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Role of sarcopenia in Temporal progression trajectory of cardiometabolic diseases: a prospective study in UK biobank

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Abstract

Background Although sarcopenia has been linked to a range of cardiometabolic diseases (CMDs, including coronary heart disease [CHD], stroke, and diabetes here), its role in the temporal progression from healthy to single CMD, subsequently to cardiometabolic multimorbidity (CMM, coexistence of ≥ 2 CMDs in an individual), and further to death remains unclear. In this study, we aimed to examine the associations of sarcopenia with the risk of CMDs, CMM, and mortality along the CMD progression trajectory.

Methods We used data from UK Biobank of 413,326 participants free of CMDs at baseline. Multi-state models were used to analyze the transition-specific associations of sarcopenia status measured by handgrip strength, muscle mass, and gait speed (according to the 2019 European Working Group of Sarcopenia in Older People 2) with the progression from no CMD to single CMD, CMM, and ultimately to death. The role of specific sarcopenia components was also assessed.

Results During a median follow-up of 13.1 years, 51,705 participants experienced ≥ 1 CMD, 6,003 had CMM, and 24,495 died. Compared with people free of sarcopenia, participants with confirmed/severe sarcopenia had higher risk experiencing transitions from no CMD to single CMD or death (hazard ratio [HR] 1.42 and 2.08) and also higher risk from single CMD to CMM progression or death (HR 1.69 and 2.05). Significant associations were observed for participants with probable sarcopenia with smaller effect sizes. All three sarcopenia components increased the risk of most transitions, and stronger associations were observed for low gait speed. In stratified analyses, the associations between sarcopenia and mortality-related transitions were modified by specific lifestyles.

Conclusions Sarcopenia is an independent risk factor of CMD, CMM progression, and all-cause mortality among middle-aged and older people.

Keywords Sarcopenia, Cardiometabolic diseases, Cardiometabolic Multimorbidity, UK biobank, Multi-state model

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Background

With the rapid population aging, cardiometabolic diseases (CMDs), a cluster of diseases including diabetes, coronary heart disease (CHD), and stroke, are becoming a rising public health burden worldwide. Owing to continued improvements in the management of chronic diseases, people are living longer with CMDs and are increasingly common to accumulate more than one of these conditions over a lifetime. Cardiometabolic multimorbidity (CMM), which refers to the co-occurrence of at least two CMDs in the same person, is one of the most common multimorbidity patterns [1–3] and affects an estimated 30% of older adults [4]. Compared with single CMD, CMM has a greater influence on adverse health-related outcomes [3]. For instance, a study demonstrated that patients with only one CMD had a life expectancy 6 to 10 years shorter than those without CMDs at age of 60 years, whereas patients with CMM had a life expectancy shorter by up to 15 years [3]. Considering the adverse health-related outcomes attributed to CMM, it is essential to identify potential risk factors and take efficient prevention measures to promote healthy aging.

Sarcopenia is now considered as an important risk factor for the development of chronic disease [5–7]. The recent consensus definition by the European Working Group on Sarcopenia in the Elderly 2 (EWGSOP2) in 2019 assists in the clinical recognition of sarcopenia in several ways [8–9]. Firstly, it proposed recommended cut-off points for low muscle strength and low muscle mass. Second, it introduces the concept of "probable sarcopenia", which means low muscle strength resulting in poor performance on grip strength or chair rise tests, as a basis for initiating intervention when muscle mass cannot be assessed. Finally, it emphasizes that sarcopenia is predominantly an age-related condition, but is also thought to occur at a young age following long-term conditions [10]. Up to date, a limited number of evidence confirms that both possible sarcopenia and sarcopenia are associated with the risk of CMDs. However, existing studies mainly focused on single CMDs and the link between sarcopenia and CMM is poorly understood. Furthermore, prior studies mainly investigated the impact of sarcopenia on the development or prognosis of single CMDs in separate analyses [5–7, 11–12], limiting the ability to assess and compare the roles of sarcopenia in the temporal trajectories of CMM including transitions from free of CMD to single CMD, subsequently to CMM and finally to death. Despite increasing awareness of deleterious effect of sarcopenia on single CMDs, appreciation of its effect on the incidence, progression, and prognosis of CMM simultaneously is still scarce, which is of great importance for the evidence-based prevention and intervention of CMDs and CMM.

