

# Update on the Etiology, Assessment, and Management of COPD Cachexia: Considerations for the Clinician

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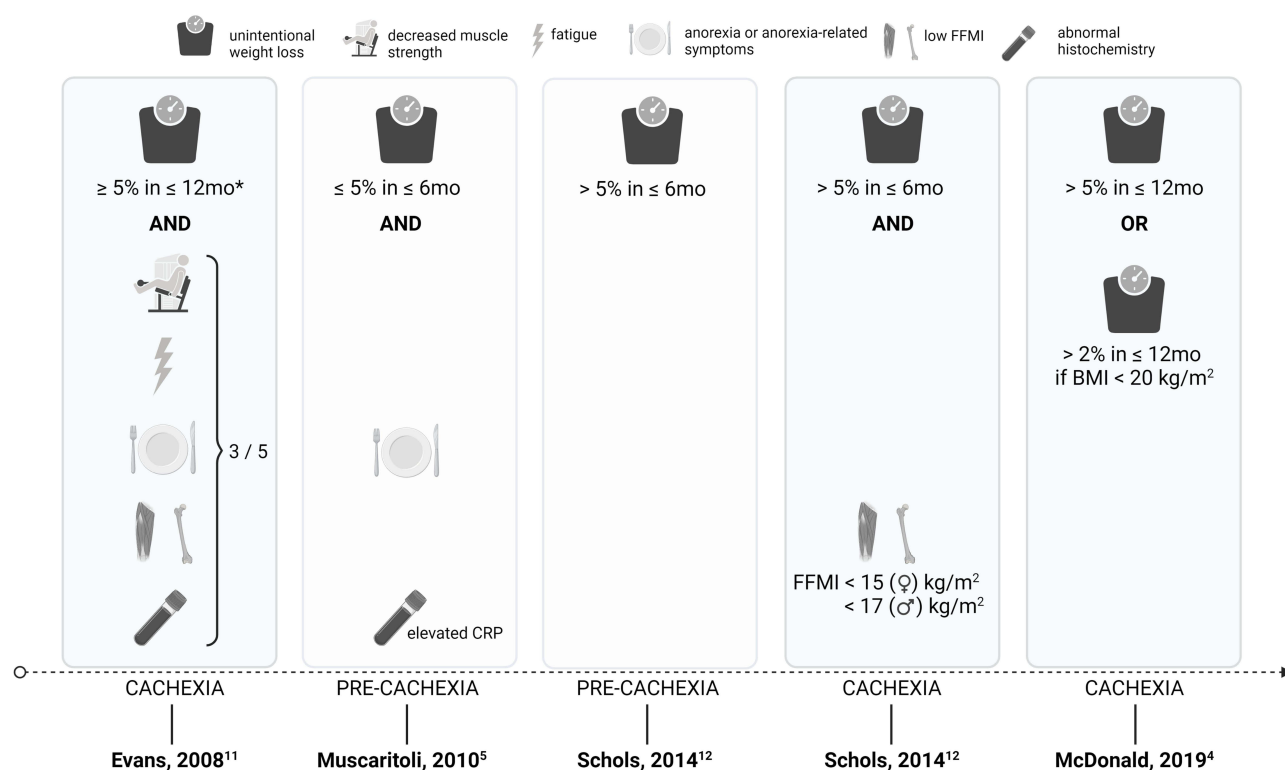
**Abstract:** Cachexia is a commonly observed but frequently neglected extra-pulmonary manifestation in patients with chronic obstructive pulmonary disease (COPD). Cachexia is a multifactorial syndrome characterized by severe loss of body weight, muscle, and fat, as well as increased protein catabolism. COPD cachexia places a high burden on patients (eg, increased mortality risk and disease burden, reduced exercise capacity and quality of life) and the healthcare system (eg, increased number, length, and cost of hospitalizations). The etiology of COPD cachexia involves a complex interplay of non-modifiable and modifiable factors (eg, smoking, hypoxemia, hypercapnia, physical inactivity, energy imbalance, and exacerbations). Addressing these modifiable factors is needed to prevent and treat COPD cachexia. Oral nutritional supplementation combined with exercise training should be the primary multimodal treatment approach. Adding a pharmacological agent might be considered in some, but not all, patients with COPD cachexia. Clinicians and researchers should use longitudinal measures (eg, weight loss, muscle mass loss) instead of cross-sectional measures (eg, low body mass index or fat-free mass index) where possible to evaluate patients with COPD cachexia. Lastly, in future research, more detailed phenotyping of cachectic patients to enable a better comparison of included patients between studies, prospective longitudinal studies, and more focus on the impact of exacerbations and the role of biomarkers in COPD cachexia, are highly recommended.

**Keywords:** chronic obstructive pulmonary disease, muscle, weight loss, nutrition, pulmonary rehabilitation

## Introduction

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and irreversible respiratory disease accompanied by extra-pulmonary manifestations that significantly impact morbidity and mortality.<sup>1</sup> Cachexia is prevalent in many chronic diseases (eg, cancer, chronic kidney disease, chronic heart failure)<sup>2</sup> and is an important extra-pulmonary manifestation observed in patients with COPD.<sup>2-4</sup> In COPD, cachexia is a multifactorial syndrome characterized by severe loss of body weight, muscle, and fat, as well as increased protein catabolism.<sup>5</sup> An estimated 1.4 million patients with COPD in Europe suffer from cachexia;<sup>2,4</sup> these patients have a 2- to 3-fold higher mortality risk<sup>3,4</sup> and suffer from a greater disease burden (eg, reduced lung function<sup>3,6,7</sup> or more emphysema)<sup>4</sup> than those without cachexia. In addition to its impact on patients, cachexia poses an increased load on the healthcare system in terms of number, length, and cost of hospitalizations.<sup>8,9</sup> The considerable impact of COPD cachexia on patients and the healthcare system highlights the clinical relevance of the COPD cachexia syndrome and underscores the need to improve prevention and treatment.

In the past decade, several international working groups focusing on chronic diseases and cancer have proposed definitions of cachexia to facilitate diagnosis and management (Figure 1).<sup>5,10-12</sup> However, scientific and clinical



**Figure 1** Graphical overview of published criteria to diagnose cachexia in patients with COPD. Given the variability in the definition of cachexia, it is important to note that this review covers a wide spectrum of patients and is not limited to a single definition of COPD cachexia. For specific diagnostic criteria and cut off values, the authors refer to the publications from Evans (2008), Muscaritoli (2010), Schols (2014) and McDonald (2019). Pre-cachexia criteria = light; Cachexia criteria = dark. \*In cases where weight loss cannot be documented, a body mass index (BMI) <20 kg/m<sup>2</sup> is sufficient. Based on Evans (2008), fatigue is interpreted as physical and/or mental weariness resulting from exertion and an inability to continue exercise at the same intensity with a resultant deterioration in performance. Based on Evans (2008) and Muscaritoli (2010), anorexia or anorexia-related symptoms are interpreted as limited food intake or poor appetite. Based on Evans (2008) and Muscaritoli (2010), abnormal histochemistry is interpreted as increased inflammatory markers, though anemia or low serum albumin may also be present. Created with BioRender.com.

