Diagnosis, prevalence, and clinical impact of sarcopenia in COPD: a systematic review and meta-analysis

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Abstract

Sarcopenia prevalence and its clinical impact are reportedly variable in chronic obstructive pulmonary disease (COPD) due partly to definition criteria. This review aimed to identify the criteria used to diagnose sarcopenia and the prevalence and impact of sarcopenia on health outcomes in people with COPD. This review was registered in PROSPERO (CRD42018092576). Five electronic databases were searched to August 2018 to identify studies related to sarcopenia and COPD. Study quality was assessed using validated instruments matched to study designs. Sarcopenia prevalence was determined using authors’ definitions. Comparisons were made between people who did and did not have sarcopenia for pulmonary function, exercise capacity, quality of life, muscle strength, gait speed, physical activity levels, inflammation/oxidative stress, and mortality. Twenty-three studies (70% cross-sectional) from Europe (10), Asia (9), and North and South America (4) involving 9637 participants aged ≥40 years were included (69.5% men). Sarcopenia criteria were typically concordant with recommendations of European and Asian consensus bodies. Overall sarcopenia prevalence varied from 15.5% (95% confidence interval (CI) 11.8–19.1) combined muscle mass, strength, and/or physical performance criteria) to 34% (95%CI 20.6–47.3; muscle mass criteria alone) (P = 0.009 between subgroups) and was greater in people with more severe [37.6% (95%CI 24.8–50.4)] versus less severe [19.1% (95%CI 10.2–28.0)] lung disease (P = 0.020), but similar between men [41.0% (95%CI 26.2–55.9%)] and women [31.9% (95%CI 7.0–56.8%)] (P = 0.538). People with sarcopenia had lower predicted forced expiratory volume in the first second (mean difference −7.1%; 95%CI −9.0 to −5.1%) and poorer exercise tolerance (standardized mean difference −0.8; 95%CI −1.4 to −0.2) and quality of life (standardized mean difference 0.26; 95%CI 0.2–0.4) compared with those who did not (P < 0.001 for all). No clear relationship was observed between sarcopenia and inflammatory or oxidative stress biomarkers. Incident mortality was unreported in the literature. Sarcopenia is prevalent in a significant proportion of people with COPD and negatively impacts upon important clinical outcomes. Opportunities exist to optimize its early detection and management and to evaluate its impact on mortality in this patient group.

Keywords Sarcopenia; COPD; Prevalence; Diagnosis; Aging

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Introduction

Chronic obstructive pulmonary disease (COPD) is a condition characterized by chronic inflammation\(^1\) and extrapulmonary changes that negatively affect physical function (e.g. lower levels of physical activity\(^2\) and reductions in muscle mass and strength\(^3,4\)\)) and quality of life.\(^5,6\) The presence of such factors is also closely related to the presence of sarcopenia,\(^7\) a syndrome characterized by lower muscle mass, muscle strength, and physical performance.\(^7\) Sarcopenia is a significant contributor to frailty in the elderly population and is associated with increased rates of falls, hospitalization, and mortality.\(^8,9\) It has been estimated to occur in approximately 5–13% of the ‘healthy’ older population.\(^4,7\)

People with COPD appear to have an increased risk of developing sarcopenia, with prevalence estimates ranging from 15%\(^2\) to 55%.\(^10\) In this patient group, sarcopenia appears to confer a negative impact upon clinical outcomes related to function and health\(^1,3,11–13\) and its prevalence appears to increase with increasing COPD-related impairment. Although sarcopenia has also been shown to contribute towards poorer prognosis in people with COPD,\(^2,3\) the real clinical impact has not yet been analysed. Additionally, the wide-ranging prevalence estimates of sarcopenia in COPD, however, make its true impact somewhat difficult to accurately ascertain.

A significant factor contributing to this large variability appears to be choice of definition criteria.\(^2,3,14\) International recommendations exist for the diagnosis of sarcopenia in older people such as those proposed by the European Working Group of Sarcopenia in Older People (EWGSOP)\(^7\) and the Asian Group of Sarcopenia,\(^15\) yet these have not been featured in published literature in the field of COPD. Considering the prevalence of both sarcopenia and COPD increase with increasing age, the impact of sarcopenia on a broader range of clinically important COPD-related outcomes is also not currently clear. This review therefore aimed to evaluate the literature pertaining specifically to people with COPD to identify the criteria used to diagnose sarcopenia, estimate its prevalence, and evaluate its impact upon health outcomes.

