Title: Protocol: Sarcopenia and Frailty in Chronic Obstructive Pulmonary Disease: a systematic review

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Contributions:
- Study conception and design: CC, SC, MB, RH, MUP, CAC
- Acquisition of data: SC, MB, AP, MD, JM, CC, RH
- Analysis and interpretation of data: CC, SC, MB, RH, MUP, CAC
- Drafting of manuscript: CC, SC, MB
- Critical revision: CC, SC, MB, RH, AFP, MAD, JM, MUP, CAC
- Final approval: CC, SC, MB, RH, AFP, MAD, JM, MUP, CAC
In this protocol, we endorse PRISMA-P 2015 (Preferred Reporting Items of Systematic Review and Meta-Analysis Protocols 2015) statement (1,2).

BACKGROUND

Description of the conditions

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is a prevalent respiratory condition that is associated with significant mortality and morbidity (3), being the fourth leading cause of death worldwide (4). The primary risk factor for COPD is inhalation of agents such as tobacco or biomass smoke, but occupational dusts and fumes and exposure to air pollution have also been reported to be independent risk factors (5). Inhalation of these agents is associated with airway inflammation, presenting as bronchiolitis and emphysema (6). These structural changes cause impairment of expiratory flow and lead to resting and exercise hyperinflation (7), and they are related to the occurrence of progressive symptoms, such as dyspnea, cough and sputum production (6,7).

The natural history of COPD is characterized by exacerbations or episodes of clinical and lung function deterioration associated with an increase in airway and systemic inflammation (8). Acute exacerbations are now the main outcome evaluated in clinical trials as they are associated with increased respiratory and cardiovascular mortality, long-term decline in lung function and poorer quality of life (9), effects that are greater in those patients who have a frequent exacerbator phenotype (10).

Pharmacological and non-pharmacological therapy for COPD is therefore aimed at improving lung function, exercise capacity and quality of life, relieving symptoms and preventing exacerbations (11).

Skeletal muscle dysfunction is a well-recognized manifestation of COPD and common changes in the muscular system include quadriceps weakness, atrophy and fiber type shift, each of which offers prognostic information independent of lung function (12-15). One mechanism through which skeletal muscle dysfunction may
contribute to poor outcome is by precipitating so-called ‘geriatric syndromes’—age-related multifactorial health conditions—most notably sarcopenia and frailty (16-18).

A geriatric syndrome is a term used to describe common conditions occurring as result of impairments across multiple physiological systems, which ultimately lead to vulnerability, poor reserve and significant morbidity and mortality. Geriatric syndromes do not fit typical patterns of disease but are manifested by number of frequently observed characteristics (19-21).

**Sarcopenia**

The term sarcopenia was first coined by Rosenberg et al. in 1989 as a progressive loss of skeletal muscle mass with aging (22); although several definitions have been proposed, the algorithm for sarcopenia published by the European Working Group on Sarcopenia in Older People (EWGSOP) in 2010 has incorporated the presence of either low gait speed or low grip strength for the diagnosis (23) (figure 1).

The prevalence of sarcopenia is reported to be up to 29 % for older community-dwelling adults and up to 33 % for individuals living in long-term care institutions, depending on the definition used, and it is associated with subsequent morbidity, mortality and substantial financial cost from physical disability, falls, fractures, poor quality of life, depression and hospitalizations (24).

As there is now widespread agreement that sarcopenia should be defined as a combination of low muscle mass and loss of function (table 1), a new ICD code (ICD-10-M62.84) recognizes sarcopenia as a separately reportable condition (26).

Current research on sarcopenia treatment is focusing on nutritional exercise/activity based and other novel interventions for improving the quality and quantity of skeletal muscle in older people. Some studies demonstrated that resistance training combined with nutritional supplements can improve muscle function (26-28).
Frailty

Based on a recent consensus definition, frailty can be defined as a multi-system impairment associated with increased vulnerability to stressors (30) and the classic frailty phenotype definition by Fried et al. requires the presence of three or more of five features (low gait speed, low grip strength, weight loss, self-reported low physical activity and exhaustion) to diagnose the condition or the pre-frailty state (i.e., 1 or 2) (31) (table 2).

