

Multimorbidity increases the risk for sarcopenia onset:
Longitudinal analyses from the English Longitudinal Study of Ageing

Running head: multimorbidity and sarcopenia

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ABSTRACT

Background: Cross-sectional studies have demonstrated that multimorbidity is associated with sarcopenia. However, to date, this association has not been extensively investigated longitudinally. Therefore, the aim of the present paper was to explore the association between multimorbidity at baseline and sarcopenia onset over 12 years of follow-up in a large representative sample of the English older adult population.

Methods: Representative data from the English Longitudinal Study of Ageing (ELSA) were analyzed. Multimorbidity at baseline was defined as ≥ 2 medical conditions, of 17 conditions included. Participants were considered to have sarcopenia if they had low handgrip strength and skeletal muscle mass (i.e., lower skeletal mass index) at waves 4, 6, 8. Multivariable logistic regression analysis was conducted to assess prospective associations between multimorbidity at baseline and sarcopenia at follow-up.

Results: 2873 older participants (mean age: 69.1 years, 54% females) who did not have sarcopenia at baseline were included. The prevalence of multimorbidity at baseline was 57.3%. Over twelve years of follow-up, 394 participants (=13.7% of the initial population) became sarcopenic. The presence of multimorbidity at baseline was associated with an increased risk of sarcopenia during follow-up (OR=2.06; 95%CI: 1.61-2.62) in the univariable analysis, and even after adjusting for multiple potential confounders (OR=1.23; 95%CI: 1.01-1.61).

Conclusions: In this large representative sample of older adults from the UK, multimorbidity at baseline was associated with a higher risk of sarcopenia during twelve-year follow-up. It may be prudent to target those with multimorbidity to aid in the prevention of sarcopenia.

Key Words: Multimorbidity; Sarcopenia; ELSA; Older Adults; Epidemiology; Aging; Comorbidity; Cohort; Prospective.

INTRODUCTION

Sarcopenia refers to “age-related muscle loss, affecting a combination of appendicular muscle mass, muscle strength, and/or physical performance measures” (1) and is now widely considered to be a disease since its introduction in the ICD-10-CM in 2016.(2) Sarcopenia is most prevalent amongst older adults. For example, a recent meta-analysis including community-dwelling adults aged ≥ 55 years reported a prevalence of at least 10%.(3) Given that muscle mass accounts for up to 60% of body mass, pathological changes to this metabolically active tissue can have profound consequences on the older adult.(4) For example, an umbrella review with integrated meta-analyses identified that sarcopenia is associated with high risk of mortality, disability, and falls, supported by a highly suggestive evidence.(5) Consequently, sarcopenia is associated with significantly high health care costs. (5) Considering the high prevalence of sarcopenia in older adults, the detrimental effects on health, and the considerable health care costs, it is important to identify risk factors of sarcopenia in older adults to inform targeted intervention.

To date, there is growing interest in the role of multimorbidity as a risk factor for sarcopenia. Multimorbidity may be defined as the presence of two or more long-term health conditions(6) and its prevalence increases with age. Multimorbidity is feasibly associated with sarcopenia via factors such as chronic low-grade inflammation.(7) Indeed, chronic low-grade inflammation contributes to the loss of muscle mass, strength and functionality, which are components of sarcopenia, by affecting both muscle protein breakdown and synthesis through several signaling pathways.(8) To the best of the authors’ knowledge, just two studies have focused specifically on the association between multimorbidity and sarcopenia. One cross-sectional study in a sample of 499,046 UK adults aged 40-70 years found that multimorbidity was associated with nearly twice the odds of probable sarcopenia [odds ratio, OR 1.96 (95% CI: 1.91, 2.02)].(9) In another study including 10,118 Korean adults aged ≥ 40 years, it was found that there was a significant association between sarcopenia and multimorbidity [odds ratio (OR): 1.49, 95% confidence interval (CI): 1.31–1.70].(10) However, a key

limitation of these existing studies is that they are cross-sectional in nature meaning that it is not known whether multimorbidity leads to sarcopenia or vice versa. Prospective longitudinal studies are therefore required to determine the direction of the association

Given this background, the aim of the present study was to investigate the association between multimorbidity at baseline and new onset sarcopenia over 12 years of follow-up in a large representative sample of English older adult population.

