





Sarcopenia in COPD: a systematic review and meta-analysis

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We confirmed a high prevalence of sarcopenia in COPD patients, with varying prevalence across population settings. We recommend adhering to the sarcopenia consensus criteria to systematically evaluate the muscle health of COPD patients. <http://bit.ly/2KA6weh>

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ABSTRACT COPD is associated with a progressive loss of muscle mass and function. However, there is an unmet need to define and standardise methods to estimate the prevalence of sarcopenia in COPD patients. We performed a systematic review and meta-analysis of the prevalence of this extrapulmonary manifestation in COPD patients. We searched Embase, Medline (Ovid), CINAHL (EBSCO), Web of Science, Scopus and Google Scholar for studies published up to January 17, 2019, assessing sarcopenia in COPD patients based on low muscle mass and decreased muscle function. Interventional studies, *in vitro* experiments, protocols or reviews and meta-analyses were excluded. We estimated heterogeneity (I^2) and assessed significance (Q) using a Chi-squared test for estimates obtained from random-effects models.

4465 articles were initially identified. After removing the duplicates and applying the selection criteria, we reviewed 62 full-text articles. Finally, 10 articles ($n=2565$ COPD patients) were included in this systematic review and meta-analyses. Overall, the prevalence of sarcopenia in patients with COPD was 21.6% (95% CI 14.6–30.9%, $I^2=94\%$), ranging from 8% in population-based to 21% in clinic-based studies, and 63% in COPD patients residing in nursing homes.

Sarcopenia is frequently observed in COPD patients, with varying prevalence across population settings. Sarcopenia in COPD should be assessed using standardised tests and cut-off points from sarcopenia consensus criteria for clinical practice and international comparisons.

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Introduction

COPD is a heterogeneous, complex and multisystem disease, with a vast number of intra- and extrapulmonary manifestations [1–5]. The clinical assessment of COPD patients is also complicated by the presence of multi-morbid conditions due to shared risk factors with other diseases [3, 6]. The extrapulmonary manifestations are increasingly recognised as important contributors to functional decline in patients with COPD [2, 3]. Functional impairment is associated with muscle weakness and body weight loss in COPD patients [5–7]. Irrespective of the method used to assess muscle mass [8], it is well known that patients with COPD suffer from loss of muscle mass [9–29]. Indeed, loss of muscle mass and muscle strength can be greater in patients with moderate-to severe COPD [7, 30] or during acute COPD exacerbations [31], especially loss of muscle from the lower limbs [6, 7, 32].

Low muscle mass and loss of muscle function have been described as the main components of sarcopenia [33–38], which was originally defined as a multifactorial geriatric syndrome [39]. However, there has been increasing recognition of this muscle disorder as a disease-related rather than just age-related condition [40]. The 2018 European Working Group of Sarcopenia in Older People (EWGSOP2) have reinforced the importance of distinguishing “secondary sarcopenia” when factors other than ageing are involved from “primary sarcopenia” or age-related sarcopenia [38]. Sarcopenia can result from underlying diseases such as COPD or other conditions characterised by chronic inflammation [38]. Although COPD occurs mainly in middle-aged and older people, sarcopenia in COPD can occur independent of age [41]. Therefore, early detection of sarcopenia might be pivotal, given that it has therapeutic implications such as pulmonary rehabilitation and management of respiratory failure in COPD patients.

Although many aspects of the pathophysiology of sarcopenia are better understood now than a decade ago [38], the precise aetiology of sarcopenia and underlying explanatory mechanisms are still not fully established [42, 43]. However, physical inactivity, weight loss, inflammatory cytokines, inadequate energy intake, oxidative stress and reduced blood flow to muscles are common features linked with sarcopenia [43] as well as COPD [3, 5, 44]. For instance, it is well known that limb muscle dysfunction in COPD contributes to loss of muscle strength [7]. Despite the heterogeneity in the muscle fibre proportions in COPD patients [45], there is a shift from type I to II fibres, which correlates inversely with disease severity [7]. By contrast, age-related loss of muscle strength and mass are mainly attributed to muscle fibre denervation and loss of type II fibres [46].

In the last decade, different international consensus criteria of sarcopenia [33–38] have focused clinically and operationally on the measurements and thresholds of sarcopenia (table 1). For instance, five out of six sarcopenia consensus statements recommend muscle mass measurement as a first criterion to define sarcopenia. Only the updated EWGSOP2 recommends including muscle strength as the main criterion of sarcopenia, and labelling the patient as having “probable sarcopenia” [38] when muscle strength is compromised.

Using these consensus criteria, it has recently been reported that 10% of healthy older adults have sarcopenia [47]. However, the prevalence of sarcopenia varies widely (0.9%–32.8%) among different study populations [48]. No global estimates of the prevalence of sarcopenia in COPD patients with the consensus definitions have previously been reported. Estimating the overall prevalence of sarcopenia, according to the contemporary operational definitions recommended by multidisciplinary consensus, will provide further insight into its burden in COPD.

Therefore, we conducted a systematic review and meta-analysis to appraise the best available evidence on the prevalence of sarcopenia among COPD patients based on the consensus definitions.