We therefore conducted this study based on UK Biobank cohort with multi-state models to investigate the associations of sarcopenia with transitions from free of CMD to single CMD, to CMM, and further to death.

Methods

Study population and design

The current study was based on UK Biobank, a large-scale prospective cohort of over 500,000 participants aged 40–69 years from U.K., which has been described in detail previously [13]. Since 2006, UK Biobank regularly collected detailed information of participants through touchscreen questionnaire, verbal interview, physical measurements, and biological sampling and accessed a series of electrical records to derive health-related outcomes. UK Biobank have obtained informed consents from participants and were approved by the North West Multi-centre Research Ethics Committee (updated ref 21/NW/0157, 18 June 2021).

Data from 502,133 participants was available. We included participants without CMD history (detailed definition in Table S1) at recruitment ($n = 446{,}703$), and those who had missing information in sarcopenia measurements ($n = 10{,}092$), covariates ($n = 23{,}278$), or outcome date ($n = 7$) were excluded, leaving 413,326 participants remained.

Assessment of sarcopenia

Sarcopenia status was defined according to decline in muscle strength (grip strength), mass (appendicular lean mass [ALM]), and function (gait speed) according to the 2019 European Working Group on Sarcopenia in Older People 2 (EWGSOP2) [8–9]. In UK Biobank, grip strength of both hands was measured using a Jamar J00105 hydraulic hand dynamometer. Participants were required to hold the dynamometer against their side and bent to a 90° angle and the maximum value for each hand was recorded. For estimation of grip strength in sarcopenia assessment, the maximum value of both hands was used. Low grip strength was defined as a grip strength < 16 kg (female) or < 27 kg (male), and participants who skipped the measurement because of health problems were also considered with low grip strength [10].

Appendicular fat-free mass (AFM, kg) was calculated as the summed values of fat-free mass of limbs which were estimated by impedance measurement with Tanita BC418MA body composition analyzer. ALM (kg) was estimated according to AFM values as: $\mathrm{ALM} = (0.958 \times \mathrm{ALM}) - (0.166 \times \mathrm{G}) - 0.308$, in which G = 0 for female and 1 for male [10]. Standing height (m) was measured using a Seca 202 device, and we used ALM adjusted by height squared to define low

muscle mass as <7 kg/m^2 for male and 5.5 kg/m^2 for female according to the EWGSOP2 definition [8–9].

Participants who had low grip strength were firstly considered with "probable sarcopenia", irrespective of measurements of muscle mass. For those with low grip strength and low muscle mass, they were considered with "confirmed sarcopenia". There was no objective measurement of gait speed available in UK Biobank, so we used the self-report walking speed obtained via touchscreen questionnaires. Participants were asked "How would you describe your usual walking pace?", and those who were unable to walk or walked at a slow pace were defined with low physical performance [14]. Participants who satisfied all criteria were diagnosed with "severe sarcopenia". Because of the limited sample size of people who had severe sarcopenia ($n=312$, 0.08%), participants with confirmed or severe sarcopenia were combined as a group with confirmed/severe sarcopenia in the following analyses.

Ascertainment of CMDs, CMM, and death

We ascertained the occurrences of CMDs including CHD, stroke, and diabetes based on electrical inpatient diagnosis and operation codes (details shown in Table S1). The incidence of diseases during follow-up was determined by comparing the corresponding diagnosed date with date at recruitment, and CMM outcome was defined with the co-occurrence of at least 2 CMDs during follow-up. The date of single CMD and CMM was ascertained according to the diagnosed date of the first and second CMD. For the ascertainment of mortality, UK Biobank derived related event, date, and causes by linking to the National Health serves across U.K., and the latest follow-up was ended in April 2022 [13].

