Sarcopenic obesity, weight loss, and mortality: The English Longitudinal Study of Ageing

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Abbreviations

Body mass index **(BMI)**

Centre of Epidemiological Studies Depression **(CES-D)**

English Longitudinal Study of Ageing (**ELSA**)

Hazard ratio (**HR**)

National Institutes of Health Biomarkers Consortium **(FNIH)**

Abstract

Background: Age-related sarcopenia describes loss of muscle strength and often accompanies an increase in adiposity in elderly participants.

Objectives: We examined the association of sarcopenic obesity, and changes in muscle strength and weight with risk of mortality.

Design: Participants were 6,864 community dwelling men and women (mean±SD age 66.2 ± 9.5 years, 45.6% men) from the English Longitudinal Study of Ageing. Handgrip strength and body mass index were measured at baseline and at four years follow-up. Individual participant data were linked with death records from National Health Service registries. Sarcopenic obesity was defined as obese individuals (body mass index [BMI] ≥ 30 kg/m^2) in the lowest tertile of sex specific grip strength (<35.3 kg men; < 19.6kg women).

Results: Over an average follow up of 8 years there were 906 deaths. Compared with the reference group (normal BMI and highest hand grip tertile), the risk of all-cause mortality increased with reducing grip strength within each BMI category. For participants in the lowest hand grip tertile there was little difference in risk between normal BMI (Hazard ratio=3.25; 95% CI, 1.86, 5.65), overweight (2.50;1.44, 4.35), and obese (2.66; 1.86, 3.80), after adjustment for covariates. Compared to participants with stable weight and grip strength, risk of all-cause mortality was significantly greater in those experiencing weight loss over 4 years (2.21;1.32, 3.71) and reduced hand grip strength (1.53;1.07, 2.17), with the highest risk in those with weight loss and reduced strength (3.77; 2.54, 5.60).

Conclusion: Sarcopenic obesity did not confer any greater risk than sarcopenia alone. Weight loss in combination with sarcopenia presented the greatest risk of mortality.

Introduction

Age-related sarcopenia is a syndrome characterized by a progressive loss of skeletal muscle mass and quality (or strength) resulting in impaired physical performance (1,2). Age-related loss of muscle mass is often accompanied by gain in adipose tissue, thus sarcopenic obesity describes a clinical entity in which these two states are thought to act together to increase risk more than the additive effect of the two factors alone in the pathophysiology of both metabolic, functional impairments, and mortality risk (3-9).

There is limited evidence on the association between sarcopenic obesity and mortality, although data from several cohort studies suggest that sarcopenic obesity does not confer any greater risk than sarcopenia alone (8,9). In constrast, other cohort data have shown that the combination of obesity and high hand grip strength is associated with lower risk of mortality in older adults (10). Nevertheless, when obesity was defined from waist circumference and high triglycerides, the combination of abdominal obesity and sarcopenia was associated with the highest risk of mortality (11). These studies, however, relied on a single baseline clinical visit to assess sarcopenia and body composition, and did not examine changes over time. Indeed, changes in sarcopenia status can be best captured using repeat longitudinal clinical assessments. The aim of our study was therefore to first examine the association of sarcopenia and obesity at baseline with mortality over 8 years follow up; second we examined associations between changes in muscle strength and weight on risk of mortality. Analyses were performed on a well characterised community sample of older adults. In our study we defined “sarcopenia” using the lowest sex specific tertile of hand grip strength.

Methods

Study sample and procedures

The English Longitudinal Study of Ageing (ELSA) is an ongoing cohort study of a nationally representative sample of the English population born on or before 29 February 1952 living in private households (12). A multi-stage stratified probability sampling method was used to recruit the sample. Participants gave full, informed written consent to take part in the study and ethical approval was obtained from the London Multi-Centre Research Ethics Committee. For the purposes of the present analyses, data collected in 2004/05 (wave 2) were used as the baseline, as this was the first occasion on which clinical information was gathered. An identical clinical assessment was repeated four years later at wave 4 (2008/09) and the individual participant data were linked with death records from National Health Service registries for all consenting respondents (96.5% of the sample) up to February 2012. For the key exposure measure, grip strength, there were no upper age limits although respondents were excluded if they had swelling or inflammation, severe pain, or a recent injury or surgery to the hand in the preceding 6 months.