Rockwood and Mitniski proposed a model based on the arithmetic accumulation of deficits occurring with ageing. The so-called Frailty Index (FI) is generated as the ratio between the number of deficits the individual presents divided by the total of deficits considered in the computation. The assumptions of the model are that the items to be included should be associated with health status, increase with age, not saturate too early, adequately cover the multiple aspects of the health status, and be sufficiently numerous (at least 30 to guarantee the robustness of the estimation) (32, 33).

These two instruments are evidently very different in their constructs, but also in their objectives; the frailty phenotype is more focused at screening the physical domain of frailty, the deficit accumulation model stems from the results of a comprehensive geriatric assessment (16,34).

A recent systematic review found a total of 67 different frailty instruments, nine of which were had accumulated over 200 citations; Fried’s phenotype was the most widely used and cited, followed by the FI from Rockwood (35).

The prevalence of physical frailty increases with aging from under 5% in community dwelling persons aged 65-75 years to about 25% in persons who are 85 years of age or older (36); a pooled analysis of nine studies with a total of 1373 nursing home patients reported prevalence of frailty of 52.3% (95%CI 37.9%-66.5%) (37). In Latin America, frailty is very common among older people, with a review of 29 studies and 43,083 individuals reporting a prevalence of 19.6% (95%CI 15.4-24.3%) (38).
Agreeing an operational definition for frailty has also been controversial, and in the current International Classification of Diseases (ICD), frailty is listed simply as a condition of 'age-related physical disability' (ICD-10-R54) (30). There is substantial evidence that frailty reveals great power in predicting adverse clinical outcomes, not only in the general older population or patients at geriatric wards but also in patients with specific medical conditions, such as cardiac, liver and kidney disease as well as diabetes mellitus, osteoarthritis, trauma patients, patients undergoing surgery and critically ill patients (40). Thereby, frailty itself is associated with a wide range of different adverse clinical outcomes including high mortality in the mentioned groups of patients, partly independent of multiple potential confounders and detected also in younger patients (40).

**How the conditions might be related**

While frailty and sarcopenia overlap, about a third of people with sarcopenia do not have frailty, and similarly, all frail persons do not have sarcopenia (40,41). Although both conditions are conventionally considered secondary to aging, chronic diseases, such as COPD, can accelerate their occurrence (42,43).

According to a recent proposed conceptual model, sarcopenia is said to be the biological substrate of physical frailty and some refer to sarcopenia and frailty as two sides of the same coin (43-47). Skeletal muscle plays a preeminent role in frailty since, not only it is crucial for strength and mobility, but also it is one of the primary sources of mitochondrial energy production and the primary reservoir for amino acids in the body (43-47).

In times of stress, as could be an acute exacerbation of COPD, the sarcopenic patient can`t mobilize amino acids commensurate with the 400% increased demand required to synthesize proteins for wound healing, immune function, and acute phase reactants. The combination of anabolic insufficiency and catabolic stressors is aggravated by bedrest and malnutrition, creating a perfect storm for rapid muscle loss and culminating in profound deconditioning with prolonged recovery and
multiple complications; even a small loss of 5% muscle mass can have a devastating and long-lasting impact for the frail patient (43-47).

Aging-related chronic diseases such as pulmonary diseases, cardiovascular diseases and diabetes compromise metabolic balance, cardiovascular performance and pulmonary function leading to increased vulnerability of the organism when exposed to low-intensity stressors. This scenario represents the phenotypic manifestation of frailty. Conversely, the presence of frailty negatively conditions the progression and outcome of chronic diseases in older patients (43-47).

These chronic diseases would additionally impact skeletal muscle mass and function leading to sarcopenia which is closely related to poor physical performance and frailty. In this context, reduced regenerative capacity due to inefficient satellite cell function, malperfusion, increased oxidative stress, mitochondrial dysfunction and inflammation composes the aging-related skeletal muscle alterations in sarcopenia associated to the frailty phenotype; inflammation appears as a common determinant for chronic diseases, sarcopenia and frailty. Chronic diseases also share an impact on hormonal regulation, mainly on testosterone levels, which are key for muscle physiology and related to poor physical performance and frailty when they are reduced (43-47).