**Abbreviations:** CRP, C-reactive protein; FFMI, fat-free mass index; BMI, body mass index; mo, months.

respiratory communities have not systematically incorporated the diagnosis and management of cachexia in patients with COPD in research and practice.<sup>3</sup> This oversight has led to an underappreciation of the prevalence and a suboptimal or neglected clinical management of the COPD cachexia syndrome. Understanding the factors that contribute to COPD cachexia is necessary to conceptualize effective prevention and treatment strategies. Therefore, the primary objective of this narrative review is to provide an update on the current scientific evidence on COPD cachexia etiology, assessment, and management. In addition, recommendations for clinical practice and future directions for research are provided. Given the variability in the definition of cachexia (Figure 1), it is important to note that this review covers a wide spectrum of patients and is not limited to a single definition of COPD cachexia.

## COPD Cachexia

### Diagnosis and Clinical Phenotype

In the 15 years since Evans et al published their consensus definition of cachexia,<sup>11</sup> research on the diagnosis and presentation of cachexia in COPD, including the importance of treating comorbid conditions, has evolved significantly. However, COPD cachexia is still primarily characterized using cross-sectional anthropometric measurements that are readily available in clinical offices. Low body mass index (BMI) and low fat-free mass index (FFMI) have long been recognized as risk factors for increased mortality in patients with COPD;<sup>13,14</sup> however, patients with COPD who are experiencing weight loss, even among those who are overweight or obese, have a higher risk of death in comparison to those with stable weight.<sup>4</sup> So, it is important to recognize that, despite the classically cachectic patient being seen as severely underweight, cachexia can develop in patients

with COPD across the BMI spectrum.<sup>4</sup> For this reason, cross-sectional measurements of BMI and FFMI are often inferior to longitudinal measures of loss of body weight and fat-free mass (FFM) for predicting mortality.<sup>3</sup>

Screening for COPD cachexia can be as straightforward as tracking a patient's weight across clinical visits; active monitoring of weight trends over time is essential, even among patients with obesity. However, in obese patients, unintentional weight loss may be applauded instead of recognized as a harbinger of worsened outcomes. Two large studies have found that the BMI category (normal, overweight, or obese) is a modifier of the risk of mortality among patients with COPD cachexia.<sup>4,15</sup> However, several other studies of COPD have shown no statistically significant increased mortality contribution from BMI category above that associated with weight-loss.<sup>3,14,16</sup> Concurrent monitoring of the loss of FFM is essential as patients may lose FFM independent of BMI.<sup>16</sup> Measurement of FFM typically requires techniques such as dual x-ray absorptiometry (DXA) and bioelectrical impedance (BIA), which are often used in research but not generally accessible in pulmonary clinics.<sup>17,18</sup>

Routine body composition monitoring for cachexia is most evolved in cancer, where patients frequently receive whole body scans. Cancer cachexia studies typically rely on assessment of muscle mass at the L3 vertebrae which is not typically available on chest computed tomography (CT) scans in COPD designed to capture lung abnormalities. However, pectoralis muscle area (PMA) and first lumbar level (L1) muscle mass can be measured on chest CT scans, which are commonly acquired during acute hospitalizations or as part of a lung cancer screening program in patients with COPD.<sup>19</sup> PMA is more highly correlated with COPD disease severity and functional outcomes than BMI,<sup>20</sup> and loss of PMA is associated with increased mortality in patients with COPD.<sup>16</sup> Research in patients with non-small cell lung cancer showed that L1 muscle mass correlates very strongly ( $r = 0.90$ ) with L3 muscle mass, which is considered the reference but is often not evident on chest CT, and L1 muscle mass loss predicts overall survival.<sup>21</sup> Screening for longitudinal changes in FFM based on PMA or L1 muscle mass on routine chest CT scans is feasible. A large study of longitudinal PMA in more than 10,000 current and former smokers demonstrated increased risk of mortality independent of baseline BMI and disease severity which indicates therapies targeting muscle maintenance may be of benefit early in the disease course.<sup>16</sup>

Clinical studies indicate that patients with COPD cachexia suffer from more severe disease in terms of pulmonary and physical functioning outcomes compared to those without cachexia. More specifically, patients with COPD cachexia have worse airway obstruction<sup>3,4,7,13,14,22</sup>, and more severe impairment in exercise capacity<sup>3,23</sup> and functional outcomes such as walk distance and handgrip strength.<sup>24,25</sup> In addition, cachexia is more prevalent in patients with more extensive emphysema on CT imaging. However, it is important to note that cachexia can develop in patients with COPD without emphysema.<sup>26</sup>

Further, the multifactorial components of COPD cachexia contribute to the increased likelihood of other extra-pulmonary manifestations in cachectic patients or those at risk of becoming cachectic. For example, metabolically, patients with COPD and cachexia have elevated inflammation and growth hormone resistance compared to non-cachectic patients,<sup>6,27,28</sup> while the presence of insulin resistance in cachectic patients remains debatable.<sup>6,29</sup> Additionally, low body weight (defined as BMI  $<21$  kg/m<sup>2</sup>) has also been associated with a higher likelihood of reporting symptoms of depression in patients with COPD.<sup>30,31</sup> In contrast, a higher risk of anxiety symptoms has not been reported.<sup>30,32</sup>

Overall, patients with COPD and cachexia (defined as low muscle mass) appear to have a worse quality of life than patients without cachexia,<sup>20,24,33</sup> however, some studies have not reported this association.<sup>3,32</sup>

## Pathophysiological Mechanisms and Etiology of COPD Cachexia

### Pathophysiological Mechanisms

The molecular triggers and mechanisms contributing to weight loss and muscle mass loss in COPD cachexia have become increasingly evident in the last decade. We provide a brief summary here, as these mechanisms have been reviewed in detail elsewhere.<sup>27,34–36</sup>

Inflammation and oxidative/nitrosative stress are well-established triggers of muscle wasting and dysfunction in cachexia<sup>27,37</sup> that catalyze an imbalance in protein and myonuclear turnover, leading to weight and muscle loss (atrophy) in cachectic patients with COPD.<sup>27,34</sup> Protein breakdown is increased,<sup>34</sup> with a compensatory increase in protein synthesis.<sup>38</sup> In addition, cachectic patients with COPD have a more pronounced loss of oxidative muscle capacity than