Handgrip and body mass index

Handgrip strength (kg) of the dominant hand was assessed using the Smedley hand-held dynamometer (Stoelting Co, IL, USA), using the average of three measurements. Participants were required to hold the device at a right angle to their body and exert maximum force for a couple of seconds when instructed. Successive trials were alternated between dominant and non-dominant hands. Nurses measured participants' body weight without shoes and in light clothing to the nearest 0.1 kg using Tanita electronic scales (Tanita Co, IL, USA), and height was measured using a stadiometer with the Frankfurt plane

in the horizontal position; body mass index (BMI) was calculated using the standard formula [weight (kg)/height^2 (m^2)].

Covariates

At baseline, trained interviewers collected information on self –reported cigarette smoking (current, previous or non-smoker), the self –reported frequency of participation in physical activities (more than once per week, once per week, one to three times per month, hardly ever), self –reported physician-diagnosed cardiovascular diseases, longstanding illness, depressive symptoms (assessed using the self–reported 8-item Centre of Epidemiological Studies Depression (CES-D) scale (13). Based on previous work in ELSA showing robust dose-response associations with mortality (14), physical activity was further categorised into three groups classified as: inactive (no moderate or vigorous at least once a week); moderate activity at least once a week (but no vigorous), and vigorous activity at least once a week. Depressive symptoms were categorised as a binary variable (CES-D score 0 – 3 [ref]; or > 3). Self-reported wealth was used as our measure of socioeconomic status. The wealth variable comprised the total value of the participant's home (excluding mortgage), financial assets such as savings, business assets, and physical wealth such as artwork or jewellery, which has been shown to best capture the material resources available to older adults (15). Wealth was grouped into quintiles relative to the ELSA sample.

Statistical analysis

We created sex specific tertiles of grip strength; the range of handgrip strength at baseline in men was 4 – 35.3 (median [IQR]= 29.7 [7.7]), 35.4 – 44.2 (39.7 [4.0]), >44.2 (48.7 [6.0]) kg for low, intermediate and high tertiles, respectively. The corresponding ranges in women

were 4 – 19.6 (16.0 [5.0]), 19.7 – 24.9 (22.3 [2.7]), >24.9 (28.3 [4.3]) kg, respectively. Sarcopenic obesity was defined as obese individuals (BMI ≥ 30 kg/m^2) in the lowest tertile of sex specific grip strength (<35.3 kg men; < 19.6kg women). Non-obese were defined as BMI 18.5 – 29.99 kg/m^2 and underweight participants were excluded to prevent possible reverse causation (as underweight is often a marker of serious illness) (16). We used Cox proportional hazards regression models to examine associations between sarcopenic obesity and death. Age at death was recorded and years were the time scale for the follow-up. For consenting participants with no record of an event, the data were censored at February 2012. The proportional hazards assumption was examined by using plots of the Nelson-Aalen cumulative hazard estimates. In preliminary analyses, there was no evidence of effect modification according to sex, thus data for men and women were pooled and sex-adjusted. We estimated models that were initially adjusted for age and sex. The final models were additionally adjusted for physical activity, smoking, depressive symptoms, long standing illness, and wealth. These covariates were selected a priori based on previous literature (8,9). The analyses described above were repeated using Foundation for the National Institutes of Health Biomarkers Consortium (FNIH) sex-specific handgrip strength cutoffs (men <26 kg; women <16kg) to define sarcopenia (1). We performed sensitivity analyses excluding participants who died in the first two years of follow up and those with doctor diagnosed cardiovascular diseases at baseline. In the final set of analyses we examined the association between changes in hand grip strength and weight on risk of mortality. Weight change was defined as an increase or reduction in 5% of initial body mass (17), and loss of grip strength was defined as reduction in 5% of initial hand grip between clinical assessment waves 2 to 4. All analyses were conducted using SPSS (version 22).