Assessment of covariates

Covariates were assessed according to the baseline touchscreen questionnaires, verbal interview, and physical measurements of UK Biobank, including information in demographic (sex, age, race, Townsend Deprivation Index [TDI], weight), lifestyle (diet, smoking history, alcohol consumption, physical activity levels, and sleep duration), and clinical factors (hypertension history). The definition of covariates above is presented in Table S2 in details.

Statistical analysis

The baseline characteristics of participants were presented in categorization of sarcopenia status. Continuous variates with normal distribution were expressed as mean (standard deviation [SD]), and those with abnormal distribution were expressed as median (interquartile range [IQR]). Categorical variates were expressed as number (percentage, %).

Considering the theoretical progression process of CMDs [2], we assumed that participants without CMDs at baseline might experience various transitions along the progression trajectory from no CMD to single CMD, subsequent CMM, and death. Unidirectional multi-state models with Markov assumption, extended from competing risk statistical models [15], were used to estimate the transition-specific role of sarcopenia status along the progression trajectory of CMDs. Multi-state models were developed using R package mstate [16]. Four different states with five transitions were designed in the multi-state models as the following: (a) no CMD– first single CMD; (b) no CMD– death; (c) first single CMD– CMM; (d) first single CMD– death; (e) CMM– death. Since the occurrence and date of diseases were ascertained according to inpatient diagnosis records, some participants might experience two distinct states at the same timepoint (i.e., overlapping, $n=3{,}447$). For those with overlapping states, their date of the conceptually prior state was calculated as the recorded date minus 0.5 day. In the multi-state models, we set age as time scale, and designed two adjustment settings: model 1: sex, race, and weight were adjusted; model 2: TDI, diet, smoking status, alcohol consumption, physical activity levels, sleep duration, and hypertension history were additionally adjusted. The exposure, sarcopenia status, was firstly entered in the model as a categorical variable: no sarcopenia (reference), probable sarcopenia, and confirmed/severe sarcopenia. Then the fulfilled number of sarcopenia components was entered as a continuous variable to estimate the dose-dependent association, and the role of specific sarcopenia components including low handgrip strength, low muscle mass, and low gait speed were also estimated as binary variables.

To investigate whether healthy lifestyles modified the adverse role of sarcopenia, we further conducted stratified analyses based on multi-state models according to healthy diet (no or yes), smoking status (never/previous or current), alcohol consumption (<3 times/week or ≥ 3 times/week), sleep duration (<7 or >8 h/day or 7–8 h/day), and physical activity (meeting guidelines or not). Likelihood ratio tests were used to assess the interaction. We also performed sensitivity analyses to confirm the robustness of our analyses. First, we removed people who experienced morbidity or mortality outcomes during the first two years of follow-up to account for potential reverse causality. Second, we additionally adjusted for sedentary duration per day and family history of CMDs. Third, we excluded people who arrived at two distinct states at the same timepoint. Finally, we modified the date calculation of those who arrived two distinct states at the same timepoint to minus1.0 day.

Table 1 Baseline characteristics according to sarcopenia status at baseline

Characteristics	Overall	Sarcopenia Status [a]		
		No sarcopenia	Probable	Confirmed/severe
Participants, No. (%)	413,547	395,219 (95.6)	17,568 (4.2)	760 (0.2)
Age (years), mean (SD)	56.51 (8.08)	56.35 (8.08)	59.93 (7.30)	62.27 (6.55)
Male, No. (%)	179,470 (43.4)	173,270 (43.8)	5710 (32.5)	490 (64.5)
White, No. (%)	395,010 (95.5)	378,149 (95.7)	16,209 (92.3)	652 (85.8)
Townsend Deprivation Index, median (IQR)	-2.27 (-3.71, 0.22)	-2.30 (-3.72, 0.18)	-1.71 (-3.38, 1.17)	-0.19 (-2.63, 2.95)
Body mass index (kg/m^2), mean (SD)	27.05 (4.55)	27.03 (4.53)	27.21 (4.81)	32.60 (6.37)
Healthy diet, No. (%)	232,678 (56.3)	222,158 (56.2)	10,144 (57.7)	376 (49.5)
Current smoking, No. (%)	41,415 (10.0)	39,609 (10.0)	1752 (10.0)	54 (7.1)
Alcohol consumption ≥ 3 times/week, No. (%)	187,071 (45.2)	180,722 (45.7)	6110 (34.8)	239 (31.4)
Meeting physical activity guidelines, No. (%)	320,958 (77.6)	307,882 (77.9)	12,576 (71.6)	500 (65.8)
Sleep duration (hours/day), mean (SD)	7.15 (1.06)	7.15 (1.04)	7.15 (1.30)	7.24 (1.53)
Hypertension history, No. (%)	91,286 (22.1)	86,052 (21.8)	4884 (27.8)	350 (46.1)

