Physical capability markers used to define sarcopenia and their association with cardiovascular and respiratory outcomes and all-cause mortality: A prospective study from UK Biobank

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Abstract

Introduction- It is unclear whether a different combination of physical capability markers used to define sarcopenia results in a stronger association with health outcomes. Aim: To compare the associations between different combinations of physical capability markers of sarcopenia with cardiovascular and respiratory outcomes and all-cause mortality.

Study design- 469,830 UK Biobank participants were included in this prospective study. Four groups were derived based on combinations of three physical capability markers used to define sarcopenia or severe sarcopenia: gait speed, grip strength and muscle mass. Outcomes studied were all-cause mortality, as well as incidence and mortality from cardiovascular disease (CVD), respiratory disease and chronic obstructive pulmonary disease (COPD).

Results- All combinations of physical capability markers used to define sarcopenia or severe sarcopenia identified individuals at increased risk of respiratory disease and all-cause mortality. However, the definition most strongly associated with a wide range of adverse health outcomes was the combination of slow gait speed plus low muscle mass, followed by severe sarcopenia, and the combination of slow gait speed plus low grip strength. The current definition of sarcopenia (low grip strength plus low muscle mass) had the weakest associations with all-cause (HR: 1.35 [95% CI: 1.07 to 1.71]) and respiratory mortality (HR: 1.88 [95% CI: 1.15 to 3.10]), as well as respiratory disease (HR:1.38 [95% CI: 1.11 to 1.73]) and COPD incidence (HR:2.08 [95% CI: 1.14 to 3.79]).

Conclusions- Associations of sarcopenia with adverse outcomes were strongest when sarcopenia was defined as slow gait speed plus low muscle mass, followed by severe sarcopenia, suggesting that this combination of physical capability markers should be still considered in the diagnosis of sarcopenia.

Keywords: mortality; incidence; muscle strength; EWGSOP2

1. Introduction

Low grip (muscle) strength, low muscle mass and slow walking pace (gait speed) have been shown to be strong independent predictors of morbidity and mortality in middle-aged and old-aged populations [1-3]. These markers of physical capability are all known to decline after the age of ~35 years, and with the rapid growth of ageing populations, the number of individuals with low levels of physical capability is also expected to be increased rapidly. This, in turn, will increase the number of people who are at higher risk of developing non-communicable diseases [4]. Although markers of physical capability are generally investigated in isolation, combinations of these predictors are used to define conditions, such as sarcopenia. In 1989, Irwin Rosenberg was the first to recognise the age-related decline in lean body mass and coined the term "sarcopenia" (from the Greek 'sarx' for flesh + 'penia' for loss) [5, 6]. Nowadays, sarcopenia is defined as a complex syndrome characterised by a progressive loss of muscle strength along with a higher risk of disability and reduction in quality of life [7] and it is one of the 150 musculoskeletal conditions that contribute to disability worldwide [8]. Furthermore, the International Classification of Disease (ICD-10) has recognised sarcopenia as an independent condition since September 2016 [9].

Although sarcopenia has been clinically recognised as a frailty marker, a global consensus on an operational definition has not been reached. This could explain the wide variation in reported sarcopenia prevalence, ranging from 3% to 30% for older adults aged 60 years or older [10]. In the last ten years, there have been several attempts to standardise the operational definition and cut-off points for sarcopenia, most of which have used combinations of measures of muscle mass, muscle strength and gait speed [11-13]. The most recent statement, by the European Working Group on Sarcopenia in Older People 2019

(EWGSOP2), has proposed that sarcopenia should be defined as low muscle strength plus low muscle mass, with severe sarcopenia including the addition of slow gait speed [7].

Although the associations between sarcopenia and all-cause mortality, chronic obstructive pulmonary disease (COPD) [14, 15], and cardiovascular diseases (CVD)[16, 17] have been previously studied, it is unclear whether a different combination of physical capability markers results in a stronger association with health outcomes. The aim of this study, therefore, was to compare the association of different combinations of physical capability markers used to define sarcopenia with cardiovascular and respiratory outcomes as well as all-cause mortality in UK Biobank, a large prospective cohort study of middle-aged adults.