Results

A total of 8,688 participants (82% of wave 1 participants) attended the wave 2 (baseline) clinical assessment. The analytic sample comprised 6,864 men and women (aged 66.2 ± (SD) 9.5 years, 45.6% men) (see **Figure 1**). Compared with the analytic sample, the excluded participants were older (66.2±9.5 vs. 70.7±11.4 yrs, p<0.001), less wealthy (lowest wealth quintile; 15.2 vs 21.4%, p<0.001), and less vigorously active (29.1 vs. 18.7%, p<0.001), although they reported similar prevalence of cardiovascular disease (18.0 vs 16.1%, p=0.17) and smoking (16.2 vs 18.2%, p=0.13).

The baseline characteristics are displayed in **Table 1**. Participants in the highest tertile of grip strength (non-obese and obese) were younger than participants with medium and low grip strength. Non-obese participants with high grip strength were more physically active, wealthier, displayed lower levels of depressive symptoms and reported less disease than other participants.

During an average follow up of 7.6 years (median, 8.1; range 0 – 8.1 yrs) there were 906 deaths. We observed a "U"-shaped association between BMI and mortality, with the overweight category demonstrating lowest risk of mortality (**see Supplemental Table 1**). In comparison with the highest tertile for grip strength there was a linear increase (p-trend <0.001) in mortality risk for the middle (HR=1.71; 95% CI, 1.32, 2.21) and lower tertiles (2.20; 1.70, 2.85).

Compared with the reference group (normal BMI and highest hand grip strength tertile), the risk of all-cause mortality increased with reducing grip strength within each BMI category. For participants in the lowest hand grip tertile there was little difference in risk between

normal BMI (3.25; 1.86, 5.65), overweight (2.50;1.44, 4.35), and obese (2.66; 1.86, 3.80), after adjustment for covariates (**Table 2,** Model 2). In additional analyses we categorised participants using FNIH sex-specific handgrip strength cut-offs (men <26 kg; women <16kg) to identify sarcopenia, and 12.7% of the sample met the threshold. Compared with the reference group (non-obese and non-sarcopenic), the increased risk of all-cause mortality was similar in sarcopenic (age/sex adjusted HR, 1.22; 1.02, 1.45) and in sarcopenic obese (1.22; 0.93, 1.61), although associations did not persist after adjustment for all covariates (physical activity, smoking, depressive symptoms, long standing illness, and wealth) **(Supplemental Table 2)**. Results were similar in sensitivity analyses excluding participants who died in first two years of follow up and those with doctor diagnosed cardiovascular diseases at baseline (**Supplemental Table 3**).

Around 11.5% of the sample gained weight and 12.0% lost weight over 4 years follow-up, and 52.8% experienced at least a 5% reduction in handgrip strength. **Table 3** demonstrates that all-cause mortality risk was significantly greater in participants experiencing weight loss over 4 years (2.21; 1.32, 3.71) and reduced hand grip strength (1.53;1.07, 2.17), with the highest risk in those with weight loss and strength reduction (3.77; 2.54, 5.60). No excess risk was observed in either of the weight gain groups. Three measures were used to investigate biological interaction between weight loss and sarcopenia in relation to mortality (18): the relative excess risk due to interaction (RERI); the attributable portion due to interaction (AP); and the synergy index (S) (RERI and AP would be equal to 0 and S would be equal to 1 if there were no biological interaction). The interaction was modelled as 2 × 2 categories, comprising a binary weight loss variable (yes or no) and binary grip strength loss variable (yes or no). Although there appeared to be some evidence of biological interaction,

(RERI=0.23, 95% CI: -1.56, 2.02; AP= 0.07, 95% CI: -0.46, 0.60; S=1.11, 95% CI: 0.48, 2.55) the effect estimates were not statistically significant.

Discussion

The main aim of this study was to examine associations between sarcopenic obesity and mortality. A novel addition to the area was to examine the association between changes in muscle strength and weight on risk of mortality. Our main findings showed sarcopenic obesity did not confer any greater risk than sarcopenia alone. In fact, body mass index was a poor predictor of mortality. In contrast, using data from repeat clinical assessments, we showed that weight loss in combination with loss of muscle strength presented the greatest risk. Loss of lean muscle mass and gain in adiposity is considered a hallmark of ageing. That weight gain combined with loss of muscle strength was not associated with risk of mortality in the present study challenges commonly held belief in the area.