Methodology

Data sources and search strategy

The protocol for this review was registered in PROSPERO (CRD42018092576). Five electronic databases (i.e. PubMed, LILACS, EMBASE, The Cochrane Library, and Scielo) were searched from inception until August 2018 using the following free-text and subject heading terms: ‘COPD’, ‘pulmonary disease, chronic obstructive’, ‘chronic obstructive lung disease’, ‘COAD’, ‘chronic obstructive airway disease’, and ‘sarcopeni*’ (Supporting Information, Table S1). Hand searching of reference lists from included articles was also conducted to identify additional potential studies. To be eligible for inclusion, studies must have been conducted on adults with COPD (aged ≥40 years), defined according to authors, irrespective of disease severity (GOLD: Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease\(^16\) and reported upon a diagnosis of sarcopenia, defined according to any criteria provided it was stated in the methodology. Considering the nature of our research question, we included observational (e.g. cohort) and cross-sectional studies and clinical trials (whether randomized or not). Abstracts and publications published in languages other than English, Spanish, or Portuguese were not eligible for inclusion.

The principal outcomes for this review were (i) the criteria used to define sarcopenia and its prevalence and (ii) clinical data from studies that provided comparative data between people with COPD who did and did not have sarcopenia, as follows: (a) quality of life, from either generic or respiratory-specific quality of life questionnaires; (b) physical function, derived from common clinical tests of exercise capacity, muscle strength, and balance; (c) physical activity levels, measured by objective physical activity monitors; (d) pulmonary function, measured by spirometry (e.g. FEV\(_1\)% predicted); (e) inflammatory or oxidative stress biomarkers [e.g. interleukin (IL)-6, tumour necrosis factor-alpha, C-reactive protein, catalase, paraxonase-1]; and (f) all-cause mortality.

Data management and quality appraisal

Database search yields were collated within a bibliographical reference manager software (StArt v.3.03\(^17\)), and duplicates were discarded. Citations were screened for eligibility upon title and abstract by two independent reviewers (W.S.L and A.A.M) and classified as either ‘include’, ‘exclude’, or ‘maybe’. Those deemed ‘include’ or ‘maybe’ were reviewed in full text to derive a final yield, with any disagreements resolved via a third, independent assessor (V.S.P). This process was summarized in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations.\(^18\) Data were extracted by two members of the team (W.S.L and A.A.M) using standardized templates appropriate for the study objectives.

Study quality was appraised using validated instruments tailored according to study design, as follows: (i) National Institutes of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies, to assess the quality of cohort and cross-sectional studies; (ii) PEDro scale to assess the quality of randomized clinical trials; and (iii) Joanna Briggs Institute Critical Appraisal Checklist for Quasi-Experimental Studies to assess the quality of non-randomized controlled trials.

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**Statistical analysis**

An overall estimate of sarcopenia prevalence was derived by pooling the proportion of patients with COPD who had detected sarcopenia in individual studies in a meta-analysis. For this purpose, only one prevalence estimate was used from each study. Where individual studies reported different types of sarcopenia (e.g. sarcopenia with normal body mass index, sarcopenic obesity, severe sarcopenia), an aggregated value, if able to be determined, or the most ‘conventional’ type was used. In order to avoid double counting, estimates from individual studies that evaluated sarcopenia via multiple diagnostic criteria (e.g. comparisons of different cut-off thresholds within a single cohort) were pooled using their primary stated method or that which most closely resembled the current EWGSOP recommendation. Where able to be conducted, separate subgroup analyses were conducted to compare prevalence effect estimates between sarcopenia definitions (1 vs >1 diagnostic criteria), gender (male versus female), and disease severity (GOLD I–II versus III–IV), evaluated via $\chi^2$ test. This meta-analysis was performed via the ‘metaprop’ command in Stata SE 14.2 (Texas, USA) with 95% confidence intervals (CIs) calculated using the score (Wilson) method and a random-effects model (DerSimonian and Laird method) utilized due to the variability in sarcopenia definitions across studies.

Clinical outcome data from studies comparing people with COPD who did and did not have sarcopenia were meta-analysed via Review Manager 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen 2014). Continuous outcome data evaluated using homogenous metrics (e.g. same test instrument) were summarized as mean differences, while data arising from heterogenous metrics (e.g. same construct, different instrument) were summarized as standardized mean differences (SMDs) and 95%CI. A random-effects model was used as the principal method of analysis, with statistical heterogeneity described via the $I^2$ statistic and interpreted according to Deeks and colleagues (values <25% considered low, 50–75% moderate, and >75% high).

