

Obesity in



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further exploring the
complex interaction

Safir Zewari

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Obesity in COPD

further exploring the complex interaction

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Content

Chapter 1	General introduction and thesis outline	7
Chapter 2	Obesity in COPD: Revealed and Unrevealed Issues	23
Chapter 3	Obesity in COPD: Comorbidities with Practical Consequences?	51
Chapter 4	Adiposity increases weight-bearing exercise-induced dyspnea despite favoring resting lung hyperinflation in COPD.	75
Chapter 5	Sleep hypoventilation is common in diurnal normocapnic COPD patients with severe or very severe obstruction and is not associated with body mass index.	95
Chapter 6	General discussion	113
Chapter 7	Summary	134
	Nederlandse samenvatting	136
Appendices	List of publications	140
	Research Data Management	141
	Curriculum vitae	142
	Word of gratitude (dankwoord)	143



Chapter 1

Introduction and thesis outline

According to the World Health Organization (WHO), chronic obstructive pulmonary disease (COPD) is recognized as a major non-communicable disease (NCD). Alongside chronic respiratory disease, the four primary types of NCDs include cardiovascular diseases, cancer and diabetes. While obesity itself is not classified as a NCD, it is a significant risk factor for developing other NCDs such as cardiovascular diseases (1). Given that NCDs are significant contributors to global mortality and morbidity, it remains of great interest to understand the interplay between COPD and obesity. As COPD and obesity are already highly complex as sole conditions, their coexistence in one and the same person adds even more complexity in terms of symptoms, physiology, comorbidity, and clinical outcomes. The interaction between COPD and obesity may in some respects even seem paradoxical. This thesis aims to further explore aspects of the complex interplay between COPD and obesity. This chapter provides a brief introduction to each condition separately and reflects on clinically relevant issues when COPD and obesity coexist.

COPD

COPD has been defined by the Global initiative for Obstructive Lung Disease (GOLD) as a *“heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, sputum production) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction”* (2). Environmental and genetic risk factors contribute to the development of COPD including tobacco smoking, inhalation of toxic particles and gases, abnormal lung development and genetic mutations leading to α 1-antitrypsin deficiency (2). The primary diagnostic tool for COPD is spirometry; a pulmonary function test that measures the ratio of post-bronchodilator forced expiratory volume in one second to forced vital capacity (FEV_1/FVC ratio) and determines the presence of non-fully reversible airflow limitation.

The global prevalence of COPD is estimated at ~10% according to a recently published systematic review, including 162 studies across 65 countries (3). Despite significant progress in understanding the pathogenesis of COPD, the prevalence of this condition has shown a relative increase of ~6% between 1990 and 2017 (4), while projections indicate that the prevalence of COPD will continue to rise in the future (5,6). The significant disease burden of COPD is demonstrated by findings from the Global Burden of Disease Study, indicating

that COPD contributed to 74.4 million disability-adjusted life years (DALYs) worldwide in 2019 [6]. Furthermore, while patients with COPD have higher prevalence and number of comorbidities compared to non-COPD controls (7), they are also subjected to increased mortality. Indeed, according to the latest WHO factsheet, COPD was the third leading cause of death worldwide, causing 3.23 million deaths in 2019 (8). Also, COPD has an enormous economic burden accounting for 6% of the total healthcare spending (€38.6 billion annually) in the European Union and for 56% of the total cost of treating respiratory diseases (9). While a significant part of the economic burden is caused by direct treatment costs, a Danish study has shown that a substantial portion of COPD-related expenses are attributed to hospital admissions for comorbid conditions such as cardiovascular disease (10).

Physiologically, in addition to the diagnostic criterion of non-fully reversible airflow limitation, lung hyperinflation is among the impairments that characterize COPD (2). The loss of elastic recoil due to emphysema combined with expiratory flow limitation limiting lung emptying during expiration, results in lung hyperinflation. This phenomenon can be further worsened during exercise leading to dynamic hyperinflation (11). Lung hyperinflation has been associated with increased dyspnea, exercise intolerance and morbidity (12). Therefore, it is important to take this parameter into consideration when evaluating the clinical effects of obesity on COPD. This could lead to new insight and therapeutic interventions.

