Sarcopenic obesity and the risk of hospitalization or death from coronavirus disease 2019: findings from UK Biobank

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Abstract

Background  Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2. The role of skeletal muscle mass in modulating immune response is well documented. Whilst obesity is well established as a key factor in COVID-19 and outcome, no study has examined the influence of both sarcopenia (low muscle mass) and obesity, termed ‘sarcopenic obesity’ on the risk of severe COVID-19.

Methods  This study uses data from UK Biobank. Probable sarcopenia was defined as low handgrip strength. Sarcopenic obesity was mutually exclusively defined as the presence of obesity and low muscle mass [based on two established criteria: appendicular lean mass (ALM) adjusted for either (i) height or (ii) body mass index]. Severe COVID-19 was defined by a positive severe acute respiratory syndrome coronavirus 2 test result in a hospital setting and/or death with a primary cause reported as COVID-19. Fully adjusted logistic regression models were used to analyse the associations between sarcopenic status and severe COVID-19. This work was conducted under UK Biobank Application Number 52553.

Results  We analysed data from 490 301 UK Biobank participants (median age 70.0 years, 46% male); 2203 (0.4%) had severe COVID-19. Individuals with probable sarcopenia were 64% more likely to have had severe COVID-19 (odds ratio 1.638; \(P < 0.001\)). Obesity increased the likelihood of severe COVID-19 by 76% (\(P < 0.001\)). Using either ALM index or ALM/body mass index to define low muscle mass, those with sarcopenic obesity were 2.6 times more likely to have severe COVID-19 (odds ratio 2.619; \(P < 0.001\)). Sarcopenia alone did not increase the risk of COVID-19.

Conclusions  Sarcopenic obesity may increase the risk of severe COVID-19, over that of obesity alone. The mechanisms for this are complex but could be a result of a reduction in respiratory functioning, immune response, and ability to respond to metabolic stress.

Keywords  Coronavirus disease 2019; Sarcopenia; Obesity; Sarcopenic obesity

Introduction  Coronavirus disease 2019 (COVID-19), an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), reached pandemic status due to its infectivity and fatality.\(^1\) As of 29 April 2021, in the UK, there have been over 4 million confirmed cases resulting in over 127 000 deaths.\(^2\) Age, sex, ethnicity, frailty, and the pre-existence of multiple co-morbidities have been identified as important components associated with poor prognosis in

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COVID-19.\textsuperscript{1,3–5} Obesity has been recognized as a risk factor in previous infectious outbreaks and is highly prevalent in individuals with COVID-19.\textsuperscript{6} Obesity is now well established as a key factor of severe COVID-19 and COVID-19-related mortality,\textsuperscript{7–12} likely due to adverse changes in pulmonary function and reductions in immune system function concomitant with excessive adiposity,\textsuperscript{13} which exacerbate the direct effects of COVID-19-induced pneumonia.

The impact of COVID-19 on sarcopenia, characterized by reduced muscle mass and muscle strength, has received substantial interest in the literature, although work has predominantly focused on how COVID-19 and its consequential social restrictions (e.g. physical activity) can cause acute loss of muscle and function.\textsuperscript{14,15} The role of skeletal muscle mass in modulating immune response and supporting metabolic stress responses are well documented. Patients with sarcopenia have been shown to have compromised intercostal muscle strength and respiratory function, which are detrimental in the treatment of severe pneumonia and acute respiratory distress syndrome.\textsuperscript{16} have higher incidence of community-acquired and in-hospital pneumonia, and are reported to have reduced ability to respond to systemic stress when facing acute infection, major surgeries, and other illness.\textsuperscript{14,17,18} Currently, no study has investigated the relationship between sarcopenia and risk of severe COVID-19.\textsuperscript{14} It is likely that individuals with sarcopenia respond poorly to infection with COVID-19 because of impaired immune potential.