**Results**

A detailed summary of the literature search is provided in Figure 1. Two hundred and seventy-two unique records were identified through database searching, resulting in 23
articles involving 9637 participants included in the final review. Of these, seventeen adopted a cross-sectional design, five were observational cohort studies, and one was a non-randomized clinical trial. Most studies included patients with differing histories of smoking (those who never smoked and former and current smokers). Comparative data between people with COPD who did and did not have sarcopenia were available from 17 studies. The overall quality of included studies was ‘moderate’ (full details in Table S2). Characteristics of included studies are presented in Table 1. The review sample spanned a diverse range of populations, including ten studies from Europe, nine from Asia, and four from South America. Most participants were men (69.5%).

Methods used to assess sarcopenia

A summary of diagnostic criteria used to assess sarcopenia in the included studies is presented in Table 1. Measures of low muscle mass (LMM),1,2,9,32–34,39 low muscle strength (LMS),1,2,9,32–34,39 and low physical performance (LPP),2,9,32–34,37–39 were used as the basis of diagnosis. Fourteen studies used LMM as the sole criteria to diagnose sarcopenia, while LMM was combined with LMS and/or LPP in nine studies.1,2,9,32–34,37–39 Those studies utilized different cut-off points and methods to identify LMM, LMS, and LPP. Muscle mass was measured by dual-energy X-ray absorptiometry (sixteen studies),13,21,22,24–26,28,33–38,40 bioelectrical impedance analysis (six studies),1,2,23,27,31,32,39 and calf circumference (one study).29 Muscle strength was measured via handgrip dynamometry (seven studies).1,2,9,32–34,39 Physical performance was measured via gait speed (four studies)23,29,32,39 and 6 min walk test (6MWT) (four studies).33,34,37,38 The different cut-off thresholds used to define ‘positive’ responses to each test are presented in Table 2. Muscle mass, muscle strength, and physical performance were most commonly evaluated according to cut-off thresholds recommended by the EWGSOPO2 and the Asian Group of Sarcopenia.15 Comparisons between the main guidelines used to detect sarcopenia in individuals with COPD are available in Table S3.

Sarcopenia prevalence

Data were available for meta-analysis from 22 studies involving 9416 participants. The overall pooled prevalence estimate of sarcopenia in people with COPD was 27.5% (95%CI 18.4–36.5; Figure 2). These effect estimates were significantly higher in studies that used a single criterion [LMM; 34%, (95%CI 20.6–47.3)] than those that used >1 criteria [LMM + LMS and/or LPP; 15.5% (95%CI 11.8–19.1)]. The high statistical heterogeneity in this analysis ($I^2 = 99.3\%$) meant that individual study weighting was uniform (range 4.1–4.7%). In the studies that provided data specific to gender, sarcopenia was found to be higher in men [41.0% (95%CI 26.2–55.9)] than in women [31.9% (95%CI 7.0–56.8)]; however, this difference was not statistically significant ($P = 0.538$) and gender did not predict effect size in meta-regression (Figures S1–S2). In the studies that provided data specific to disease severity, sarcopenia was found to be significantly higher in patients with more severe disease [GOLD stages III–IV; 37.6% (95%CI 24.8–50.4)] than those with less severe disease [GOLD stages I–II; 19.1% (95%CI 10.2–28.0)], with test for between-group differences ($P = 0.020$) with the proportion of participants having more severe disease being strongly predictive of effect sizes in meta-regression with high explanatory power [regression coefficient 0.715 (95%CI 0.342–1.088), $P = 0.006$; adjusted $R^2 = 90.1\%$ (Figures S3–S4).

Impact of sarcopenia on clinical outcomes

Data from 11 studies involving 5367 participants were available for meta-analysis of pulmonary function, showing that those with sarcopenia had, on average, poorer FEV$_1$% predicted than those without sarcopenia [mean difference $-7.07\%$ (95%CI $-9.03$ to $-5.11$); $I^2 = 83\%$, Figure 3A].

Data from six studies involving 2252 participants were available for outcomes related to exercise capacity. These were measured via the 6MWT,1,2,7,28 incremental shuttle walk test,2 and cardiopulmonary incremental cycle test.25,36 Having sarcopenia was associated with poorer performance compared with those without sarcopenia [SMD $-0.77$ (95%CI $-1.35$ to $-0.18$); $I^2 = 96\%$, Figure 3B].

Four studies involving 1996 participants reported data on quality of life via the COPD Assessment Test,1,2 and St George’s Respiratory Disease Questionnaire2,7,28 was included in the meta-analysis. Having sarcopenia was associated with poorer quality of life [SMD $0.42$ (95%CI $0.07$–$0.77$); $I^2 = 85\%$, Figure 3C]. Other studies not included in the meta-analysis reported similar findings33,35 (Table 3).