2. Methods

Between April 2007 and December 2010, UK Biobank recruited over 500,000 participants (5.5% response rate), aged 37-73 years from the general population [18]. Participants attended one of 22 assessment centres across England, Wales and Scotland [19, 20] where they completed a touch-screen questionnaire, had physical measurements taken, and provided biological samples, as described in detail elsewhere [19, 20].

The outcomes in the current study were all-cause mortality and incidence and mortality for CVD and respiratory diseases, and the exposures were different combinations of physical capability markers used to define sarcopenia. Due to ethnic differences in the reference values for these markers, inclusion in the study was restricted to participants of a white European background.

2.1 Procedures

Date of death was obtained from death certificates held by the National Health Service (NHS) Information Centre (England and Wales) and the NHS Central Register Scotland (Scotland). Dates and causes of hospital admissions were identified via record linkage to Health Episode Statistics (HES) (England and Wales) and the Scottish Morbidity Records (SMR01) (Scotland). Details of the linkage procedure can be found at http://www.ic.nhs.uk/services/medical-research-information-service. Follow-up data started in March 2008 and were available until 31 January 2018 for participants in England or Wales, and 30 May 2017 for participants in Scotland. Follow-up was censored on these for deaths.

Incident CVD was defined as a hospital admission or death with ICD10 (International Classification of Diseases, 10th revision) codes I60, I61, I63, I64, I21, I21.4, and I21.9. Respiratory disease was defined as ICD10 codes J09-J98, and COPD was defined as ICD10 code J44.

2.2 Physical capability markers groups

The 2019 EWGSOP2 statements define sarcopenia as the combination of low grip strength plus low muscle mass and severe sarcopenia as both in combination with slow gait speed [7]. To compare the association of different combinations of physical capability markers used to define sarcopenia with the health outcomes of interest, we derived four groups, two of which were the current EWGSOP2 definition of sarcopenia and severe sarcopenia and the other two being the remaining combinations of physical capability markers (Supplementary Figure 1). The four groups were therefore as follows: a) slow gait speed plus low grip strength only (gait-grip group), b) slow gait speed plus low muscle mass only (gait-muscle group), c) low grip strength plus low muscle mass only (grip-muscle group or current sarcopenia definition), and

d) low grip strength plus low muscle mass plus slow walking speed (severe sarcopenia). The four groups were mutually exclusive.

Details about measures and the cut-off points for each physical capability marker as well as other sociodemographic, lifestyle and health measures are available in supplementary methods.

2.3 Statistical analyses

Associations of the combination of physical capability markers with cause-specific incidence and mortality were investigated using Cox-proportional hazard models (individuals with a normal range for all physical capability markers were used as the reference group). Associations between individual physical capability markers and cause-specific incidence and mortality are also reported. The results are reported as hazard ratios (HR) and their 95% confidence intervals. The proportional hazard assumption was checked by tests based on Schoenfeld residuals. All analyses were performed using a 2-year landmark analysis. The models for CVD and respiratory incidence and mortality were performed excluding participants with medical diagnoses of CVD, or respiratory disease, respectively.

We produced three models that included an increasing number of covariates: “model 1” (minimally adjusted) included sociodemographic covariates (age, sex and deprivation); “model 2” (maximally adjusted) was adjusted as in model 1, but also included prevalent diseases (hypertension, diabetes, depression, major illness, cancer, as well as CVD and respiratory disease when these were not the outcome) and lifestyle factors (smoking, sleep duration, waist circumference [WC], total physical activity, total discretionary sedentary time and dietary intake including alcohol, fruit and vegetable, oily fish, red meat and processed

meat intake). Sensitivity analyses, where all 71,778 participants with comorbidities at baseline (such as CVD, cancer, COPD, diabetes and depression) were excluded from the analyses irrespective of the outcome, were conducted to evaluate the association between combinations of physical capability markers and health outcomes among apparently "healthy" individuals (model 3).