Previous evidence has suggested that overweight and obesity are not as adverse in elderly populations (10,19), and that muscle mass may be more strongly associated with mortality than obesity (8,20). However, results may be biased when using BMI assessed from a single time point as morbidity is a positive function of the duration of obesity, and effects may be obscured when obese participants fall into normal weight categories due to rapid weight loss from underlying disease (21). In the present study obesity itself was not associated with mortality when compared to a normal weight reference category alone, although the results changed when the reference category was refined to include non-obese with grip strength in the highest tertile.

Low grip strength may be explained by factors other than low muscle mass, such as underlying disease and general health status (22). Indeed, many individuals with weakness may not have low muscle mass. This had led to suggestions of a distinct term, dynapenia (23). Nevertheless, associations between grip strength and mortality have been consistently observed in cohort studies (24), including some with follow-up of over 20 years in which the prevalence of sub-clinical disease and existing comorbidities at baseline was low. Data on skeletal muscle mass were not available in the present cohort and we relied on measurements of muscle strength alone. Nevertheless, while lean mass and strength (muscle quality) may not decline at the same rate, loss of lean mass is strongly associated with strength decline in both men and women (25). We used the suggested cut points for weakness according to the FNIH criteria (1). However, only 12.7% of the sample met the threshold for weakness based on their handgrip thus limiting our statistical power. Recent evidence has suggested aerobic fitness may have additive and multiplicative interactions with muscle strength in relation to all-cause mortality (26), although such data were not available in the present study.

ELSA is a nationally representative cohort, although the present sample included younger and healthier participants than the overall cohort due to loss of older, more disadvantaged men and women. Thus the present findings might reflect a conservative estimate of the true effects. The covariates were self-reported, and imprecise measurement may have led to residual confounding.

203 In conclusion, sarcopenic obesity did not confer any greater mortality risk than sarcopenia
204 alone in a sample of community dwelling older adults. Weight loss in combination with a
205 reduction in muscle strength presented the greatest risk.

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Author contributions

Hamer had full access to the data, and takes responsibility for the integrity and accuracy of the results. Hamer drafted the paper, performed analyses and designed the study. O'Donovan contributed to the concept and design of the study and critical revision of the manuscript.

Conflict of interest

None of the authors have any competing interests to declare.

Data sharing statement

Full ELSA data are available at the UK data archive http://www.data-archive.ac.uk/ .

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Table 1. Characteristics of the sample at baseline. Data presented as percentages within group unless stated

Variable	Sex-specific hand grip tertile[1] stratified by obesity					
	Non-obese (BMI 18.5 – 29.99 Kg/m^2)			Obese (≥30 kg/m^2)		
	High	Intermediate	Low	High	Intermediate	Low
N	1464	1625	1769	685	663	658
Age, yrs (mean±SD)	60.8± 6.2	65.5± 8.4	72.4± 10.1	60.6± 6.3	65.4± 8.0	70.2± 9.1
Sex (% men)	38.3	50.5	50.3	40.9	45.6	38.1
Physical activity						
Inactive	9.4	14.5	30.1	17.7	24.9	41.8
Moderate	47.7	51.3	50.3	54.0	52.0	41.6
Vigorous	42.9	34.3	19.7	28.3	23.1	16.6
Smoking						
Never	40.3	37.9	34.3	33.8	37.4	35.5
Ex-smoker	41.5	45.3	48.9	51.5	47.3	51.4
Current	18.2	16.8	16.8	14.6	15.3	13.1
Wealth[2] quintile						
1st (poorest)	7.7	10.8	21.0	13.1	17.8	28.6
2nd	14.6	17.2	20.9	17.1	20.1	22.3
3rd	21.1	20.2	20.0	23.5	22.5	21.0
4th	26.9	24.5	18.8	23.6	22.6	16.6
5th (richest)	29.6	27.3	19.4	22.6	17.0	11.6
Depressive symptoms						
CES-D score 0 - 3	89.9	88.4	81.7	86.9	86.1	78.6
CES-D score >3	10.1	11.6	18.3	13.1	13.9	21.4
Chronic illness						
None	59.2	52.2	37.6	47.9	40.7	26.7
Yes	40.8	47.8	62.4	52.1	59.3	73.3
Prevalent CVD[3]						
None	86.8	81.1	74.0	82.0	75.9	70.2
Yes	13.2	18.9	26.0	18.0	24.1	29.8
Body mass index, kg/m^2 (mean± SD)	25.8±2.5	25.7±2.6	25.4±2.7	33.9±3.8	33.8±3.9	33.9±3.8