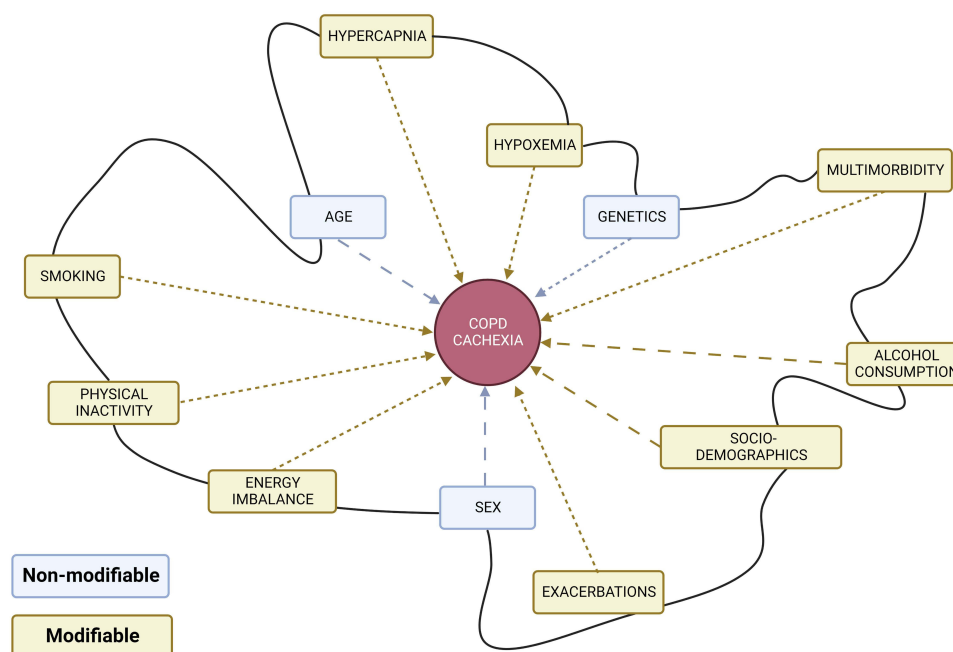
patients without cachexia.<sup>34,39–41</sup> Recent research has further demonstrated that sarcopenic patients with COPD have more endoplasmic reticulum stress (a possible driver of muscle atrophy) compared to non-sarcopenic patients.<sup>42</sup> Additionally, cachectic patients with COPD have dysregulated micro-RNA expression related to muscle proliferation and differentiation during myogenesis compared to patients without cachexia.<sup>43</sup>

The molecular and cellular mechanisms responsible for fat mass loss, mostly observed in patients with advanced COPD and particularly emphysematous COPD,<sup>26</sup> have received less attention. Most scientific work has focused on the role of adipokines, cell-signaling molecules (cytokines), produced by the adipose tissue. For example, leptin, a major influencer of energy balance through its effects on regulation of appetite and food intake, was found to be lower in the circulation of emphysematous patients compared to chronic bronchitis patients.<sup>44</sup> Further, an association was noted between reduced serum leptin levels, increased serum adiponectin levels, and increased resting energy expenditure in patients with COPD, though this analysis was not limited to patients with cachexia.<sup>45</sup> More recent research has investigated other adipokines, including adiponectin and zinc alpha 2-glycoprotein (ZAG), and reported that serum levels of both adipokines were significantly higher in patients with COPD with cachexia compared to those without cachexia.<sup>46</sup> Adiponectin and ZAG were also associated with weight loss.<sup>46</sup> Brown adipose tissue (BAT) activity has been suggested as a possible mechanism leading to a hypermetabolic state in patients with emphysema;<sup>47</sup> however, Sanders et al recently discovered that BAT activity was not different between hypermetabolic patients with COPD and age, sex, and BMI-matched healthy controls.<sup>48</sup> Lastly, upregulation of inflammatory and proapoptotic adipose tissue markers has not been observed in cachectic patients with COPD.<sup>29</sup>

Other proposed COPD cachexia triggers and mechanisms include altered brain responses to food stimuli, altered gut integrity, and reduced splanchnic extraction.<sup>34</sup>

## Etiology

The etiology of COPD cachexia involves a complex interplay of non-modifiable and modifiable factors,<sup>49</sup> depicted in Figure 2. Which factors cause, accelerate or impair the recovery of cachexia remains to be determined. Identifying modifiable factors, however, is crucial as it drives the development of therapeutic approaches and may permit early detection of cachexia and initiation of treatment.



**Figure 2** Conceptual framework of etiological factors involved in COPD cachexia. The complex interplay of these factors is depicted via the irregularly shaped black line that links all factors to each other. It illustrates that each factor possibly influences other factors. For every patient with COPD cachexia, the factors involved and their interplay (and consequently the shape of the black line) will be different. Wider space between dashed line = scientific evidence is not consistent or not currently available in patients with COPD. Created with BioRender.com.

## Non-Modifiable Factors

**Age and sex** – Neither age and sex have been reproducibly shown to differ between COPD patients with and without cachexia.<sup>3,4,7,9,14,25,32</sup>

**Genetics** – Genetic predisposition to COPD and/or addiction to tobacco smoking are well-established, including monogenic and complex genetic etiologies.<sup>50–54</sup> Among the monogenic etiologies, individuals with alpha-1 antitrypsin deficiency (AATD), caused by genetic variation in the *SERPINA1* gene, are at increased risk of developing COPD as well as cachexia. This emphasises the importance of early AATD diagnosis and counseling for smoking cessation.<sup>55</sup> Yet the majority of AATD patients go undiagnosed: in a recent study of 458,164 European-ancestry participants from the UK Biobank, only 6.4% of subjects with the heterozygous recessive PIZZ genotype, the most common genetic variation causing AATD, had been diagnosed with AATD.<sup>56</sup> In addition to being at high risk for worsened airway obstruction, carriers of the PIZZ genotype are more likely to have cachexia and have a higher mortality risk. One challenge in investigating and identifying genetic predictors of COPD cachexia is that genetic variants typically have low to moderate effect sizes, which requires large samples of patients with COPD with and without cachexia to achieve the necessary power to scan the genome. For this reason, early genetic studies focused on candidate genes in patients with COPD who were not thoroughly phenotyped for cachexia. Candidate genes with variants associated with cachexia traits in COPD include angiotensin-converting enzyme (ACE),<sup>57</sup> bradykinin receptor,<sup>58</sup> vitamin D receptor,<sup>59</sup> and secretory phospholipase-A2,<sup>60</sup> as well as genes responsible for initiating the inflammatory cascade such as interleukin-1 $\beta$  (IL-1 $\beta$ ), interleukin-6 (IL-6), and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ).<sup>60</sup> The first genome-wide association study of longitudinal weight loss in 4308 patients with COPD identified significant gene-level associations with *EFNA1* and *BAIAP2*.<sup>61</sup> Interestingly, *EFNA2* encodes the membrane-bound protein ephrin-A2, which is involved in regulating developmental processes and homeostasis in adult tissue such as skeletal muscle. *BAIAP2* encodes the 53 kD insulin-responsive protein (IRSp53), a negative regulator of myogenic differentiation. At the single gene variant level, the rs35368512 variant, intergenic to *GRXCR1* and *LINC02383*, was associated with an increased likelihood of weight loss but only among African-American patients with COPD. The study also used an integrative approach to mine the underlying proteome network and found that genetic variation associated with weight loss in COPD may influence skeletal muscle regeneration and tissue remodeling. However, additional genetic investigations in larger samples of patients of diverse ancestry with COPD with and without cachexia are needed.