Dyspnea is the most common symptom experienced by patients with COPD and is associated with negative health outcomes such as disability and anxiety (13). Generally, as COPD progresses, dyspnea worsens and becomes a significant burden on daily life activities (14). The GOLD clinical classification has integrated the modified Medical Research Council scale (mMRC) as a measure of dyspnea; however, it is important to acknowledge that dyspnea is a multidimensional symptom of which various measures are available to assess its presence and severity (15). While mMRC is used to evaluate the impact of dyspnea on daily activities, ratings such as Borg scale are used to assess the intensity of the perceptual experience (15). Multiple complex mechanisms contribute to the perception of dyspnea in patients with COPD, including pulmonary function impairments, as well as peripheral muscle dysfunction, deconditioning, dysfunctional breathing, and comorbidities such as cardiovascular diseases (16,17). This complex array of contributing factors makes it difficult to fully comprehend the exact mechanisms that

cause dyspnea. However, it is generally believed that neuromechanical dissociation, which refers to a mismatch between increased inspiratory neural drive (afferent signals) and an inadequate mechanical response of the respiratory system (efferent signals) plays an important role in the perception of dyspnea (18).

Obesity

Obesity has been defined by the WHO as abnormal or excessive fat accumulation that presents a risk to health, with a body mass index (BMI) $\geq 30.0 \text{ kg/m}^2$ (19). The prevalence of obesity has nearly tripled between 1975 and 2016, indicating an alarming increase in this preventable condition (19). The global prevalence of obesity is projected to rise even further in the future, reaching 18% in men and 21% in women by 2025 (20).

Obesity poses a substantial global health burden and is a major risk factor for NCDs, including cardiovascular disease, certain types of cancer and type 2 diabetes mellitus. An analysis of 57 prospective studies including nearly 900,000 adults has shown that obesity is associated with increased mortality, with a reduction of median survival by 2–4 years in adults with BMI 30–35 kg/m^2 and even by 8–10 years with BMI 40–45 kg/m^2 (21). High BMI is projected to be among the five leading global risk factors for years of life lost (YLL) by 2040 (22). Furthermore, obesity is associated with many comorbidities leading to lower quality of life and a high economic burden (23). While BMI is often used as the sole measure of obesity, it is important to acknowledge that high BMI does not necessarily always lead to worse clinical outcomes. For example, being overweight or obese has been associated with better survival in some chronic diseases such as severe COPD, lower mortality in ICU patients receiving mechanical ventilation and not always lead to increased cardiometabolic risk (24–26). This highlights the importance of also taking other body composition measures including muscle mass, fat mass and location of fat tissue into account in obesity research.

Obesity also has an impact on pulmonary function, mainly as a result of a mass effect of subcutaneous thoracic and intra-abdominal visceral adipose tissue (27,28). This results in reduced static lung volumes, which contrasts with the hyperinflation commonly observed in COPD (29). Especially in severe obesity (BMI $>45 \text{ kg/m}^2$) there may be even a restrictive pulmonary function

with reduced total lung capacity (TLC). However, this is not typically observed in milder stages of obesity, where usually only the functional residual capacity (FRC) and consequently expiratory reserve volume (ERV) are decreased, while TLC is preserved (30). Furthermore, while diffusion capacity of the lungs for carbon monoxide (DL_{CO}) is usually reduced in COPD, it is usually increased in obesity, probably because of increased lung blood volume, basal lung perfusion and cardiac output (31).

Dyspnea is often reported by obese individuals (32–34) and it is demonstrated that they are twice as likely to have a mMRC score of 2–4 compared to individuals with a normal BMI (35). While the mechanisms leading to dyspnea in obesity are not fully clear, it has been suggested that in part it can be explained by the reduced static lung volumes due to increased chest wall and abdominal mass leading to a restrictive ventilatory defect (36). Furthermore, increased work of breathing due to carrying of excess weight has been mentioned in earlier reports as a potential cause (37). Data from 16,171 participants from the NHANES III survey revealed that obesity was associated with increased dyspnea despite lower prevalence of airflow obstruction. In this study the obese ($BMI > 31 \text{ kg/m}^2$) cohort had the least number of subjects with $FEV1/FVC < \text{lower limit of predicted}$ while reporting more often dyspnea during exertion compared to cohorts with lower BMI (38). These results indicate a less significant role for airflow obstruction as a cause of dyspnea in obesity.

When COPD and obesity coexist

While the prevalence of both COPD and obesity has increased and are projected to continue increasing in the future, there is uncertainty about the prevalence of obesity in the COPD population. Available data regarding obesity prevalence in COPD shows a notable degree of variability ranging between 13–54% (39–47). Furthermore, while some studies suggest a higher prevalence of obesity in patients with COPD compared to non-COPD individuals (40,41,43), other studies demonstrate the opposite trend (42,47). Comparing data on prevalence rates remains challenging due to numerous factors that can influence the outcomes, including study methodology, participant characteristics, genetic and socio-demographic differences. For a deeper understanding of the interaction between COPD and obesity, it is essential to have insight into the co-prevalence of these conditions.

