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REVIEW

# Body weight and mortality in COPD: focus on the obesity paradox

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**Abstract**
*Abstract* The positive association between overweight, obesity, and cardiovascular and all-cause mortality is well established, even though this relation is typically U shaped with an increased risk also in low-weight subjects. However, being overweight or obese has been associated with a better prognosis in subjects suffering from chronic diseases, id est the "obesity paradox". In both community-dwelling and hospitalized patients with COPD, several studies have reported a significant protective effect of obesity on all-cause mortality, indicating that also in obstructive pulmonary diseases, an obesity paradox may be present. Interestingly, the "paradox" is more evident for subjects with severe bronchial obstruction (i.e., a lower FEV1), while in mild–moderate conditions, the weight-related mortality shows a behavior similar to that observed in the general population. Several factors may confound the relation between COPD, obesity and mortality. The lower FEV1 found in obese people may be linked to a restrictive defect rather than to an obstructive one. Due to the modified chest wall mechanical properties—related to increased fat mass—obese COPD patients may present, respect to their lean counterpart, a lower lung hyperinflation which is associated with higher mortality. The traditional classification of COPD attributes to obese "blue bloaters" a low-grade emphysema in opposition to lean "pink puffers"; the fact that emphysema extent is related to mortality may bias the relationship between weight and survival. It is also to underline that the majority of the studies, consider BMI rather than body composition (a better predictor of mortality) when studying the intriguing relation between weight, COPD, and mortality. Reverse bias has also to be taken into account, hypothesizing that an unintentional weight loss may be the deleterious factor related to mortality, rather than considering obesity a protective one. Further prospective studies are needed to shed light on the complexity of this emerging issue.
*Level of evidence* Level V: Narrative Review.

**Keywords** Overweight · Obesity · Visceral obesity · Obesity paradox · Pulmonary function · COPD

## Introduction

Obesity is a global problem that has been increasing in recent years in dramatic proportion in both children and adults [1]. It is well established that obesity is associated with a number of comorbidities [2, 3], and being overweight and obese has been shown to be related to an increased risk for mortality. Furthermore, it is widely accepted that obesity has deleterious effects on pulmonary function, respiratory mechanics, gas exchange, control of breathing, and exercise capacity. It is also known that several respiratory conditions, such as obstructive sleep apneas (OSAS), asthma, chronic obstructive pulmonary disease (COPD), and pulmonary embolism, have been linked to obesity [4].

Contrary to the findings in a healthy population, being overweight or obese has been associated with a better prognosis in subjects suffering from chronic diseases. Indeed,

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various studies have found an inverse relationship between body mass index (BMI) and mortality in CVD (cardiovascular disease), HF (Heart Failure), chronic kidney disease, type 2 diabetes mellitus (DM), and pulmonary hypertension [5, 6]. This unexpected association has been defined as "obesity paradox", a term coined by Gruberg et al. [7].

On these premises, it is conceivable that similar findings could potentially be seen among subjects with COPD. However, the obesity paradox in COPD has been only partially reviewed. Previous papers on this topic were mainly focused on nutritional aspects [8] or on the influence of BMI, rather than obesity, on mortality [9], while other works have only summarized the main aspects of the problem, with particular regard to comorbidities [6].

Moreover, some conclusions are conflicting and not all the patients' characteristics (such as disease phenotype, body composition, and exercise tolerance) are taken into account as factors possibly influencing the paradox.

The aim of this review is twofold: first, to describe the possible relationship between obesity and COPD and second, to describe the concept of obesity paradox as it relates to respiratory system, by summarizing the existing literature available in this area.

## Search strategy and selection criteria

The article is a narrative overview of the relationships between COPD and obesity and their impact on mortality. We used as sources MEDLINE/PubMed, EMBASE, and Cochrane Library, from the beginning to April 2017. Keywords include "overweight", "obesity", "visceral obesity", "obesity paradox", "pulmonary function", and "COPD" and combinations of these terms. Both observational and experimental clinical trials, as well as reviews, commentaries, and perspectives published in peer-reviewed journals were considered in a first screening for relevance. A primary inspection included title and abstract review, and articles were excluded mainly for not discussing the topic of interest. In addition, we hand-searched references from the accessed articles.

