estimated hazard ratios (HRs) and their corresponding 95% CI. The proportional hazards assumption of each included variates in the models was checked with the Schoenfeld residual test, and no violations were observed. Model 1 was without adjustment; Model 2 was adjusted for age, education, marital status, residence, smoking, and drinking; Model 3 was adjusted for model 2 plus VAI, baseline eGFR, hypertension, dyslipidemia, kidney disease, baseline stroke, heart disease, and diabetes; Model 4 was adjusted for model 3 plus HGS.

All analysis were carried out using R version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria) and the IBM SPSS Statistics software version 27 (IBM Corporation, Armonk, NY, USA). $P<0.05$ for a two-tailed test served as the threshold for statistical significance.

RESULTS

Baseline characteriskics of participants by tertiles of NCCR

The baseline characteriskics of enrolled participants are summarized in Table 1. The average age of the population was 59.81±9.54 years old at recruitment. As the levels of NCCR increased, there was a consistent and statistically significant decrease in BMI, SBP, DBP, HGS, and VAI (all $P<0.001$). Additionally, the proportions of individuals with baseline hypertension, dyslipidemia, and heart disease were decreased progressively with higher NCCR tertiles (all $P<0.01$). In contrast, the proportion of rural population was gradually increased with increasing NCCR levels (all $P<0.05$). Notably, no significant differences were observed in the baseline proportions of diabetes, stroke, or kidney disease among the three NCCR tertiles. Regarding laboratory biomarkers, TG were lower in the higher NCCR tertiles ($P=0.009$), while TC and HDL were progressively greater (all $P<0.001$).

Association between NCCR levels and incident CMM

After a median follow-up period of 4 years, 227 (3.9%) participants developed CMM (Supplementary Figs. 2 and 3). Notably, the incidence of CMM gradually was decreased across increasing tertiles of NCCR in the overall population as well as within gender subgroups (all P for trend <0.05) (Fig. 1A-C). The association of baseline NCCR levels and incident CMM was further analyzed by logistic analysis. As shown in Table 2, per SD increase in NCCR was inversely associated with risk of CMM in the whole population after adjusting for potential confounders. Their association remained significant after additionally controlling for HGS (OR, 0.72; 95% CI, 0.62 to 0.85; $P<0.001$). Moreover, the ORs for CMM were gradually decreased with rising NCCR tertiles. When the analysis was stratified by gender, distinct sex-specific relationships emerged. In females, the multivariable-adjusted OR for incident CMM was 0.68 (95% CI, 0.55 to 0.84) per SD increase of NCCR after adjusting for potential confounders ($P<0.001$). Following full adjustment, the ORs for CMM in the middle and highest tertiles compared to the lowest tertile were 0.42 (95% CI, 0.26 to 0.66) and 0.40 (95% CI, 0.25 to 0.63), respectively. In contrast, among males, while an initial negative association was observed between the highest versus lowest NCCR teritle and CMM risk in model 2 ($P=0.024$), this relationship was diminished upon further adjustment for baseline metabolic diseases. Cubic spline analysis provided further insights, revealing a significant reverse J-shaped relationship between NCCR and CMM risk specifically in females, but not in males, after accounting for potential confounders (P overall <0.001 and P nonlinearity=0.013 for females) (Fig. 2).

Kaplan–Meier survival curves (Supplementary Fig. 4) emphasized these findings, demonstrating that females in the lowest NCCR tertile had the highest cumulative incidence of CMM (log-rank $P<0.0001$). Compared to females in the lowest NCCR tertile, those in the middle and highest tertiles had adjusted HRs of 0.46 (95% CI, 0.29 to 0.71) and 0.45 (95% CI, 0.29 to 0.71), respectively, for incident CMM (Supplementary Table 1). These results underscore the potential protective role of higher NCCR levels against CMM development, particularly among females.

Joint effect of BMI and NCCR on risk of CMM

The joint analysis of BMI and NCCR on the risk of CMM provides valuable insights into the potential interaction between these two factors. By classifying participants into four subgroups based on their BMI and NCCR levels, the study reveals that the incidence of CMM gradually decreases across these

Table 1. Baseline characteriskics of enrolled participants according to NCCR tertiles

Variable	Total	NCCR tertiles			*P* value
		Lowest	Middle	Highest	
Number	5,849	1,946	1,954	1,949	
Age, yr	59.81±9.54	60.01±9.60	59.66±9.45	59.77±9.58	0.508
Female sex	3,121 (53.4)	1,038 (53.3)	1,042 (53.3)	1,041 (53.4)	0.998
Weight, kg	58.23±11.30	65.61±11.36	57.50±8.73	51.58±8.90	<0.001
Height, m	1.58±0.09	1.60±0.08	1.58±0.08	1.55±0.08	<0.001
BMI, kg/m^2	23.37±3.79	25.70±4.08	23.10±2.89	21.32±2.89	<0.001
SBP, mm Hg	129.51±21.63	76.67±12.33	74.64±11.96	73.46±11.95	<0.001
DBP, mm Hg	74.92±12.15	132.40±21.55	129.23±21.38	126.91±21.63	<0.001
Smoking[a]	1,786 (30.6)	569 (29.3)	595 (30.6)	622 (32.0)	0.181
Drinking[b]	2,268 (38.8)	733 (37.7)	789 (40.4)	746 (38.3)	0.180
Married	4,840 (82.7)	1,639 (84.2)	1,616 (82.7)	1,585 (81.3)	0.057
Education					0.007
Less than lower secondary education	5,356 (91.6)	1,746 (89.7)	1,808 (92.5)	1,802 (92.5)	
Upper secondary & vocational training	438 (7.5)	174 (8.9)	131 (6.7)	133 (6.8)	
Tertiary education	55 (0.9)	26 (1.3)	15 (0.8)	14 (0.7)	
Residence					0.003
Rural	3,941 (67.4)	1,260 (64.7)	1,320 (67.6)	1,361 (69.8)	
Urban	1,908 (32.6)	686 (35.3)	634 (32.4)	588 (30.2)	
HGS, kg	30.0 (24.2–38.5)	31.0 (25.0–39.2)	31.0 (25.0–39.0)	30.0 (23.5–37.0)	<0.001
TC, mg/dL	190.98 (167.40–215.34)	186.73 (163.53–212.63)	190.21 (167.78–213.79)	194.46 (171.26–220.36)	<0.001
TG, mg/dL	104.43 (74.34–150.45)	107.53 (77.88–153.11)	103.55 (75.23–146.03)	100.89 (70.80–152.22)	0.009
LDL-C, mg/dL	114.82 (93.17–137.63)	114.05 (92.01–136.86)	116.75 (95.30–138.02)	114.05 (93.17–138.40)	0.141
HDL-C, mg/dL	49.87 (40.98–60.31)	47.55 (39.43–57.31)	50.26 (41.37–59.92)	52.19 (42.14–63.40)	<0.001
FPG, mg/dL	108.69±32.34	108.27±28.66	108.23±31.61	109.56±36.29	0.344
HbA1c, %	5.10 (4.90–5.40)	5.20 (4.90–5.40)	5.10 (4.90–5.40)	5.10 (4.90–5.40)	<0.001
LAP	26.27 (14.11–46.62)	35.15 (20.16–57.95)	25.68 (14.91–43.67)	18.98 (9.78–37.35)	<0.001
VAI	1.32 (0.76–2.38)	1.47 (0.86–2.55)	1.29 (0.78–2.32)	1.19 (0.67–2.29)	<0.001
Creatinine, mg/dL	0.78±0.18	0.72±0.17	0.78±0.17	0.83±0.18	<0.001
Cystatin C, mg/dL	1.01±0.23	1.09±0.23	1.01±0.20	0.93±0.21	<0.001
CCR	0.789±0.195	0.670±0.134	0.776±0.126	0.920±0.220	<0.001
NCCR	0.139±0.038	0.103±0.015	0.135±0.009	0.179±0.032	<0.001
Basal eGFR, mL/min/1.73 m^2	85.47 (73.95–96.46)	83.38 (72.12–93.88)	85.74 (74.21–96.00)	87.50 (75.56–99.09)	<0.001
Baseline hypertension	2,376 (40.6)	948 (48.7)	773 (39.6)	655 (33.6)	<0.001
Baseline dyslipidemia	2,437 (41.7)	871 (44.8)	790 (40.4)	776 (39.8)	0.003
Baseline kidney disease[c]	398 (6.8)	114 (5.9)	145 (7.4)	139 (7.2)	0.122
Baseline diabetes	848 (14.5)	249 (12.8)	233 (11.9)	250 (12.8)	0.626
Baseline stroke	89 (1.5)	35 (1.8)	30 (1.5)	24 (1.2)	0.351
Baseline heart disease	615 (10.5)	255 (13.1)	200 (10.2)	160 (8.2)	<0.001