The presence of both sarcopenia and obesity is termed ‘sarcopenic obesity’\textsuperscript{19} and has been associated with increased risk of disability, institutionalization, mortality, and metabolic diseases compared with sarcopenia or obesity alone.\textsuperscript{20,21} Consequently, given the potential adverse consequences of both obesity and sarcopenia on risk of severe COVID-19, it may be reasonable to expect that sarcopenic obesity could result in more serious prognosis and infection risk. To our knowledge, there have been no community-based studies on the association between sarcopenic status and risk of severe COVID-19. In this study, we aimed to compare the association between sarcopenic status, alone and in combination with obesity, and risk of severe COVID-19 resulting in hospital admission or death in UK Biobank.

Methods

Data source

This study uses data from UK Biobank. Over 500 000 participants, aged 37–73 years from the general population, were recruited into UK Biobank study between March 2006 and December 2010. Participants attended one of 22 assessment centres across the UK where they completed a touchscreen questionnaire, had physical measurements taken, and provided biological samples, as described in detail elsewhere.\textsuperscript{22} UK Biobank was approved by the North West Multi-Centre Research Ethics Committee (11/NW/0382). All participants provided written informed consent to participate in the UK Biobank study. This work was conducted under the UK Biobank Application Number 52553.

Exposure

Our exposure of interest was sarcopenic obesity status as reported at baseline. We undertook our analysis using two different sarcopenia criteria proposed by the European Working Group of Sarcopenia in Older People (EWGSOP2) and Foundation for the National Institutes of Health Sarcopenia Project. The role of dynapenia, a condition characterized by an age-related decline in muscle strength, is now considered a principal determinant of ‘probable sarcopenia’.\textsuperscript{23} As per the EWGSOP2, in our sample, probable sarcopenia was defined as low handgrip strength (HGS) (\textless{}16 kg in women and \textless{}27 kg in men).\textsuperscript{23} A single maximum HGS score was taken from the highest value attained from both hands.

Low muscle mass was defined as an appendicular lean mass (ALM) below specific cut-off indices. ALM was derived from the sum of fat-free mass (FFM) of the arms and legs taken from bioelectrical impedance analysis data assessed during baseline assessment visit. For this measure, participants stood barefoot on the device (Tanita BC418MA), holding both metal handles. ALM was calculated using a previous published equation,\textsuperscript{24} which estimated ALM from the appendicular FFM values: ALM (kg) = (0.958 \times (Appendicular FFM (kg)) – (0.166 \times G) – 0.308, with G taking value 0 if female and 1 if male.

Sarcopenia was defined as either

(i) ALM index (ALM/height\textsuperscript{2}) \textless{}7.26 kg/m\textsuperscript{2} for men and \textless{}5.45 kg/m\textsuperscript{2} for women as per EWGSOP2 criteria\textsuperscript{23} or
(ii) ALM/body mass index (BMI) \textless{}0.789 in men and \textless{}0.512 in women as per Foundation for the National Institutes of Health Sarcopenia Project criteria.\textsuperscript{25}

Sarcopenic obesity was mutually exclusively defined as the presence of obesity and low muscle mass (using both ALM index definitions). Obesity was defined as excessive body fat % (BF%) using cut-offs of >25% in men and >35% in women.\textsuperscript{21} We defined obesity using adiposity (i.e. BF%) rather than BMI, which can be confounded by the inclusion of lean mass. A ‘normal’ reference group consisted of those without sarcopenia, obesity, or sarcopenic obesity as per the definitions earlier.
**Outcomes**

Public Health England provided the SARS-CoV-2 test results (available from 16 March 2020), including the specimen date, origin (evidence that the individual was an inpatient or not), and result (positive or negative) of the test. Latest test result data were available up until 2 February 2021. Records were linked to inpatient Hospital Episode Statistics and national mortality registers (latest mortality data were available up to 16 February 2021). As per previous studies, the outcome of interest was a positive test result for SARS-CoV-2 in those admitted to hospital and/or death with a primary cause reported as COVID-19 (ICD-10 Code U07.1). It has previously been noted that a positive test result for SARS-CoV-2 in those admitted to hospital can act as a marker of disease severity within UK Biobank, although the actual severity of the disease is not recorded within the linked test dataset. By focusing on hospital cases and deaths, we limit the potential bias due to differential ascertainment (as these cases likely reflect more severe COVID-19 disease) and exclude those who were tested because they were a healthcare worker. Therefore, for descriptive purposes only, we refer to the composite of a test result for SARS-CoV-2 in those admitted to hospital or death from COVID-19 as indicating ‘severe’ COVID-19 disease. Participants were excluded from the dataset if they were not alive during the pandemic (i.e. died before 11 March 2020, the date pandemic declared by the World Health Organization).