Methodology

Search strategy and data sources

This systematic review and meta-analysis adheres to the schema of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [49, 50]. We performed an electronic search of Embase.com, Medline (Ovid), CINAHL (EBSCO), Web of Science, Scopus and Google Scholar to identify all relevant articles relating to sarcopenia and COPD. We searched all records published from inception through to January 17, 2019, in collaboration with a medical information specialist (GdJ). Terms related to COPD (*e.g.* “chronic obstructive pulmonary disease”) and key terms were combined with synonyms of sarcopenia (*e.g.* “muscle atrophy”). We further hand-searched bibliographies of relevant publications to identify potential articles missed by the principal search. Full search terms are listed in supplementary table S1.

This systematic review is registered in the International Prospective Register of Systematic Reviews (PROSPERO), number CDR42018095480.

TABLE 1 Criteria and cut-off points to diagnose sarcopenia according to the main consensus criteria groups

Consensus group	Main criteria definition	Lean muscle mass	Muscle function			
			Handgrip strength	Gait speed m·s ⁻¹	SPPB	TUG
ESPEN SIG [33]	Low muscle mass plus low gait speed	2sd below mean of young adults of the same sex and ethnic background		<0.8 (4MGS)		
EWGSOP [34]	Low muscle mass plus low muscle strength or low gait speed	ASMI: DXA score Male $\leq 7.26 \text{ kg}\cdot\text{m}^{-2}$ Female $\leq 5.54 \text{ kg}\cdot\text{m}^{-2}$ (2sd below mean of young adults) BIA score: Male $8.87 \text{ kg}\cdot\text{m}^{-2}$ Female $6.42 \text{ kg}\cdot\text{m}^{-2}$ (2sd below mean of young adults)	Male <30 kg Female <20 kg	<0.8 (4MGS)	≤ 8	
IWGS task force [35]	Low ASMI plus low gait speed	ASMI: Male $\leq 7.23 \text{ kg}\cdot\text{m}^{-2}$ Female $\leq 5.67 \text{ kg}\cdot\text{m}^{-2}$		<1 (4MGS)		
FNIH [36]	Low ALM/BMI plus low handgrip	ALM/BMI Male <0.789 Female <0.512	Male <26 kg Female <16 kg kg/BMI Male <1 Female <0.56	<0.8 (4MGS, 6MWT)		
AWGS [37]	Low ASMI plus low gait speed or low handgrip	ASMI: Male $\leq 7.0 \text{ kg}\cdot\text{m}^{-2}$ Female $\leq 5.4 \text{ kg}\cdot\text{m}^{-2}$	Male <26 kg Female <18 kg	≤ 0.8 (6MWT)		
EWGSOP2 [38]	Low muscle strength plus low muscle mass; severity of sarcopenia involve low physical performance	ASMI: Male <7.0 $\text{kg}\cdot\text{m}^{-2}$ Female <5.5 $\text{kg}\cdot\text{m}^{-2}$	Male <27 kg Female <16 kg	≤ 0.8	≤ 8	≥ 20 s

SPPB: Short Physical Performance Battery; TUG: timed up and go test; ESPEN SIG: European Society of Clinical Nutrition and Metabolism Special Interest Group ("cachexia-anorexia in chronic wasting diseases"); EWGSOP: European Working Group on Sarcopenia in Older People; IWGS: International Working Group on Sarcopenia; FNIH: Foundation for the National Institutes of Health; AWGS: Asian Working Group on Sarcopenia; 4MGS: 4-min gait speed; ASMI: appendicular skeletal muscle mass index; DXA: dual-energy X-ray absorptiometry; BIA: bioelectrical impedance analysis; BMI: body mass index; ALM: appendicular lean mass; 6MWT: 6-min walk test.

Selection criteria

For this systematic review, we used the following inclusion criteria: 1) all studies had to be case-control, longitudinal or cross-sectional designs; 2) assessment of sarcopenia had to be implemented according to the sarcopenia consensus criteria (muscle mass and muscle strength or physical performance are combined); 3) measurement of lean mass or muscle mass had to be assessed by at least one of four main methods [8] (bioelectrical impedance analysis, dual-energy X-ray absorptiometry, magnetic resonance imaging or computed tomography); 4) the prevalence of sarcopenia (primary outcome) in COPD patients had to be reported.

To provide additional insight into the prevalence of sarcopenia in COPD patients, we also investigated the associations of sarcopenia (if available in the study, e.g. odds ratio) and COPD as a secondary outcome measure.

We limited our inclusion to original publications, without language restriction, and excluded experimental studies, reviews and meta-analyses, comments, guidelines, editorials or letters and case reports. Furthermore, studies that referred to other populations were excluded (i.e. asthma or cystic fibrosis) (supplementary table S2).

Two independent co-authors (EB and KT) screened all the articles by title and abstract. Disagreements were resolved by consensus between both co-authors together with a third co-author (LL). The citations were classified as "eligible", "uncertain about eligibility" or "excluded" and stored in an EndNote file. The full text of articles classed as "eligible" and "uncertain about eligibility" was reviewed and appraised

independently by two co-authors (EB and KT), and disagreements were solved through revision and consultation with a fourth independent co-author (JDS).

Data synthesis

We used a predefined data collection form in which we summarised relevant information on characteristics of the study population (age, sex, setting), outcome assessment (prevalence of sarcopenia, definition of sarcopenia using any of the consensus criteria, cut-off points, and methods to measure handgrip and mass muscle) and the effect estimate of association (if available in the study; odds ratio adjusted for most confounders) with the corresponding precision estimate (95% confidence interval). When relevant data were not available, the corresponding authors of the selected publications were contacted to complement the electronic searches.