Values are presented as mean±standard deviation, number (%), or median (range).
NCCR, normalized creatinine-to-cystatin C ratio; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HGS, handgrip strength; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; LAP, lipid accumulation product; VAI, visceral adiposity index; CCR, creatinine-to-cystatin C ratio; eGFR, estimated glomerular filtration rate.
[a]There were 20 participants without smoking information, [b]There were two participants without drinking information, [c]There were 21 participants without baseline kidney disease information.

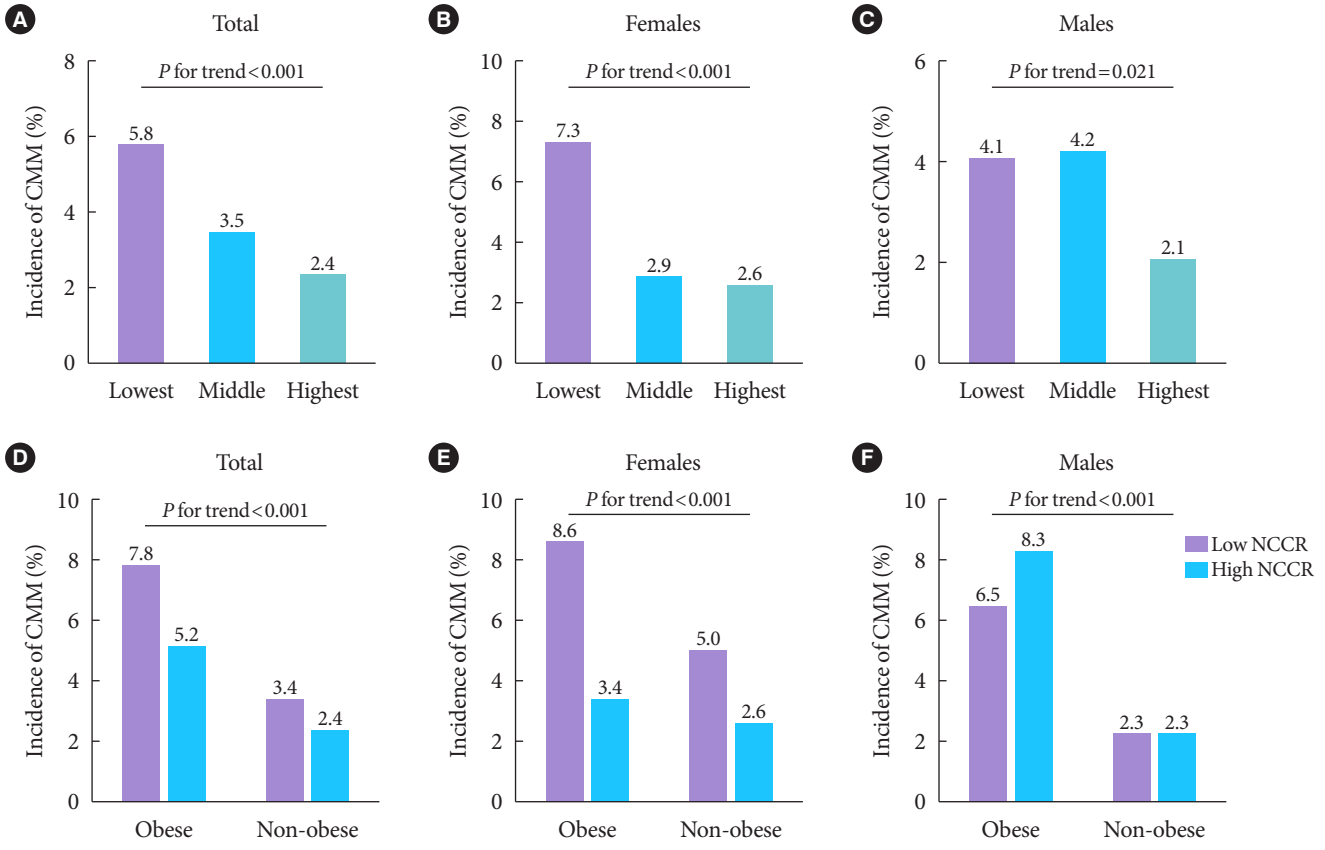

Fig. 1. The incidence of cardiometabolic multimorbidity (CMM) according to normalized creatinine-to-cystatin C ratio (NCCR) and body mass index (BMI) levels. (A) The incidence of CMM across NCCR tertiles in total participants. (B) The incidence of CMM across NCCR tertiles in females. (C) The incidence of CMM across NCCR tertiles in males. (D) The incidence of CMM across joint combination of BMI and NCCR subgroups in total participants. (E) The incidence of CMM across joint combination of BMI and NCCR subgroups in females. (F) The incidence of CMM across joint combination of BMI and NCCR subgroups in males.