**Statistical analysis**

Analysis was based on a whole population level approach as described previously for UK Biobank analysis, with severe COVID-19 cases compared with the remaining UK Biobank population. Fully adjusted logistic regression models were used to analyse the associations between sarcopenic status (defined using either criterion) and severe COVID-19. A sensitivity analysis examining the association of each ALM index individually was also performed. The results are reported as odds ratios (ORs) with their 95% confidence intervals (95% CIs).

**Results**

**Participant characteristics**

In total, data (with exposure and confounders) were available for 490,301 participants, of which 2203 (0.4%) had severe COVID-19. Characteristics of participants, stratified by COVID-19 status, are reported in Table 1. The median age was 70 years, with ~50% of the cohort male. The majority of participants were White.

| Total n | No COVID-19-associated admission or death | Severe COVID-19 |
|---------|------------------------------------------|-----------------|
| 488 098 | 2203                                     |

**Table 1** Basic participant characteristics stratified by severe COVID-19 status

| Total n | No COVID-19-associated admission or death | Severe COVID-19 |
|---------|------------------------------------------|-----------------|
| 488 098 | 2203                                     |
| Age (years) | 70.0 (13.0) | 70.0 (16.0) |
| Sex (male), n (%) | 225 559 (46%) | 1146 (52%) |
| Ethnicity | White | 462 460 (95%) | 1986 (90%) |
| | Non-White | 25 638 (5%) | 217 (10%) |
| No. with ≥1 cancer illnesses, n (%) | 40 271 (8%) | 201 (9%) |
| No. with ≥1 non-cancer illnesses, n (%) | 363 966 (75%) | 1783 (81%) |
| Townsend deprivation index | –2.2 (4.2) | –1.2 (5.0) |
| Probable sarcopenia | 26 444 (5%) | 189 (9%) |
| Low muscle mass | Low ALM/height² index | 8296 (2%) | 25 (1%) |
| | Low ALM/BMI | 8223 (2%) | 70 (3%) |
| | Either index | 9267 (2%) | 75 (4%) |
| Obesity | 270 063 (57%) | 1501 (70%) |

ALM, appendicular lean mass; BMI, body mass index; COVID-19, coronavirus disease 2019.

Data shown as median and inter-quartile range or n (%). Cancer illnesses included any incidence of cancer including bowel, skin, prostate, and leukaemia; non-cancer illnesses included cardiovascular disease, respiratory conditions, diabetes, and neurodegenerative disease.
Probable sarcopenia and risk of severe coronavirus disease 2019

Probable sarcopenia was present in 189 (8.6%) of those with severe COVID-19, compared with 26,444 (5.4%) in those without severe COVID-19. Individuals with probable sarcopenia were 64% more likely to have had severe COVID-19 (adjusted OR 1.638 [95% CI: 1.411–1.903]; \( P < 0.001 \)), compared with those without probable sarcopenia (Figure 1 and Supporting Information, Tables S1 and S2). There was no significant effect of obesity on the association between probable sarcopenia and risk of severe COVID-19 (\( P = 0.839 \)) (Table S3).

Sarcopenic obesity and risk of severe coronavirus disease 2019

Using either index to define low muscle mass, data were available for 478,683 participants, of which 21,33 (0.4%) had severe COVID-19. In participants with severe COVID-19, 616 (28.9%) had no sarcopenia, obesity, or sarcopenic obesity [compared with 199,646 (41.9%) in those without severe COVID-19]. Sixteen (0.8%) severe COVID-19 cases had sarcopenia (vs. 6964, 1.5%), 1426 (66.9%) were obese (vs. 260,673, 54.7%), and 75 (3.5%) had sarcopenic obesity (vs. 9267, 1.9%; Table S4).