In other words, sarcopenia and frailty condition have a biological substrate at the level of muscle (i.e. low muscle mass), easily and objectively measurable with available techniques. At the clinical level, the manifestations of frailty and sarcopenia, such as slow gait speed, impaired balance, and weakness, are also measurable in an objective manner with specific assessment scales, such as the Short Physical Performance Battery (SPPB). This set of biological, clinical manifestations, and functional performance are similar as the diagnostic path that is usually performed for other common age-related degenerative conditions, such as congestive heart failure, COPD, and peripheral artery disease. This eventually implies that older persons with frailty and sarcopenia can easily be identified as subjects with target organ damage (i.e. low muscle mass), specific clinical phenotype, and impaired physical performance (43-47).
The identification of sarcopenia as a major component of physical frailty indicates that interventions specifically targeting the skeletal muscle such as nutrition, adequate amount of physical activity and exercise as well as pharmacological interventions may offer preventive and therapeutic advantages (43-47).

A recent randomized controlled trial conducted at two community hospitals in 289 older adults showed that a 6-month integrated care program with exercise, nutrition and psychological interventions improved frailty and sarcopenia status among community-dwelling elders, with high-intensity training yielding greater improvements (48); these interventions are part of pulmonary rehabilitation and integrated care recommended in COPD (49).

In the field of pulmonary diseases, research in sarcopenia and frailty is a novel area (18,50). Systematic reviews have shown that smoking is related to the development of sarcopenia (51) and frailty (52) and there is evidence that the presence of sarcopenia is a significant contributor to morbidity in patients with lung cancer (53) and lung transplantation (54) and that frail adults who become critically ill are more likely develop chronic critical illness or severe disability and have higher in-hospital and long-term mortality rates (50).

**Why is important to do this review**

Sarcopenia and frailty are the new geriatric giants and their prevalence is substantial in most geriatric settings (18,55). In older people, sarcopenia and frailty have proved to be useful tools for risk stratification, prognostication and to direct interventions aimed at preventing functional decline towards those carrying the greatest risk, as both are consistently associated with increased risk of important unfavorable outcomes (43,55).

Systematic reviews have shown that sarcopenia in community-dwelling older subjects is correlated with low nutritional status (56), cognitive impairment (57), poor health related quality of life (58), and increased mortality (59); in chronic diseases,
evidence have shown that sarcopenia is an independent predictor for outcome in liver transplantation patients and could be used for risk assessment (60), at cancer diagnosis is associated with worse survival in patients with solid tumors (61), and identified before surgery is associated with impaired overall survival in gastrointestinal and hepatopancreatobiliary malignancies (62).

The presence of frailty in community-dwelling older has been related to higher inflammatory parameters and in particular CRP and IL-6 (63), poor nutritional status (64), poor quality of life (65), depression (66,67), higher risk of hospitalization (68,69) or nursing home admission (68,70), and is a significant predictor of future falls (71), fractures (72), incident and worsening activities of daily living and instrumental activities of daily living disabilities (73), Alzheimer disease and all dementia (74), cardiovascular mortality (75) and global mortality (76); in patients undergoing surgical intervention, frailty is associated with poorer outcomes with regard to mortality and return to independence (77) and higher likelihood of experiencing mortality, morbidity, functional decline, and MACCE (major adverse cardiac and cerebrovascular events) following cardiac surgery (78). In chronic diseases, systematic reviews have reported that frailty is prevalent in patients with chronic kidney disease (79,80), heart failure (81), cancer patients (82) and HIV (83) and it is associated with high rates of co-morbidity and increased risk of hospitalization and/or mortality (79-83).

In COPD, these syndromes have only recently been evaluated (18,50) but there is no systematic review published to date about sarcopenia or frailty in COPD (18,50). However, early findings have sparked interest in the field, particularly those relating to prevalence, prediction of poor outcomes and information for choosing appropriate treatment and care planning, for example, in relation to lung transplant (54).