Also, the impact of obesity on the prevalence of other comorbidities in COPD remains incompletely understood. There is increasing data indicating different patterns of comorbidities in COPD compared to non-COPD subjects. These studies indicate that cardiovascular, metabolic, and cognitive comorbidities are relatively common in COPD (7,48). However, the role of co-existing obesity on these comorbidities is a subject of ongoing research. In daily practice it is important to have a full understanding of comorbidities in obese COPD patients in order to initiate timely preventive and treatment interventions.

As mentioned, obesity and COPD have several seemingly contradictory effects on pulmonary function. The impact of obesity on pulmonary function in COPD patients has been studied in a large study where FRC was significantly lower in obese patients with COPD compared to normal-weight COPD patients. (45). While both RV and ERV contribute to lower FRC values, the decline in ERV appears to be particularly significant in obese COPD patients. Other studies support this finding and demonstrate that obese COPD patients have less lung hyperinflation compared to their normal-weight peers (49–53). Since lung hyperinflation is associated with increased respiratory symptoms and mortality in COPD (54), COPD patients with obesity might benefit from less hyperinflation compared to normal-weight COPD patients. The lesser extent of hyperinflation might play a role in the phenomena called the “obesity paradox” where obese patients with severe COPD have lower mortality rates compared to non-obese patients (55). However, research on this topic is ongoing and it is unclear to what extent the reduced hyperinflation in obese patients with COPD benefit them in regard to dyspnea and other outcomes.

The impact of obesity on dyspnea in patients with COPD remains an area of ongoing research. Studies examining dyspnea in weight-supported symptom-limited cycling tests indicate that obesity does not lead to increased dyspnea in COPD (49,51,56). However, conflicting results have been reported in studies that assess dyspnea during weight-bearing exercise or daily life, as measured by Borg scores during six-minute walking test (6MWT) or mMRC. Some studies indicate that obese and normal-weight patients with COPD experience similar levels of dyspnea (57–60), while others report increased dyspnea in the obese group (61–64). When comparing dyspnea, it is important that factors that directly and indirectly influence this symptom are considered. As COPD is a heterogeneous condition with a broad range of pathophysiologic phenotypes, not only the extent of expiratory airflow limitation and hyperinflation, but also the extent of emphysema which in turn leads to lower DL_{CO} needs to be

considered in the results. In obese patients factors beyond BMI, such as body composition and adipose tissue distribution, also seem to influence symptom perception and need to be considered. A study by Ischaki et al. for example demonstrated that fat-free mass indices were more accurate in expressing variables of disease severity in COPD (65). Finally, factors like age, gender and comorbidities might bias results and are ideally equally distributed when comparing symptoms between groups of normal weight and obese COPD patients.

Finally, breathing during sleep can be affected by both COPD and obesity. Especially, hypoventilation during sleep is of interest as it is a potential target for treatment with non-invasive ventilation (NIV) (66,67). During sleep a mild increase of PaCO_2 and decrease of PaO_2 occurs in healthy individuals, especially during Rapid Eye Movement (REM) sleep stage as a result of loss of the wakefulness drive, increased airway resistance and diminished chemosensitivity (68). However, these changes do not lead to sleep hypoventilation (SH), which is defined as an increase in PaCO_2 (or surrogate) to a value >55 mmHg (7.3 kPa) for ≥ 10 minutes, or an increase in $\text{PaCO}_2 \geq 10$ mmHg (1.3 kPa) above the awake supine value to a value exceeding 50 mmHg (6.7 kPa) for ≥ 10 minutes (69). The physiologic changes during sleep can be exacerbated in patients with COPD due to additional factors leading to ventilatory failure, like increased upper airway resistance, mechanical disadvantages imposed by hyperinflation, respiratory muscle dysfunction and ventilation-perfusion mismatch, which collectively increase the risk of SH (70,71). Obesity itself can also increase the risk of sleep hypoventilation due to several complex mechanisms, including increased work of breathing, impaired respiratory mechanics (reduced chest wall and respiratory system compliance due to excessive body weight) and decreased respiratory muscle performance (72). Whether obesity is a risk factor for developing SH in patients with COPD remains a topic of ongoing research. While data in COPD patients with diurnal hypercapnia suggest that obesity is correlated with increased prevalence of SH (73,74), data on the impact of obesity in COPD patients with diurnal normocapnia is limited. SH is believed to be a precursor of chronic hypercapnic respiratory failure (70,75) and nocturnal gas exchange impairments are associated with adverse events in patients with COPD, including pulmonary hypertension, cardiac arrhythmias, increased exacerbation risk and mortality (76–79). Therefore, it is important to explore the prevalence of SH in patients with COPD. This particularly applies for patients with diurnal normocapnia as data in this group is scarce. Additionally, exploring potential association

between obesity and SH in this cohort, as well as identifying other contributory factors, is necessary for identifying patients at risk for SH.