Notes: [a] Sarcopenia at baseline were ascertained according to the 2019 European Working Group of Sarcopenia in Older People 2. Since the limited sample size, participants with confirmed or severe sarcopenia were combined as a category

SD means standard deviation; IQR means interquartile range

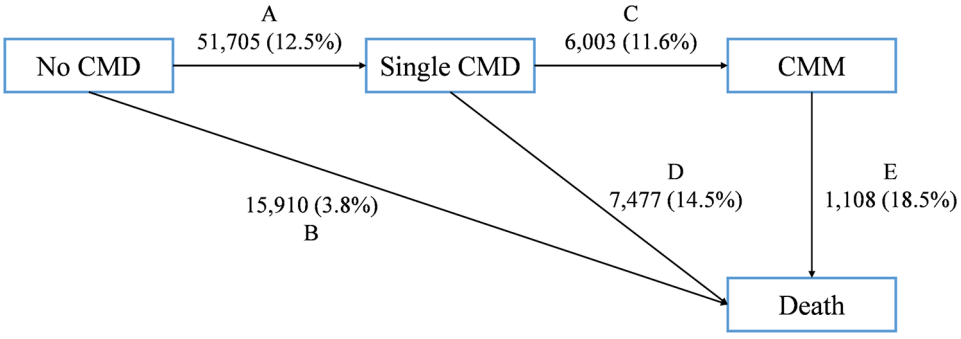

Fig. 1 Graphic scheme of temporal progression trajectory of CMD in multistate model. Note: Multistate model with 4 states and 5 transitions. The numbers (percentages) of participants experiencing each transition are labeled. A total of 413,326 participants were included at the initial state at baseline. No CMD, without coronary heart disease, stroke, and diabetes; CMD, cardiometabolic disease (defined by coronary heart disease, stroke, and diabetes in this study); CMM, cardiometabolic multimorbidity

All analysis were conducted using R software (V.4.1.0). P values were two-sided, and statistical significance was reached when $P < 0.05$.

Results

Descriptive analyses

Baseline characteristics according to sarcopenia status at baseline are shown in Table 1. The mean age (SD) of 413,326 participants included was 56.51 (8.08) years, with 179,387 (43.4%) male and 394,811 (95.5%) white. 395,010 (95.6%) people didn't have sarcopenia, 16,619 (4.0%) people had probable sarcopenia, and 1,697 (0.4%) had confirmed/severe sarcopenia. Compared with people free of sarcopenia, patients with either probable or confirmed/severe sarcopenia were prone to be older, and non-white. They were more likely to have hypertension history, higher TDI and BMI, lower alcohol consumption frequency and physical activity levels.

During a median follow-up of 13.10 years, 51,705 (12.5%) participants experienced CMDs, and 15,910 (3.8%) died without CMD. Among participants with CMDs, 6,003 (11.6%) developed CMM further, and 7,477 (14.5%) died with single CMD. In addition, 1,108 participants experienced the whole trajectory of CMD progression from no CMD to single CMD, to CMM, and death ultimately (Fig. 1).