MATERIALS AND METHODS

Study population

This study is based on data from four waves (Wave 2, 4, 6, 8) of the English Longitudinal Study of Ageing (ELSA), which is a prospective and nationally representative cohort of men and women living in England.(11) Only data from these four waves were used as they were the only waves which included data on sarcopenia. Wave 2 (baseline survey) was conducted between 2004-2005, Wave 4 between 2008-2009, Wave 6 between 2012-2013, and Wave 8 between 2016-2017. The ELSA was approved by the London Multicentre Research Ethics Committee (MREC/01/2/91). Informed consent was obtained from all participants.

Multimorbidity (exposure variable)

At baseline (Wave 2), the presence of medical conditions was collected using self-reported information on doctor diagnosed diabetes, hypertension, stroke, myocardial infarction, congestive heart failure, angina, lung disease, asthma, arthritis, osteoporosis, cancer, Parkinson's disease, Alzheimer's disease, other dementias, and eye conditions including macular degeneration and glaucoma. We also defined depression using the Center for Epidemiologic Studies Depression Scale (CES-D), with a score over 4 points indicating depression.(12) The total number of chronic conditions was then summed and multimorbidity was defined as ≥ 2 chronic conditions, in line with previously used definitions. (6)

Sarcopenia (dependent variable)

Following the criteria of the revised European consensus on the definition and diagnosis of sarcopenia(13), this condition was defined as having weak handgrip strength (defined as $<27\text{kg}$ for men and $<16\text{kg}$ for women using the average value of three handgrip measurements of the dominant hand)(13) and low skeletal muscle mass (SMM) as reflected by lower skeletal mass index (SMI). SMM was calculated based on the equation proposed by Lee and colleagues(14): $\text{SMM} =$

$0.244 * \text{weight} + 7.8 * \text{height} + 6.6 * \text{sex} - 0.098 * \text{age} + \text{race} - 3.3$ (where female=0 and male=1; race=0 [White and Hispanic], race=1.9 [Black] and race=-1.6 [Asian]). SMM was further divided by body mass index (BMI) based on weight and height measured by a trained nurse, to create a SMI.(15) Low SMM was defined as the lowest quartile of the SMI based, on sex-stratified values.(16) The same algorithm was used to define sarcopenia at baseline and also at all follow-ups (wave 4, 6, 8).

Covariates

The selection of covariates was based on their previously reported associations with the exposure (sarcopenia) and outcome (multimorbidity) and included the following: age; sex; years of education (considered as continuous variable); ethnicity (whites vs. non-whites); marital status (married vs. other status); smoking status (ever vs. never); physical activity level (high vs. moderate/low/sedentary); presence of obesity, classified according to the World Health Organization criteria as having a body mass index $\geq 30 \text{ Kg/m}^2$ vs. other categories. All these variables were assessed at baseline.

Statistical analyses

The data were weighted using the person-level longitudinal weight, core sample, wave 2 (<http://www.ifs.org.uk/ELSA>). The analyses were restricted to those aged ≥ 60 years at baseline as sarcopenia is an age-related condition. Means and standard deviations (SD) were used to describe quantitative measures, while percentages and counts were used for categorical variables. Characteristics of the study participants at baseline (wave 2) were compared according to the presence of multimorbidity at baseline with the use of Chi-squared or Fisher exact tests for categorical variables, and independent T-test for continuous variables.

The analyses were restricted to those who did not have sarcopenia at baseline to assess the prospective risk of sarcopenia among people who are free of this condition at baseline. The association between

multimorbidity at baseline or the number of chronic conditions as a continuous variable and incident sarcopenia (i.e., sarcopenia at follow up) was assessed using univariable and multivariable logistic regression analysis and reported as odds ratios (OR) and 95% confidence intervals (95% CI). The multivariable analysis was adjusted for age, sex, ethnicity, marital status, smoking status, physical activity, and presence of obesity. In the fully-adjusted model, we included factors significantly different between people with multimorbidity and those without and/or associated with incident sarcopenia in univariate analyses, using a conservative p-value <0.10 . To test the robustness of our findings, we ran several sensitivity analyses (i.e, by gender, race, marital and smoking status, physical activity level, obesity and median age and by the presence or not of specific medical conditions), as reported in **Supplementary Table 1**.