## Obesity and COPD

### Epidemiology

Several studies focused on the relationship between body composition and COPD, with increasing interest in the association with obesity [8, 10]. Some studies support the coexistence of obesity and COPD. In subjects evaluated in the frame of the Canadian Health Survey [11], obesity resulted significantly more prevalent in COPD subjects (24.6%) in respect to those without chronic bronchial obstruction (17.1%). An even higher prevalence of obesity was reported in a cohort of early stage COPD patients in the USA [12]. Fifty-four percent of subjects had BMI measurement greater than 30 compared to the 20–24% reported prevalence for the general adult population of that region. However, not all studies confirm these data. In the PLATINO Study [13], a population-based survey performed in Latin America, COPD subjects were more frequently underweight or normal weight compared to non-COPD controls. The prevalence of obesity in those with COPD was 23%, compared to 32% in subjects without COPD.

### Obesity, inflammation, metabolic syndrome, and COPD

Systemic inflammation is a major characteristic of COPD [14] and increased serum levels of different proinflammatory molecules have been reported, with augmented levels of oxidative stress too [15, 16]. However, systemic inflammation is not present in all patients with COPD. In the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) study, 16% of COPD subjects had persistent systemic inflammation at baseline [17]. Interestingly, these patients were more frequently obese, with a mean BMI of 29.4, compared to a mean BMI of 25.6 in the group with no inflammation. Systemic inflammation has been previously related to an excess in fat mass in COPD. In particular, tumor necrosis factor-α, interleukin (IL)-6, and leptin plasma levels are significantly increased in overweight/obese patients compared with normal-weight patients [18] and the likelihood of having elevated C-reactive protein (CRP) was 3.3 times higher in obese compared to normal-weight patients, [19]. In addition, abdominal fat mass is positively associated with CRP levels in patients with COPD [20]. Moreover, visceral fat mass is higher in non-obese COPD patients in comparison with controls, with increased IL-6 levels too [21]. It is to point out that it is not determined if this contributes to the pathophysiology of COPD.

Metabolic Syndrome (MetS) is a complex disorder defined by the presence of abdominal obesity variably associated with elevated triglyceride, glucose, and blood pressure levels and reduced C-HDL serum concentration [22]. In a recent meta-analysis of 19 surveys involving 4208 COPD patients, the pooled prevalence of MetS was 34% [23]. Previous studies in the general population reported an association between MetS and impairment of lung function with lower FEV1 (forced expiratory volume in 1 s) and FVC (forced vital capacity) [24]. Interestingly, among COPD patients, those with MetS presented higher BMI and higher FEV1 than their counterparts without MetS [23].

The more recent literature indicates that MetS may increase the risk of a COPD exacerbation with associated

hyperglycemia, hypertriglyceridemia, and CRP elevation [25].

In conclusion, inflammation is a key component of COPD and obesity and it plays an important role in the etiology of MetS. On the other side, MetS can worsen the inflammatory status of the patient, in a self-perpetuating vicious circle. Moreover, other factors such as physical inactivity and steroid therapy may also be relevant in the development of MetS in COPD subjects [24].

## Overweight, obesity, and respiratory function

Obesity is known to contribute to different respiratory illnesses, including asthma, OSAS, pulmonary embolism, and hypoventilation syndrome [26].

The excess in body weight predisposes obese individuals to have reduced pulmonary system compliance and increased elastic loading of the inspiratory muscles with increased work of breathing. In obesity, there is an abnormal pulmonary gas exchange linked to increased regional ventilation/perfusion mismatching due to microatelectasias and airway closure. Abdominal and thoracic fats are likely to have direct effects on the movements of diaphragm and chest wall, whereas hips' and thighs' fat is unlikely to have any mechanical influence on the lungs [27, 28].

In eucapnic obesity, ERV (Expiratory Reserve Volume) and FRC (Functional Residual Capacity) have been shown to decrease exponentially with increasing BMI [29]. Vital capacity and residual volume are slightly reduced or unchanged, whereas there is some evidence that increasing body weight is associated with modest reduction in TLC (Total Lung Capacity), probably related to reduction in thoracic expansion [30].

Spirometric variables (FEV1 and FVC) tend to decrease with increasing BMI [31, 32]. Nevertheless, the effect is small, so that both parameters are usually within the normal range in obese adults [27, 33]. The FEV1/FVC ratio is preserved, indicating that the major effect of obesity is on lung volumes with no influence on airway obstruction; airway reactivity is usually unchanged. Respiratory resistance is increased in obesity [34], indicating that airway caliber is reduced during the tidal breathing cycle. However, specific airway resistance (calculated by adjusting for lung volume) is in the normal range [34, 35].

Studies in obese patients concerning the alveolar/capillary CO (Carbon Monoxyde) diffusion usually show an unchanged diffusing capacity [36].

## Body weight and mortality in COPD: the obesity paradox

Several studies have reported a significant effect of obesity on all-cause mortality in patients with COPD, with mortality being lower in obese patients. These studies have been carried out both in community-based settings and hospitalized patients [37–41].