Multi-state model

The associations of sarcopenia status with specific transitions of CMD progression trajectory are presented in Table 2. Overall, compared with people free of sarcopenia, patients with sarcopenia status had an accelerated trajectory of CMD progression to ultimate death, irrespective of sarcopenia degrees. For transitions from no CMD, probable sarcopenia was associated with higher risk of the first CMD (hazard ratio [HR] 1.39, 95% confidence interval [CI] 1.34–1.44) and death (HR 1.29, 95% CI 1.21–1.38), while the HRs of confirmed/severe sarcopenia were 1.42 (95% CI 1.25–1.62) for first CMD and 2.08 (95% CI 1.78–2.42) for death. Among patients

Table 2 Association between sarcopenia and specific transition of cmds progression in multi-state models

Transitions	Sarcopenia status [a]	Initial model [b]			Full-adjusted model [c]		
		HR	95% CI	*P*	HR	95% CI	*P*
No CMD to single CMD	No sarcopenia	Reference			Reference		
	Probable sarcopenia	1.49	(1.44; 1.55)	< 0.001	1.39	(1.34; 1.44)	< 0.001
	Confirmed/severe sarcopenia	1.56	(1.38; 1.77)	< 0.001	1.42	(1.25; 1.62)	< 0.001
	Per 1 additional trait [d]	1.48	(1.46; 1.51)	< 0.001	1.37	(1.34; 1.39)	< 0.001
No CMD to death	No sarcopenia	Reference			Reference		
	Probable sarcopenia	1.35	(1.26; 1.44)	< 0.001	1.29	(1.21; 1.38)	< 0.001
	Confirmed/severe sarcopenia	2.32	(1.99; 2.71)	< 0.001	2.08	(1.78; 2.42)	< 0.001
	Per 1 additional trait	1.62	(1.58; 1.67)	< 0.001	1.51	(1.46; 1.55)	< 0.001
Single CMD to CMM	No sarcopenia	Reference			Reference		
	Probable sarcopenia	1.35	(1.23; 1.48)	< 0.001	1.29	(1.17; 1.42)	< 0.001
	Confirmed/severe sarcopenia	1.80	(1.27; 2.54)	< 0.001	1.69	(1.20; 2.39)	0.003
	Per 1 additional trait	1.31	(1.25; 1.37)	< 0.001	1.23	(1.18; 1.30)	< 0.001
Single CMD to death	No sarcopenia	Reference			Reference		
	Probable sarcopenia	1.34	(1.22; 1.46)	< 0.001	1.31	(1.20; 1.43)	< 0.001
	Confirmed/severe sarcopenia	2.22	(1.75; 2.81)	< 0.001	2.05	(1.62; 2.61)	< 0.001
	Per 1 additional trait	1.46	(1.40; 1.52)	< 0.001	1.39	(1.33; 1.45)	< 0.001
CMM to death	No sarcopenia	Reference			Reference		
	Probable sarcopenia	1.26	(1.02; 1.55)	0.030	1.22	(0.99; 1.51)	0.062
	Confirmed/severe sarcopenia	1.80	(0.89; 3.63)	0.102	1.75	(0.87; 3.54)	0.119
	Per 1 additional trait	1.42	(1.29; 1.56)	< 0.001	1.34	(1.22; 1.49)	< 0.001

Notes: Results were generated in multi-state models. In all models, age was included as the time scale

[a] Sarcopenia at baseline were ascertained according to the 2019 European Working Group of Sarcopenia in Older People 2. Since the limited sample size, participants with confirmed or severe sarcopenia were combined as a category

[b] Initial model: adjusted for sex, race, and weight

[c] Full-adjusted model: further adjusted for Townsend Deprivation Index, diet, smoking status, alcohol consumption frequency, meeting physical activity guidelines, sleep duration, and hypertension at baseline

[d] HRs for per one additional fulfilled component in measurement of sarcopenia

CMD means cardiometabolic disease (defined by coronary heart disease, stroke, and diabetes in this study); CMM means cardiometabolic multimorbidity; HR means hazard ratio; CI means confidence interval

with the first CMD, those with confirmed/severe sarcopenia had a higher risk of CMM progression (HR 1.69, 95% CI 1.20–2.39) and 2 times higher risk of death (HR 2.05, 95% CI 1.62–2.61), and similar patterns were also observed for probable sarcopenia. And for transition from CMM to death, similar but non-significant trend was observed for probable sarcopenia (HR 1.22, 95% CI 0.99–1.51) and confirmed/severe sarcopenia (HR 1.75, 95% CI 0.87–3.54). When the number of fulfilled sarcopenia components was included as a continuous variable, per component increment was significantly associated with all transitions in the multi-state models.