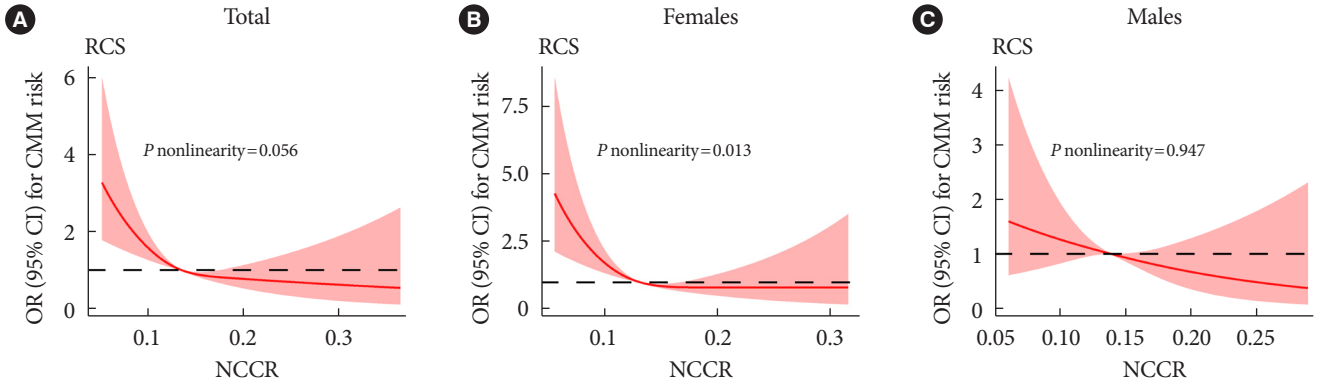

Fig. 2. The restricted cubic spline (RCS) curve for the association between normalized creatinine-to-cystatin C ratio (NCCR) and cardiometabolic multimorbidity (CMM) risk. (A) Total participants, (B) females, (C) males. Model was adjusted for age, gender, education, marriage, residence, smoking, drinking, visceral adiposity index, baseline estimated glomerular filtration rate, hypertension, dyslipidemia, kidney disease, baseline stroke, heart disease, diabetes, and handgrip strength. OR, odds ratio; CI, confidence interval.

Table 2. Normalized creatinine-to-cystatin C ratio and risk of CMM

Variable	Lowest tertile	Middle tertile	Highest tertile	Per SD increase
Total (event/total)	113/1,946	68/1,954	46/1,949	227/5,849
Model 1	1 (ref)	0.55 (0.40–0.74)	0.38 (0.27–0.54)	0.65 (0.55–0.76)
P value	-	<0.001	<0.001	<0.001
Model 2	1 (ref)	0.60 (0.44–0.82)	0.40 (0.28–0.57)	0.67 (0.57–0.78)
P value	-	0.001	<0.001	<0.001
Model 3	1 (ref)	0.65 (0.47–0.91)	0.48 (0.33–0.69)	0.73 (0.62–0.85)
P value	-	0.011	<0.001	<0.001
Model 4	1 (ref)	0.65 (0.47–0.90)	0.47 (0.32–0.68)	0.72 (0.62–0.85)
P value	-	0.010	<0.001	<0.001
Female (event/total)	76/1,038	30/1,042	27/1,041	133/3,121
Model 1	1 (ref)	0.38 (0.24–0.58)	0.34 (0.22–0.53)	0.62 (0.50–0.76)
P value	-	<0.001	<0.001	<0.001
Model 2	1 (ref)	0.39 (0.25–0.60)	0.34 (0.22–0.54)	0.63 (0.51–0.77)
P value	-	<0.001	<0.001	<0.001
Model 3	1 (ref)	0.43 (0.27–0.67)	0.39 (0.25–0.63)	0.68 (0.55–0.83)
P value	-	<0.001	<0.001	<0.001
Model 4	1 (ref)	0.42 (0.26–0.66)	0.40 (0.25–0.63)	0.68 (0.55–0.84)
P value	-	<0.001	<0.001	<0.001
Male (event/total)	37/908	38/912	19/908	94/2,728
Model 1	1 (ref)	1.02 (0.65–1.63)	0.50 (0.29–0.88)	0.72 (0.56–0.92)
P value	-	0.992	0.016	0.008
Model 2	1 (ref)	1.04 (0.65–1.66)	0.52 (0.30–0.92)	0.73 (0.57–0.93)
P value	-	0.868	0.024	0.012
Model 3	1 (ref)	1.12 (0.678–1.85)	0.64 (0.35–1.18)	0.80 (0.62–1.03)
P value	-	0.670	0.154	0.084
Model 4	1 (ref)	1.12 (0.67–1.86)	0.62 (0.33–1.15)	0.78 (0.60–1.02)
P value	-	0.674	0.127	0.071

Values are presented as odds ratio (95% confidence interval). Model 1: crude model; Model 2: adjusted for age, gender, education, marriage, residence, smoking, and drinking; Model 3: adjusted for model 2 plus visceral adiposity index, baseline estimated glomerular filtration rate, hypertension, dyslipidemia, kidney disease, baseline stroke, heart disease, and diabetes; Model 4: adjusted for model 3 plus handgrip strength.
CMM, cardiometabolic multimorbidity; SD, standard deviation.

subgroups, with the lowest incidence observed in the NOB+HNCCR subgroup (Fig. 1D-F). In females, the protective effect of high NCCR is evident, with a 59% reduced risk of CMM in obese participants with high NCCR compared to those with low NCCR (P=0.004) (Table 3). Additionally, among females with low NCCR, non-obese individuals had a lower risk of CMM compared to obese individuals (OR, 0.55; 95% CI, 0.31 to 0.98). The CMM risk was the lowest in participants with co-existing non-obesity and high NCCR level (OR, 0.31; 95% CI, 0.20 to 0.49; P<0.001). In males, only the non-obese individuals with high NCCR level exhibited a reduced risk of CMM compared to obese individuals with low NCCR level (OR, 0.48; 95% CI, 0.26 to 0.88; P=0.018). However, it is worth noting that non-obese males generally had a lower incidence of CMM regardless of their NCCR levels (Fig. 1F).

The Cox regression analysis further supported these findings, revealing the lowest risk of CMM in females with co-existing non-obesity and high NCCR levels, with an adjusted HR of 0.37 (95% CI, 0.24 to 0.56; P<0.001) (Supplementary Table 2). In summary, the joint analysis highlighted the importance