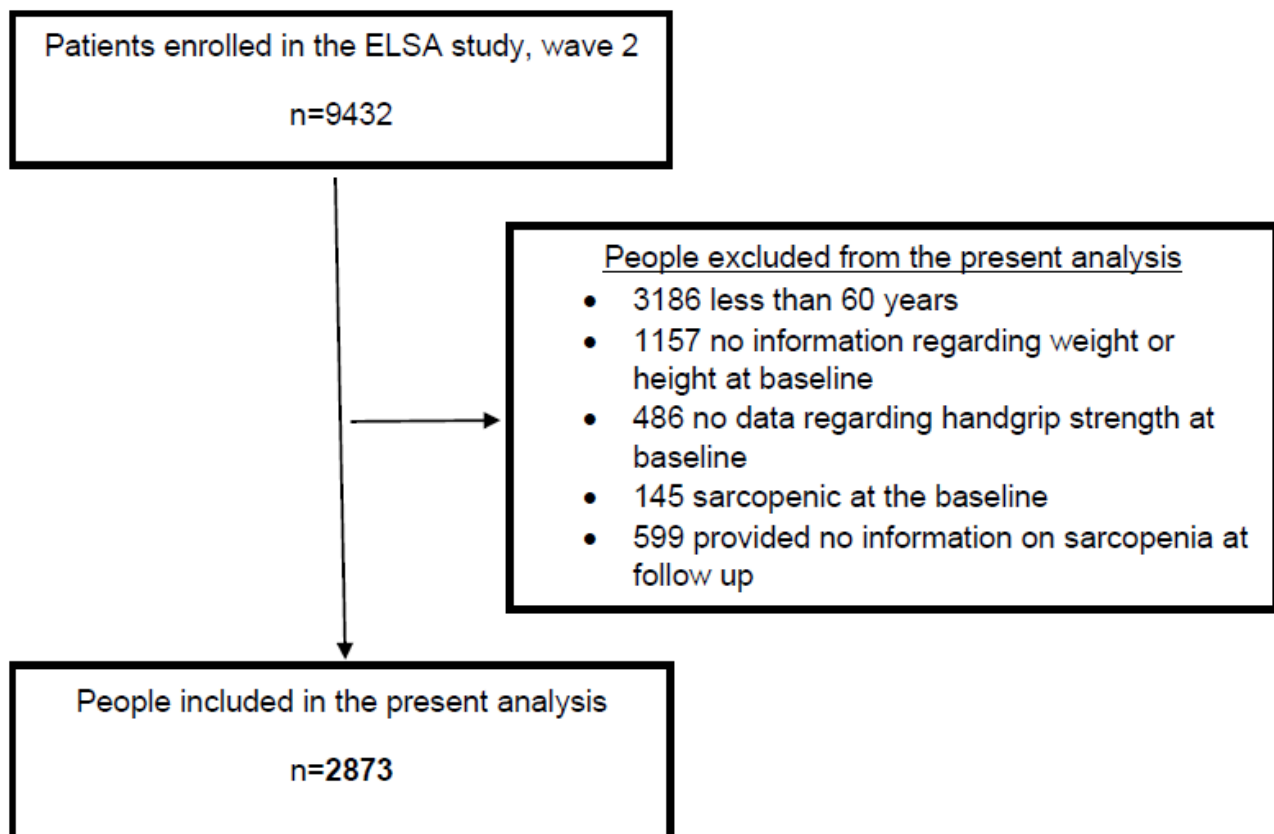
All statistical tests were two-tailed, and a p-value < 0.05 was statistically significant. All analyses were performed using SPSS 21.0 version software.

RESULTS

Sample selection

Of the 9,432 participants included in wave 2 (baseline) of the ELSA study, 3,186 were excluded for being younger than 60 years, 1,157 since no information regarding body composition was available, 486 since no data regarding handgrip strength was available, and 145 because they already had sarcopenia at baseline. Furthermore, 599 were also deleted as they provided no information on sarcopenia during any of the follow-up assessments. Therefore, our analytic study population included 2,873 older individuals (**Figure 1**, unweighted data).