Risk of bias assessment

We assessed the quality of the selected studies using an adapted version of the scale developed by Hoy *et al.* [51] for prevalence estimates. The tool consists of 10 items addressing external and internal validity. Moreover, we used an adapted Newcastle–Ottawa Scale [52] for cross-sectional studies that measured association between prevalence of sarcopenia and COPD. Two co-authors (EB and KT) independently rated each of the items of both scales into a global score adding all the items rated as low risk. Therefore, higher scores indicated lower risk of bias (supplementary table S3).

Statistical analysis

We summarised prevalence of sarcopenia across studies as its estimator (prevalence) and confidence intervals and present data in tables of study characteristics.

Meta-analysis on the prevalence of sarcopenia in COPD patients was undertaken using a random-effects model, using the packages *meta* and *metaprop* in R (version 3.5.1; R Foundation for Statistical Computing, Vienna, Austria).

Heterogeneity across studies was defined by an I^2 of >50% [53]. Given that the preliminary analyses demonstrated high heterogeneity, we stratified our analysis by population setting to explore potential sources of heterogeneity. We used a funnel plot adjusted for population setting to also measure publication bias [54].

Results

Search results

Our search yielded 4465 records, of which 2315 duplicates were removed, resulting in 2150 unique articles. We read the full text of 62 articles, and determined that 10 of them were eligible for inclusion in this meta-analysis (figure 1) [55–64].

Characteristics of studies included

Among the 10 eligible studies published between 2012 and 2018, six were performed only in COPD patients without a control group [55–57, 59, 60, 63], two reported data on population-based prevalence [58, 61] and two were nursing home based [62, 64]. Four studies were from Europe [55, 58, 63, 64], four from Asia [57, 59, 60, 62] and two from South America [56, 61]. The total number of COPD participants involved in all selected studies was 2565, with a mean age ranging from 62 to 84 years at study entry (table 2).

Eight of the selected studies used the EWGSOP definition of sarcopenia [55, 58–64], and two of them applied the Foundation for the National Institutes of Health (FNIH) and the Asian Working Group on Sarcopenia consensus (table 1) [56, 57]. When we analysed the components of sarcopenia in these 10 studies, we found large variability in the methods and cut-off points, especially for lean mass. All these studies assessed lean mass by dual-energy X-ray absorptiometry or bioelectrical impedance rather than magnetic resonance imaging or computed tomography, although one used calf circumference to measure lean mass (table 2) [61].

Quality assessment

Quality assessment scores of all included observational studies are listed according to prevalence, and two of them according to association estimators (supplementary tables S4 and S5). Regarding methodological quality of the prevalence estimator, seven (70%) had moderate risk of bias and three (30%) had low risk of bias.

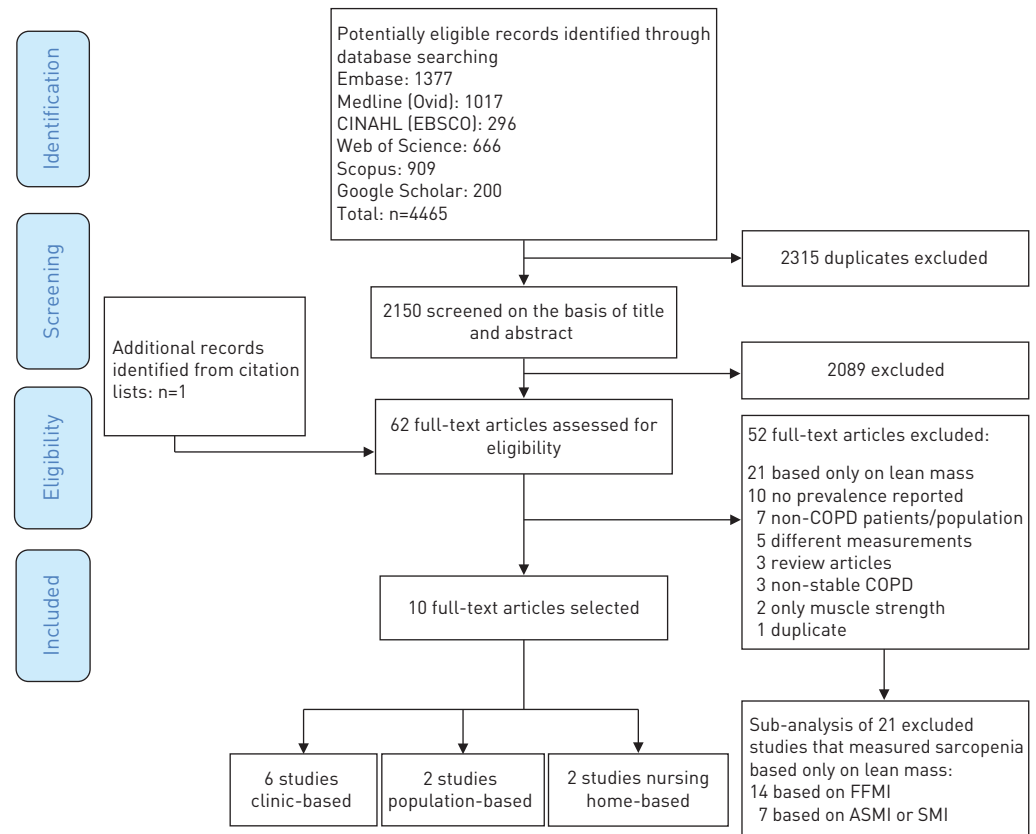


FIGURE 1 Flow diagram of the study selection process. FFMI: fat-free mass index; ASMI: appendicular skeletal muscle mass index; SMI: skeletal muscle mass index.