To investigate whether the association between combinations of physical capability markers used to define sarcopenia and health outcomes differed by age and sex, we fitted a multiplicative interaction term between sarcopenia and these sociodemographic variables. Where these were statistically significant, subgroup analyses were performed, stratified by age category (below and above 60 years) and sex as appropriate.

All analyses were performed using STATA 16 statistical software (StataCorp LP). P-values below 0.05 were regarded as statistically significant.

3. Results

Of the 502,535 participants recruited to UK Biobank, 469,830 (93.5%) had full data available on exposure, outcomes and covariates. The mean follow-up period was 6.9 years (interquartile range: 6.3–7.5) after the landmark period for all-cause and cause-specific mortality, and 6.0 years (interquartile range: 5.4–6.7) for cardiovascular and respiratory disease incidence. Over the follow-up period, 14,786 (3.1%) participants died; 2,548 (0.5%) from CVD and 2,577 (0.5%) from respiratory diseases. Additionally, 19,332 (4.1%) participants developed cardiovascular disease, 16,105 (3.4%) respiratory disease, and 1,605 (0.3%) COPD. The specific numbers of deaths/events for each physical capability marker and their combinations are presented in the Supplementary Table 1.

The study population's characteristics by the four physical capability markers groups are summarised in Table 1. Overall, in comparison to people without any form of sarcopenia, people with any combination of physical capability markers were older, more deprived and more likely to be female. For all groups, other than the grip-muscle group (current sarcopenia definition), participants were more likely to be current smokers and were less physically active. Those defined by low grip strength plus low muscle mass had the lowest body weight, and WC and those defined by slow gait speed plus low grip strength had the highest prevalence of obesity, central obesity, diabetes, CVD and hypertension. However, people with severe sarcopenia had the highest prevalence of fractures and falls in the last 5-years and 1-year, respectively. The main characteristics of the population by individual physical capability markers (gait speed or grip strength or muscle mass) are presented in Supplementary Table 2.

The associations between the individual physical capability markers used to define sarcopenia and health outcomes are presented in Figure 1 and Supplementary Table 3. These results show that slow gait speed had the strongest associations with health outcomes. Low grip strength and low muscle mass were associated with similar risk estimate for outcomes except for COPD, whereas individuals with low muscle mass had similar risks to those observed for slow gait speed.

As shown in Figure 2, severe sarcopenia had the strongest association with all-cause mortality (HR: 3.02 [95% CI: 2.34 to 3.91]), whilst the combination of slow gait speed plus low muscle mass (gait-muscle group) showed the strongest association with CVD (HR: 3.47 [95% CI: 2.03 to 5.91]), and respiratory mortality (HR: 5.73 [95% CI: 3.83 to 8.57]). Severe sarcopenia and the combination of slow gait speed plus low grip strength were also associated with CVD and

respiratory mortality, but the magnitude of these associations were lower in comparison to the gait-muscle group (Figure 2). However, the combination of low grip strength plus low muscle mass, i.e. the current sarcopenia definition, had the lowest magnitude of associations compared to other combinations of physical capability markers. Individuals with low grip plus low muscle mass had a 35% and 88% higher risk of all-cause and respiratory diseases mortality compared to the reference group. No associations were observed between this group and CVD mortality.

All combinations of physical capability markers were associated with a higher incidence risk of respiratory diseases (Figure 3), with the strongest association observed for those classified as severely sarcopenic (HR: 2.74 [95% CI: 2.06 to 3.65]). In terms of COPD incidence, the gait-muscle group had 4.16 times higher risk than people with normal physical capability markers (HR: 4.16 [95% CI 2.59 to 6.70]), followed by those with severe sarcopenia (HR: 3.85 [95% CI: 2.24 to 6.62]) and the gait-grip group (HR: 2.42 [95% CI: 2.01 to 2.91]). A lower magnitude of association was found for CVD incidence in the gait-muscle group (HR: 1.62 [95% CI: 1.20 to 2.17]), followed by the gait-grip group (HR: 1.38 [95% CI: 1.27 to 1.50]). However, no associations with CVD were found for the severe sarcopenia group and the grip-muscle group. When participants with major comorbidities at baseline were excluded from the analyses, the magnitude of the associations with all health outcomes increased for the gait-muscle group and the gait-grip group.