[1]In men, the range of handgrip strength at baseline was 4 – 35.3, 35.4 – 44.2, >44.2 kg for low, intermediate and high tertiles, respectively. The corresponding ranges in women were 4 – 19.6, 19.7 – 24.9, >24.9 kg, respectively.

[2]The wealth variable comprised the total value of the participant's home (excluding mortgage), financial assets such as savings, business assets, and physical wealth such as artwork or jewellery, which was grouped into quintiles relative to the present sample.

[3]doctor diagnosed cardiovascular diseases [CVD] (angina, heart disease, heart failure, heart murmur, arrhythmia, stroke)

Table 2. Hazard ratios (95% CI)[1] for the association between hand grip strength and mortality stratified by obesity status, over 8 yrs follow-up (n=6,864).

Grip strength tertile[2]	**Normal BMI (18.5 – 24.99 Kg/m^2)**	**Overweight BMI (25.0 – 29.99 Kg/m^2)**	**Obese BMI (≥ 30 Kg/m^2)**
Model 1			
High	1.00 **(reference)**	0.98 (0.52, 1.87)	1.97 (1.27, 3.05)
Intermediate	2.51 (1.41, 4.49)	2.00 (1.14, 3.51)	2.57 (1.76, 3.76)
Low	3.91 (2.24, 6.80)	2.90 (1.67, 5.04)	3.31 (2.34, 4.72)
Model 2			
High	1.00 **(reference)**	0.98 (0.52, 1.87)	1.81 (1.17, 2.81)
Intermediate	2.43 (1.36, 4.44)	1.92 (1.09, 3.37)	2.23 (1.52, 3.26)
Low	3.25 (1.86, 5.65)	2.50 (1.44, 4.35)	2.66 (1.86, 3.80)

Model 1; Hazard ratios(HR) adjusted for age, sex.

Model 2; adjusted for age, sex , physical activity, smoking, wealth, depressive symptoms, long standing illnesses.

[1] Cox proportional hazards regression models were used to analyse the data.

[2] *In men, the range of handgrip strength at baseline was 4 – 35.3, 35.4 – 44.2, >44.2 kg for low, intermediate and high tertiles, respectively. The corresponding ranges in women were 4 – 19.6, 19.7 – 24.9, >24.9 kg, respectively.*

Table 3. Hazard ratios (95% CI) for the association of 4 year changes in handgrip strength and weight with mortality (n=4,474)[1].

Weight change[2]	**Grip strength change[3]**	
Model 1	*Stable (n=2110)*	*Lost (n=2364)*
Stable (n=3422)	1.00 **(reference)**	1.54 (1.08, 2.18)
Gain (n=514)	2.14 (1.11, 4.15)	1.91 (1.00, 3.69)
Lost (n=538)	2.44 (1.47, 4.06)	4.18 (2.82, 6.18)
Model 2		
Stable (n=3422)	1.00 **(reference)**	1.53 (1.07, 2.17)
Gain (n=514)	1.84 (0.95, 3.58)	1.74 (0.90, 3.38)
Lost (n=538)	2.21 (1.32, 3.71)	3.77 (2.54, 5.60)

Model 1; Hazard ratios(HR) adjusted for age, sex.

Model 2; adjusted for age, sex , physical activity, smoking, wealth, depressive symptoms, long standing illnesses.

[1] *sample contains only participants that attended clinical assessments at both baseline (wave 2) and four years follow up (wave 4).*

[2]*Weight change defined as increase or reduction in 5% of initial body mass between clinical assessment waves 2 to 4;*

[3]*Loss of grip strength defined as reduction in 5% of initial grip measure between clinical assessment waves 2 to 4. Participants that increased grip strength were combined with those remaining stable.*

Figure legend

Figure 1. Selection of participants