Prevalence of sarcopenia in COPD patients

The prevalence of sarcopenia in COPD patients ranged from 7.9% to 66.7%. There was substantial heterogeneity between studies ($I^2=94\%$, $p<0.01$), which could largely be accounted for by two studies [62, 64]. These two nursing home-based studies, which had the smallest combined sample size ($n=46$ COPD patients) of any study included, reported the highest prevalence of sarcopenia. When excluding these studies in a sensitivity analysis, the prevalence of sarcopenia was 16.5% (95% CI 11.4%–23.2%), with high heterogeneity ($I^2=92\%$, $p<0.01$) (supplementary figure S1).

Therefore, we included the 10 studies and stratified our analysis according to the three main population settings: 1) clinic based, 2) population based and 3) nursing home based. Stratifying our analysis resulted in a reduction of heterogeneity within the three population settings. Consequently, the pooled prevalence of sarcopenia was 21.6% (95% CI 14.6%–30.9%) (figure 2 and supplementary table S6). There was symmetry for the funnel plot describing publication bias in these 10 selected studies when stratified by population setting (supplementary figure S2).

Additionally, we meta-analysed all the excluded studies that measured only the lean mass component of sarcopenia given that, prior to 2010, having a low lean mass was considered to represent sarcopenia (figure 1) [34, 38, 40]. These studies applied two main muscle indices: appendicular skeletal muscle mass index (ASMI), also referred as skeletal mass index (SMI) [9–15], and fat-free mass index (FFMI) [16–29]. The prevalence of low lean mass based on ASMI in COPD patients was 31.0% (95% CI 28.2%–34.2%, $I^2=65\%$, $p<0.01$). According to FFMI, the prevalence of low lean mass in COPD patients was 23.4% (95% CI 18.6%–29.0%, $I^2=96\%$, $p<0.01$) (supplementary figure S3; supplementary tables S7, S8, S9). After performing this division by index muscle, the I^2 statistics (65% and 96% respectively, $p<0.01$), although lower than when using the sarcopenia consensus criteria, still indicated heterogeneity.

Association of sarcopenia and COPD

In addition to the prevalence of sarcopenia described in the aforementioned studies, despite the considerable variation of the cut-off points, the association of sarcopenia with COPD was tested in two studies. BORDA *et al.* [61] investigated the association of sarcopenia in 250 COPD/asthma participants, and

TABLE 2 Main characteristics of the cross-sectional selected studies in the meta-analysis

First author [ref.]	Country	Subjects n	Male	Age years	Setting	Consensus group	Prevalence % (n)	Components of sarcopenia					
								Lean mass		Muscle strength		Physical performance	
								Method	Cut-off	Method	Cut-off kg	Method	Cut-off m·s ⁻¹
De Blasio [55]	Italy	COPD: 263	70.3	69.8±8.0	Clinical	EWGSOP	24 (63)	BIA (SMI)	M: ≤8.50 kg·m ⁻² F: ≤5.75 kg·m ⁻²	HGS	NS	4MGS	<0.8
Munhoz da Rocha Lemos Costa [56]	Brazil	COPD: 121	46.3	67.9±8.6	Clinical	FNIH	12.4 (15)	DXA (ALM/BMI)	M: <0.789 F: <0.512		NS	6MWT	≤0.8
Limpawattanas [57]	Thailand	COPD: 121	92.6	>65	Clinical	AWGS	24 (29)	DXA (ASMI)	M: ≤7.0 kg·m ⁻² F: ≤5.4 kg·m ⁻²	HGS	M: 26 F: 18	6MWT	<0.8
Trajanoska [58]	Netherlands	COPD: 882 All population: 5911		69.2±9.1	Population	EWGSOP	COPD: 7.9 (70) All population: 4.4 (260)	DXA (SMI)	M: ≤7.25 kg·m ⁻² F: ≤5.67 kg·m ⁻²	HGS	M: ≤29 (if BMI ≤24) ≤30 (if BMI ≤24.1–28) ≤32 (if BMI >28) F: ≤17 (if BMI ≤23) ≤17.3 (if BMI ≤23.1–26) ≤18 (if BMI ≤26.1–29) ≤21 (if BMI >29)	GAITRite	M: <0.65 (if height ≤173 cm) <0.76 (if height >173 cm) F: <0.65 (if height ≤159 cm) <0.76 (if height >159 cm)
Byun [59]	Korea	COPD: 80	83.8	68.4±8.9	Clinical	EWGSOP	25 (20)	BIA (SMI)	Below 25 th of mean population	HGS	M: ≤30 F: ≤20		NS
Lian [60]	China	COPD: 96	58.3	62.4±7.9	Clinical	EWGSOP	28.1 (27)	BIA (SMI)	M: ≤7.01 kg·m ⁻² F: ≤5.43 kg·m ⁻²	HGS	M: ≤35.04 F: ≤21.82		NS
Borda [61]	Colombia	COPD/asthma: 334 No COPD/asthma: 1666	32.9	>60	Population	EWGSOP	COPD/asthma: 11 (28) No COPD/asthma: 6.9 (77)	CC	<31 cm		NS	4MGS	
Tasar [#] [62]	Turkey	COPD: 33 All population: 211	69.7	73.9±7.2	Nursing home	EWGSOP	COPD: 66.7 (22) All population 33.6 (71)	BIA (FFM/BSA)	Below the 20 th percentile of mean population	HGS	M: ≤30 F: ≤20	6MWT	≤0.8
Jones [63]	UK	COPD: 622	58.8	73±8	Clinical	EWGSOP	14.5 (90)	BIA (SMI)	M: ≤8.50 kg·m ⁻² F: ≤5.75 kg·m ⁻²	HGS	M: <30 F: <20	4MGS	<0.8
Landi [64]	Italy	COPD: 13 All population: 122	68	84±7.3	Nursing home	EWGSOP	COPD: 53.4 (7) All population: 32.8 (40)	BIA (SMI)	M: <8.87 kg·m ⁻² F: <6.42 kg·m ⁻²	HGS	M: <30 F: <20	4MGS	≤0.8