Figure 1. Flow-chart of the selection of participants



The mean age of the 2,867 participants was $69.1 \pm \text{SD } 6.7$ years (range: 60-90), 54.0% were females. Overall, the prevalence of multimorbidity at baseline was 57.3%, with a median number of medical conditions of 2 (range: 0-8). **Table 1** shows the main descriptive characteristics of the participants included, according to the presence or absence of multimorbidity at baseline. People having multimorbidity (n=1,645) were significantly older, more frequently females, married, and smokers, and less educated than their counterparts (n=1,228) ($p < 0.0001$ for all these comparisons). As expected, people with multimorbidity were less frequently physically active, were more obese and had worse status in terms of the individual components of sarcopenia (i.e., SMMI, handgrip strength) (**Table 1**).

Table 1. Baseline characteristics by presence or absence of multimorbidity

Parameter	Presence of MM (n=1645)	Absence of MM (n=1228)	p-value	Missing data (number)
Age (mean, SD)	70.2 (6.7)	67.4 (6.0)	<0.0001	0
Female gender (n, %)	974 (59.2)	598 (48.9)	<0.0001	0
Years of education (mean, SD)	6.8 (6.9)	7.9 (6.9)	<0.0001	115
Whites (n, %)	1623 (98.7)	1210 (99)	0.49	0
Married (n, %)	1037 (63.1)	897 (73.4)	<0.0001	133
Ever smoked (n, %)	1044 (63.5)	700 (57.3)	0.001	0
High physical activity level (n, %)	262 (15.9)	314 (25.7)	<0.0001	2
SMMI (kg/m ²) (Mean, SD)	0.85 (0.21)	0.92 (0.22)	<0.0001	0
Body mass index (kg/m ²) (Mean, SD)	28.4 (4.7)	27.3 (4.1)	<0.0001	0
Handgrip strength (Kg) (Mean, SD)	27.6 (10.0)	31.3 (10.0)	<0.0001	0

Abbreviations: SD: standard deviation; SMMI: skeletal muscle mass index; MM: Multimorbidity.

Table 2 shows the association between multimorbidity at wave 2 and incident sarcopenia. In the univariable analysis, multimorbidity at wave 2 was associated with a higher incidence of sarcopenia by about two times (OR=2.06; 95%CI: 1.61-2.62; $p<0.0001$): this association remained statistically significant after adjusting for seven potential confounders (OR=1.23; 95%CI: 1.01-1.61; $p=0.03$) (**Table 2**). A one-unit increase in medical conditions at baseline was associated with an increased risk of sarcopenia during follow-up, even after adjusting for potential confounders (OR=1.09; 95%CI: 1.002-1.19; $p=0.04$) (**Table 2**).

Table 2. Association between multimorbidity or number of chronic conditions at baseline and incident sarcopenia (weighted data)

	Univariable		Fully-adjusted	
	model	p-value	model ¹	p-value
	(OR, 95% CI)		(OR, 95% CI)	
No multimorbidity	Reference	-	Reference	-
Multimorbidity	2.06 (1.61-2.62)	<0.0001	1.23 (1.01-1.61)	0.03
Increase in one medical condition	1.30 (1.21-1.39)	<0.0001	1.09 (1.002-1.19)	0.04

Data are reported as odds ratios (ORs) with their 95% confidence intervals (CIs).

¹Fully-adjusted model included: age (as continuous variable); gender; years of education (as continuous variable); ethnicity (whites vs. non-whites); marital status (married vs. other status); smoking status (ever vs. never); physical activity level (high vs. others); presence of obesity vs. underweight/normal weight/overweight.

DISCUSSION

In this longitudinal analysis using a large representative sample of the UK older adult population, after adjustment for potential confounders, it was found that those with multimorbidity at baseline had a 1.33 higher risk of sarcopenia over twelve years of follow-up, compared to those without multimorbidity at baseline. Furthermore, an increase in one condition at baseline was associated with a 1.11 times higher risk for new onset sarcopenia after adjustment.