The study by Landbo et al. was the first to examine the relation between BMI and mortality in subjects with COPD in a large, randomly selected population sample [42] (Fig. 1). They found an independent effect of BMI on both all-cause and COPD-related mortality. Of interest, obesity was associated with a 20–34% increase in the relative risk (RR) of all-cause mortality in patients with mild-to-moderate COPD, compared to normal-BMI patients with similar disease severity. However, the relative risk of all-cause mortality and COPD-related mortality was 0.62 and 0.31,

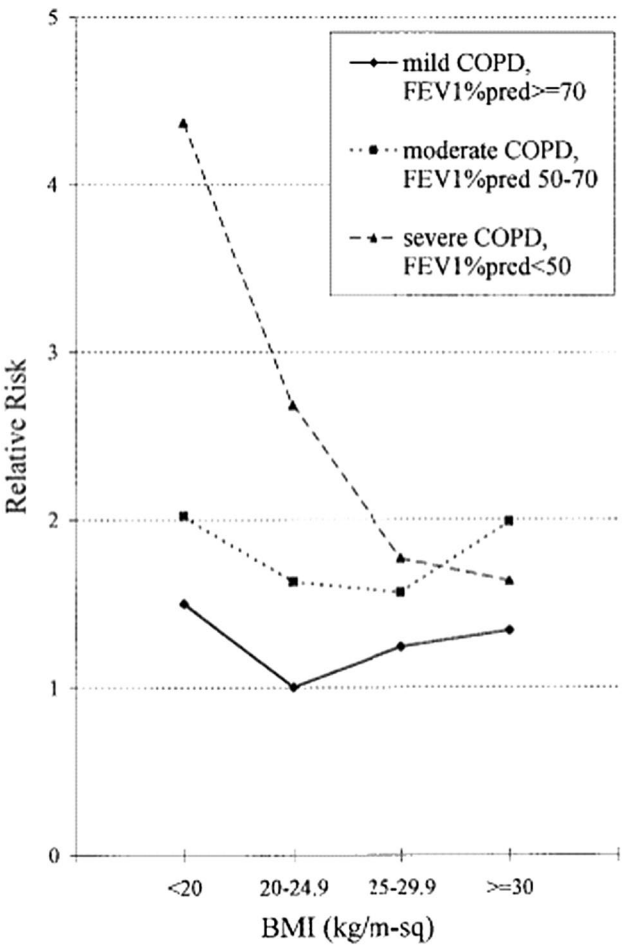


**Fig. 1** All-cause mortality by BMI in subjects with mild, moderate and severe COPD. Normal-weight subjects (BMI 20–24.9 kg/m$^2$) with mild COPD were used for reference. Reprinted with permission of the American Thoracic Society. Copyright © 2017 American Thoracic Society [42]

respectively, in patients with severe COPD compared to normal-weight patients with severe disease. This suggests that obesity may exert different effects depending on the degree of bronchial obstruction: obesity has a protective effect in severe COPD patients, but in those with mild-to-moderate disease, a BMI > 30 is associated with a worse prognosis.

Cao et al. performed a meta-analysis on 22 studies comprising 21,150 participants with COPD [43]. Compared with patients having normal BMI, overweight (RR 0.47, 95% CI 0.33–0.68), and obese (RR 0.59, 95% CI 0.38–0.91), patients were associated with lower mortality. It is to point out that the authors showed that the BMI category associated with the lower risk of mortality was 25 kg/m$^2$ or more, indicating that even individuals with a normal BMI have a higher risk of mortality.

Several studies investigated the relationship between weight and mortality in COPD patients during hospitalization or after discharge [40, 44–47]. Among others, a recent study enrolled 968 patients hospitalized for acute exacerbation of COPD and followed them for a median time of 3.26 years [40]. After adjustment for several possible confounders (including GOLD stage), the authors found that higher BMI was predictive of survival, with each 1 kg/m$^2$ unit increase in BMI associated with 5% lower chance of death (hazard ratio 0.95, 95% CI 0.93–0.97). Importantly, they demonstrated that the optimal BMI with the lowest risk of death was in the overweight category (BMI of 25.09–26.56 kg/m$^2$).

Zapatero et al. evaluated 313,233 patients hospitalized for acute exacerbation of chronic obstructive pulmonary disease [44]. They showed that obesity reduced the in-hospital mortality risk and the possibility of early re-admittance. Going into detail, the authors observed that obese patients with COPD have an almost 50% lower risk of death during hospitalization than patients with normal weight.