Data are presented as % or mean±SD, unless otherwise stated. EWGSOP: European Working Group Older People; M: male; F: female; BIA: bioelectrical impedance analysis; SMI: skeletal muscle index; NS: not specified; HGS: handgrip strength; 4MGS: 4-min gait speed; FNIH: Foundation for the National Institute of Health; DXA: dual-energy X-ray absorptiometry; ALM: appendicular lean mass; BMI: body mass index; 6MWT: 6-min walk test; AWGS: Asian Working Group on Sarcopenia; ASMI: appendicular skeletal muscle mass index; GAITRite: 5.79-m-long electronic walkway; CC: calf circumference; FFM: fat-free mass; BSA: body surface area. [#]: data directly obtained from authors.

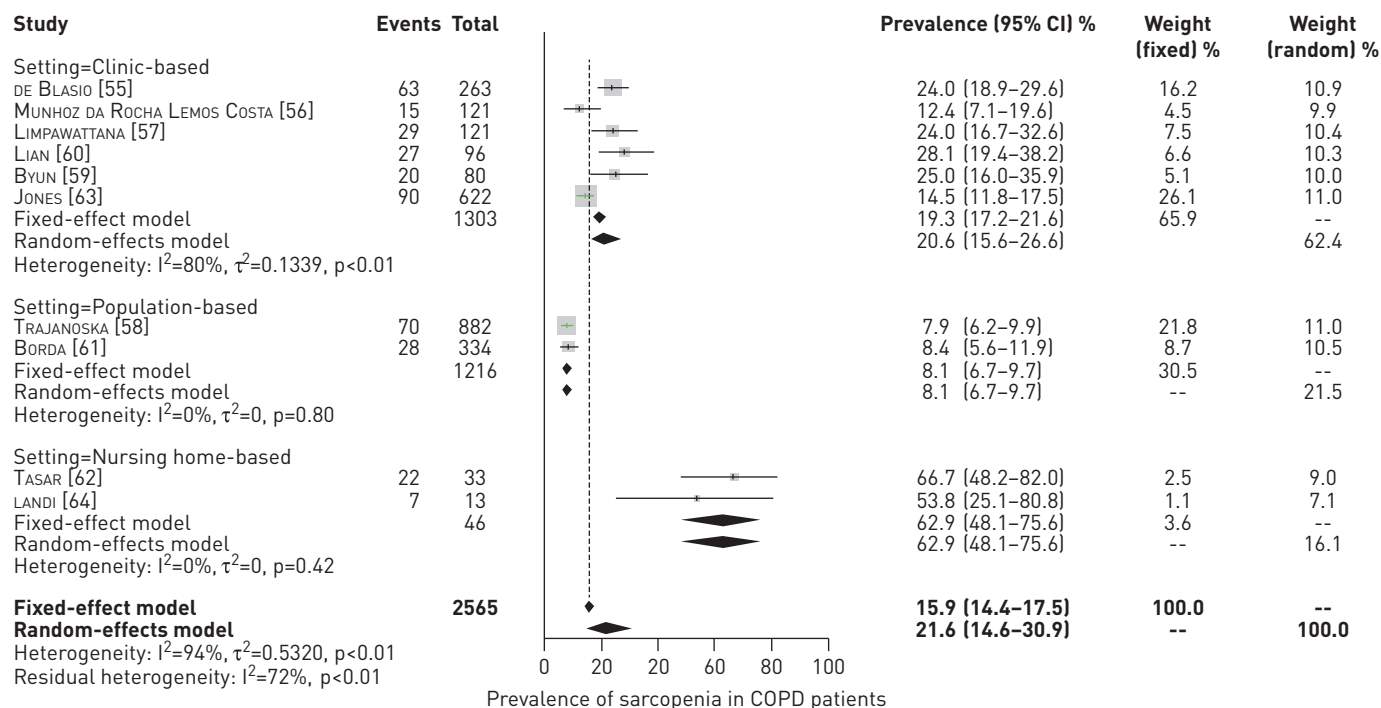


FIGURE 2 Fixed- and random-effects meta-analysis results for the prevalence of sarcopenia in patients with COPD, according to population setting. The authors directly provided the prevalence estimate for the study by TASAR *et al.* [62].

the odds ratio for sarcopenia was 2.01 (95% CI 1.21–3.35), independent of sex, age, educational level and body mass index (BMI). Moreover, TASAR *et al.* [62] reported that the odds ratio for elderly people with COPD to have sarcopenia was 1.69 (95% CI 0.83–3.43).