There were significant interactions between age and the gait-grip group for all-cause mortality, and respiratory mortality and incidence, and between age and severe sarcopenia in relation to CVD incidence. In these cases, the magnitude of the associations was slightly bigger for younger individuals compared to older individuals (Supplementary Table 6).

Interactions were also observed in relation to sex (Supplementary Table 7). Associations for all-cause mortality and respiratory incidence with all physical capability groups were stronger in men than women. However, women had stronger associations with CVD mortality for all physical capability groups (except grip-muscle group) (Supplementary Table 7).

4. Discussion

Sarcopenia is a progressive, complex disorder associated with the development of a number of diseases and contributes to frailty, disability, morbidity and mortality. As detailed previously, there are many diagnostic criteria used to define sarcopenia [11-13]. In this study, we used the three physical capability markers (gait speed, grip strength and muscle mass) used in EWGSOP2 to derive four different combinations of physical capability markers, including the current definition of sarcopenia and severe sarcopenia [7].

The main finding of this study was that all combinations of physical capability markers used to define sarcopenia or severe sarcopenia identified individuals at increased risk of respiratory disease and all-cause mortality. However, the definition most strongly associated with a wide range of adverse health outcomes was the combination of slow gait speed plus low muscle mass, followed by severe sarcopenia, and the combination of slow gait speed plus low grip strength. Individuals with these characteristics were at significantly higher risk of developing CVD, respiratory disease and COPD incidence as well as all-cause, CVD and respiratory mortality. Nevertheless, the new EWGSOP2 guidelines proposed that low muscle strength (or grip strength) plus low muscle mass should be used to diagnose sarcopenia [7].

Whilst the loss of muscle mass was the first and is the most widely recognised characteristic of sarcopenia, strength and gait may be better measures of sarcopenia severity and its risk to health. In fact, Bachettini el al. showed that gait speed was the only criterion independently associated with mortality in the definition of sarcopenia using the EWGSOP2 definition (76% higher risk of mortality) [21] and Ganna & Ingelsson demonstrated that the self-reported walking pace – along with the self-reported health – was the strongest predictor of mortality

in both men and women [22]. Therefore, a definition, and diagnosis, based on slow gait speed and/or low grip strength may be more meaningful for use in clinical practice and research since both are quick tests for the sarcopenia diagnosis. In particular, slow gait speed and low grip strength appeared to be the main drivers of the observed associations with health outcomes more than low muscle mass. In fact, Sim et al. demonstrated that different definitions of sarcopenia were not associated with falls-related hospitalisations in older Australian women; however, when each physical capability marker was examined individually, both grip strength and physical function, but not muscle mass, were associated with falls-related hospitalisation [23]. Comparable results were observed for mortality in the same cohort [24]. However, despite its potential as a diagnostic tool, grip strength may not respond to treatment well, and its use in the continual monitoring of sarcopenic patients can be limited [25].

In terms of muscle mass, we should note that other measurements on muscle mass could provide a better prognostic value. For instance, Cawthon et al. highlighted that when muscle mass was determined by creatine concentration, people in the lowest quartile of muscle mass had a higher risk of mortality for all-cause, cancer and CVD [26]. However, this method is still not recognised as a measurement of muscle mass by the EWGSOP2 [7].

In our study, the current definition of sarcopenia and severe sarcopenia were both more prevalent in women; however, were associated with a stronger risk of adverse health outcomes in men. Women experience an earlier loss of muscle mass and a major decline in sex-specific hormones that are important for the muscle maintenance, and therefore they could be more susceptible to experiencing sarcopenia early in life; however, men have a greater decline in skeletal muscle mass with advancing age [27]. This muscle loss is

accompanied by a significant decrease in muscle strength which is intensified when there is poor nutrition (e.g. low intake of protein) and lower levels of physical activity [27].