Table 3. Joint effect of BMI and NCCR on the risk of CMM

Variable	Obese		Non-obese	
	Low NCCR	High NCCR	Low NCCR	High NCCR
Total (event/total)	82/1,047	37/706	31/899	77/3,197
Model 1	1 (ref)	0.65 (0.44–0.97)	0.42 (0.28–0.64)	0.29 (0.21–0.40)
P value	-	0.036	<0.001	<0.001
Model 2	1 (ref)	0.70 (0.46–1.04)	0.38 (0.25–0.59)	0.28 (0.20–0.39)
P value	-	0.076	<0.001	<0.001
Model 3	1 (ref)	0.66 (0.43–1.01)	0.50 (0.31–0.79)	0.38 (0.26–0.53)
P value	-	0.055	0.003	<0.001
Model 4	1 (ref)	0.67 (0.43–1.02)	0.49 (0.30–0.77)	0.37 (0.26–0.52)
P value	-	0.063	0.002	<0.001
Female (event/total)	57/661	15/440	19/377	42/1,643
Model 1	1 (ref)	0.37 (0.21–0.67)	0.56 (0.33–0.96)	0.28 (0.19–0.42)
P value	-	0.001	0.035	<0.001
Model 2	1 (ref)	0.42 (0.23–0.76)	0.49 (0.28–0.85)	0.26 (0.17–0.39)
P value	-	0.004	0.011	<0.001
Model 3	1 (ref)	0.40 (0.22–0.73)	0.53 (0.30–0.94)	0.32 (0.20–0.49)
P value	-	0.003	0.031	<0.001
Model 4	1 (ref)	0.41 (0.23–0.76)	0.55 (0.31–0.98)	0.31 (0.20–0.49)
P value	-	0.004	0.043	<0.001
Male (event/total)	25/386	22/266	12/522	35/1,554
Model 1	1 (ref)	1.30 (0.72–2.36)	0.34 (0.17–0.69)	0.33 (0.20–0.56)
P value	-	0.385	0.003	<0.001
Model 2	1 (ref)	1.31 (0.72–2.39)	0.31 (0.15–0.64)	0.32 (0.19–0.55)
P value	-	0.375	0.001	<0.001
Model 3	1 (ref)	1.23 (0.64–2.37)	0.52 (0.24–1.13)	0.53 (0.29–0.96)
P value	-	0.541	0.100	0.035
Model 4	1 (ref)	1.21 (0.62–2.37)	0.45 (0.21–1.00)	0.48 (0.26–0.88)
P value	-	0.570	0.051	0.018

Values are presented as odds ratio (95% confidence interval). Model 1: crude model; Model 2: adjusted for age, gender, education, marriage, residence, smoking, and drinking; Model 3: adjusted for model 2 plus visceral adiposity index, baseline estimated glomerular filtration rate, hypertension, dyslipidemia, kidney disease, baseline stroke, heart disease, and diabetes; Model 4: adjusted for model 3 plus handgrip strength.
BMI, body mass index; NCCR, normalized creatinine-to-cystatin C ratio; CMM, cardiometabolic multimorbidity.

of considering both BMI and NCCR when assessing CMM risk and the protective effect of high NCCR was more pronounced in females.

Stratification analysis on the association between NCCR and incident CMM

The further analysis according to the component of CMM at recruitment provided additional insights into the relationship between NCCR and CMM risk (Fig. 3 and Supplementary Fig. 3). In participants with none CMM component at baseline, the highest tertile of NCCR was associated with 53% reduced risk of CMM compared to the lowest tertile (Fig. 3A). In participants with one CMM component at baseline, both the middle and highest NCCR tertiles were associated with lower risk of incident CMM compared to the lowest tertile, with reduction of 34% and 55%, respectively (all $P<0.05$). This indicated that even in the presence of one CMM component, a higher NCCR level was still associated with the risk of CMM.

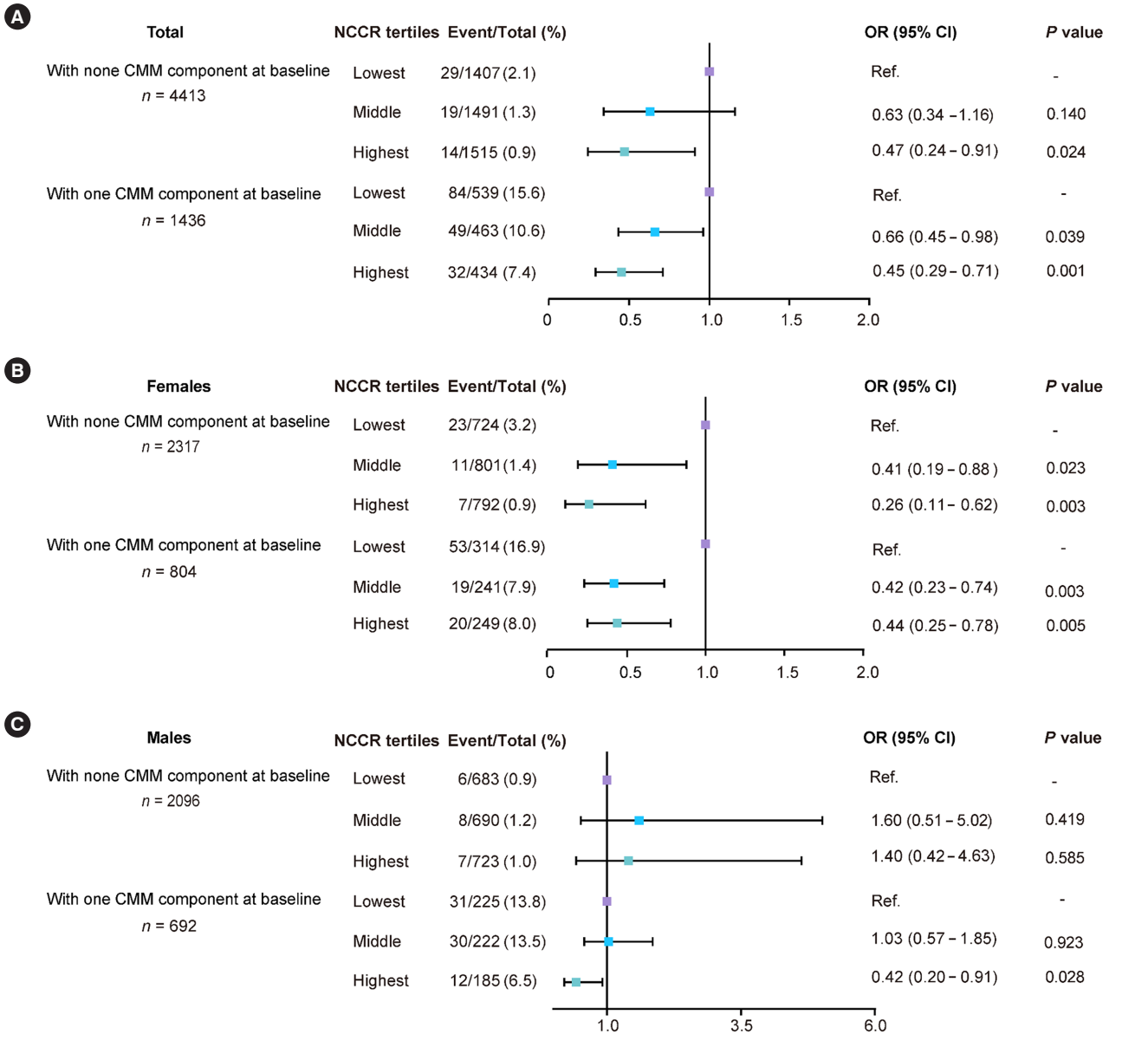

Fig. 3. The forest map of the association between normalized creatinine-to-cystatin C ratio (NCCR) tertiles and cardiometabolic multimorbidity (CMM) risk with none or one cardiometabolic disease at baseline. (A) Total population, (B) females, (C) males. Creatinine-to-cystatin C ratio tertiles were categrized by gender (female: <0.1179, ≥0.1179 and <0.1466, ≥0.1466; male: <0.1254, ≥0.1254 and <0.1518, ≥0.1518). Model was adjusted for age, gender, education, marriage, residence, smoking, drinking, visceral adiposity index, baseline estimated glomerular filtration rate, hypertension, dyslipidemia, kidney disease, baseline stroke, heart disease, diabetes, and handgrip strength. OR, odds ratio; CI, confidence interval.