Factors associated with sarcopenia in COPD patients

Some of the main factors associated with sarcopenia in COPD patients were age [56, 59, 60], especially among the older group (≥ 75 years old) [57]; systemic inflammatory biomarkers (high-sensitivity tumour necrosis factor- α (hsTNF- α)) [59]; and BMI, either separately (both high [57] and low [59]) or as part of the BODE index (BMI, airflow obstruction, dyspnoea and exercise) [56] (supplementary table S10).

Smoking, one of the main risk factors for COPD, was associated with sarcopenia in one study [60], whereas in two other studies it was not [56, 57]. In addition, JONES *et al.* [63] did not find a difference in smoking status between COPD patients with and without sarcopenia.

Severity of COPD [57], severity of dyspnoea [57] and cardiovascular disease [59] were the main clinical outcomes associated with sarcopenia in COPD patients. DE BLASIO *et al.* [55] reported that 58.7% of COPD patients with sarcopenia were also malnourished. In the study of JONES *et al.* [63], COPD patients with sarcopenia had more severe airflow obstruction (low forced expiratory volume in 1 s (FEV₁)) and reduced physical activity, functional performance and exercise capacity.

When the components of sarcopenia were analysed separately, BYUN *et al.* [59] found that handgrip and SMI were negatively correlated with serum interleukin-6 ($r = -0.27$ and $r = -0.23$, respectively) and hsTNF- α ($r = -0.35$ and $r = -0.25$, respectively).

Discussion

Overall, we found that ~22% of individuals with COPD had sarcopenia. The prevalence estimates of sarcopenia varied between 12.4% and 28.1% in clinical settings, and 7.9% and 8.4% in population-based settings. Prevalence was highest in nursing home settings, ranging from 53.8% to 66.7%. We observed large heterogeneity across studies, attributed to important differences in methods and cut-off points used to assess muscle mass, and particularly the distinct population settings. Therefore, differences between study settings (*i.e.* community dwelling *versus* institutionalised patients) should be considered when assessing the risk of sarcopenia in COPD patients.

In COPD patients, BONE *et al.* [42] have previously described the importance of sarcopenia based on consensus criteria. However, to the best of our knowledge, this systematic review including a meta-analysis is

the first to assess the prevalence of sarcopenia in patients with COPD. This meta-analysis notes the heterogeneity induced by the different methods used to assess sarcopenia and the type of population setting.

Clinic-based studies

The vast majority of the selected studies reporting prevalence of sarcopenia in COPD patients were clinic based, with high heterogeneity between studies ($I^2=80\%$, $p<0.01$). Notably, two studies using the same cut-off points and methods to measure sarcopenia in COPD patients [55, 63] reported prevalence estimates with big discrepancies (~10% difference). However, the study by DE BLASIO *et al.* [55] ($n=263$) included more male COPD patients (70%), and the sarcopenic group ($n=26$) had more deteriorated lung function (FEV_1 % pred 30.9%, 95% CI 26.1%–35.7%) than that of JONES *et al.* [63] ($n=622$) (sarcopenic group ($n=90$), FEV_1 % pred 43.5%, 95% CI 37.4%–50.2%).

Population-based studies

The prevalence of sarcopenia in COPD population-based studies was lower than in clinical settings. This finding can be explained by the fact that COPD cases from the population are more often in an early stage of the disease or even asymptomatic. Two population-based studies reported the prevalence of sarcopenia in COPD [58, 61]; although they used the same consensus criteria [34], there was no uniformity in the measurement methods used, particularly for lean mass. TRAJANOSKA *et al.* [58] performed a specific calculation of each component of sarcopenia, based on BMI and height, for male and female patients. By contrast, BORDA *et al.* [61] calculated low lean mass based on calf circumference for both sexes in patients with COPD/asthma. This makes comparison between the two studies difficult.

Nursing home-based studies

The high prevalence of sarcopenia in COPD patients from nursing homes can be explained by two main factors. First, the selected studies had small sample sizes (<50 participants). Second, according to the mean age, these participants were older than the age range mean of the clinic- and population-based studies. However, while the prevalence of sarcopenia increases notably with ageing, the high prevalence within COPD patients is unlikely to be explained by age alone. There are biological mechanisms by which respiratory impairment contributes to muscle deterioration [7], *e.g.* patients with more severe emphysema have lower muscle mass [30].

Sarcopenia consensus statements

We found six international sarcopenia consensus criteria that can be applied in clinical and research fields [33–38]. All of these criteria are based on lean mass and physical performance related to muscle loss, but there is still a lack of uniformity in measurement standards, and especially in cut-off points across these criteria. However, the cut-off points for lean mass and handgrip strength measurements from two of the consensus criteria (EWGSOP2 and FNIH) are practically equivalent [36, 38].

The majority of our selected studies ($n=8$) [55, 58–64] applied the EWGSOP criteria to define sarcopenia in COPD patients. According to the updated EWGSOP2 [38] recommendations, muscle strength can be considered as the principal determinant of sarcopenia, mainly because it can facilitate early identification of sarcopenia in clinical practice. EWGSOP2 have modified and simplified the cut-off points to identify primary and secondary sarcopenia in a broad population [40]. Consequently, we suggest using the EWGSOP2 practical algorithm for case finding, diagnosis of sarcopenia and determining sarcopenia severity in COPD patients. We encourage clinicians to start by systematically assessing handgrip in all COPD patients, which is easily performed, rather than with other tests that can be influenced by COPD due to ventilator restrictions.