Sarcopenia was initially considered a disease of ageing but is now understood to begin before older ages [7]. In our study, we demonstrated that the associations were slightly stronger in participants aged < 60 years. Our findings, therefore, reinforce the need for earlier detection of sarcopenia and altered physical capability markers in clinical practice.

In terms of health outcomes, other studies have identified similar associations between different combinations of physical capability markers used to define sarcopenia and health outcomes [14-17]. Zhang et al. showed that sarcopenia was associated with an increased risk for all-cause mortality among older nursing home residents (HR: 1.86 [95% CI: 1.42 to 2.45]) [28]. By contrast, Kittiskulnam et al. determined that neither sarcopenia nor low muscle mass were a good predictor of mortality among patients on haemodialysis; however, when gait speed or grip strength were used, a positive association was identified [29]. These findings are similar to our study because, although we found a positive association with a different classification of sarcopenia, low grip strength and slow gait speed, no associations between low muscle mass (the previously more important criterion) and the outcomes were identified.

Finally, the majority of the strongest associations were with respiratory outcomes. It has been postulated that both ageing and sarcopenia may be associated with reduced power of the diaphragm muscle, which, in turn, impairs expulsive airway clearance [30]. Jones et al., after studying 622 stable patients with COPD, determined that sarcopenia, defined by EWGSOP criteria, has an impact on the functional and health status in these patients, specifically those with reduced functional performance, exercise capacity and quality of life [14].

Strengths and limitations

UK Biobank is not representative of the UK population in terms of lifestyle and prevalent disease [31]. Therefore, whilst estimates of effect sizes can be generalised, summary statistics should not be. However, the use of UK Biobank allowed us to test our research question in a very large general population cohort as well as the opportunity to work with information collected using validated and standardised methods. On the other hand, dual-energy X-ray absorptiometry (DXA) is the most commonly used method for deriving muscle mass because it can provide a reproducible estimation of the appendicular skeletal muscle mass in a few minutes. In the UK Biobank study, muscle mass was measured using bioimpedance, but this method has been shown to correlate well with DXA ($r=0.868$, $p<0.0001$). Finally, walking pace was self-reported. Whilst this is potentially a source of bias, it is more easily replicated in clinical practice. Future studies are needed to establish whether it is a reasonable proxy of objectively measured walking speed.

In conclusion, even though different combinations of physical capability markers were associated with CVD, respiratory, COPD incidence and all-cause, CVD and respiratory mortality, there were differences in the strength of association. Notably, the EWGSOP2 definition was not significantly associated with both fatal and nonfatal CVD. The strongest associations were observed for the combination of slow gait speed plus low muscle mass. These findings suggest that slow gait speed, which was omitted in defining sarcopenia in the current EWGSOP2, may be an important physical capability marker of sarcopenia and its use should not be limited to the definition of severe sarcopenia.

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Authorship contribution

F.P-R, SRG, JPP and C.C-M contributed to the conception and design of the study, advised on all statistical aspects, and interpreted the data. F.P-R performed the literature search. F.P-R performed the analyses with support from SRG, J. PP and C.C-M. All authors critically reviewed this and previous drafts. All authors approved the final draft for submission. SRG, JPP and C.C-M contributed equally to this work and are joint senior authors. C.C.-M. is the guarantor.

Data statement

All UK Biobank information is available online on the webpage www.ukbiobank. Data access are available through applications. This research was conducted using the application number 7155.