When analyzed by gender, females with either no or one CMM component at baseline showed reduced risks of CMM across both the middle and highest NCCR tertiles (Fig. 3B). While for males, the negative relationship between the highest NCCR tertile and CMM risk was only observed in participants with one CMM component (OR, 0.42; 95% CI, 0.20 to 0.91; P=0.028) (Fig. 3C).

More analysis was conducted according to the specific component of CMM at the end of follow-up. The results revealed that each SD increase in NCCR was associated with a 46% reduction in the risk of stroke+heart disease (P=0.024) and a 27% reduction in the risk of diabetes+heart disease (P=0.001)

in the overall population (Supplementary Table 3). Besides, the association between CMM and NCCR did not vary substantially by subgroups based on age, marital status, history of smoking, drinking, or chronic diseases (Supplementary Table 4). To be mentioned, the relationship between NCCR and incident CMM were only significant in participants from rural areas, not in urban residents (Supplementary Table 4).

DISCUSSION

This is the first prospective study to explore the relationship between NCCR and incident CMM in Chinese middle-age and older population. Our gender-stratified analysis uncovered a compelling inverse correlation between NCCR and CMM risk, particularly pronounced among female participants who had no or just one CMM component at baseline. While this association was somewhat attenuated in males, it remained statistically significant among those with a single CMM component initially. Moreover, our findings underscore the lowest risk of CMM in non-obese subjects with high NCCR levels in both genders. Taken together, our study suggested an association between NCCR as a simple and precise surrogate index and the long-term risk of CMM in Chinese middle-age and older population, with particularly pronounced implications for women's health.

Both muscle mass and muscle strength were important components to definite sarcopenia. Previous studies, both from China and other ethics, has demonstrated robust association between HGS and the risk of single cardiometabolic disease or CMM [1,37-39]. However, there are debates about the association between muscle mass and cardiometabolic disease [8,13, 26,40], with some studies reporting significant correlations while other studies yielding contrast observations [28,40]. For instance, one study from CHARLS indicated no association between muscle mass and CMM [13]. This discrepancy may stem from the fact that many studies have relied solely on height-adjusted muscle mass, which reflects absolute muscle quantity but fails to account for the confounding influence of fat mass on metabolic outcomes. Consequently, recent investigations have emphasized the superiority of weight-adjusted muscle mass as a more accurate indicator of relative muscle mass, which is more closely tied to insulin resistance and metabolic dysfunction [9,25-27]. For instance, a study from National Health and Nutrition Examination Survey (NHANES) III revealed that it was weight-adjusted muscle mass, rather than height-adjusted, that was associated with an elevated risk of NAFLD [41]. Similarly, other studies also have confirmed the paramount importance of relative skeletal muscle mass over absolute muscle mass in the development of MS [8,11,42]. That's why recent studies suggested using weight-adjusted muscle mass in the definition of sarcopenia, as height-standardized muscle mass may underestimate the prevalence of sarcopenia in overweight and obese people [43,44].

As common markers for evaluating renal function, both serum creatinine and cystatin C are widely used in clinical practice [32]. While serum creatinine levels are influenced by muscle mass, cystatin C remains relatively stable due to its ubiquitous expression across tissues. Therefore, CCR was found as a precise surrogate index for estimating muscle mass as validated by gold standard methods like CT or DEXA in diverse populations from numerous studies [14-19]. One previous analysis has demonstrated a well-correlation between NCCR and weight-adjusted muscle mass through BIA [29]. Additionally, a large-scale study has uncovered a predictive link between NCCR and incident diabetes in the Chinese population [30]. In line with these findings, our study underscores a strong association between baseline NCCR and long-term CMM risk. Notably, this relationship remains significant after accounting for HGS, reinforcing the independent association between NCCR and the incidence of CMM. Furthermore, we found that their relationships remained not only in middle-age and older women with none CMM component but also in those with existing one cardiometabolic diseases at baseline, further emphasizing the significance of NCCR on CMM risk, at least in females.

Our study observed a trend of higher CMM incidence among females compared to males, especially in those with one CMM component at baseline. One plausible explanation for this gender disparity could be the inherent difference in muscle mass, as men tend to possess more muscle mass than BMI- and age-matched women [45]. Gender-specific effects of sex hormones may be another important contributor. It is noteworthy that a substantial portion of the female participants in our study maybe postmenopausal, given their age of 45 years or older. Plenty of previous studies have suggested higher risk of MS and CVD in postmenopausal women compared to their male counterparts of similar age [45-47]. It is also worth emphasizing that we found a stronger association between NCCR levels and CMM incidence in females compared to males. This observation aligns with previous research that has uncovered sex differences in the relationship between

muscle mass and metabolic diseases. For instance, an analysis of the Look Action for Health in Diabetes (AHEAD) trial indicated that low muscle mass has deleterious effects on HbA1c specifically in females but not males [48]. Furthermore, two separate studies from China reported significant associations between CCR/WC ratio or muscle mass and the incidence of T2DM in females, with these associations weakened in males [49,50]. These findings underscore the importance of considering gender-specific factors when assessing the risk of CMM and the potential role of NCCR in this regard.

Our study has uncovered significant associations between higher NCCR with reduced risk of CMM among both obese and non-obese females when compared to obese individuals with low NCCR levels. This finding was in line with previous research [25,26]. For instance, results from the Korean Genome Epidemiology Study revealed that weight-adjusted muscle mass was strongly associated with diabetes in middle-age and older adults, irrespective of obesity status [25]. Besides, the study from Korea National Health and Nutrition Examination Survey (KNHANES) revealed the synergistic effect of sarcopenia and obesity on the increased risk of albuminuria [12]. Another study indicated that both low muscle mass and central obesity independently predispose individuals to NAFLD and CVD [48]. Consistently, the CMM risk was the lowest in participants with co-existing non-obesity and high NCCR level in both genders of our study. Collectively, these observations underscore the importance of assessing skeletal muscle mass, which may offer valuable information beyond BMI, facilitating a more refined risk stratification for CMM in middle-age and older Asian populations, including those with a low BMI. One explanation is that low muscle mass, either independently or in conjunction with increased fat deposition, is hypothesized to promote β-cell exhaustion, resulting in early β-cell failure. This, subsequently, promotes insulin resistance and reduces insulin sensitivity [25]. Notably, the incidence of CMM appears to be more closely linked to obesity than NCCR levels in males, emphasizing the gender-specific contribution of fat mass and muscle mass in modulating CMM risks.