## Modifiable Factors

**Smoking** – Chief among the modifiable risk factors for COPD cachexia is continued tobacco smoking. Even among adults without COPD, longitudinal fat mass and muscle mass loss patterns are associated with tobacco smoking.<sup>62</sup> Among patients with COPD, low BMI and muscle wasting are frequently, but not universally, associated with active smoking.<sup>3,7,9,32,63,64</sup> The cellular mechanisms of the effects of smoking on skeletal muscle are not completely clear, but greater tobacco smoke exposure is associated with greater evidence of mitochondrial DNA damage, and the muscle from patients with COPD show increased levels of cytochrome c oxidase (COX) deficiency and blunted compensatory transcriptional responses.<sup>65</sup> There is also evidence to suggest that m. vastus lateralis fibers of patients with COPD cachexia may undergo repeated cycles of denervation suggestively caused by decades of tobacco smoke exposure,<sup>66</sup> although studies on the m. rectus abdominis in patients with cancer-associated cachexia show no evidence of denervation.<sup>67</sup> Degens et al previously reviewed the extensive literature regarding skeletal muscle dysfunction secondary to active smoking (human and animal model) and concluded that smoking contributes to the development of muscle dysfunction, and that future studies need to investigate whether smoking cessation restores muscle function in patients with COPD.<sup>68</sup> Other studies have suggested that physical activity may modulate tobacco smoke's effects on skeletal muscle in mouse models.<sup>69,70</sup> There may also be a differential temporal association of tobacco smoking with wasting in different tissues, as recent mouse and tissue culture data indicate earlier onset of adipose tissue wasting when compared to wasting of skeletal muscle. Future in vivo studies characterizing longitudinal changes in body composition in response to tobacco smoke exposure could help to identify temporal heterogeneity in the wasting of various tissue types.<sup>71</sup>

**Hypoxemia** – Cachexia is more likely to be present in patients with COPD who demonstrate more severe airway obstruction and emphysema, which limits the body's access to oxygen, contributing to alveolar hypoxia and consequent



hypoxemia. For these reasons, hypoxia and hypoxemia are suspected to play a crucial role in the pathogenesis of COPD cachexia.<sup>49,72</sup> Hypoxia influences relevant cachexia mechanisms such as appetite and maintenance of skeletal muscle mass and function.<sup>73</sup> Hypoxemia can be monitored clinically, and lower resting oxygen saturation has been associated with lower body weight in patients with COPD.<sup>74,75</sup> A study in healthy young male volunteers found that hypoxemia (14.1% inspired oxygen) and forced inactivity, compared with normoxic forced inactivity, resulted in more significant thigh muscle cross-sectional area (CSA) loss, a greater increase in the proportion of type IIx muscle fibers, and a greater decrease in the proportion of type I muscle fibers.<sup>76</sup> A similar fiber type shift is seen in patients with COPD and is associated with greater disease severity.<sup>77</sup>

**Hypercapnia** – The chronic buildup of carbon dioxide in blood, called hypercapnia, is associated with worse nutritional status in COPD.<sup>74</sup> Hypercapnia is found to be more likely among patients with COPD and BMI <20 kg/m<sup>2</sup> with respiratory failure.<sup>78</sup> Interestingly, after receiving non-invasive positive pressure ventilation (NPPV) overnight, those with BMI <20 kg/m<sup>2</sup> experienced weight gain independent of changes in blood gas and lung function levels. The mechanisms behind this beneficial effect of NPPV on body weight remain unclear. A reduction in the energy requirements by nocturnal unloading of the respiratory musculature is a plausible hypothesis to explain this improvement.<sup>78</sup> Recent data supports this hypothesis, indicated by weight gain in patients with severe COPD and BMI < 21 kg/m<sup>2</sup> after undergoing bronchoscopic lung volume reduction.<sup>79,80</sup> Further studies to replicate these results are merited.

**Physical inactivity** – Physical inactivity contributes to a decline in muscle mass and function, and indirectly contributes to cachexia. While physical inactivity is the strongest predictor of all-cause mortality in patients with COPD,<sup>81</sup> its role in COPD cachexia is surprisingly scarcely investigated. Muscle dysfunction in patients with COPD, however, has been extensively characterized.<sup>36</sup> Physical inactivity is seen as a major driver of muscle dysfunction in patients with COPD, with many muscle characteristics similar to those observed after immobilization (disuse of the muscles).<sup>36</sup> Additionally, studies of exercise training interventions have reproducibly shown improvements in muscle mass in patients with COPD.<sup>82</sup> However, the number of exercise training studies including cachectic patients with COPD is limited. Observational evidence investigating the relationship between physical inactivity and muscle mass loss leads to contradictory conclusions. A recent systematic review<sup>33</sup> showed that patients with COPD and lower-limb sarcopenia had significantly lower levels of subjectively (self-reported)<sup>83–86</sup> and objectively (accelerometry)<sup>83</sup> measured physical activity. Further, Matkovic et al demonstrated that patients with COPD and poor physical activity have a lower FFMI and lean mass index; however, these were not independently associated with poor physical activity in a multivariate analysis.<sup>87</sup> Observational cross-sectional evidence has shown weak positive associations between FFMI, rectus femoris CSA, and physical activity level ( $r = 0.134$  to  $0.286$ ) in patients with COPD.<sup>88,89</sup> Multivariate analysis showed that FFMI was not an independent predictor of physical activity in patients with COPD;<sup>90</sup> however, in GOLD stage I patients, physical activity was associated (independently from airflow limitation) by rectus femoris CSA,<sup>91</sup> suggesting that muscle wasting is present even in early disease. Until now, observational studies investigating physical inactivity in patients with COPD and cachexia have been limited by cross-sectional data and small sample sizes. Longitudinal observational studies of physical activity in patients with COPD with cachexia are needed to elaborate on the dynamic process of cachexia and the role of physical inactivity to address causation. For example, it is unclear whether inactive patients with COPD are more prone to develop cachexia or whether patients with cachexia are more likely to be inactive. Lastly, low physical activity is associated with increased systemic inflammation, an essential trigger of cachexia in patients with COPD.<sup>92–94</sup> Conversely, improvements in systemic inflammation have been reported in patients with COPD who were able to increase their physical activity.<sup>95</sup>

**Energy imbalance** – Factors contributing to the observed energy imbalance (energy expenditure vs energy availability) in cachectic patients with COPD is described in a comprehensive review by Sanders et al.<sup>34</sup> An increased resting energy expenditure is reported in patients with COPD cachexia.<sup>96,97</sup> Additionally, cachectic patients with COPD have higher energy demands when performing physical activity in comparison to healthy controls.<sup>98,99</sup> When combined with the observed respiratory mechanical inefficiency, due to hyperinflation, which increases the work of breathing, the higher energy demand might lead to increased activity-induced energy expenditure (AEE). Research regarding AEE in cachectic patients with COPD is, however, lacking. Compensation for the elevated energy expenditure is necessary to maintain energy balance and to avoid wasting of muscle and fat mass. Dietary intake in patients with COPD who are losing weight are reported to be

comparable to weight-stable patients but insufficient to counterbalance the elevated energy expenditure.<sup>100</sup> Unfortunately, extensive research focusing on dietary intake in patients with cachexia is currently scarce. In relation to dietary intake, nutrition impact symptoms (eg, constipation, changes in the taste of food, loss of appetite) can be assessed and those symptoms are more frequently reported in patients with low FFMI compared to patients with normal FFMI.<sup>6</sup> Additionally, nutrition impact symptoms and reduced food intake (measured as <75% food intake compared to usual) have shown to be associated with involuntary weight loss in patients with COPD,<sup>101</sup> suggesting that nutrition impact symptoms and reduced food intake could significantly contribute to the development of cachexia in this population.