A summary of findings related to the remaining review outcomes is presented in Table 3; however, quantitative meta-analysis was not possible due to lack of sufficient data. Compared with non-sarcopenic individuals, those with sarcopenia had worse physical function (as measured by tests of balance, gait speed, strength, and general daily function),2,21,39 lower levels of daily physical activity,2,22,30,35 increased levels of dyspnoea during daily activities,1,2 and a heightened mortality risk, as measured via body mass index, obstruction, dyspnoea, and exercise tolerance (BODE) index.1,2,38 Sarcopenia was more prevalent in the fourth quartile of BODE, ranging from 25% to 63.6%,1,2,38 With respect to inflammatory biomarkers, C-reactive protein, IL-6, and tumour necrosis factor-alpha were reported to be higher1,25,39 or not different27,28 in subjects with sarcopenia compared with those without it. No differences were
Table 1  Characteristics of the included studies regarding the prevalence of sarcopenia in subjects with chronic obstructive pulmonary disease

| First author and year | Country | Study design | Sample size | Age (mean ± SD) | Male, n (%) | Smoking status (never/former/current), n | GOLD (%) | Total, n (%) | Male, n (%) | Criteria (assessment method to detect sarcopenia) |
|-----------------------|---------|--------------|-------------|----------------|-------------|-----------------------------------------|-----------|--------------|-------------|-------------------------------------------------|
| Sergi et al. 200621   | Italy   | Cross-sectional | 40          | 75.7 ± 5.3     | 40 (100%)   | —                                    | —         | 103/231/240 | 15 (38%)   | LMM (DXA) |
| Koo et al. 201422     | Korea   | Cross-sectional | 574         | 64.0 ± 0.6     | 574 (100%)  | —                                    | —         | 195 (27%)    | 155 (100%) | LMM (DXA) |
| Gologanu et al. 201423| Romania | Cross-sectional | 36          | 65.6 ± 7.5     | 12 (33%)    | —                                    | —         | 3 (8%)       | —          | LMM (BIA) |
| Jones et al. 20152    | UK      | Clinical non-randomized | 622    | — | 354 (57%) | 7/170/43 | — | 90 (14%) | 57 (63%) | LMM (BIA), LMS (HGS), LPP (4MGMS), LMM (DXA) |
| Costa et al. 201524   | Brazil  | Cross-sectional | 91          | 67.4 ± 8.7     | 41 (45%)    | 91 former smokers | —         | 437 (87%)  | 239 (55%) | LMM (DXA) |
| Van de Bool et al. 201525 | Netherlands | Retrospective | 505         | 64 (median)    | 288 (57%)  | 13/360/132 | —         | 437 (87%)  | 239 (55%) | LMM (DXA) |
| Chung et al. 201526   | Korea   | Retrospective | 1039        | 64.5 ± 9.4 (male) | 760 (73%) | 129/136/771 | —         | 283 (27%)  | 249 (88%) | LMM (DXA) |
| Joppa et al. 201627   | ECLIPSE (12 countries and USA) | Cross-sectional | 2000 | 63.5 ± 7.1 | 1314 (66%) | — | — | 682 (34%) | 509 (75%) | LMM (BIA) |
| Van de Bool et al. 2016 (van de Bool et al. 2016) | Netherlands | Cross-sectional | 45 | 42-77 | 29 (64%) | — | — | 14 (31%) | 13 (92%) | LMM (DXA) |
| Lipovec et al. 201628 | Slovenia | Prospective observational | 112 | 66 ± 8 | 74 (66%) | 92 current smokers | — | 61 (54%) | 44 (72%) | LMM (DXA) |
| Borda et al. 201629   | Colombia | Cross-sectional | 334         | 71.1 ± 8.05    | 110 (33%)  | —                                    | —         | 28 (8%)     | —          | LMM (CC), LMS (HGS), LPP (3.4MGMS), LMM (DXA) |
| Lee et al. 201630     | Korea   | Cross-sectional | 858         | —              | —          | —                                    | —         | 286 (33%)   | 226 (79%) | LMM (DXA) |
| Pothirat et al. 201631| Thailand | Cross-sectional | 121         | —              | —          | —                                    | —         | 12 (10%)    | —          | LMM (BIA) |
| Maddock et al. 201632 | UK      | Prospective cohort | 816 | 69.8 ± 9.7 | 484 (59%) | — | — | 101 (12%) | — | LMM (BIA), LMS (HGS), LPP (4MGMS), LMM (DXA) |
| Hwang et al. 201713   | Korea   | Cross-sectional | 777         | 63.9 ± 10.6    | 777 (100%) | 0/185/592 | — | 41 (5.3%) | 41 (100%) | LMM (DXA) |
| Limpawattana et al. 201733 | Thailand | Cross-sectional | 121         | —              | 112 (92.6%) | 7/104/10 | — | 29 (24%) | 29 (100%) | LMM (DXA) |
| Byun et al. 20171     | Korea   | Cross-sectional | 80          | 68.4 ± 8.9     | 67 (83.8%) | —                                    | —         | 20 (25%)    | 17 (83%) | LMM (BIA), LMS (HGS), LMM (DXA) |
| Limpawattana et al. 201734 | Thailand | Cross-sectional | 121         | 70 ± 9        | 112 (92.6%) | 7/104/10 | — | 29 (24%) | 29 (100%) | LMM (DXA) |
| Lee et al. 201735     | Korea   | Cross-sectional | 748         | —              | —          | —                                    | —         | 251 (34%)   | 203 (81%) | LMM (DXA) |