A recent meta-analysis by Guo et al. summarized the evidence about the relation between BMI and mortality in COPD. Thirteen studies have been included in the meta-analysis, with the final result that overweight subjects have a decreased risk of mortality. The lowest risk of mortality is for a BMI of 30 kg/m$^2$ [9].

Finally, it is important to underline that weight modifications and weight loss may have a strong impact in COPD patients. As first described by Prescott et al., weight loss is associated with a higher mortality in COPD subjects in the general population [rate ratio (RR) for weight loss > 3 BMI units 1.63, 95% CI 1.38–1.92]. Moreover, while the risk of COPD-related death is increased with weight loss [RR 2.14 (95% CI 1.18–3.89)], this does not happen with weight gain [RR 0.95 (95% CI 0.43–2.08)]. Then, subjects with severe COPD show a significant mortality risk modification ($p = 0.045$) considering both the baseline BMI and the weight change: weight gain is associated with a better survival in normal-to-underweight subjects (BMI < 25), while for the overweight and obese (BMI > 25), best survival was seen in stable weight [45].

Table 1 shows the most important studies assessing the "Obesity Paradox" in COPD patients in the general population.

**Table 1** Most important studied assessing the "Obesity Paradox" in the general population

| Study | Publication year | Design | Sample size | Age<br>Mean (SD), range, years | Results |
|---|---|---|---|---|---|
| Schols et al. [48] | 1998 | Retrospective and Prospective | 400/203 | 65 (0.5 SEM) | Significantly better survival in obese patients |
| Landbo et al. [42] | 1999 | Prospective | 2132 | 21–89 | All-cause mortality decrease with increasing BMI in severe COPD |
| Chailleux et al. [49] | 2003 | Prospective | 4088 | 68 (9, men)<br>70 (10, women) | Best survival rate for obese patients |
| Ringbaek et al. [50] | 2004 | Prospective | 221 | NA | Tendency for lower mortality in obese subjects (limited number) |
| Ringbaek et al. [51] | 2005 | Prospective | 869 | 57.7 (8.5 men)<br>55.8 (9, women) | Lower RR for any cause of death in obese COPD patients |
| Marti et al. [52] | 2006 | Prospective | 128 | 68.9 (9.7) | Lowest risk of mortality for overweight and obese subjects |
| Schembri et al. [53] | 2009 | Prospective | 3343 | NA | Lower respiratory death rate in obese subjects |
| Jordan et al. [54] | 2010 | Prospective | 2439 | 64.28 | Lower all-cause mortality in class-1 obese subjects |
| Collins et al. [55] | 2010 | Retrospective | 424 | NA | Significant negative trend between BMI and mortality with lowest mortality in obese subjects |

## Possible mechanisms and confounders at the basis of the paradox

The mechanisms underlying the obesity paradox remain unresolved. Why does obesity improve survival in patients with COPD and why is a higher BMI associated with fewer respiratory-related deaths?

### Low FEV1: restrictive vs obstructive defect

The studies evaluating the changes in lung function relative to BMI found that, among healthy young adults, FEV1 and FVC decrease both with higher baseline BMI and with increasing BMI over time and that those subjects who reduced their BMI also increased these lung-function parameters. On these premises [8, 29, 56], it is possible to affirm that obesity in itself contributes to low FEV1, leading to obese subjects to be wrongly classified as having a worse bronchial obstruction compared to their real clinical stage of COPD. Therefore, the obesity paradox may be related to an apparent effect on bronchial obstruction of BMI. In other words, the lower FEV1 found in obese people may be linked, at least in part, to a restrictive defect and not only to an obstructive one.

### Hyperinflation in obese patients with COPD

The impact of the combination of COPD and obesity on respiratory pathophysiology and symptom intensity is not well known. There is evidence that the presence of airway obstruction does not alter the relationship between BMI and lung volumes—such as ERV and FRC—as found in healthy people [36, 57], which means that an increase in BMI is associated with an exponential decrease in these lung volumes, as reported in the previous paragraph. As a possible consequence, obese COPD patients present less lung hyperinflation and a higher inspiratory capacity and inspiratory capacity/TLC ratio, in comparison with lean COPD subjects matched for FEV1 [58]. It has been suggested that these mechanical changes may carry some prognostic advantages to obese COPD patients. In fact, indices of lung hyperinflation, such as reduced inspiratory capacity and inspiratory capacity/TLC ratio, seem to be predictors of increased mortality. Moreover, the above-mentioned mechanical changes (i.e., reduced hyperinflation) may produce potential benefits during physical activity [58]. Indeed, symptom-limited peak oxygen uptake during incremental cycling exercise ($VO_2$, expressed as a percentage of the predicted normal value corrected for ideal body weight) is greater in obese than in normal-weight COPD patients [57]. Since $VO_2$ is an indicator of cardiorespiratory fitness and a strong predictor of mortality, it is tempting to speculate that its increase can partially explain the better outcomes found in obese COPD patients [59].