To classify the severity of sarcopenia, EWGSOP2 recommends different tests, *e.g.* gait speed, 400-m walk test, Short Physical Performance Battery and timed up and go test (TUG), with corresponding cut-off points. In COPD patients, an optimal test should be targeted for each case. For instance, the TUG test has not been associated with airflow limitation, in contrast to the 6-min walk distance [65]. Therefore, the TUG test could be implemented in cases of COPD with more severe ventilatory impairment. Similarly, a cut-off point (11.2 s) different from the EWGSOP2 recommendation (20 s) has been suggested for use as an abnormal TUG time for COPD patients [66]. Nevertheless, additional studies are needed to establish which functional test and cut-offs should be used across different stages of COPD. Given that these updated recommendations have only recently been introduced, their performance within COPD patients has not yet been performed and warrants future studies.

When we analysed each element of sarcopenia across studies, muscle mass was the component with most variability in its measurements, mainly due to muscle indices and cut-off points. For instance, in Asian populations, BYUN *et al.* [59] used a SMI below 2SD of the mean of the Korean population, whereas

LIAN *et al.* [60] used cut-offs close to the ASMI. To diagnose sarcopenia in patients with COPD, dual X-ray absorptiometry and bioelectrical impedance analysis were used to measure lean mass. However, no consensus has been reached concerning cut-off points of lean mass across different international (working) groups for the diagnosis of sarcopenia. Therefore, for both SMI and ASMI, the cut-off points require further validation and standardisation. There is more consistency across the sarcopenia consensus criteria groups for assessing muscle function, although a wide range of cut-off points have been recommended (e.g. handgrip in males ranges from 26 kg to 30 kg). In addition, cut-offs for gait speed were essentially the same (\leq or $<0.8 \text{ m}\cdot\text{s}^{-1}$). Only the method to measure gait speed differed across studies: some articles used the 6-min walk test and others 4-m gait speed ($\text{m}\cdot\text{s}^{-1}$). However, 4-m gait speed is significantly correlated with the 6-min walk test in COPD patients [67]. Studies are required to further establish the role and interaction of each sarcopenia component in COPD patients.

Factors associated with sarcopenia in COPD patients

We only found two studies that reported an association between sarcopenia and COPD [58, 61], even after adjustment for age, sex and BMI. Additionally, TRAJANOSKA *et al.* [58] reported that the difference in sarcopenia prevalence between COPD and non-COPD individuals was independent of age, sex, smoking and corticosteroid use.

Multiple factors were associated with the presence of sarcopenia in COPD patients in the selected studies. These factors included age, severity of COPD, BMI, BODE index, dyspnoea and elevated inflammatory biomarkers, such as TNF- α [56, 57, 59, 60]. However, the direct effect of smoking on sarcopenia, an established risk factor for COPD, showed different associations across studies. For instance, only one study [60] reported an association between smoking and sarcopenia among COPD patients, whereas two other studies did not [56, 57]. Likewise, in support of a negative association, another study did not find differences in smoking across COPD patients with and without sarcopenia [63]. One explanation for these discrepancies might originate from distinct smoking classification across studies; while LIAN *et al.* [60] used cumulative smoking exposure (*i.e.* a long-term history of smoking, defined as ≥ 10 cigarettes/day for 10 years), all other studies categorised smoking status as never, past and current.

None of these studies reported sex differences in the prevalence of sarcopenia, in contrast to what has been shown in previous studies on COPD patients that mainly focused on lean mass (and not on sarcopenia) [13, 22]. Moreover, COPD patients with sarcopenia had lower FEV₁, lower exercise capacity and lower physical activity than patients without sarcopenia [63]. Therefore, in terms of sarcopenia in COPD patients, factors including age, severity of COPD, BMI, BODE index, dyspnoea and hsTNF- α might add value to preventive strategies, especially when these strategies are modifiable. Likewise, other factors such as corticosteroid use, protein intake and alcohol use were not considered and as such these should be of interest for future research.

CRUZ-JENTOFT *et al.* [38] consider sarcopenia as “secondary” when another factor besides ageing is present. They state that secondary sarcopenia can occur due to a systemic disease (*i.e.* COPD), physical inactivity and inadequate energy intake, among other factors [38]. However, there is not any distinction in recommendations of methods and cut-offs for distinguishing primary and secondary sarcopenia. It is important to consider that across these selected studies, age was associated with sarcopenia, which is also in line with the fact that COPD patients with sarcopenia are older. Only one study did not find age differences in COPD patients with and without sarcopenia [55]. Nevertheless, patients in all of these studies were aged >60 years. Therefore, an overlap between primary and secondary sarcopenia in COPD patients can be expected and is difficult to differentiate. Additionally, sarcopenia is increasingly recognised as a progressive and generalised muscular disorder related to long-term conditions presenting during midlife, such as COPD [40]. Nevertheless, sarcopenia in COPD patients seems to be more disease-related than age-related, as supported by distinct physiopathological processes related to ageing and COPD. With ageing there is a transition of the muscle fibres from type II to type I [68], involving intra- and inter-muscular adipose tissue [69]. In contrast, in COPD there is mainly a shift from type I to type II fibres [7] that can be responsible for dyspnoea symptomatology and/or low performance during exercise tests. Further understanding of the main molecular and cellular mechanisms underlying the onset of sarcopenia in COPD patients could support the optimisation of assessment tools for sarcopenia in COPD.