(Continues)
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| First author and year | Country | Study design | Sample size | Age (mean ± SD) | Male, n (%) | Smoking status (never/former/current), n | GOLD (%) | Prevalence of sarcopenia | Criteria (assessment method to detect sarcopenia) |
|----------------------|---------|--------------|-------------|----------------|-------------|----------------------------------------|---------|--------------------------|-----------------------------------------------|
| Kneppers et al. 2017 | Slovenia | Prospective cohort | 92 | — | — | — | 23 current smokers | LMM (DXA) | 13 (11%) | 6 (5%) | 29 (74%) | LMM (DXA) |
| et al. 2017 | — | — | — | — | — | — | — | — | — | — | LPP (6MWT) |
| Costa et al. 2017 | Brazil | Cross-sectional | 121 | 67.9 ± 8.6 | 56 (46%) | 23 current smokers | LMM (DXA) | 11 (9%) | 15 (12%) | 39 (42%) | LMM (DXA) |
| Costa et al. 2018 | Brazil | Cross-sectional | 121 | 67.9 ± 8.6 | 56 (46%) | — | — | — | — | 15 (12%) | LPP (6MWT) |

3.4 MGS, 3.4 m gait speed; 4MGS, 4 m gait speed; 6MWT, 6 min walking test; BIA, bioelectrical impedance analysis; CC, calf circumference; DXA, dual-energy X-ray absorptiometry; HGS, handgrip strength; LMM, lower muscle mass; LMS, lower muscle strength; LPP, lower physical performance; SD, standard deviation.

**Discussion**

This systematic review and meta-analysis offers unique insight into the clinical relevance of sarcopenia for people with COPD. It describes the prevalence of the condition and how this is impacted by use of different criteria, cut-off thresholds and definitions based upon independent assessment of sarcopenia in COPD. Definitions of COPD, age and disease severity are commonly used within the studies included in this literature.

Two predominant strategies appear to be in use to classify sarcopenia in COPD: definitions based upon independent assessment of sarcopenia in COPD, and definitions based upon independent assessment of sarcopenia in COPD that include age and disease severity in the definition. While this reduces the incidence of detecting a positive diagnosis, it is likely to reduce the incidence of detecting a positive diagnosis by 3%. Use of both LMM and LPP, or LPP and LMS, is likely to reduce the incidence of detecting a positive diagnosis by 15%. Such variability has been previously reported in community-dwelling older adults and is associated with oxidative stress.

By detecting levels of inflammation and IL-8, these findings were consistent with the lower limb and the chest wall.

Table 1 (continued)
Table 2 Criteria and cut-off points used to detect sarcopenia in individuals with chronic obstructive pulmonary disease in the different studies

| Lower muscle mass | References |
|-------------------|------------|
| DXA | Van de Boel et al. 2015,25 Lipovec et al. 2016,28 Kneppers et al. 2017,30 and van de Boel et al.40 Costa et al. 201524 and Costa et al. 201737 |
| BIA | Costa et al. 201524 and Costa et al. 201737 Lee and Choi30 Limpawattana et al.,33,34 and Lee et al.35 Costa et al. 201737 and Costa et al. 201838 Byun et al.,39 Hwang et al.,13 Sergi et al.21 Chung et al.,26 and van de Boel et al.40 Koo et al.32 Costa et al. 201524 and Costa et al. 201737 Jones et al.,2 Maddocks et al.,32 and de Blasio et al.39 Gologanu et al.23 and Pothirat et al.31 Joppa et al.27 Byun et al.1 Borda et al.29 |
| HGS | Byun et al.,1 Jones et al.,2 Maddocks et al.,32 and de Blasio et al.39 Limpawattana et al.,33,34 Borda et al.29 |
| Lower physical performance | |
| 4MGS | Jones et al.,2 Maddocks et al.,32 and de Blasio et al.39 Borda et al.29 Limpawattana et al.,33,34 Costa et al. 201737 Costa et al. 201838 |
| 3.4MGS | |
| 6MWT | |