**Alcohol consumption** – Excessive alcohol consumption might also contribute to COPD cachexia. Animal models of COPD<sup>102,103</sup> and cancer,<sup>104,105</sup> as well as human<sup>106,107</sup> studies, have repeatedly shown that excessive alcohol consumption leads to muscle loss as protein synthesis is inhibited and protein breakdown is enhanced.<sup>103,108</sup> In addition, patients with COPD may have increased rates of excessive alcohol use compared to age-matched controls,<sup>109</sup> suggesting that excessive alcohol consumption could contribute to the development of COPD cachexia. However, this hypothesis has not been tested, and future research is needed to explore the contribution of alcohol consumption to COPD cachexia.

**Exacerbations** – The number of COPD exacerbations a patient has experienced in the prior year is associated with an increased risk of cachexia (defined as unintentional weight loss of >5% over the preceding 6 months and with reduced FFMI).<sup>3</sup> Gene expression studies on muscle tissue from the m. vastus lateralis of patients with COPD during acute exacerbation versus those with stable disease showed increased expression of genes associated with ubiquitin-dependent protein catabolism, one of the leading culprits in the pathophysiology of COPD cachexia, and down-regulation of genes in the mitochondrial respiratory chain.<sup>110</sup> The proximal cause of these changes is uncertain as corticosteroids are frequently prescribed for acute exacerbations, and systemic corticosteroid exposure has been directly linked to reduced quadriceps strength after a COPD exacerbation<sup>111</sup> and during stable disease.<sup>112</sup>

**Social-demographic factors** – Social factors such as access to care, ability to afford medication and food, proximity to environmental pathogens, and other social determinants of health show significant effects across the medical spectrum.<sup>113</sup> Little data is available to describe the impact of these factors on the development and prognosis of cachexia in patients with COPD. Attaway et al used a national database in the United States to demonstrate increased prevalence of COPD in more rural and economically deprived areas; however, geographic differences between COPD patients with and without a muscle loss phenotype were relatively minor.<sup>9</sup>

**Multimorbidity** – Finally, it is important to conceptualize cachexia within a broader context of multimorbidity in patients with COPD. Vanfleteren et al described a pattern of comorbidity clustering in 215 patients with COPD, including a cluster of cachectic patients that showed associations with osteoporosis and renal disease.<sup>32</sup> These associations were not borne out in a later clustering analysis conducted by the same group.<sup>7</sup> Within the scientific community, there is a movement towards recognizing extra-pulmonary manifestations of COPD as related symptoms of an overarching systemic disease centered in the lungs but inextricably linked to the function of many other organs.<sup>114,115</sup> Recognizing the burden of multimorbidity in COPD, and screening patients for these extra-pulmonary manifestations, could allow for earlier identification and treatment of comorbidities and more holistic care for the patient.<sup>115</sup>

## Therapeutic Approaches to COPD Cachexia

The deleterious effects of cachexia on morbidity and mortality in patients with COPD underscore the importance of identifying effective therapeutic approaches. After cachexia is diagnosed in a patient with COPD, an initial structured nutritional assessment is required, which is ideally repeated regularly along with longitudinal measurements of body weight, body composition, and nutritional intake impact symptoms. These nutritional assessments should prompt multimodal intervention strategies encompassing nutritional support, muscle activation by exercise training, and/or targeted pharmacological interventions in select subpopulations.

## Nutritional Therapy

Poor dietary quality may accelerate disturbances in body composition in patients with COPD and contribute to the development of cachexia. In terms of caloric content, patients with COPD generally have a normal dietary intake compared with healthy individuals.<sup>116</sup> Nevertheless, this intake may be inadequate for meeting the elevated energy

requirements of patients with COPD.<sup>117–119</sup> Exacerbation of COPD may further impair energy balance due to decreased dietary intake combined with increased resting energy expenditure during acute illness.<sup>120</sup> To compensate for increased energy requirements and prevent weight loss, patients with COPD may need to adapt their dietary intake to an energy-enriched diet. However, since a high caloric load may stress the impaired ventilatory capacity, smaller meals spread throughout the day should be recommended.<sup>121</sup> In addition, muscle protein synthesis should be stimulated to maintain muscle mass. Muscle protein synthesis depends on the availability of amino acids in the bloodstream. Therefore, a diet with sufficient proteins amounting to at least 1.2 g per kg body weight might be necessary to achieve an anabolic response.<sup>122</sup> High-quality proteins, such as casein, leucine, and whey protein, elicit an increased anabolic response after acute or short-term ingestion in patients with COPD.<sup>123–126</sup> However, the long-term benefits of high-quality protein ingestion and the beneficial effects of its metabolites (eg, beta-hydroxy-beta-methylbutyrate) still need to be investigated.<sup>127</sup>

**Nutritional supplementation** – To treat cachexia, oral nutritional supplements (medical drinks/snacks) could supplement the diet when nutrient requirements cannot be satisfied through habitual dietary intake or when a temporary boost is needed. A recent Cochrane review on supplementation with medical nutrition in patients with COPD showed moderate-quality evidence that nutritional supplementation promotes weight gain among patients with COPD, especially if malnourished.<sup>128</sup> With high-quality proteins to stimulate the regenerative response of muscles, these supplements might need to be enriched with additional vitamins, minerals, and trace elements to combat nutrient deficiencies. Vitamin D deficiency, measured as serum levels of 25-hydroxyvitamin D, is frequently reported in patients with COPD and worsens with disease severity.<sup>129</sup> Supplementing vitamin D in patients with COPD may positively affect bone health and improve muscle strength by regulating mitochondrial dynamics and enzyme production,<sup>130,131</sup> however, the specific effects of vitamin D in the cachectic patient with COPD remain unclear. Low intake of omega-3 polyunsaturated fatty acids (n-3 PUFAs) is also reported in patients with COPD.<sup>132</sup> In addition to their anti-inflammatory effects, PUFAs are the natural ligands of peroxisome proliferator-activated receptors (PPARs) and may potentially boost muscle mitochondrial metabolism by stimulating PPAR and PPAR gamma coactivator-1 alpha (PGC-1 $\alpha$ ) signaling or inhibiting classic nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B) signaling. In addition, a placebo-controlled randomized controlled trial (RCT) in cachectic patients with COPD showed decreased exercise fatigue and dyspnea after 12 weeks of a targeted medical nutrition therapy<sup>133</sup> enriched with whey protein, n-3 PUFAs, and vitamin D. Nutrition therapy was compared with an isocaloric diet including milk protein instead of whey protein and sunflower oil instead of fish oil with high levels of n-3 PUFAs.