As stated, both COPD and obesity individually impact pulmonary function, dyspnea, breathing during sleep, comorbidity, morbidity and mortality. When COPD and obesity coexist, their interplay generates a complex interaction that modifies the outcomes of each of these variables. As more studies are emerging, there are several discrepancies and gaps in the available knowledge on various aspects of the interplay between COPD and obesity. These include the prevalence of obesity in COPD, the impact of obesity on the occurrence of other comorbidities in COPD, and impact of obesity on dyspnea and sleep hypoventilation in COPD. This thesis aims to address these aspects and thereby to improve our understanding of the complex interplay between obesity and COPD.

Thesis outline

This thesis further explores various aspects of the interplay between obesity and COPD, including prevalence, comorbidities, dyspnea, pulmonary function and sleep hypoventilation.

The narrative review in **Chapter 2** provides an overview of the impact of obesity in COPD. The prevalence of obesity in COPD, impact of obesity on dyspnea, pulmonary function and exercise capacity are discussed. Furthermore, the impact of obesity on COPD exacerbations is discussed. This review provides insight on the current knowledge in these fields and identifies knowledge gaps requiring further study.

The prevalence of obesity in a large cohort of patients with COPD visiting the outpatient clinic was assessed in **Chapter 3**. Furthermore, an extensive array of comorbidities is compared between obese and non-obese COPD patients.

The impacts of BMI, body fat distribution and body composition on dyspnea in patients with COPD are studied in **Chapter 4**. In this cross-sectional study 80 obese COPD patients and 80 age- and FEV₁-matched normal-weight COPD patients were included. The effect of obesity on weight-bearing exercise-induced dyspnea and pulmonary function was assessed.

The main objective of **Chapter 5** was to evaluate the association between BMI and prevalence of sleep hypoventilation in patients with COPD. In this observational study polysomnography with transcutaneous $p\text{CO}_2$ measurements were performed in 56 diurnal normocapnic patients with severe COPD. Furthermore, the association between SH and other body composition measures was studied.

In **Chapter 6**, a general discussion of the findings of this thesis is presented.

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Chapter 2

Obesity in COPD: revealed and unrevealed issues

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Abstract

The interactions between obesity and COPD are being increasingly explored. In part, this is due to the globally increasing prevalence rates of obesity. The prevalence of obesity in COPD patients is variable and it seems that obesity is more common in COPD patients compared with subjects who do not have COPD. However further studies are encouraged in this area due to observed inconsistencies in the current data. In this review we focus on the knowledge of the effects of obesity on dyspnea, pulmonary function, exercise capacity and exacerbation risk. Reduction of dyspnea is one of the main therapy targets in COPD care. There is still no consensus as to whether obesity has a negative or even a positive effect on dyspnea in COPD patients. It is hypothesized that obese COPD patients might benefit from favorable respiratory mechanics (less lung hyperinflation). However, despite less hyperinflation, obesity seems to have a negative influence in exercise capacity measured with weight-bearing tests. This negative influence is not seen with weight supported exercise such as cycling. With respect to severe exacerbations obesity seems to be associated with better survival.

In summary, it is concluded that due to differences in study methodology and cohort selection there are still too many knowledge gaps to develop guidelines for clinical practice. Further exploration is needed to get conclusive answers.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) and Obesity are two major health problems. According to the World Health Organization (WHO), the prevalence of obesity (Body Mass Index (BMI) ≥ 30 kg/m²) has doubled since 1980, reaching 600 billion in 2014 (1). The prevalence of obesity among COPD patients is variable (2); however, obesity seems to be more common in Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages I-II and less prevalent in GOLD IV (3). While the prevalence of both conditions are projected to increase in the near future (4,5), clear guidelines on a clinical approach to obese COPD patients are lacking.