Obese individuals were 1.8 times more likely to have severe COVID-19 [adjusted OR 1.761 (95% CI: 1.602–1.935); \( P < 0.001 \)]. Individuals with sarcopenic obesity were 2.6 times more likely to have severe COVID-19 [adjusted OR: 2.880 (95% CI: 2.248–3.691); \( P < 0.001 \)] (Figure 1 and Table S5). Sarcopenia alone did not increase the risk of severe COVID-19.

Discussion

Although evidence suggests that obesity is a key risk factor for severe COVID-19, no data exist on the association of sarcopenia and COVID-19 and also, importantly, when obesity occurs in the presence of sarcopenia (or low muscle mass), termed ‘sarcopenic obesity’. Using UK Biobank, we examined the association with different measures of sarcopenia and sarcopenic obesity with risk of severe COVID-19. We found that (i) individuals with probable sarcopenia (defined as low HGS) were at higher risk of severe COVID-19 compared with those without probable sarcopenia and (ii) sarcopenic obesity significantly increased the likelihood of severe COVID-19 above that of obesity alone (regardless of low muscle mass definition).

Figure 1 Odds ratios for risk of severe coronavirus disease 2019 across sarcopenia status. Data presented as odds ratios and 95% confidence intervals (CIs). Adjusted for current age, sex, ethnicity, Townsend deprivation index, and number of cancer and non-cancer illnesses. Probable sarcopenia was defined as low handgrip strength (<16 kg in women and <27 kg in men); sarcopenic obesity was defined as the presence of obesity and sarcopenia [defined as either low muscle using appendicular lean mass (ALM)/height index or ALM/body mass index]; a ‘normal’ reference group consisted of those without sarcopenia, obesity, or sarcopenic obesity.
It is well established that obesity is a significant risk factor in severe COVID-19 and COVID-19-related mortality.\(^7\)\(^-\)\(^12\) The link between obesity and COVID-19 is multifaceted: obesity is associated with decreased expiratory reserve volume, functional capacity, and respiratory system compliance. In patients with increased abdominal obesity, pulmonary function is further compromised in supine patients by decreased diaphragmatic excursion, making ventilation more difficult. Furthermore, increased inflammatory cytokines associated with obesity may contribute to the increased morbidity associated with obesity in COVID-19 infections.\(^13\) Our data support the previous work showing that obesity remains a significant risk factor in COVID-19.

Sarcopenia is characterized by reduced muscle mass and muscle strength. Although the exact criteria to define it differ, reduced skeletal muscle mass is a fundamental feature across all definitions. There is robust evidence for an impaired immune response in patients with sarcopenia, including a higher incidence of community-acquired and in-hospital pneumonia, and an increased risk of infectious complications following surgeries.\(^14\),\(^17\),\(^18\) A key mechanism underlying the impaired immunity in individuals with sarcopenia refers to the abnormal myokines, such as interleukin (IL)-15, IL-17, and IL-6. Cytokines, such as IL-6, facilitate muscle atrophy by blunting muscle anabolism and directly mediate muscle catabolism and also may modulate the proliferation and function of both innate and adaptive immune cells.\(^30\) In particular, elevated IL-6 levels have been consistently reported in studies of COVID-19, and excessive IL-6 may explain the overly activated pro-inflammatory Th17 cells observed in COVID-19 patients.\(^31\) During severe infection, skeletal muscle is catabolized to provide the immune system, liver, and gut with amino acids, especially glutamine\(^22\); patients with sarcopenia have a decreased availability of such protein mobilization. Furthermore, compromised intercostal muscle strength and respiratory function could further exacerbate a failure in ventilatory function. In the context of severe COVID-19 risk, therefore, it is likely that skeletal muscle has an important role in respiratory functioning, modulating immune response, and supporting metabolic stress.\(^14\)