3.4 MGS, 3.4 m gait speed; 4MGS, 4 m gait speed; 6MWT, 6 min walking test; ASMI, appendicular skeletal muscle index; ATS, American Thoracic Society; AWGS, Asian Working Group for Sarcopenia; BIA, bioelectrical impedance analysis; BMI, body mass index; CC, calf circumference; DXA, dual-energy X-ray absorptiometry; EWGSOP, European Working Group on Sarcopenia in Older People; FNHI, The Foundation for the National Institutes of Health Sarcopenia Project; HGS, handgrip strength; SMI, skeletal muscle mass index.

review (Tables 1 and 2). Despite this, we observed 12 different cut-off points used to classify test results as normal or abnormal. The most commonly used criteria were those of Newman et al.34 and Baumgartner et al.,55 which are also considered by the EWGSOP.7 Borda et al.29 measured muscle mass with calf circumference, which conforms simplicity as a screening method for sarcopenia,56,57 but it is not recommended.7,15,19,43,49 Similar advice is also available for the assessment of muscle strength (handgrip force) and physical performance (gait speed),7,15 yet inconsistencies were again apparent. For example, gait speed was assessed using the 4 m gait speed22,29,32,39 and the 6MWT.33,34,37,38 While the same cut-off was used to diagnose sarcopenia across both tests (<0.8 m/s), the two tests are vastly different. The 4 m gait speed is typically performed at usual walking speed across a 4 m distance (although variations also exist at different walk speeds and track lengths), while the 6MWT is typically performed on a 30 m walking track with participants encouraged to walk as far as they can (often faster than normal speed) in order to assess exercise tolerance.58 Deriving a measure of walking speed from the 6MWT [i.e. total distance (m) divided by 360 (s)] poses a significant risk of inaccurate interpretation. For example, it could not distinguish between people walking slowly and fast but stopping to rest during the test. The prevalence of sarcopenia in the studies that used this approach33,34,37,38 may therefore have been underestimated. It is thus crucial that future research not only implement consistent tests to diagnose sarcopenia, but also adopt standardized cut-off thresholds to facilitate accurate test interpretation.

Sarcopenia had a consistently negative impact on a range of COPD-related clinical outcomes, including exercise capacity, balance, quadriceps, and handgrip strength, gait speed, and physical activity levels.2,12,30,35,38 It was also associated with increased symptom burden and poorer quality of life.1,2,30,35 It is interesting that the two studies that measured dyspnoea (Medical Research Council scale)1,2 classified sarcopenia according to physical function alone, as it raises the possibility that functional impairment may associate more strongly with dyspnoea than LMM.21 This also raises...
some challenging issues related to clinical management strategies. As associations do not imply causation or directionality, should interventions targeting improvement in health outcomes for people with COPD who have sarcopenia be directed towards mitigating the defining features of sarcopenia (e.g. muscle mass and physical performance) or their associated manifestations (e.g. low physical activity levels, poor balance, impaired lung function)? To our knowledge, the precise impact of sarcopenia (and its severity) upon intervention effectiveness targeting these other areas has received scant attention to date in COPD. Sarcopenia has, however, been highlighted as an important ‘treatable trait’ in adult respiratory medicine.\(^5\)\(^6\)\(^7\) One of the few studies to explore this area was conducted by Jones \(et\ al.\)^2 \(^2\) who demonstrated that pulmonary rehabilitation, a comprehensive, multicomponent exercise-based intervention, improved a range of clinical outcomes and reduced the incidence of sarcopenia in a cohort of patients with COPD. More research is clearly warranted to further validate the findings of Jones and colleagues, including the use of other recommended adjunctive therapies such as nutritional supplementation.\(^7\)\(^6\)\(^0\)\(^6\)\(^1\)