Combining obesity with COPD leads to an interesting paradox. While on one hand obesity seems to be associated with increased morbidity (6), overweight and obese COPD patients tend to have lower mortality rates compared to their normal weight counterparts (7). Some physiologic and metabolic explanations may contribute to this phenomenon, but the exact mechanism remains unclear (8). With emerging data, more insight is gained regarding the complex interaction between these conditions. However, there are important knowledge gaps and unrevealed issues (9,10) which limits our understanding. Currently, these gaps prevent conclusive guidelines for daily practice regarding the management of obese COPD patients (11).

The aim of this paper is to give a brief overview of the prevalence of obesity in COPD and its consequences on certain clinically important domains. The differences between COPD patients with obesity and those with normal weight concerning dyspnea, main pulmonary function parameters, exercise capacity, and exacerbation risk will be reviewed. Limitations of available data regarding these issues will be outlined and knowledge gaps which need further exploration will be discussed.

Methods

For the purpose of this narrative review we carried out a search in PubMed covering all papers published through November 2016. The following search terms were used:

For articles covering COPD:

1. ("Lung Diseases, Obstructive"[Mesh:NoExp] OR "Pulmonary Disease, Chronic Obstructive"[Mesh] OR "Pulmonary Emphysema"[Mesh] OR COPD[tiab] OR Chronic Obstructive Pulmonary Disease[tiab] OR Chronic Obstructive Lung Disease[tiab] OR Chronic Airflow Obstructions[tiab] OR Chronic Airflow Obstruction[tiab])

For articles covering obesity:

2. ("Obesity"[Mesh:NoExp] OR "Obesity, Morbid"[Mesh] OR "Obesity, Abdominal"[Mesh] OR "Body Weight Changes"[Mesh] OR "Overweight"[Mesh:NoExp] OR Obesity[tiab] OR Obese[tiab] OR Overweight[tiab])

1424 papers in English or Dutch were found with the search terms in Pubmed. The titles and abstracts of the papers of the last 10 years were screened by the first author. Then the articles were read in full text by 2 authors and selected on relevance to the various topics of our overview such as prevalence of obesity in COPD, impact of obesity on dyspnea, pulmonary function and exercise capacity. If for a particular topic only few studies could be selected than papers published > 10 years ago were also screened and included. Finally, the selected papers were evaluated in detail and discussed with the other coauthors.

Is obesity more or less common in COPD?

The prevalence of obesity in COPD has been studied in several countries (12). Only two studies included both COPD and non-COPD subjects and could therefore directly compare the prevalence rates of obesity between COPD and non-COPD subjects (13,14). Vozoris et al. used self-reported data of 95,707 individuals participating in the Canadian National Health Survey to compare the prevalence of obesity among COPD (N=3,470) and non-COPD subjects (14). Obesity was significantly more prevalent in COPD compared to

non-COPD (24.6% vs. 17.1% respectively, $p < 0.0001$). In contrast, the other study that compared the prevalence of obesity both in COPD and non-COPD subjects, indicates that obesity is less prevalent in COPD compared to non-COPD (13). In this study interviews and spirometry were performed in 5,314 individuals (759 COPD patients) in five Latin American cities. The prevalence of obesity in COPD was 23% compared to 31% in non-COPD subjects ($p < 0.001$). Both studies indicate similar occurrence rates of obesity in COPD (23-25%), however the studies disagree on whether obesity is less or more common in COPD compared to non-COPD.

Two Dutch studies evaluated the prevalence in a group of only COPD patients (3,15). Steuten et al. (3) studied 317 COPD patients in a primary care population. Pulmonary function, using a hand held spirometer, and anthropometrical measurements were performed. The prevalence of obesity in this population appeared to be 18%. Furthermore, obesity was more common in GOLD stages I and II (16–24%) and least prevalent in GOLD stage IV (6%). In another study conducted in the Netherlands, Vanfleteren recruited 213 clinically stable COPD patients (GOLD II-IV) from a pulmonary rehabilitation program (15). In this single-center prospective study 23% of COPD patients were obese. In comparison, the estimated prevalence of obesity among the general adult population in the Netherlands during the time of this study was 12.7% (16). Hence, it appears that obesity was more common in COPD patients than in the general Dutch population although no direct comparison was made.