### Emphysema

It has been demonstrated in COPD patients that emphysema extent is associated with a loss of both free fat mass and fat mass and consequently with a lower body weight [60]. Furthermore, it is interesting to underline that Lung Volume Reduction Surgery (LVRS) for emphysema significantly increases BMI, which correlates with positive changes in health status [61]. On these premises, it is conceivable to hypothesize a lower extent of emphysema in overweight–obese patients, even though studies on this issue are scanty. Moreover, the extent of emphysema has been linked to all-cause and COPD-related mortality, independently of airflow limitation [62, 63]. Therefore, it is possible that the protective effect of obesity against mortality in COPD patients is related to a low-grade emphysema, rather than to the excess of weight. This hypothesis, mainly speculative, needs further studies, since to our knowledge, there is no investigation evaluating the combined effects of body composition, airflow limitation and extent of emphysema on mortality. Anyway, we have to mention the traditional classification of COPD subjects in "blue bloaters" and "pink puffers": the former lean with emphysema, the latter obese with bronchitis.

### BMI vs body composition

BMI can be a misleading indicator for survival or health outcomes in COPD patients, since it does not carry any information about the body composition: the amount of metabolically and functionally active (Free Fat Mass) FFM, rather than body weight or fat mass, seems to be positively associated with survival. The study by Schols et al. [64] supports this hypothesis, showing that FFM is an independent predictor of mortality in COPD, irrespective of FM. Of interest, a study by Marquis et al. [65] showed that a small mid-thigh cross-sectional area, measured with computed tomography, was associated with increased mortality risk during a 3-year follow-up in COPD patients.

Since the capability of a patient in performing physical activities is related to FFM, it is important to highline the role of Cardiorespiratory Fitness (CRF) as a potential modifier of the obesity paradox, also in COPD: the impact of BMI on mortality tends to lower for increasing fitness of the subjects. McAuley et al. demonstrated that cardiorespiratory fitness level altered the obesity paradox: unfit men were roughly twice as likely to die as fit men regardless of obesity status, and fit men who were obese survived as well as non obese/fit men [59].

Another limitation to consider BMI a measure of obesity is that it cannot discriminate regional fat distribution (*id est* abdominal from gluteo-femoral fat). Waist circumference is strongly correlated to abdominal obesity which is associated with chronic diseases more than gluteo-femoral obesity [66].

Moreover, a recent pooled analysis from 11 prospective cohort studies, enrolling more than 650,000 white adults, showed that a higher waist circumference is positively associated with higher mortality for all BMI levels, ranging from 20 to 50 kg/m$^2$ [67].

### Other confounders

Smoking and reverse causality are major confounders in estimating the association between weight and mortality. The role of smoking as a potential confounder for obesity paradox in CVD has been hypothesized [68, 69], and this can be important in COPD too. Stokes and Preston showed that in CVDs, overweight/obese individuals are less likely to smoke than normal-weight counterparts. A similar behavior may be present in COPD, although to our knowledge, no data are available at this regard.

In addition, a "reverse causality" bias is possible, meaning that weight loss may be a consequence of illness. In other words, a lower weight may be a result of more severe disease, associated with higher mortality [64]. Therefore, it is possible to speculate that a decreasing weight is the deleterious factor for mortality, rather than overweight/obesity is a protective one.

## Conclusions

A patent evidence supports the fact that being underweight is associated with poor survival in COPD. Therefore, it is not unexpected that normal-weight COPD subjects have a better prognosis. In contrast, it is surprising that there are data supporting the evidence of a protective effect of overweight and obesity on mortality. It is of interest that this seems true mainly in patients with a more severe airway obstruction.

It is possible that an excess in body weight may have a real protective effect in COPD patients. However, several factors may bias this hypothesis. The influence of obesity per se on both respiratory mechanics and pulmonary volumes, the extent of emphysema and the role of muscle mass rather than BMI may all be important in partly justifying the paradox. Future prospective studies, focusing directly on obesity in COPD, with a particular regard to body composition, weight changes, and COPD phenotypes are needed to shed light on the complexity of this intriguing issue.

**Compliance with ethical standards**

**Conflict of interest** The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

**Ethical approval** This article does not contain any studies with human participants or animals performed by any of the authors.

**Informed consent** For this type of study formal consent is not required.

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