We were not able to investigate actual mortality in those who had sarcopenia due to a lack of available evidence. However, it is plausible that sarcopenia might associate with increased mortality in this population, considering that it associated with poorer prognosis and a higher prevalence in patients with more severe lung disease (37.6% in GOLD stages III–IV compared with 19.1% in those with GOLD stages I–II). Leivseth \(et\ al.\)^6\(^2\) reported that people with GOLD stages III and IV disease severity had a more than sixfold increased risk of mortality in women and a more than double increased risk in men over 15 years of follow-up. Heightened mortality risk was also observed in individuals with COPD evaluated via BODE,\(^1\)\(^2\)\(^4\)\(^2\)\(^4\)\(^3\)\(^8\) which is a widely used, valid tool for predicting risk of death in COPD.\(^6\)\(^3\)\(^4\) Costa \(et\ al.\)^2\(^4\) reported an increased prevalence of sarcopenia (odds ratio 3.89; 95%CI 1.21–12.46) in those with GOLD stages III and IV, and these quartiles are related with lower 4 year survival (18–57%).\(^6\)\(^3\)

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**Figure 2** Prevalence of sarcopenia in chronic obstructive pulmonary disease according to different criteria. CI, confidence interval; ES, effect size (prevalence %); I\(^2\), I\(^2\)\(^h\) heterogeneity statistic. Random effects model used for analysis.
Sarcopenia also related to poorer quality of life and pulmonary and physical function, which are known factors associated with heightened mortality risk in COPD. Sarcopenia has been associated with premature mortality in community-dwelling older adults in a cohort study with 4425 older adults during a median 14.4 year follow-up (hazard ratio 1.32; 95%CI 1.13–1.47). However, the lack of COPD-specific data suggests that this remains an area in need of addressing in future research.

This systematic review has highlighted the clinical relevance of including measurements of muscle mass, muscle strength, and physical performance in individuals with COPD, as these variables clearly associate with sarcopenia, exacerbations, and poor prognosis. The more widespread implementation of these measures in clinical practice could help identify patients with COPD at increased risk of future healthcare use related to exacerbations. This is also an important priority from a public health economic perspective. In Europe, on average, the healthcare system spends €6725 per year per person (95%CI €6590–€6863) for each exacerbation of this disease. In older people, sarcopenia is consistently associated with increased risk of incident disability, falls, hospitalization, and mortality.

Sarcopenia has been associated with increased breathlessness, exacerbation frequency, and frailty in individuals with COPD. Hospitalizations also hasten deconditioning and muscle weakness, thereby worsening the sarcopenic state. Earlier identification of sarcopenia may therefore help direct preventive healthcare to positively impact upon its healthcare burden.

We were unable to demonstrate a clear relationship between sarcopenia and inflammatory biomarkers across the included studies. Some authors reported no differences between sarcopenic and non-sarcopenic patients with COPD, while Byun et al. observed higher levels of C-reactive protein, IL-6, and tumour necrosis factor-alpha. No studies evaluated the effect of sarcopenia on oxidative stress, despite convincing evidence of pathophysiological changes occurring in the COPD literature and known associations between sarcopenia, oxidative stress, and inflammation.
Table 3. Clinical impact of the sarcopenia in different variables in subjects with chronic obstructive pulmonary disease

| Categories                        | Variables                          | Compared with individuals with COPD without sarcopenia |
|-----------------------------------|------------------------------------|--------------------------------------------------------|
|                                    |                                    | Saropenia (1 criterion) | Saropenia (>1 criterion) |
| Health-related quality of life     | EQ-5D index (score)                | Worse<sup>30,35</sup> |                         |
| Physical function                  | SPPB (score)                       | Worse<sup>2</sup> |                         |
|                                    | 5STS (s)                           | Worse<sup>2</sup> |                         |
|                                    | GS (kg)                            | Worse<sup>2</sup> |                         |
|                                    | GS (m/s)                           | Worse<sup>2</sup> |                         |
| Physical activity level            | Time in moderate and high activity (min/day) | Worse<sup>22</sup> |                         |
|                                    | Total energy expenditure (kcal/week) | Worse<sup>2</sup> |                         |
|                                    | Daily Steps (steps/day)            | N.d.<sup>2</sup> |                         |
| Dyspnoea                           | MRC (score)                        | N.d.<sup>21</sup> | Worse<sup>1,2</sup> |
| Risk of mortality                  | Prevalence in BODE quartile 3 or 4 | Higher<sup>24</sup> | Higher<sup>1,2,38</sup> |
| Inflammation                       | CRP (mg/L)                         | Augmented<sup>25</sup>/N.d.<sup>27,28</sup> | Augmented<sup>29</sup> |
|                                    | Fibrinogen (mg/L)                  | N.d.<sup>27</sup> |                         |
|                                    | IL-6 (pg/mL)                       | N.d.<sup>27</sup> |                         |
|                                    | IL-8 (pg/mL)                       | N.d.<sup>27</sup> |                         |
|                                    | TNF-α (pg/mL)                      | N.d.<sup>27</sup> |                         |

S5TS, five-repetition sit-to-stand test; 6MWT, 6 min walking test; BODE, body mass index, obstruction, dyspnoea, and exercise tolerance index; CAT, COPD Assessment Test; CRP, C-reactive protein; EQ-5D index, EuroQol five-dimensional; GS, gait speed; HGS, handgrip strength; IL, interleukin; ISWT, incremental shuttle walk test; MRC, Medical Research Council; N.d., no significant difference; QS, quadriiceps strength; SGRQ, St George’s respiratory disease questionnaire; SPPB, short physical performance battery; TNF-α, tumour necrosis factor-alpha.