**Nutrition supplementation combined with exercise** – Combining nutritional supplementation with pulmonary rehabilitation (PR) might enhance the beneficial effects of PR. For example, PUFA supplementation during an 8-week rehabilitation program significantly improved endurance exercise capacity in comparison to placebo in patients with COPD, even after adjustment for FFM.<sup>134</sup> A more recent RCT—the NUTRAIN trial—investigated whether targeted nutritional supplementation enhances outcomes of exercise training in patients with COPD with low muscle mass.<sup>135</sup> In the trial, a multimodal drink enriched with leucine, vitamin D, and n-3 PUFAs significantly improved or maintained body weight, inspiratory muscle strength, and physical activity but did not enhance the effects of a 12-week rehabilitation program on muscle mass, muscle strength, and physical performance.

**Opportunities for nutritional therapeutics** – While most studies of nutritional interventions for COPD cachexia have focused on short-term efficacy (1–3 months) in clinically stable disease or as an adjunct to PR, only a few studies have investigated the benefits of nutritional supplementation during the maintenance phase after PR. For example, the NUTRAIN trial and the INTERCOM trial showed that during the 12- to 24-month maintenance phase after PR, nutritional interventions did not seem to enhance the long-term outcome of exercise training on physical capacity but did improve plasma levels of the supplemented nutrients, total body weight, physical activity, and generic health status. Notably, these outcomes were achieved at an acceptable cost for patients with high disease burden.<sup>136,137</sup> Lastly, the effect of nutrition therapy during and after an acute exacerbation still is a wholly neglected area of research. This is noteworthy as, during an acute exacerbation, disease-related factors such as inflammation, hypoxia, inactivity, and glucocorticosteroid treatment converge and intensify.<sup>138</sup> Additionally, the gap between energy intake and energy expenditure becomes wider during acute exacerbations, then slowly decreases upon recovery.<sup>120,139,140</sup> Only one study



has proven the feasibility and efficacy of nutritional supplementation in maintaining energy balance and increasing protein intake in hospitalized patients with COPD.<sup>139</sup> Still, the therapeutic window of opportunity after an acute exacerbation warrants further investigation.

## Exercise Training

Exercise training is recommended in many diseases associated with skeletal muscle wasting.<sup>141</sup> Exercise should be routinely offered to patients with COPD as part of PR, supported by a significant and robust evidence base in both stable and acute COPD populations. The established benefits of PR in general COPD populations include improved exercise capacity, symptom burden, and health status, and, in the post-acute setting, a lower risk of hospital admission.<sup>142</sup> Exercise training also clearly improves skeletal muscle function and morphology in patients with COPD<sup>36,82,142,143</sup> through upregulation of factors governing skeletal muscle hypertrophy and regeneration, with a variable effect on systemic or local muscle inflammation.<sup>144,145</sup> Increased fiber CSA, reduced proportion of type IIx fibers, increased oxidative capacity, and reduced exercise-induced lactic acid production are also observed after exercise training in patients with COPD.<sup>36,146</sup> Notably, independent of the exercise modality used, programs using training at higher intensity or with longer duration produce greater physiological training effects.

**Endurance training modalities** – While the optimal program length is unknown, 8 weeks of endurance training, with at least 2–3 one-hour sessions per week, at >40% of maximal work rate (cycling) is recommended to achieve meaningful benefits.<sup>36,142</sup> The goal should be to provide a potent training stimulus at the limit of the patient's capacity.<sup>147</sup> Many patients with COPD, including those with cachexia, find it challenging to sustain a moderate-to-high-intensity training load for the target training duration, for example due to intolerable breathlessness. Different training strategies can allow symptomatic patients to better tolerate training loads that offer an effective stimulus for adaptation. These include interval training, where repeated bouts of high-intensity exercise are interspersed with recovery periods (passive or active recovery)<sup>148</sup>, and partitioned training, where exercising a smaller muscle mass (eg, single-leg cycling or knee extension) reduces the load on the respiratory system.<sup>149–152</sup>

**Resistance training modalities** – A systematic review of resistance training in patients with COPD found increases in muscle strength and mass after short-term programs; typically, these programs involved 12 weeks of training, with at least 2–3 sessions each week, at progressive loads of 30–90% of one-repetition maximum.<sup>153–155</sup> Catabolic, anabolic and transcription factor protein expression responses to resistance training are blunted in patients with COPD compared to healthy controls, but these seem not tightly coupled to gains in lean mass.<sup>156</sup> Hypoxemia has been suggested to play a role in the variable adaptive response of the skeletal muscle in patients with COPD.<sup>157</sup> As with endurance training, limiting symptoms may prevent patients with COPD from undertaking planned training protocols, and alternative training modalities can be helpful to increase the total work done. Neuromuscular electrical stimulation offers an effective form of resistance training,<sup>158</sup> where an external current is applied over the target muscles to induce contractions.<sup>159</sup> It places a low metabolic load on the respiratory system, and is thus particularly suited to severely breathless patients.

**Combined exercise modalities** – In practice, combining endurance and resistance training would optimize overall gains, eg, in functional capacity, along with increases in muscle mass and function to counteract the adverse effects of cachexia. Careful tailoring of the exercise prescription with attention paid to exercise modality can improve patient outcomes, including the most severe cases.<sup>160</sup> A recent case report in a patient with very severe COPD, chronic respiratory failure, and cachexia showed impressive gains in weight (including lean mass), function (strength, exercise capacity, mobility), health status, and psychological well-being from comprehensive and personalized PR.<sup>161</sup> The effects of exercise, anabolic and beyond, rapidly wane once the training stimulus is stopped,<sup>162</sup> so attention to behavior changes and/or maintenance strategies is paramount. This requires a consideration of exercise program features that may improve longer-term access, adherence, and efficacy. Low-cost, home-based and telerehabilitation models may have a role; however, these models also have a smaller evidence base and lack the well-defined process and outcomes of center-based PR.<sup>163</sup> Finally, as described previously exercise should be combined with nutritional intervention in a multimodal approach, as exemplified in the NUTRAIN and INTERCOM trials,<sup>136,137</sup> to target the wide range of etiological factors involved in cachexia, including energy imbalance and low nutrient availability.<sup>34</sup>

**Exercise responses in COPD cachexia** – Despite the impressive gains in the abovementioned case report,<sup>161</sup> individual responses to exercise training in COPD are variable and cannot be readily predicted by any clinical phenotype.<sup>83,164</sup> Some, but not all, cachectic patients with COPD retain the capacity to improve functional exercise performance with exercise training. In an in-depth physiological study, Vogiatzis et al compared 10 cachectic and 19 non-cachectic patients with COPD before and after high-intensity cycling training (45 min, 3x weekly) over 10 weeks.<sup>165</sup> The endurance, high-intensity interval program improved peak work rate and 6-min walk distance (6MWD) in both groups. Mean muscle fiber CSA also increased in both groups, though significantly less in cachectic patients. A blunted muscle remodeling response was found at the group level, with less reduction in the proportion of type IIb fibers, less increased muscle capillary/fiber ratio, and less increased insulin-like growth factor I (IGF-I) protein levels in the cachectic group.<sup>165</sup> This blunted response to high-intensity endurance exercise in COPD cachexia supports the inclusion of resistance training in managing COPD cachexia. Indeed, combined endurance and resistance training approaches seem highly relevant and should focus on the critical features of the cachexia syndrome (eg, reduced muscle mass, reduced FFMI, and/or reduced muscle strength).<sup>16,58,166</sup>

## Pharmacological Intervention

In addition to nutritional support and exercise training, pharmacological agents have been identified as potential therapeutic options for cachectic patients with COPD. Even though research is sparse,<sup>167–171</sup> the efficacy of different pharmacological agents has been investigated and is listed below.