While earlier mentioned data are consistent in prevalence rates of obesity in COPD (18%-25%), there are also data indicating higher prevalence rates. Recently, Lambert et al. analyzed data from a multicenter cohort study in the United States (COPDGene) including 3,631 patients with spirometry confirmed COPD. Within this cohort, 35% of patients were classified as obese. Eisner reported an even higher prevalence of obesity in COPD in Northern California (17). The COPD cohort (N=355) was prospectively analyzed; spirometry and anthropometrical measurements were performed. In this study, obesity was highly prevalent (54%) among the COPD patients. Furthermore, the prevalence of obesity was considerably higher in this study compared to the general population of the same state (20–24%). Finally Koniski et al. reported that 29.6% of 996 COPD patients were obese in a cross-sectional survey from 10 countries in the Middle East region (18). This study did not perform spirometry to confirm diagnosis and relied on self-reported data.

What can we conclude?

In summary, available data regarding the prevalence of obesity in COPD patients are variable, ranging from 18% to 54%. There are only few studies with a direct comparison of COPD patients and non-COPD subjects in regard to the prevalence rates. These studies disagree on whether obesity is more or less prevalent in COPD compared to non-COPD (13,14). However, including studies which have made an indirect comparison, it seems that the prevalence of obesity is higher in COPD patients compared to non-COPD subjects. Nevertheless, this issue still needs further exploration.

Future considerations

Some factors might explain the variability in results between the studies. First, there seems to be a link between the degree of airflow limitation and the prevalence of obesity. Obesity seems to be less common in severe COPD (3). Thus, ideally studies should include large cohorts of COPD patients with all levels of airflow obstruction (GOLD I-IV). Second, gender may play a role in the prevalence of obesity. Several studies indicate that obesity is more prevalent in women (13,14,19). It is noteworthy that the proportion of females was higher in the study with the highest prevalence of obesity in COPD patients (17). Third, it is relevant how information is retrieved regarding the diagnosis of COPD and BMI. Studies with a relatively large sample size have included patients with self-reported diagnoses and BMI to define COPD and obesity (14,18). Utilization of self-reported data is a popular methodology in studies; however, it is proven to be less reliable (20–24). Using physician based diagnosis and Pulmonary Function Tests (PFT) to confirm the diagnosis is important. Although it is more difficult to execute, especially in larger cohorts, it gives a more reliable view than self-reported data. Finally, genetic and sociodemographic differences play a role when looking at prevalence rates. Future studies need to consider all these aspects in order to provide a realistic view of the occurrence rates of obesity in COPD (Table 1).

For clinical practice, it is also interesting to know whether there is a causal link between obesity and COPD. To date, our understanding is limited regarding this issue, mainly due to the cross-sectional design of available studies. Therefore, it remains unclear whether COPD is a risk factor for developing obesity, due to a sedentary lifestyle or if obesity is a risk factor for developing COPD, due to their combined pathophysiology of inflammation. Longitudinal studies are required in the future to provide more insight into this issue.

Do obese COPD patients experience more or less dyspnea?

Dyspnea is one of the predominant complaints of patients with COPD (25). Obesity itself is also associated with dyspnea (26–30). As a consequence, it might be assumed that obese COPD patients experience more dyspnea than COPD patients with a normal weight. However, studies exploring this issue show conflicting results (6,31–37). Some studies indicate that obesity does not affect dyspnea in COPD, whereas others suggest a negative role for obesity. The evidence for both findings will be discussed below.

Obese COPD patients have similar levels of dyspnea compared to COPD patients with a normal weight:

Ora et al. conducted a prospective study investigating the relationship between dyspnea and obesity during incremental cycle exercise in COPD patients (37). This study compared 18 obese (mean BMI $\pm$ SD, 35 ± 4 kg/m²) and 18 normal weight (mean BMI $\pm$ SD, 22 ± 2 kg/m²) patients with COPD. The groups were matched for forced expiratory volume in 1 second (mean FEV₁ 49% pred.) and diffusing capacity of the lungs for carbon monoxide (mean DL_{CO}, % predicted > 70% in both groups). The groups were also well matched for age, smoking history (pack years) and gender. The Baseline dyspnea index and Borg dyspnea scale were used to assess dyspnea. Obese patients did not experience more dyspnea at rest or during exercise compared to patients with a normal weight. In fact, at certain ventilation levels during cycling, dyspnea intensity on the Borg scale was even lower in the obese group (Figure 1), though the differences remained non-significant. When comparing the lung volumes, the obese group had significantly less static and dynamic hyperinflation (Figure 2). The phenomena of less hyperinflation, thus breathing at relatively lower lung volumes, leads to a mechanical advantage in obese patients. This advantage might be partly responsible for observing less dyspnea in obese COPD patients.