Inflammation,<sup>1</sup> and age-related alterations in muscle morphology.<sup>76,78–80</sup> This would appear a valuable area for future research.

As with all studies, the findings from the present review are not without some limitations. Due to the significant heterogeneity between studies in terms of factors such as sarcopenia definitions, participant characteristics, and diagnostic cut-offs, the opportunity for meta-analysis was limited for some outcomes and clear interpretation of the clinical implications of some results was challenging. This review was unable to elucidate the direct relationship between sarcopenia and mortality due to a lack of data. This was not surprising due to the prolonged periods of follow-up required to observe such outcomes in cohorts of patients who would otherwise not typically have been at risk of imminent death. However, our observed association between sarcopenia and mortality risk (assessed via BODE) is noteworthy. While not a pre-specified focus of our review, we also feel that the lack of direct evidence highlighting the clinical impact of sarcopenia on healthcare expenditure represents an area to address in future studies. Additionally, despite this review including studies from four different continents (Asia, Europe, North America, and South America), data regarding participant race were not available, which limits its potential applicability to specific patient subgroups. In addition, it was not considered the impact of differing sarcopenia subtypes (e.g. sarcopenic obesity, severe sarcopenia), despite their clinical relevance due to a lack of suitable data. This might have plausibly explained some of the observed variability in clinical outcome data. We also synthesized prevalence data via meta-analysis in contrast to our registered protocol. This was altered in light of access to appropriate statistical software to conduct this analysis while still allowing readers to identify the raw proportions of individual studies (as stated in the protocol) in Figure 2. The overall pooled effect from the present meta-analysis (27.5%) compared favourably against the protocol-based method utilizing median estimates from individual studies (26.1%).

In conclusion, sarcopenia is a clinically important condition that is prevalent within a substantial proportion of patients with COPD. Diagnostic accuracy appears sensitive to the criteria, test methods, and cut-offs used to detect the individual components, as well as markers of disease severity. Considering the negative impact of sarcopenia upon health outcomes, there may be merit in future strategies targeting early identification of sarcopenia in the clinical assessment of people with COPD to ultimately improve management strategies aiming to mitigate its impact upon individuals’ lives.

Author contributions

W.S.L. and A.A.M. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. C.O. and S.P. contributed substantially to statistical analysis and interpretation of the results, and G.D. and V.S.P. contributed with the study design and writing of the manuscript. The authors of this manuscript certify that they comply with the ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle.<sup>31</sup>
Conflict of interest

The authors have disclosed no conflicts of interest. We declare no financial support or relationships that may pose conflict of interest. This work has not been published anywhere.

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Online supplementary material

The supplementary figures and tables can be found in the Supporting Information section of the online article.

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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: Search strategy in each database (Supplementary data)
Table S2: Quality analysis (Supplementary data)
Table S3: Different cut-off points used to identify Sarcopenia.
Figure S1: Prevalence of sarcopenia by gender.
Figure S2: Meta-regression of effect of gender (percent male) on sarcopenia prevalence.
Figure S3: Prevalence of sarcopenia, by COPD disease severity.
Figure S4: Meta-regression of effect of disease severity (GOLD stages III-IV) on sarcopenia prevalence.

Table S5: Different cut-off points used to identify Sarcopenia.
Figure S6: Prevalence of sarcopenia, by COPD disease severity.
Figure S7: Meta-regression of effect of gender (percent male) on sarcopenia prevalence.
Figure S8: Prevalence of sarcopenia, by COPD disease severity.
Figure S9: Meta-regression of effect of disease severity (GOLD stages III-IV) on sarcopenia prevalence.

Table S10: Different cut-off points used to identify Sarcopenia.
Figure S11: Prevalence of sarcopenia, by COPD disease severity.
Figure S12: Meta-regression of effect of gender (percent male) on sarcopenia prevalence.
Figure S13: Prevalence of sarcopenia, by COPD disease severity.
Figure S14: Meta-regression of effect of disease severity (GOLD stages III-IV) on sarcopenia prevalence.
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