This study has some strength. Firstly, it is a national, representative and prospective study conducted in middle-aged and older Chinese adults and followed up for 4 years. Secondly, this is the first study to explore the longitudinal relationships between NCCR and incident CMM. There are also some limitations on this study. First of all, the study was conducted in Chinese population, which may limit the generalizability of our results to other ethics. Secondly, despite of the effort to adjust for a series of covariables, residual confounding could not be completely ruled out. Thirdly, the chronic diseases, such as CMM components and kidney disease were based on self-reported questionnaires, which may also have some degree of bias. Lastly, the occurrence of heart disease or stroke was primarily self-reported during recruitment and follow-up visits, and the exact timing of these events was not recorded. Similarly, diabetes was identified by a combination of self-reported diagnosis and serum detection of HbA1c and blood glucose levels. However, serum detection was only conducted in wave 1 and wave 3. This may have led to an underestimation of CMM incidence during wave 2, due to the infrequent measurement of serum markers for diabetes. These factors might have affected the accuracy of the Kaplan–Meier curve analysis and Cox analysis in our study.

In conclusion, this study reinforced the reliability of NCCR as a surrogate indicator for predicting the initiation and progression of CMM in the Chinese middle-aged and older population, particularly among females. Furthermore, our findings emphasize the importance of both reducing fat mass and enhancing muscle mass in mitigating the risk of CMM.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2024.0100.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conception or design: G.W., J.L.
Acquisition, analysis, or interpretation of data: H.S., Z.W.
Drafting the work or revising: H.S., Z.W., G.W., J.L.
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Supplementary Table 1. Cox regression analysis for the association between NCCR and risk of CMM

NCCR	Event/ Total	Model 1		Model 2		Model 3		Model 4	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Female									
Per SD increase	133/3,121	0.63 (0.51–0.78)	<0.001	0.65 (0.53–0.80)	<0.001	0.71 (0.58–0.87)	0.001	0.71 (0.58–0.87)	0.001
Tertile									
Lowest	76/1,038	Ref	-	Ref	-	Ref	-	Ref	-
Middle	30/1,042	0.40 (0.26–0.61)	<0.001	0.41 (0.27–0.62)	<0.001	0.46 (0.30–0.71)	<0.001	0.46 (0.29–0.71)	<0.001
Highest	27/1,041	0.38 (0.25–0.59)	<0.001	0.39 (0.25–0.60)	<0.001	0.45 (0.29–0.71)	0.001	0.45 (0.29–0.71)	0.001
Male									
Per SD increase	94/2,728	0.74 (0.58–0.94)	0.014	0.75 (0.59–0.96)	0.021	0.89 (0.69–1.14)	0.354	0.88 (0.68–1.14)	0.330
Tertile									
Lowest	37/908	Ref		Ref		Ref		Ref	
Middle	38/912	1.07 (0.68–1.69)	0.764	1.08 (0.69–1.71)	0.729	1.15 (0.72–1.83)	0.570	1.17 (0.73–1.87)	0.527
Highest	19/908	0.54 (0.31–0.94)	0.029	0.56 (0.32–0.98)	0.042	0.84 (0.47–1.48)	0.538	0.82 (0.46–1.48)	0.509

Model 1: crude model; Model 2: adjusted for age, education, marriage, residence, smoking, and drinking; Model 3: adjusted for model 2 plus visceral adiposity index, baseline estimated glomerular filtration rate, hypertension, dyslipidemia, kidney disease, baseline stroke, heart disease, and diabetes; Model 4: adjusted for model 3 plus handgrip strength.
NCCR, normalized creatinine-to-cystatin C ratio; CMM, cardiometabolic multimorbidity; HR, hazard ratio; CI, confidence interval; SD, standard deviation.

Supplementary Table 2. Cox regression analysis for the association between NCCR+BMI joint groups and risk of CMM

Variable	Event/ Total	Model 1		Model 2		Model 3		Model 4	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Female	133/3,121								
OB+LNCCR	57/661	Ref	-	Ref	-	Ref	-	Ref	-
OB+HNCCR	15/440	0.39 (0.22–0.69)	0.001	0.43 (0.24–0.77)	0.004	0.42 (0.23–0.75)	0.003	0.43 (0.24–0.78)	0.005
Non-OB+LNCCR	19/377	0.57 (0.34–0.95)	0.034	0.50 (0.29–0.84)	0.010	0.58 (0.34–0.99)	0.047	0.60 (0.35–1.02)	0.061
Non-OB+HNCCR	42/1,643	0.31 (0.21–0.46)	<0.001	0.29 (0.19–0.43)	<0.001	0.37 (0.24–0.56)	<0.001	0.37 (0.24–0.56)	<0.001
Male	94/2,728								
OB+LNCCR	25/386	Ref	-	Ref	-	Ref	-	Ref	-
OB+HNCCR	22/266	1.30 (0.73–2.30)	0.373	1.31 (0.73–2.33)	0.364	1.44 (0.79–2.63)	0.229	1.45 (0.79–2.66)	0.230
Non-OB+LNCCR	12/522	0.36 (0.18–0.71)	0.003	0.32 (0.16–0.65)	0.002	0.59 (0.28–1.22)	0.154	0.52 (0.25–1.10)	0.086
Non-OB+HNCCR	35/1,554	0.37 (0.22–0.61)	<0.001	0.35 (0.21–0.60)	<0.001	0.63 (0.36–1.10)	0.104	0.60 (0.34–1.05)	0.071

Model 1: crude model; Model 2: adjusted for age, education, marriage, residence, smoking, and drinking; Model 3: adjusted for model 2 plus visceral adiposity index, baseline estimated glomerular filtration rate, hypertension, dyslipidemia, kidney disease, baseline stroke, heart disease, and diabetes; Model 4: adjusted for model 3 plus handgrip strength.
NCCR, normalized creatinine-to-cystatin C ratio; BMI, body mass index; CMM, cardiometabolic multimorbidity; HR, hazard ratio; CI, confidence interval; OB, obese; LNCCR, low NCCR; HNCCR, high NCCR.

Supplementary Table 3. The association between NCCR and risk of each specific cardiometabolic disease combination