Given the low prevalence of mutually exclusive sarcopenia (i.e. individuals with just low muscle mass) in UK Biobank,\(^24\) it was difficult to ascertain the independent effect of sarcopenia alone on severe COVID-19 risk. However, we found that there was a greater number of individuals with sarcopenic obesity, which was present in over 9000 individuals when sarcopenia was defined using either index. In particular, the prevalence of sarcopenic obesity was greater when using ALM adjusted for BMI (recommended as a more valid index of muscle mass above ALM adjusted for only height\(^25\),\(^33\)). We found that sarcopenic obesity increased the odds of severe COVID-19 approximately three times, compared with those who were just obese (1.8 times). Given the detrimental independent effects of low muscle mass and obesity, this result is perhaps unsurprising although highlights the severe detrimental effects of sarcopenic obesity. It is important to note that the risk of COVID-19 did not significantly change across either ALM index to define low muscle mass.

The interaction between sarcopenia, obesity, and sarcopenic obesity with COVID-19 is likely bidirectional. COVID-19 could be a risk factor for the incidence and progression of sarcopenic obesity because of the reduced physical activity and inadequate diet (e.g. low protein intake) caused by social isolation and restrictions in mobility. The inflammatory reaction caused by COVID-19 may also exacerbate metabolic stress and muscle catabolism,\(^14\) although we cannot infer this in our cohort here. Therapeutic approaches targeting skeletal muscle and adiposity should form a fundamental part in the treatment of COVID-19. Physical activity, especially resistance exercise, can help increase muscle mass and reduce body fat, whilst appropriate nutritional management (i.e. a balanced nutritional formula with high-quality protein—rich in leucine) can help promote muscle synthesis.\(^14\) Specialist physiotherapy targeting respiratory muscle function and lung capacity may also form an important part of COVID-19 rehabilitation.\(^34\)

Whilst UK Biobank offered a large cohort of individuals with linked data to both COVID-19 testing and outcomes, it is limited by low initial response rate (5.5%) and evidence of a ‘healthy responder’ bias.\(^35\) This ‘healthy responder’ bias may explain the low prevalence of sarcopenia as previously described.\(^24\) Sarcopenic obesity status was also taken from baseline assessments, which were performed a decade ago (between 2006 and 2010). Given that sarcopenia, and other variables such as co-morbidity, in particular is likely to worsen with age, the results presented here could underestimate the current sarcopenia prevalence and therefore overestimate the effect on severe COVID-19 risk. As discussed earlier, we chose a composite of a test result for SARS-CoV-2 in those admitted to hospital or death from COVID-19 as indicating ‘severe’ COVID-19 disease. This is due to constraints of the data available in the UK Biobank (e.g. no data available on variables such as oxygen saturation or respiratory rate). Our definition has been used in previous work investigating COVID-19 outcomes in UK Biobank.\(^26\)

In conclusion, the presence of sarcopenic obesity may increase the risk of severe COVID-19, over that of obesity alone. The mechanisms for this association are complex but could be a result of a reduction in respiratory functioning, immune response, and ability to respond to metabolic stress. Therapeutic approaches targeting both skeletal muscle and adiposity should form a key part in the treatment of COVID-19.
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The authors of this manuscript certify that they comply with the ethical guidelines for authorship and publishing in the Journal of Cachexia, Sarcopenia and Muscle. 36

Conflict of interest

None declared.

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Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Probable sarcopenia stratified by severity of COVID-19.
Table S2. Association of probable sarcopenia with risk of severe COVID-19.
Table S3. Association of probable sarcopenia with risk of severe COVID-19 stratified by obesity status.
Table S4. Sarcopenic status stratified by severe COVID-19 using either ALM indices.
Table S5. Association of sarcopenic status with risk of severe COVID-19 using either ALM indices.
Table S6. Sarcopenic status stratified by severe COVID-19 using ALM index.
Table S7. Association of sarcopenic status with risk of severe COVID-19 using ALM index.
Table S8. Sarcopenic status stratified by severe COVID-19 using ALM/BMI index.
Table S9. Association of sarcopenic status with risk of severe COVID-19 using ALM/BMI index.

Figure S1. Sarcopenic status stratified by severe COVID-19.
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