As an area of research, sarcopenia/frailty in COPD will allow of our interdisciplinary group (geriatrics and pulmonary medicine) to publish a second paper (84) and will help us to understand the occurrence and impact of these geriatric syndromes in COPD patients to propose potential areas for future research (18,50,85).
OBJECTIVES

The objective of this review is to summarize the evidence examining sarcopenia and frailty in patients with COPD, explore the relationships between these syndromes and clinically important disease outcomes (symptoms, quality of life, exercise capacity, physical activity, exacerbations, mortality, lung function) and determine the strategies used in COPD patients for their treatment.

PICOT QUESTION

P: patients with diagnosis of COPD (all severity grades)

I: structured evaluation of sarcopenia or frailty (all definitions)

C: none or subjects without sarcopenia or frailty

O: prevalence of sarcopenia and frailty in COPD, relations with important outcomes (lung function, symptoms, quality of life, exacerbations, mortality, comorbidities, others)

T: none

METHODS

Protocol registration

The review protocol is registered on the PROSPERO database (registration number CRD42016046833).

Criteria for considering studies for this review
- Types of studies

We will include randomized controlled trials (RCTs) and cohort and cross-sectional observational studies reported in full. Abstracts as well as unpublished data will not be considered. Review articles, case studies, case reports and case series will be also excluded.

- Types of participants

We will include all participants with a confirmed diagnosis of stable COPD using reliable and validated methods (i.e. GOLD 2010: smoking history of ≥10 pack-years and a post-bronchodilator FEV₁/forced vital capacity (FVC) <70%).

- Types of interventions

We will include cross-sectional and cohort studies and RCTs with patients with COPD, outpatient or inpatient, and sarcopenia or frailty assessed using systematically defined criteria.

- Types of outcome measures

Primary outcomes

• Prevalence of sarcopenia and frailty in COPD patients.
• Impact of sarcopenia and frailty on clinically important outcomes: symptoms (dyspnea, cough, fatigue), exercise capacity (i.e. 6 minutes walking tests), physical activity (i.e. validated questionnaire or number of steps), quality of life (i.e. SGRQ), exacerbations (moderate or severe) and mortality.

Secondary outcomes

• Relations of sarcopenia and frailty with lung function (i.e. post-bronchodilator VEF₁) and markers of inflammation or muscle weakness.
• Relations to comorbidities in COPD patients.
• Instruments used to evaluate sarcopenia and frailty in COPD.
• Strategies used for treatment of sarcopenia or frailty in COPD.
Information sources

Search methods for identification of studies

We will identify trials from searches of the following databases, without restriction on language or type of publication:

• Cochrane Airways Group Register of Trials (all years)

• Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library) (latest issue)

• MEDLINE (Ovid) (1950 to date)

• EMBASE (Ovid) (1974 to date)

• Physiotherapy Evidence Database (PEDro) (all years)

• ClinicalTrials.gov (http://clinicaltrials.gov/)

We will check reference lists of all primary studies and review articles for additional references.

Search strategy

We will search all records using search terms based on ‘sarcopenia’ (muscle, sarco*, wasting), ‘frailty’ (frail*, geriatric) and ‘chronic obstructive pulmonary disease (COPD, emphysema, chronic bronchitis, pulm* disease, respir*), modified according the specific vocabulary of each database.

Study Records

Selection of studies
Two group review authors (AP/MD/JM/CC for sarcopenia and SC/MB/RH for frailty), will independently screen titles and abstracts for inclusion of all the potential studies, retrieve the full-text, independently screen the full-text and identify studies for inclusion or exclusion.

We will resolve disagreements by involving a third person (MU-Z).

We will record the selection process according the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

**Data extraction and management**

We will use a data collection form for study characteristics and outcome data. Two group authors (AP/MD/JM/CC for sarcopenia and SC/MB/RH for frailty) will extract study characteristics from included studies:

1. Methods: study design, total duration of study, details of any 'run in' period, number of study centers and location, study setting, withdrawals, and date of study.

2. Participants: number enrolled, mean age, age range, gender, diagnostic criteria of COPD, baseline lung function.

3. Interventions: sarcopenia or frailty criteria.

4. Outcomes: primary and secondary outcomes and time points reported.

5. Others: funding for trial and conflicts of interest of trial authors.

We will resolve disagreements by involving a third person (MU-Z).