We further investigated the specific role of sarcopenia components in multi-state models. All three sarcopenia components increased the risk of most transitions, and the strongest association was observed for low gait speed (Table 3). It increased the risk of morbidity or mortality outcomes (HRs 1.29–1.90), affecting participants without CMD most (HR 1.59, 95% CI 1.54–1.63 for no CMD to single CMD; HR 1.90, 95% CI 1.80-2.00 for no CMD to death). The role of low handgrip strength was observed in transitions except for CMM to death, with a transition-specific HR varying from 1.23 to 1.29. For low muscle mass, significant associations existed for transitions from no CMD to single CMD, to death, and from single CMD to death.

Stratified and sensitivity analyses

The results of stratified analyses are presented in Figure S1 to S5, and the interactions between sarcopenia and lifestyles were transition-specific across the CMD progression trajectory. For participants without CMDs, the role of sarcopenia in the progression of death was modified by diet heath ($P_{interaction}$ = 0.033), smoking status ($P_{interaction}$ = 0.002), and physical activity levels ($P_{interaction}$ <0.001). People who were currently smoking, had unhealthy diet or didn't have adequate physical activity had higher sarcopenia-related risk of death. Among patients with single CMD, the associations between sarcopenia and death risk were modified by diet, smoking status, alcohol consumption frequency, and sleep duration (all $P_{interaction}$ <0.001). In addition, for the transition from CMM to death, the effect sizes were modified by alcohol consumption ($P_{interaction}$ = 0.001), while no interactive effects were observed for transitions with morbidities as the outcome.

Table 3 Association between sarcopenia components and specific transition of cmds progression in multi-state models

Transitions	Sarcopenia components	Initial model [a]			Full-adjusted model [b]		
		HR	95% CI	*P*	HR	95% CI	*P*
No CMD to single CMD	Low handgrip strength [c]	1.35	(1.30; 1.39)	< 0.001	1.29	(1.24; 1.33)	< 0.001
	Low muscle mass [d]	1.09	(1.04; 1.13)	< 0.001	1.08	(1.03; 1.12)	< 0.001
	Low gait speed [e]	1.83	(1.78; 1.88)	< 0.001	1.59	(1.54; 1.63)	< 0.001
No CMD to death	Low handgrip strength	1.25	(1.18; 1.33)	< 0.001	1.23	(1.16; 1.31)	< 0.001
	Low muscle mass	1.41	(1.32; 1.49)	< 0.001	1.36	(1.28; 1.44)	< 0.001
	Low gait speed	2.20	(2.09; 2.31)	< 0.001	1.90	(1.80; 2.00)	< 0.001
Single CMD to CMM	Low handgrip strength	1.27	(1.16; 1.40)	< 0.001	1.24	(1.13; 1.37)	< 0.001
	Low muscle mass	1.05	(0.92; 1.21)	0.461	1.04	(0.90; 1.20)	0.610
	Low gait speed	1.40	(1.31; 1.51)	< 0.001	1.29	(1.20; 1.38)	< 0.001
Single CMD to death	Low handgrip strength	1.25	(1.15; 1.36)	< 0.001	1.26	(1.16; 1.37)	< 0.001
	Low muscle mass	1.47	(1.34; 1.62)	< 0.001	1.39	(1.26; 1.53)	< 0.001
	Low gait speed	1.62	(1.52; 1.72)	< 0.001	1.49	(1.40; 1.60)	< 0.001
CMM to death	Low handgrip strength	1.11	(0.90; 1.36)	0.333	1.12	(0.91; 1.38)	0.295
	Low muscle mass	1.33	(1.00; 1.77)	0.054	1.25	(0.94; 1.67)	0.129
	Low gait speed	1.67	(1.44; 1.94)	< 0.001	1.54	(1.32; 1.79)	< 0.001

Notes: Results were generated in multi-state models. In all models, age was included as the time scale

[a] Initial model: adjusted for sex, race, and weight

[b] Full-adjusted model: further adjusted for Townsend Deprivation Index, diet, smoking status, alcohol consumption frequency, meeting physical activity guidelines, sleep duration, and hypertension at baseline