Strengths of this systematic review include the use of a predefined protocol, a comprehensive search strategy and the involvement of two independent co-authors in all stages of the process. Nevertheless, it is not free of limitations, and several topics should be taken into account when interpreting our results. First, as was previously highlighted, despite our results being centred around all sarcopenia consensus criteria, the cut-off points for its components were not uniform across studies. One explanation might be that there were different indices to measure muscle mass, and consequently there were different cut-offs. For instance, despite most of the selected studies used EWGSOP consensus criteria, they used different indices

to measure lean mass (appendicular lean mass/height², skeletal muscle mass/height², fat-free mass/body surface area); they also applied different cut-offs even for the same muscle index. Another explanation may be that they used different dual-energy X-ray absorptiometry and bioelectrical impedance analysis devices to measure lean mass. It is well known that bioelectrical impedance analysis, an inexpensive alternative to dual-energy X-ray absorptiometry, is dependent on the formula used [70], which differed among these studies. It has also been widely reported that dual-energy X-ray absorptiometry and bioelectrical impedance measurements in healthy adults provide different estimates of fat mass and fat-free mass [71]. Second, the main aim of this systematic review and meta-analysis was to provide a comprehensive overview of the current overall prevalence of sarcopenia in COPD patients, independent of the population setting. However, the six clinic-based studies used different consensus criteria and were performed in different ethnic groups, resulting in different estimates of sarcopenia prevalence. Similarly, the two population-based studies used different cut-offs and measurements, as did the nursing home studies, and the quality assessment of the selected studies varied, affecting the external validity. Therefore, our results may not be representative for COPD patients in general. Likewise, our results highlight that population-based studies on the association of main lifestyle factors (e.g. diet, physical activity, smoking) with sarcopenia in COPD patients remain limited.

More studies are needed to identify the main characteristics of COPD patients who present with sarcopenia defined by low muscle mass and function. This is particularly the case given that the updated EWGSOP2 recommendations mention that healthcare professionals have increasing possibilities for preventing, delaying, treating and even reversing sarcopenia [38]. EWGSOP2 have described that low muscle strength should be considered as “probable sarcopenia”. Therefore, systematically measuring the handgrip of each COPD patient, independent of the clinical setting, can contribute to early detection, prevention and treatment of sarcopenia. Muscle strength is determined by the velocity and type of contraction, size and motor units activated [7], which are affected early in COPD patients [7]. However, this does not mean that we should consider only handgrip for early detection of sarcopenia in patients with COPD, because the relationship between muscle mass and muscle function is nonlinear [72]. In addition, according to new recommendations of the Global Leadership Initiative on Malnutrition [73], having low muscle mass with normal muscle strength would be considered to be a result of malnutrition rather than sarcopenia.

We propose that the EWGSOP2 algorithm be used in clinical practice [38], and muscle strength assessed in all COPD patients. We call for more research directed towards defining optimal cut-off points of tests measuring muscle mass or function in patients with COPD. Importantly, multidisciplinary interventions such as pulmonary rehabilitation, which is included in the EWGSOP2 algorithm, have been shown to improve physical performance and exercise capacity in patients with COPD. The different steps of the

TABLE 3 EWGSOP2 algorithm for case finding, making a diagnosis and quantifying severity of sarcopenia in clinical practice with clinical and research considerations for COPD patients

Steps	Components	Response	Considerations for COPD patients
Step 1: Case finding	SARC-F or clinical suspicion	+ : Go to step 2 - : No sarcopenia, rescreen later	SARC-F in all COPD patients
Step 2: Assess	Muscle strength (grip strength or chair stand test)	+ : Go to step 3 plus start intervention: “probable sarcopenia” - : No sarcopenia, rescreen later	Call for research directed to define accurate cut-off points for low muscle strength in COPD patients
Step 3: Confirm	Muscle quantity or quality (DXA, BIA, CT, MRI)	+ : Go to step 4 plus intervention: “sarcopenia” - : Intervention for “probable sarcopenia”	Call for research directed to define accurate cut-off points for low muscle mass in COPD patients
Step 4: Severity	Physical performance (gait speed, SPPB, TUG, 400 m walk)	+ : “Severe sarcopenia” - : Intervention for “sarcopenia”	Call for research directed to define optimal physical performance tests and accurate cut-off points for COPD patients

EWGSOP2: 2018 European Working Group Older People; SARC-F: questionnaire with the five components of strength, assistance with walking, rise from a chair, climb stairs and falls; DXA: dual-energy X-ray absorptiometry; BIA: bioelectrical impedance analysis; CT: computed tomography; MRI: magnetic resonance imaging; SPPB: Short Physical Performance Battery; TUG: timed up and go test.

diagnostic approach to sarcopenia in patients with COPD, encompassing case finding, assessment, confirmation and determining its severity, are illustrated in table 3.

Finally, it is important to highlight that we found the overall prevalence of sarcopenia in COPD patients to be twice as high as compared to a healthy elderly population. In conclusion, sarcopenia defined as low muscle mass plus reduced muscle function is a frequent extrapulmonary condition in COPD patients. Despite the sarcopenia consensus criteria, there is still a lack of agreement in the optimal method and cut-off points to assess sarcopenia in general and in COPD patients in particular. Therefore, it is necessary to standardise the assessment methods for clinical practice and future research in COPD patients.

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