Ora et al. reconfirmed the results in a more recent study, including 12 obese and 12 age- and FEV₁ matched COPD patients with a normal weight (mean FEV₁ pred. $\pm$ 60% in both groups) (35). This study was a well-designed prospective study and both groups had comparable DL_{CO}, gender distribution and smoking history. Dyspnea at rest, using the Medical Research Council dyspnea scale (MRC), was comparable in obese and normal weight COPD patients (mean MRC 2.7 and 2.4 respectively). A larger retrospective analysis by Laviolette

et al. (36); comparing 64 obese COPD patients with 84 patients with a normal weight, confirmed the results of Ora et al. Ratings of dyspnea (Borg scale) remained similar between the groups at different ventilation levels during exercise. Despite a larger number of subjects, this study had some limitations compared to the studies performed by Ora et al. First, in this study, only male subjects were included. Moreover, the DL_{CO} was significantly better in the obese group, 19.2 ± 6.6 mL/min/mmHg ($59\% \pm 27\%$ pred.) compared with the normal weight group 15.4 ± 5.1 mL/min/mmHg ($46\% \pm 22\%$ pred.); $p=0.01$ (36). This suggests that the obese group may have benefited from less severe emphysema and thus resulting in relatively low dyspnea scores compared to the group with a normal weight.

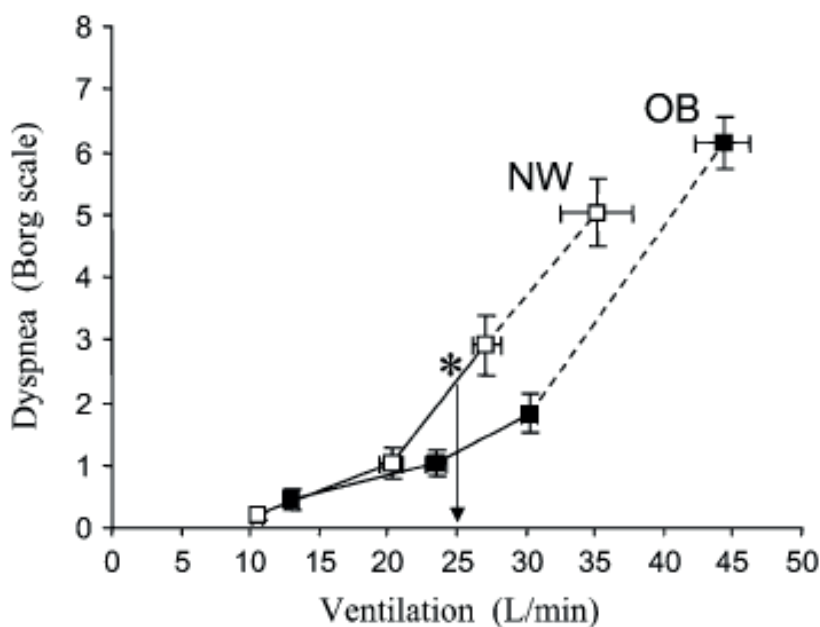


Figure 1. Reproduced from Ora J, Laveneziana P, Ofir D, Deesomchok A, Webb KA, O'Donnell DE. Combined effects of obesity and chronic obstructive pulmonary disease on dyspnea and exercise tolerance. *Am J Respir Crit Care Med.* 2009;180(10):964-71. [37]

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Obese (OB) subjects with chronic obstructive pulmonary disease (COPD) (solid squares) had a rightward shifted dyspnea/ventilation (VE) slope in comparison with normal- weight (NW) subjects with COPD (open squares). At an iso-VE of 25 L/min (vertical line with arrow), dyspnea intensity was 1.2 ± 1.1 versus 2.4 ± 1.6 Borg units in OB versus NW ($P < 0.01$).