[c] Low handgrip strength: maximum handgrip strength < 27 kg in male and < 16 kg in female. Participants who were unable to perform grip strength measurements because of health reasons were also considered with low handgrip strength

[d] Low muscle mass: appendicular lean mass adjusted for height^2 < 7 kg/m^2 in male and < 5.5 kg/m^2 in female

[e] Low gait speed: self-reported being unable to walk or their walking pace as 'slow'

CMD means cardiometabolic disease (defined by coronary heart disease, stroke, and diabetes in this study); CMM means cardiometabolic multimorbidity; HR means hazard ratio; CI means confidence interval

We conducted several sensitivity analyses to test the robustness of our results (Table S3-S6). After excluding 6,789 participants who reported CMDs or death during the first two years of follow-up (sensitivity analysis 1), further adjusting for sedentary duration and family history of CMDs (sensitivity analysis 2), excluding 1,338 participants who arrived at two states simultaneously (sensitivity analysis 3), or modifying the date calculation for participants with overlapped timepoints (sensitivity analysis 4), we observed results consistent with the main analyses.

Discussion

In this prospective study, we systematically evaluated the role of sarcopenia in the temporal progression trajectories of CMD based on UK Biobank. We found that compared with people without sarcopenia, those with confirmed or severe sarcopenia had higher risk experiencing transitions from no CMD to single CMD or death (HRs 1.42 and 2.08) and also higher risk from single CMD to CMM progression or death (HRs 1.69 and 2.05). For the number of fulfilled components of sarcopenia assessment, a dose-dependent relationship was observed in all transitions of CMD progression. All sarcopenia components were associated with an increased risk of most transitions of CMD progression, and the strongest association was observed for low gait speed. According to stratified analyses, the interactions between sarcopenia and healthy lifestyles were transition-specific across the CMD progression trajectory.

The negative impacts of sarcopenia on the temporal trajectory of CMD progression observed in this study were generally in line with previous results in single conditions. For example, a recent analysis based on the China Health and Retirement Longitudinal Study (CHARLS) demonstrated that both possible sarcopenia and sarcopenia, assessed using the Asian Working Group for Sarcopenia in 2019 criteria, were associated with a higher CVD risk among middle-aged and older Chinese adults [5], and another longitudinal study indicated that sarcopenia and components of sarcopenia were associated with greater CVD and all-cause mortality in suburb-dwelling older Chinese people [17], which were consistent with the increased risk for the transitions from no CMD to single CMD and to death observed in this study. However, these studies merely focused on single condition, and failed to examine the impacts of sarcopenia on different transition conditions of the whole progression course of CMDs. In addition, these studies did not consider the competing risk of death. As sarcopenia is an important predictor of mortality from CMDs and other causes [18–19], simply regarding those who died from CMD-free or single CMD during follow-up as censored might cause a deviation of the morbidity risk related to sarcopenia [20]. Hence, we

used the multi-state model, an extended model considering both competing risk and the various transitions of disease. As mentioned before, the multi-state model has only been applied to identify the impacts of several risk factors on the progression of CMM, including lifestyle, clinical, environmental and behavioral factors [1–2, 21–22], but not sarcopenia. To our knowledge, this study is the first to assess the associations of sarcopenia with CMD progression with applying advanced multi-state model.

Our findings have significant public health implications. First, we examined significant associations between sarcopenia and CMDs. Although the HRs associated with sarcopenia are relatively smaller than some conventional risk factors of CMDs such as lifestyle factors [1, 22], the medical burden attributable to sarcopenia is estimated to be very high in the near further due to the population aging around the world. Second, with multi-state model, we found that sarcopenia had non-negligible influences on the transition from no CMD to single CMD that had been well studied previously [23], as well as on the transition further to CMM that had not yet been explored before. Considering the excess risk of morbidity and mortality of CMM related to sarcopenia especially in low gait speed, it might be advisable to introduce CMD-targeted prevention and management for patients with existing sarcopenia. Third, we found that sarcopenia-related mortality risk was modified by lifestyles. Among participants without CMDs, stronger effect sizes were observed for those with unhealthy diet, current smoking status, and lower physical activity. For patients who already had CMDs, interactions with clinical significance existed for sleep duration and alcohol consumption frequency, and people who had sleep duration during 7–8 h/day or alcohol consumption ≥ 3 times/week were more susceptible. Overall, our findings suggest that adopting healthy lifestyles might protect people with sarcopenia severity to attenuate mortality risk, especially for those without CMDs.