**Ghrelin** – A 28-amino acid peptide hormone,<sup>36</sup> ghrelin, has received specific attention as a pharmacologic agent in COPD cachexia. Studies show that ghrelin has potential benefits in reversing the breakdown of proteins and weight loss in catabolic states like cancer cachexia<sup>172,173</sup> and it is thought to affect several vital pathways in the regulation of appetite and body composition. However, less is known about the effects of ghrelin in COPD cachexia, and available study results are conflicting. In a small sample of 7 cachectic individuals with COPD, Nagaya et al<sup>168</sup> found that a 3-week treatment with exogenously administered ghrelin resulted in improvements in body weight, food intake, lean body mass, peripheral and respiratory muscle strength, and clinically relevant improvement in 6MWD. In contrast, in a multicenter, randomized, double-blind, placebo-controlled trial, the same research group<sup>167</sup> evaluated a similar intravenous treatment of high-dose ghrelin (2 µg/kg) twice daily for 3 weeks but did not see any significant difference in 6MWD, quality of life, symptoms, body weight, food intake, or peripheral muscle strength when compared to placebo. Nevertheless, ghrelin analogues are regarded as a novel potential therapeutic option in COPD cachexia that warrants further investigation despite the somewhat conflicting and limited findings reported in the literature.<sup>34,167,168</sup>

**Megestrol acetate and testosterone** – Another potentially relevant pharmacological agent for COPD cachexia is megestrol acetate, a progestational appetite stimulant with anti-inflammatory effects.<sup>36,174</sup> In a large RCT including 145 individuals with COPD, megestrol acetate administration improved appetite, body weight, and body image but not exercise tolerance as measured by 6MWD.<sup>169</sup> In a 12-week pilot trial in 2015, Casaburi et al<sup>171</sup> treated 9 cachectic patients with COPD with oral megestrol acetate (800 mg/day) plus weekly testosterone injections (initially 125 mg in men and 40 mg in women). They found that the treatment reversed weight loss trajectories and resulted in significant gains in both lean and fat mass. Though the small sample size and lack of a control group should be noted when interpreting these findings, the promising findings warrant further research. Moreover, adding testosterone supplementation to men with COPD with low serum testosterone levels during a resistance training intervention have, when compared to resistance training alone, enabled more profound abundances of all major myosine heavy chain (MyHC) isoforms, enhanced expression of muscle IGF-1 and other components of the muscle IGF system, as well as improved maximal leg muscle strength and lean body mass.<sup>175,176</sup>

**Roflumilast** – Recent research shows that the phosphodiesterase (PDE)-4 inhibitor roflumilast may revert proteolysis and increase the antioxidant defense in cultured myotubes obtained from cachectic patients with COPD.<sup>177</sup> As this PDE-4 inhibitor is available for treating systemic inflammation and exacerbations in patients with COPD, these findings have potential clinical implications for treating muscle wasting in cachectic patients with COPD.

**Targeting key pathways** – Sanders et al<sup>34</sup> emphasizes that muscle wasting may result from protein and myonuclear turnover alterations;<sup>27,34</sup> therefore, targeting key pathways in these processes (eg, ubiquitin-proteasome system) will

likely be required to combat muscle wasting in cachectic patients with COPD.<sup>34</sup> In 2019, Polkey et al<sup>178</sup> investigated the effect of 2 doses of intravenously administered bimagrumab, a novel and fully human monoclonal antibody that inhibits myostatin (a negative skeletal muscle regulator), in patients with COPD with reduced skeletal muscle mass (without documented recent weight loss). Although the patients in the study were not diagnosed with cachexia, treatment led to increased thigh muscle volume over 24 months but had no effect on 6MWD.

In summary, the benefit of single modality pharmacological interventions for the cachectic patient with COPD is unclear, research is sparse, and the results are mixed.<sup>167–171</sup> Therefore, cachexia cannot be managed entirely by any single modality treatment intervention, including current pharmacological options. Still, pharmacological interventions may be relevant as part of a multimodal approach for some, but not all, cachectic patients with COPD, although the latter requires further investigation.<sup>170,179</sup>

## Recommendations for Practice

### Diagnosing (Pre-)Cachexia in Patients with COPD

Longitudinal assessment of weight in patients with COPD meets Wilson and Jungner's principles of screening.<sup>180</sup> Though weight measurements are routinely collected, they require the clinician's close attention in order to spark recognition and therapeutic action. In addition to weight, information from routine clinical imaging, such as lung screening CTs or DXA scans, present opportunities for monitoring muscle mass or FFM over time, generating longitudinal assessments of a patient's body composition. If clinical imaging is not available, improving clinical access to other reliable and validated body composition assessment tools (eg BIA) is advised. Additionally, protocolized inquiries about weight loss or changes in strength or functional status could be incorporated into a disease-specific review of systems, along with more classical questions about sputum production and recent exacerbations. Automated generation of alerts by the electronic medical record could help augment the vigilance of clinicians and highlight weight loss when it is first evident. Future clinical studies should quantify the effects of heightened clinical attention and novel information technology solutions for early recognition of cachexia in patients with COPD to facilitate early therapeutic intervention.

### Minimizing Modifiable Etiological Factors and Improving Patient Referral to PR

In theory, the prevention and management of COPD cachexia should start with minimizing modifiable etiological factors (Box 1). Generally, a multidisciplinary and holistic PR program considers all proposed minimization steps.<sup>181</sup> Unfortunately, PR programs are not equally extensive worldwide, and poor healthcare professional awareness and knowledge about PR is a significant barrier to patient referral.<sup>182,183</sup> In practice, therapeutic nihilism about the role of PR in the management of cachexia may prevent some healthcare professionals not recommending it to patients. Given the physiological and psychosocial benefits of PR for patients with stable and acute COPD, clinicians need to engage with patients to talk about barriers and enablers and support the uptake of PR.