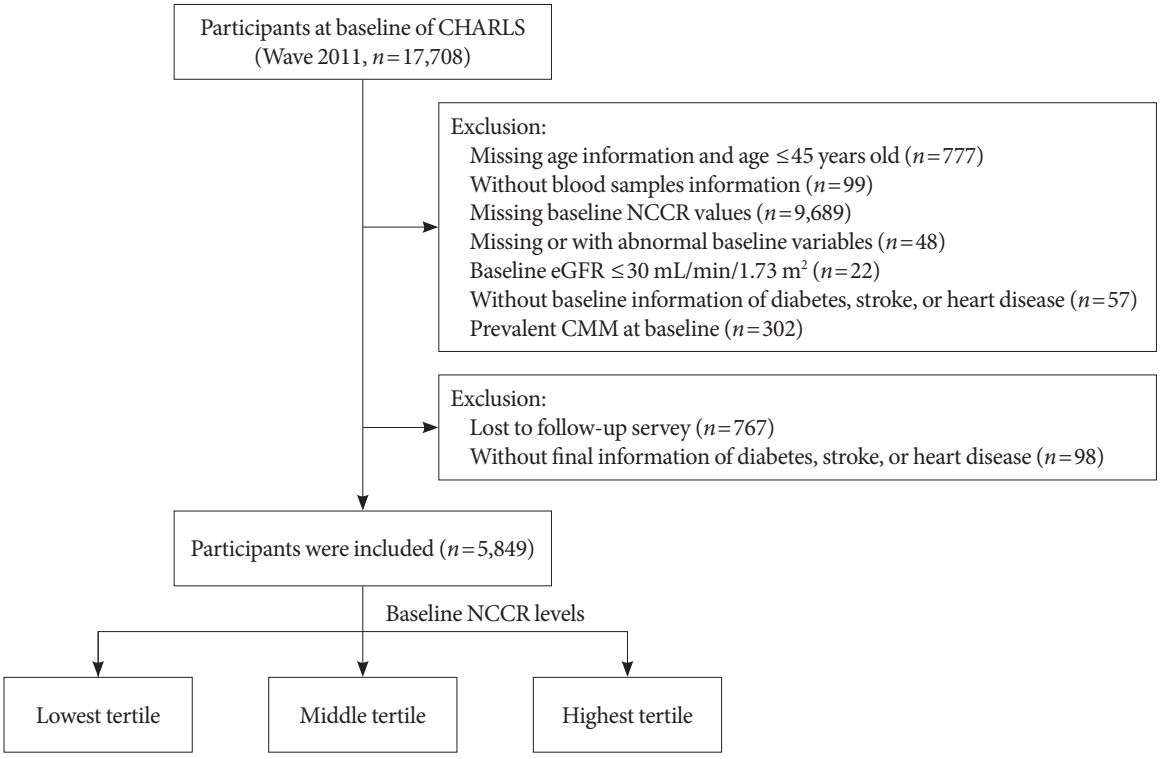
Variable	Lowest tertile	Middle tertile	Highest tertile	Per SD increase
Total	113/1,946	68/1,954	46/1,949	227/5,849
OR (95% CI)	1 (ref)	0.65 (0.47–0.90)	0.47 (0.32–0.68)	0.72 (0.62–0.85)
P value	-	0.010	<0.001	<0.001
Diabetes+stroke+heart disease	4/1,946	2/1,954	3/1,949	9/5,849
OR (95% CI)	1 (ref)	0.60 (0.10–3.65)	0.82 (0.16–4.23)	1.10 (0.58–2.06)
P value	-	0.581	0.813	0.773
Diabetes+stroke	12/1,946	9/1,954	6/1,949	27/5,849
OR (95% CI)	1 (ref)	0.78 (0.31–1.97)	0.46 (0.16–1.35)	0.73 (0.46–1.16)
P value	-	0.603	0.158	0.182
Stroke+heart disease	13/1,946	10/1,954	3/1,949	26/5,849
OR (95% CI)	1 (ref)	0.84 (0.35–2.02)	0.35 (0.10–1.27)	0.54 (0.31–0.92)
P value	-	0.691	0.110	0.024
Diabetes+heart disease	84/1,946	47/1,954	34/1,949	165/5,849
OR (95% CI)	1 (ref)	0.62 (0.42–0.90)	0.47 (0.30–0.72)	0.73 (0.61–0.88)
P value	-	0.013	<0.001	0.001

Model adjusted for age, gender, education, marriage, residence, smoking, drinking, visceral adiposity index, baseline estimated glomerular filtration rate, hypertension, dyslipidemia, kidney disease, baseline stroke, heart disease, diabetes, and handgrip strength.
NCCR, normalized creatinine-to-cystatin C ratio; SD, standard deviation; OR, odds ratio; CI, confidence interval.

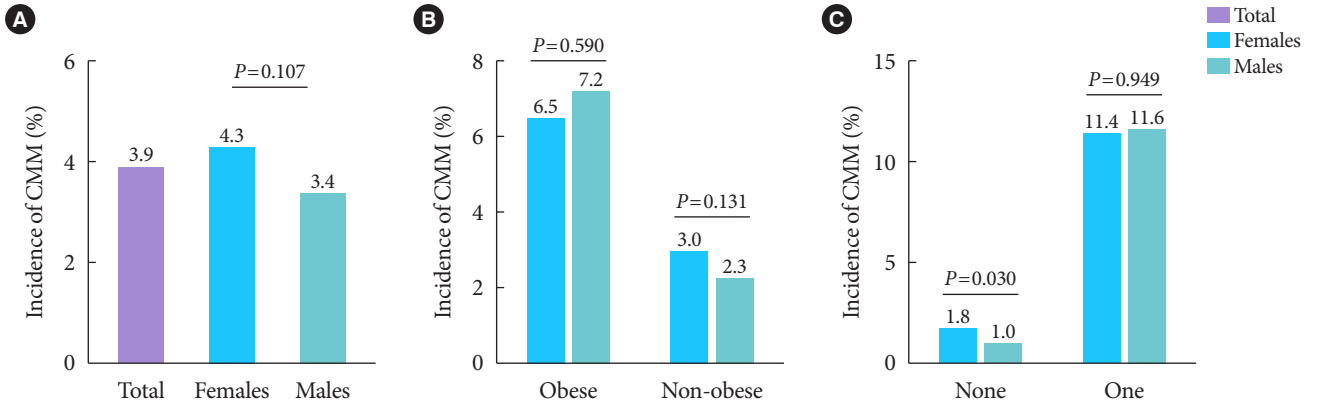
Supplementary Table 4. Subgroup analysis between the associations between normalized creatinine-to-cystatin C ratio and risk of CMM

Variable	Event/Total	Per SD increase	*P* value	*P* for interaction
Baseline CMM component				0.570
1	165/1,436	0.74 (0.61–0.90)	0.002	
0	62/4,413	0.67 (0.49–0.91)	0.010	
Age, yr				0.995
≥60	132/2,632	0.74 (0.60–0.92)	0.006	
<60	95/3,085	0.69 (0.53–0.90)	0.006	
Smoking				0.548
Yes	52/1,786	0.74 (0.52–1.05)	0.095	
No	175/4,043	0.71 (0.59–0.86)	<0.001	
Drinking				0.245
Yes	81/2,268	0.62 (0.45–0.84)	0.002	
No	146/3,579	0.78 (0.65–0.95)	0.012	
Residence				0.289
Rural	146/3,941	0.67 (0.54–0.83)	<0.001	
Urban	81/1,908	0.84 (0.65–1.08)	0.177	
Marriage				0.485
Yes	184/4,840	0.75 (0.62–0.89)	0.001	
Others	43/1,009	0.62 (0.42–0.92)	0.017	
Baseline hypertension				0.552
Yes	140/2,437	0.76 (0.61–0.93)	0.008	
No	87/3,412	0.67 (0.52–0.88)	0.004	
Baseline dyslipidemia				0.992
Yes	142/2,376	0.74 (0.60–0.91)	0.003	
No	85/3,473	0.73 (0.56–0.97)	0.028	
Baseline kidney disease				0.605
Yes	25/398	0.59 (0.34–1.02)	0.058	
No	201/5,430	0.75 (0.63–0.89)	0.001	