Conflict of interest

None

Words

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Table 1. Baseline characteristics by different combinations of physical capability markers

	Without sarcopenia (normal)	Gait-grip group	Gait-muscle group	Grip-muscle group *	Severe Sarcopenia
Socio-demographics					
Total n	394,583	8,731	564	1,678	424
Sex (Female), n (%)	207,782 (52.7)	5,378 (61.6)	505 (89.5)	1,604 (95.6)	386 (91.0)
Age (years), mean (SD)	56.1 (8.1)	60.2 (6.8)	62.0 (5.9)	63.0 (5.3)	62.0 (6.3)
Age categories					
<56 years	173,200 (43.9)	1,953 (22.4)	77 (13.7)	167 (9.9)	67 (15.8)
56 to 65 years	169,368 (42.9)	4,589 (52.5)	294 (52.1)	855 (51.0)	198 (46.7)
>65 years	52,037 (13.2)	2,192 (25.1)	193 (34.2)	656 (39.1)	159 (37.5)
Deprivation					
Lower	141,660 (35.9)	1,748 (20.0)	150 (26.6)	542 (32.3)	114 (26.9)
Middle	135,979 (34.5)	2,412 (27.7)	184 (32.6)	611 (36.5)	136 (32.1)
Higher	116,509 (29.6)	4,559 (52.3)	230 (40.8)	524 (31.2)	174 (41.0)
Smoking status, n (%)					
Never	215,924 (54.9)	3,750 (43.3)	236 (41.9)	993 (59.5)	200 (47.4)
Previous	138,609 (35.2)	3,414 (39.5)	190 (33.8)	529 (31.7)	133 (31.5)
Current	38,877 (9.9)	1,490 (17.2)	137 (24.3)	147 (8.8)	89 (21.1)
Obesity-related markers					
Height (metres), mean (SD)	1.69 (0.09)	1.64 (0.09)	1.63 (0.08)	1.61 (0.07)	1.62 (0.08)
Body weight (kg), mean (SD)	78.0 (15.2)	83.8 (18.6)	62.4 (11.0)	59.6 (8.3)	61.3 (10.3)
BMI, mean (SD)	27.1 (4.4)	31.2 (6.4)	23.6 (4.0)	22.9 (2.9)	23.5 (3.5)
BMI Categories, n (%)					
Underweight (<18.5 $kg.m^{-2}$)	1,480 (0.4)	43 (0.5)	41 (7.3)	102 (6.1)	28 (6.6)
Normal weight (18.5-24.9 $kg.m^{-2}$)	131,731 (33.5)	1,268 (14.7)	347 (61.5)	1,171 (69.8)	274 (64.6)
Overweight (25.0 to 29.9 $kg.m^{-2}$)	173,553 (44.1)	2,750 (31.9)	147 (26.1)	392 (23.3)	106 (25.0)
Obese (≥30.0 $kg.m^{-2}$)	86,692 (22.0)	4,560 (52.9)	29 (5.1)	13 (0.8)	16 (3.8)
Waist Circumference (cm)	89.7 (12.9)	99.2 (15.2)	81.7 (10.6)	78.2 (8.8)	81.4 (10.2)
Central Obesity, n (%)	121,990 (31.0)	5,638 (64.7)	120 (21.3)	224 (13.4)	99 (23.4)
% Body fat, mean (SD)	30.7 (8.3)	37.2 (9.0)	37.0 (8.1)	36.1 (6.4)	36.9 (7.5)
Fitness and Physical activity					
Total PA ($MET.h^{-1}.week^{-1}$), mean (SD)	3,018.2 (3,286.7)	1,889.2 (2,359.2)	1,821.2 (2,214.9)	2609.6 (2744.5)	1,560 (1,904.5)
Cardiorespiratory fitness (MET), mean (SD)	9.8 (2.8)	8.0 (2.5)	7.2 (1.7)	7.6 (1.8)	7.6 (1.4)
Grip Strength (kg), mean (SD)	32.5 (10.3)	14.5 (6.2)	22.2 (5.8)	12.7 (3.7)	10.9 (5.0)
TV viewing ($h.day^{-1}$), mean (SD)	2.7 (1.5)	4.0 (2.2)	3.8 (2.0)	3.2 (1.7)	4.0 (2.1)
Total Sedentary behaviour ($h.day^{-1}$) , mean (SD)	5.0 (2.2)	5.6 (2.8)	5.3 (2.5)	4.6 (2.0)	5.2 (2.4)
Health status, n (%)					
Diabetes	15,062 (3.8)	1,470 (17.0)	15 (2.7)	28 (1.7)	14 (3.3)
CVDs	106,513 (27.0)	5,022 (57.8)	232 (41.3)	443 (26.5)	176 (41.6)
High blood pressure	88,983 (22.6)	3,046 (35.0)	163 (29)	343 (20.5)	110 (26.0)