#### Box 1 Ways to Minimize Modifiable Etiological Factors

- Encourage smoking cessation
- Consider oxygen therapy to treat hypoxemia
- Consider non-invasive ventilation to treat hypercapnia
- Increase physical activity
- Improve dietary intake
- Guide energy conservation
- Reduce alcohol consumption
- Treat comorbidities
- Optimize medical treatment

Box 2 Multimodal Interventions for Cachexia in COPD

Nutritional Supplementation	Exercise Training
<ul style="list-style-type: none"><li>• A diet with at least 1.2 grams of protein per kg of body weight</li><li>• High-quality proteins (casein, leucine, whey protein)</li><li>• Smaller portions spread over the day</li><li>• Poly unsaturated fatty acids might enhance the effects of exercise training</li></ul>	<ul style="list-style-type: none"><li>• <b>Resistance training:</b> 12 weeks, at least 2–3 sessions per week, at progressive loads of 30–90% of one-repetition maximum<sup>a</sup></li><li>• <b>Endurance training:</b> 8 weeks, at least 2–3 (1-hour) sessions per week, at &gt;40% of maximal work rate (cycling) or &gt;75% of walking speed achieved during 6MWT or peak speed achieved during incremental shuttle walk test (walking).</li></ul>

**Note:** <sup>a</sup>The lower the loads used, the closer to task failure the patient needs to be when performing the exercises in order to obtain positive effects. See Schoenfeld et al for details.

**Abbreviation:** 6MWT, 6-minute walk test.

Moving Towards Multimodal Therapeutic Approaches

There is a clear consensus that single therapies are insufficient to stabilize or reverse cachexia.<sup>170,179</sup> Considering the significant etiologic complexities of COPD cachexia, a multimodal approach that combines nutritional, exercise, and (possibly) pharmacological components is likely necessary. A recent review<sup>170</sup> summarized the effect of multimodal treatment strategies tested in 5 individual studies in cachectic patients with COPD.<sup>133,136,184–186</sup> All studies that combined exercise with an oral nutritional supplement reported significant improvements in favor of the treatment groups. Thus, building on current evidence, oral nutritional supplementation combined with exercise should be the primary multimodal approach to treating the cachectic patient with COPD. Adding a pharmacological agent might be considered in some, but not all, cachectic patients with COPD<sup>170</sup> (Box 2).

Future Directions for Research

While acknowledging the challenges in COPD cachexia research studies, the following steps are recommended when designing future research studies to investigate the etiology, assessment, and management of COPD cachexia.

Enable/Facilitate Comparisons Between Studies

A key challenge in interpreting and comparing the results of observational and interventional studies is the use of different definitions of cachexia across studies, resulting in somewhat diverse patient groups. Therefore, we propose that researchers use a longitudinal definition of cachexia and recognize that cross-sectional measurements are not optimal. Furthermore, more detailed phenotyping of patients included in studies will assist in comparing patient cohorts between studies.

Provide Stronger Scientific Evidence

Observational studies on the etiology of COPD cachexia are often cross-sectional and retrospective. Instead, large-scale prospective and longitudinal studies should be conducted to provide more robust etiological evidence. In addition, multi-arm RCTs are needed to fully establish the efficacy of a specific or multimodal intervention.

Select the “Right” Outcome(s)

In previous work on COPD cachexia, functional outcomes, such as 6MWD, are commonly used, but does not seem to be responsive to cachexia interventions, including resistance training.<sup>167,169,178,187</sup> The latter, thought to have a particular role in managing COPD cachexia considering the known consequences of the disease (eg, reduced muscle mass, reduced FFMI and/or reduced muscle strength).<sup>16,58,166</sup> However, the efficacy of resistance training (at least when designed to improve muscle mass and strength)<sup>188,189</sup> would not be reflected in the functional outcome of walking distance on the 6MWT.<sup>187</sup> Instead, to evaluate resistance training intervention effects in the cachectic patient with COPD, muscle-related outcomes, including direct measurements of strength and power properties of the quadriceps, should be used due to their

relevance to muscle mass; these measurements are particularly responsive to resistance training interventions.<sup>82,190–192</sup> If a functional outcome measure is desirable, a sit-to-stand test would be more relevant, considering the requirements of this test compared to the 6MWT. For example, strength and muscle mass properties which often are affected in the cachectic patient with COPD are more closely linked to 5-time sit-to-stand performance than to 6MWT performance.<sup>193,194</sup> Sit-to-stand tests also respond to resistance training interventions designed to increase muscle mass and strength.<sup>153</sup>

Lastly, although selecting the proper functional test, and focusing on muscle-specific outcome measures is essential to capture treatment adaptations, multidimensional outcome assessment including objective and patient-centered outcomes such as quality of life should not be neglected. For example, quality of life is often worsened in patients with COPD cachexia compared to patients without cachexia.<sup>24,33</sup> Additionally, although it remains to be determined in the cachectic patient COPD, it is likely that specialized nutrition and exercise can restore muscle mass and strength through metabolic crosstalk between body organs,<sup>195</sup> highlighting the need of multidimensional outcome assessments to fully capture the treatment response in the cachectic patient with COPD.

## Evaluate Exacerbations

Only limited studies have focused on the role of cachexia during and after severe exacerbations. Disease-related detrimental factors such as systemic inflammation, hypoxia, physical inactivity, malnutrition, and glucocorticosteroid treatment converge and intensify during a severe exacerbation. Therefore, the period of an exacerbation and the recovery phase immediately following might be an excellent opportunity to intervene to prevent or treat cachexia. More studies are needed to investigate the potential and optimal therapeutic strategies for the period around COPD exacerbations.

## Discover New Biomarkers Prognostic of Cachexia Development

A major challenge with cachexia is that it remains largely discovered in end-stage COPD. By the time a patient with COPD exhibits weight loss the ideal interventional window for reversing cachexia's course may have already been missed. Additional research is needed to identify biomarkers of pre-cachexia to guide cachexia risk stratification and/or serve as sensitive endpoints in clinical trials.

Next to future steps described above, the scoping review by Orsso et al also provides excellent recommendations for future trials investigating nutrition or multimodal interventions to prevent or treat cachexia in clinical and non-clinical conditions.<sup>196</sup>

## Acknowledgments

The authors greatly acknowledge Stacey Tobin for editing and improving the English language of the work.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

Jana De Brandt is funded by the Swedish Heart and Lung Foundation (20200139 and 20210146). Joe Chiles is funded by the NIH NHLBI T32HL105346. Matthew Maddocks is funded by a National Institute for Health and Care Research (NIHR) Career Development Fellowship (CDF-2017-10-009) and NIHR Applied Research Collaboration South London (NIHR ARC South London) at King's College Hospital NHS Foundation Trust. The views expressed in this article are those of the authors and not necessarily those of the NIHR, or the Department of Health and Social Care. Merry-Lynn N. McDonald is funded by the National Institutes for Health (NIH), National Heart, Lung and Blood Institute (NHLBI), R01HL153460. André Nyberg is funded by the Swedish Research Council (2020-01296) and the Swedish Heart and Lung Foundation (20210146).



## Disclosure

The authors report no conflicts of interest in this work.

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