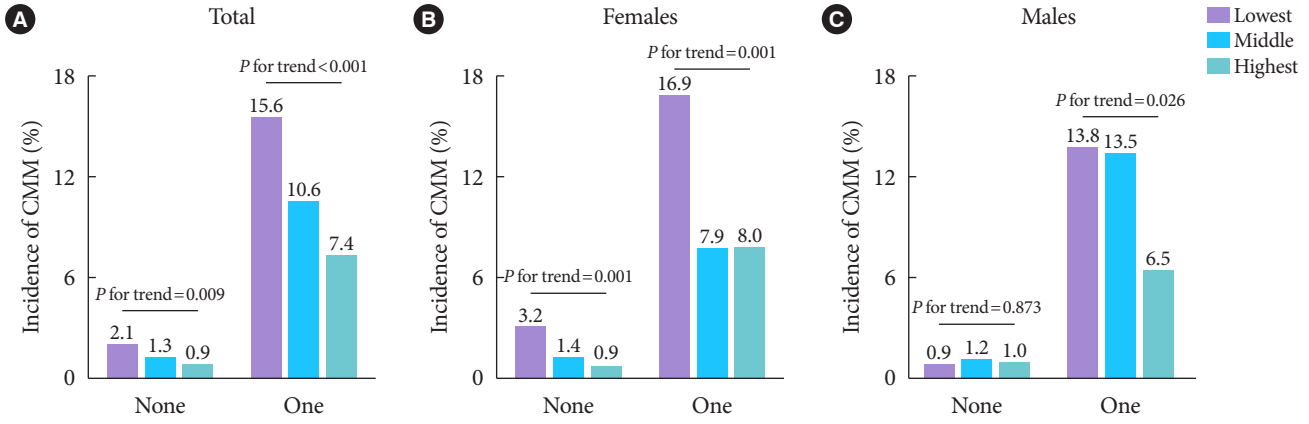
Values are presented as odds ratio (95% confidence interval). Model adjusted for age, gender, education, marriage, residence, smoking and drinking, visceral adiposity index, baseline estimated glomerular filtration rate, hypertension, dyslipidemia, kidney disease, baseline stroke, heart disease, diabetes, and handgrip strength.



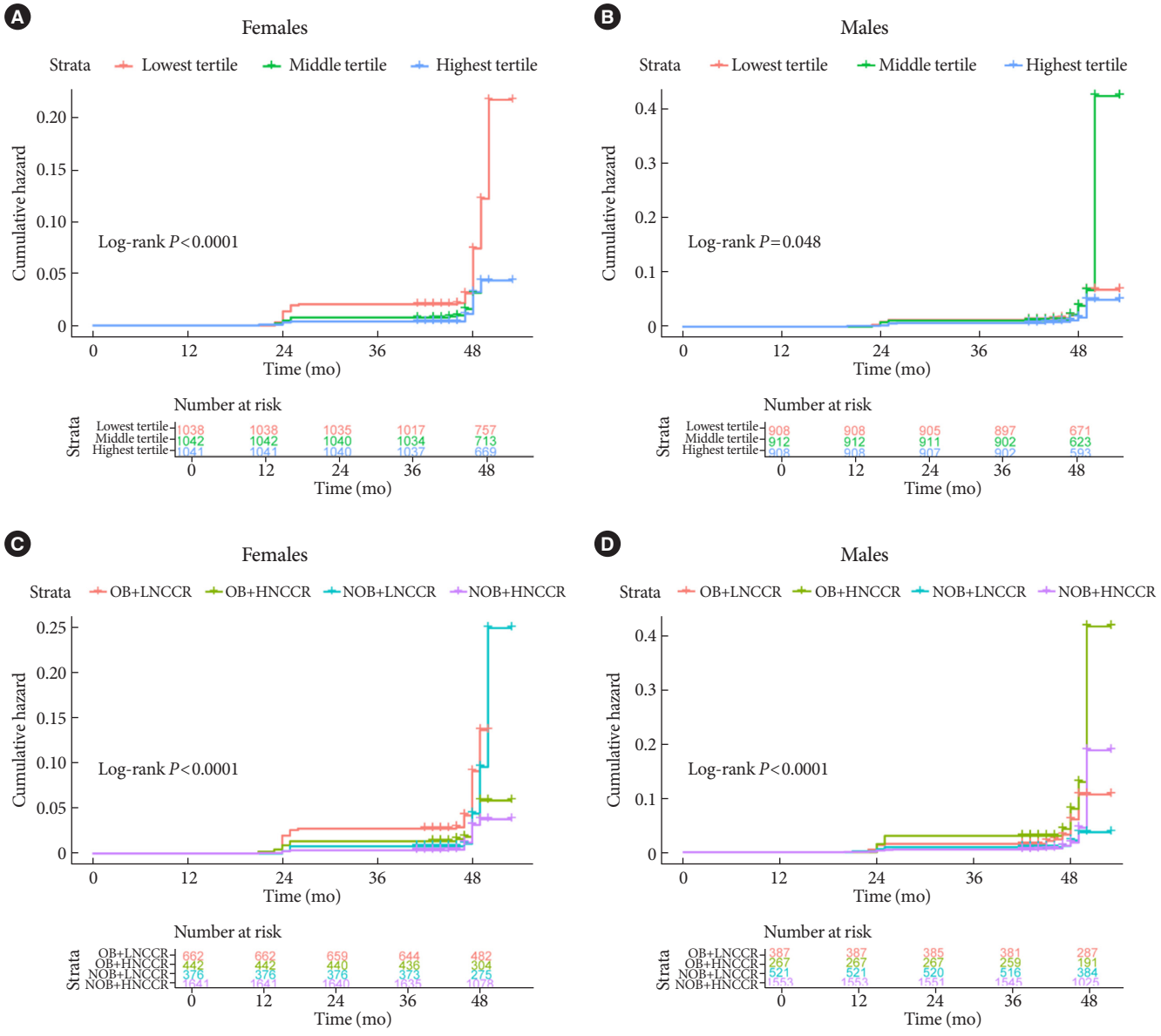
Supplementary Fig. 1. Flow chart of the study. CHARLS, China Health and Retirement Longitudinal Study; NCCR, normalized creatinine-to-cystatin C ratio; eGFR, estimated glomerular filtration rate; CMM, cardiometabolic multimorbidity.



Supplementary Fig. 2. The incidence of cardiometabolic multimorbidity (CMM) by genders. (A) The incidence of CMM in total participants by gender. (B) The incidence of CMM by gender in non-obese and obese participants. (C) The incidence of CMM by gender in participants with none or one cardiometabolic disease at baseline.



Supplementary Fig. 3. The incidence of cardiometabolic multimorbidity (CMM) by normalized creatinine-to-cystatin C ratio tertiles in participants with none or one cardiometabolic disease at baseline. (A) Total participants, (B) females, (C) males.



Supplementary Fig. 4. Kaplan–Meier curves for the cumulative incidence of cardiometabolic multimorbidity (CMM). (A) Cumulative CMM indicence by normalized creatinine-to-cystatin C ratio (NCCR) tertile in females. (B) Cumulative CMM indicence by NCCR tertile in males. (C) Cumulative CMM indicence by joint NCCR+body mass index (BMI) subgroups in females. (D) Cumulative CMM indicence by joint NCCR+BMI subgroups in males. OB, obese; LNCCR, low NCCR; HNCCR, high NCCR; NOB, non-OB.