We will double-check that data is entered correctly by comparing the data presented in the systematic review with the study reports.

**Assessment of risk of bias in included studies**
For RCT studies, two review authors (CC and RH) will independently assess risk of bias using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions. We will assess the risk of bias according the following domains:

1. Random sequence generation
2. Allocation concealment
3. Blinding of participants and evaluators
4. Blinding of outcome assessment
5. Incomplete outcome data
6. Selective outcome reporting
7. Other bias

For non-randomised studies, two review authors (CC and RH) will independently assess risk of bias using the criteria outlined in the Newcastle-Ottawa Scale (NOS) Ottawa. We will assess the risk of bias according the following domains:

1. Selection: representativeness of the exposed cohort, ascertainment of exposure, demonstration that the outcome of interest was not present at start of study.
2. Comparability: on basis of the design or analysis
3. Outcome: assessment of outcome, enough and adequacy of follow-up

For each domain, a judgement of low, unclear or high risk of bias was made. Studies were assessed as at overall low risk of bias if all individual domains were judged at low risk; studies were judged as at overall high risk of bias if any individual domain was judged at high risk; studies were judged as at overall unclear risk of bias in all other cases.
In both cases, we will resolve any disagreements by discussion. We will grade each potential source of bias as high, low or unclear and provide a quote from the study report together with an explication in a 'Risk of bias' table. When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

**Data synthesis**

**Measures of effect**

We will analyze dichotomous data as odds ratios (ORs). For continuous data, we will use mean differences (MDs) or standardized mean differences (SMDs). Where it is reported, we will use the change from baseline. Where the change from baseline is not reported, we will use the adjusted results or final score.

We will undertake meta-analyses only where the prevalence, treatments, participants and the underlying clinical question are similar enough for pooling to make sense.

We will pool data using a random-effects model to incorporate between study heterogeneity into the meta-analysis, using RevMan 5.3 (2014). Where the studies are clinically heterogeneous, we will perform a narrative synthesis.

**Summary of findings table**

We will create a 'Summary of findings' table using the primary and secondary outcomes and we will use the five Grading of Recommendations Assessment, Development and Evaluation (GRADE) considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to the studies which contribute data to the pre-specified outcomes, using GRADEpro software (2008).
Dealing with missing data

We will contact trial investigators or sponsors to verify key missing study characteristics and obtain numerical outcome data where possible. Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis.

Assessment of heterogeneity

We will use the $I^2$ statistic to measure heterogeneity among the trials in each analysis. If we identify substantial heterogeneity, we will report it and explore possible causes by prespecified subgroup analysis.

We anticipated the possibility of different cut-points for sarcopenia and frailty domains and that the domains included might not have been standardized across included studies. We therefore extracted data on the cut-points for all the reference standards and the domains included for sarcopenia and frailty, as reported by the study authors.

Assessment of reporting biases

Only if we are able pool more than 5 trials, we will create and examine a funnel plot to explore possible small study and publication biases.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses.
• Severity of COPD: we will analyze data separately for patients with mild/moderate or severe/very severe COPD, determined by GOLD 2010 classification.

We will use the formal test for subgroup interactions in Review Manager 2014.

**Sensitivity analysis**

We will perform sensitivity analyses to examine the effects of methodological quality on the pooled estimate by removing studies that are at high or unclear risk of bias for the domains of blinding and incomplete outcome data.

**Schedule of activities**

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REFERENCES


**Figure 1.** Algorithm for sarcopenia diagnosis published by the European Working Group on Sarcopenia in Older People (EWGSOP).
Table 1. Existing tools for the assessment of the three domains of sarcopenia: muscle mass, muscle strength and physical performance and their applicability in research and clinical settings.
Table 2. Criteria for the phenotypic definition of frailty developed by Fried et al.
- Weight loss: > 5 kg/a
- Exhaustion: depression scale CES-D (2 points)
- Weakness: grip strength (lowest 20%)
- Gait speed: 5 m (slowest 20%)
- Low physical activity: kcal/week (lowest 20%)