Our study shows some strengths. The chief one lies in the use of multi-state models, which allows us to assess the association of sarcopenia with each transition along CMD progression trajectory simultaneously, accounting for the competing risk from death. Additionally, we excluded participants who reported CMDs or death during the first two years of follow-up, tried adjustments for sedentary duration and family history of CMDs, excluded participants who arrived at two states simultaneously, and modified the date calculation for participants with overlapped timepoints. None of these sensitivity analyses altered the results significantly. Finally, the UK Biobank's extensive collection of individual-level data on lifestyle and sociodemographic features enabled us to account for multiple confounding factors to estimate the role of sarcopenia.

Indeed, our study also presents several limitations. Firstly, participants of UK Biobank were mostly white and not entirely representative, and the prevalence of sarcopenia status (total 4.4%, including probable and confirmed/severe) in this study was obviously lower than that of community-dwelling population in published data [24], as the "healthy volunteer bias" suggested [25]. Therefore, our findings possess uncertain generalizability when extrapolated to populations of other regions and races. Secondly, self-reported information in gait speed was used to assess sarcopenia trait, since there was no objective measurement of gait speed available in UK Biobank. Even though these measurements have been verified previously [26], we admit the existence of self-report bias, which limited the interpretation of the public health implications of this study. Thirdly, sarcopenia and other variables in this study were measured at baseline, and possible changes afterwards were not accounted for. Since sarcopenia is dynamic, temporal changes in sarcopenia status during follow-up were not captured, and considering the facts that muscle mass reduced by about 1–2% every year after age 50 and gait speed also decreased with age [24, 27], it was more common to become worse, rather than relieved. Accordingly, it may lead to an underestimation of the magnitude of sarcopenia-related associations in this study. Fourthly, limited by sample size and low prevalence of sarcopenia in this study, we did not consider occurrences and combination of specific diseases in analyses, and couldn't rule out that sarcopenia might have different associations with specific CMDs and CMM patterns. Finally, the observational nature of our study precluded causal inference, and the casual roles of modifiable sarcopenia in the prognosis of CMDs need further study.

Conclusion

In conclusion, sarcopenia was associated with increased risk of temporal progression from a healthy condition to single CMD, CMM, and death, indicating the importance of targeting sarcopenia in the primary and secondary prevention of CMM. Furthermore, sarcopenia-related mortality risk was modified by certain lifestyles across the CMD progression trajectory.

Abbreviations

CHD	Coronary heart disease
CMD	Cardiometabolic disease
CMM	Cardiometabolic multimorbidity
CVD	Cardiovascular disease
T2D	Type 2 diabetes
SD	Standard deviation
EWGSOP2	European Working Group on Sarcopenia in Older People 2

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-025-22500-1.

Supplementary Material 1

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Author contributions
YX: Data curation, Formal analysis, Writing-original draft. CZ: Formal analysis, Writing-original draft. XC: Data curation, Writing-review & editing. QH: Writing-review & editing, Visualization. TM: Conceptualization, Formal analysis, Writing-review & editing, Supervision. YB: Conceptualization, Writing-review & editing, Supervision.

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Data availability
The data that support the findings of this study are available from UK Biobank but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the website https://www.ukbiobank.ac.uk/ upon reasonable request and with permission of UK Biobank.

Declarations

Ethics approval and consent to participate
This research was conducted using UK Biobank Resource under project number 84443. The UK Biobank has been approved by the North West Multicentre Research Ethics Committee as a Research Tissue Bank, and separate ethical clearance is not required for researchers under this approval (updated ref 21/NW/0157, 18 June 2021). All participants of UK Biobank have provided written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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