One first important consideration is the relatively high prevalence of multimorbidity detected at baseline evaluation. Overall, more than half of the population included had two or more medical conditions. This finding emphasizes the importance of addressing multimorbidity in our ageing populations. The present findings both support and add to previous literature. They support previous literature through confirming that an association exists between multimorbidity and sarcopenia in a large representative sample of older English adults and add to the existing literature through demonstrating that multimorbidity at baseline is associated with a higher odds of sarcopenia over twelve years of follow-up. (9, 10)

There are several plausible mechanisms that likely explain why multimorbidity at baseline increases odds for sarcopenia at follow-up. First, as previously discussed multimorbidity is associated with higher levels of chronic low-grade inflammation(8) and chronic low-grade inflammation is likely implicated in the development of sarcopenia owing to affecting both muscle protein breakdown and synthesis through several signaling pathways.(5) Second, multimorbidity is associated with polypharmacy in order to treat multiple chronic conditions. Indeed, many medications can affect and interfere with various metabolic processes and circulatory homeostasis and this in turn can increase the risk of developing sarcopenia.(17) Third, multimorbidity is associated with a reduction of activities of daily living, which has been as well associated with a reduction in muscle mass and strength.(18) Fourth, multimorbidity has been found to be related to an increased risk of sleep

problems(19), likely owing to pain and discomfort. Whereas sleep problems have been implicated in the onset of sarcopenia owing to endocrine factors and consequent reduction in muscle health.(20) Fifth, those with multimorbidity have demonstrated high levels of sedentary time and high levels of sedentary behavior have been found to increase risk of sarcopenia. (21)

Findings from the present study suggest that it may be prudent to target those with multimorbidity to aid in the prevention of sarcopenia. Targeting lifestyle behaviors among those with multimorbidity may yield positive results. Interventions to improve sleep quality, reduce sedentary time and improve diet may be effective. Such interventions may wish to focus on behavior change techniques such as persuasion, education, and self- monitoring.(22) Moreover, clinicians should be aware of the multimorbidity-sarcopenia relationship and should screen early for this condition in multimorbid people.

The large representative sample of the UK older adult population and the longitudinal design are clear strengths of the present study. However, findings must be considered in light of the study limitations. We used a single measure of muscle strength to assess sarcopenia. Although a unified geriatric assessment tool is yet to be widely implemented to diagnose sarcopenia, handgrip strength has been commonly used to measure muscle strength, a critical component of sarcopenia.(13) It has been widely used in research and clinical settings and shown to be an independent predictor of all-cause mortality. Moreover, body composition was based on a population equation and not direct assessment, that is the gold standard. However, this has been validated against gold standard methods such as magnetic resonance imaging and dual-energy X-ray absorptiometry.(23) Other limitations include limited adjustment for sub-clinical disease process and severity of disease. Moreover, residual confounding (i.e., not to include factors that can significantly affect our results as moderators or covariates in our analyses) is possible. Finally, the nutritional status of the participant is an important

determinant of sarcopenia: although anthropometric measures were present in the ELSA, other nutritional parameters were unfortunately unavailable.

In conclusion, in this large representative sample of older adults from the UK, multimorbidity at baseline was associated with a higher risk of sarcopenia at twelve-year follow-up. It may be prudent to target those with multimorbidity to aid in the prevention of sarcopenia.

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Conflict of interest: none.

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Data sharing: The study protocol and statistical analysis plan for this project are available on request from the corresponding author. Data are available from the UK Data Service for researchers who meet the criteria for access to confidential data. Data are from waves 2 to 8 of the ELSA study. Data

and contact details may be obtained via the website <http://www.adls.ac.uk/find-administrative-data/linked-administrative-data/english-longitudinal-study-of-ageing/>

Supplementary Table 1. Sensitivity analyses performed

Factor	p-value for the interaction*
Gender	0.76
Race	0.80
Marital status	0.61
Smoking status	0.58
Physical activity level	0.36
Obesity	0.23
Median age	0.37
High blood pressure	0.12
Diabetes	0.99
Presence of cardiovascular disease	0.73
Lung disease	0.51
Asthma	0.64
Arthritis	0.76
Osteoporosis	0.55
Cancer	0.54
Parkinson's disease	0.87
Psychiatric disease	0.91
Dementia	0.99
Glaucoma	0.30
Cataract	0.94
Depression	0.16

* p-values represent the interaction multimorbidity by factor in predicting incident sarcopenia.