Fractures/ broken bones last 5 years	35,648 (9.1)	1,350 (15.6)	104 (18.6)	252 (15.1)	87 (20.6)
Falls, n (%)					
No falls	326,585 (82.9)	4,256 (49.2)	351 (62.3)	1,189 (70.9)	230 (54.4)
Only one fall	49,217 (12.5)	1,515 (17.5)	99 (17.6)	354 (21.2)	87 (20.6)
More than one fall	18,288 (4.6)	2,886 (33.3)	113 (20.1)	133 (7.9)	106 (25.1)

Gait-grip group: slow gait speed plus low grip strength only. Gait-muscle group: slow gait speed plus low muscle mass only. Grip-muscle group or current sarcopenia definition*: low grip strength plus low muscle mass only. Severe sarcopenia: having low grip strength plus low muscle mass plus slow walking speed. BMI: body mass index; n: number; PA: physical activity; MET: metabolic-equivalent; TE: total energy; SD: standard deviation; CVD: cardiovascular disease.

Figure Legends

Figure 1. Association of physical capability markers with incidence and mortality

Data presented as adjusted hazard ratio (HR) and its 95% confidence interval (95% CI) by different combinations of physical capability markers. People with a normal range for all physical capability markers were used as the reference group for the analyses.

All analyses were conducted using a 2-year landmark analyses and for Model 2, were adjusted for age, sex, deprivation, smoking status, sleep duration, WC, total physical activity, discretionary sedentary time, dietary intake (alcohol, fruit and vegetable, oily fish, red meat and processed meat intake), hypertension, diabetes, depression, comorbidities, cancer, as well as CVD and respiratory disease when these were not the outcome.

Figure 2. Association between different combinations of physical capability markers and all- and cause-specific mortality

Data presented as adjusted hazard ratio (HR) and its 95% confidence interval (95% CI) by different combinations of physical capability markers.

People with a normal range for all physical capability markers were used as the reference group for the analyses.

Gait-grip group: having slow gait speed plus low grip strength only. Gait-muscle group: having slow gait speed plus low muscle mass only. Grip-muscle group or current sarcopenia definition: having low grip strength plus low muscle mass only. Severe sarcopenia: having low grip strength plus low muscle mass plus slow walking speed.

All analyses were conducted using a 2-year landmark analyses and for Model 2 were adjusted for age, sex, deprivation, smoking status, sleep duration, WC, total physical activity, discretionary sedentary time, dietary intake (alcohol, fruit and vegetable, oily fish, red meat and processed meat intake), hypertension, diabetes, depression, comorbidities, cancer, as well as CVD and respiratory disease when these were not the outcome.

Figure 3. Association between different combinations of physical capability markers and cause-specific incidence

Data presented as adjusted hazard ratio (HR) and its 95% confidence interval (95% CI) by different combinations of physical capability markers. People with a normal range for all physical capability markers were used as the reference group for the analyses.

. Gait-grip group: having slow gait speed plus low grip strength only. Gait-muscle group: having slow gait speed plus low muscle mass only. Grip-muscle group or current sarcopenia definition: having low grip strength plus low muscle mass only. Severe sarcopenia: having low grip strength plus low muscle mass plus slow walking speed.

All analyses were conducted using a 2-year landmark analyses and for Model 2 were adjusted for age, sex, deprivation, smoking status, sleep duration, WC, total physical activity, discretionary sedentary time, dietary intake (alcohol, fruit and vegetable, oily fish, red meat and processed meat intake), hypertension, diabetes, depression, comorbidities, cancer, as well as CVD and respiratory disease when these were not the outcome.