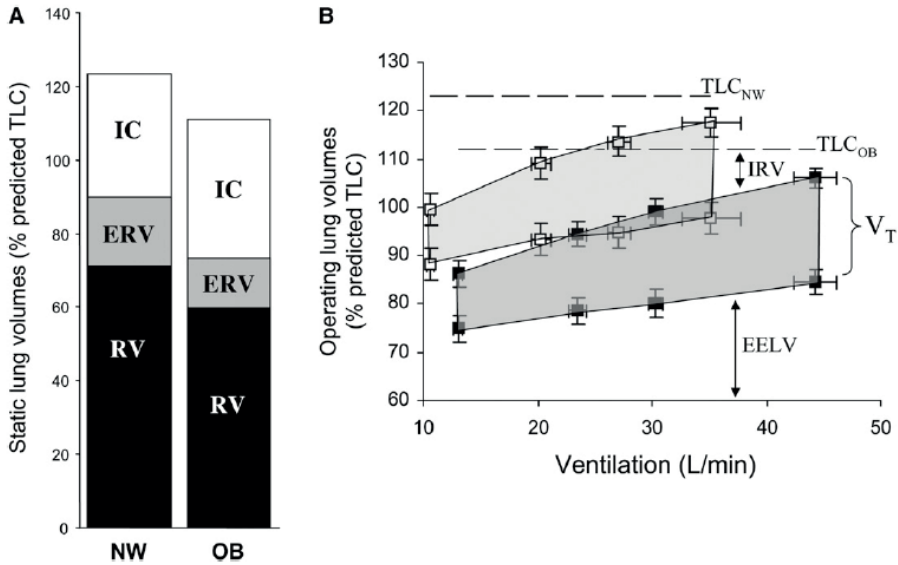


Figure 2. Reproduced from Ora J, Laveneziana P, Ofir D, Deesomchok A, Webb KA, O'Donnell DE. Combined effects of obesity and chronic obstructive pulmonary disease on dyspnea and exercise tolerance. *Am J Respir Crit Care Med.* 2009;180(10):964-71. [37]

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(A) Static lung volumes measured by body plethysmography at rest. Expiratory reserve volume (ERV) and functional residual capacity (FRC) (ERV + RV) were significantly ($P < 0.05$) lower in the obese (OB) group. (B) Lung volumes are shown from rest to peak exercise in OB patients COPD (closed squares) and in normal-weight (NW) patients with COPD (open squares). In the OB compared with the NW group, end-expiratory lung volume (EELV) (standardized as a % of predicted TLC) was consistently lower ($*P < 0.01$) at rest and throughout exercise; the OB group reached an EELV at peak exercise that was similar to that of the NW group at the pre-exercise resting level.

IC = inspiratory capacity; IRV = inspiratory reserve volume; VT = tidal volume (shaded area); RV = residual volume. Values are means $\pm$ SE.

Two more recent studies have been conducted, one performed during activities of daily life by Vaes et al. (N= 13 obese; 31 normal weight) (33) and the other during exercise by Rodriguez et al. (N= 108 obese; 143 non-obese) (32). Both studies indicate that obesity does not affect dyspnea in COPD. However, the interpretation of the results is more difficult because the groups were not well matched for important confounders. In the study by Vaes et al., gender distribution in the groups was uneven (obese: 85% male; normal weight: 45%; $p < 0.05$). Furthermore relevant information regarding smoking history, DL_{CO} and static lung volumes were lacking. In the study performed by Rodriguez, the obese group had significantly less airflow obstruction (mean FEV_1 % pred. 58% vs. 49%) and better DL_{CO} (mean % pred. 72% vs. 63%) compared to the non-obese group (32). Furthermore, no real comparison can be made between obese and normal weight patients, because the authors divided the patients in two groups: obese and non-obese, with the non-obese group having a mean BMI 26.2 kg/m², which can be categorized as overweight.

Obese COPD patients experience more dyspnea compared to COPD patients with a normal weight:

In contrast to the studies mentioned previously, there are also data indicating more dyspnea in obese COPD patients compared to COPD patients with a normal weight. The most recent and also largest study discussing this issue was performed by Lambert et al. (6). In this retrospective analysis of a large cohort, including 3,631 COPD patients (normal and overweight: N= 2,383 and obese: N= 1,248), the association between obesity and COPD outcomes was assessed. There were no significant differences in age and smoking history between the groups. Only the mean FEV_1 % pred. was higher in the obese group (obese: 53 % pred. normal and overweight: 49% pred; p value for trend < 0.001). The odds of having an mMRC ≥ 2 increased significantly with obesity, to a 4-fold increase in patients having class III obesity (p -value for trend < 0.001). Of note, static lung volumes and DL_{CO} were not obtained in this study. Furthermore, the non-obese group included both normal- and overweight COPD patients.

The results from Lambert et al. are supported by earlier reports. Cecere et al. performed data analysis on 364 veterans with COPD and categorized patients by BMI (34). Obese and overweight patients had less airflow obstruction (mean FEV_1 % pred. obese: 55.4% $\pm$ 19.9%; overweight: 50.0% $\pm$ 20.4%) than normal weight patients (mean FEV_1 % pred. 44.2% $\pm$ 19.4%; $p < 0.001$). The authors used the MRC dyspnea scale to measure the intensity of dyspnea in daily life. Despite having less severe airflow obstruction, obese COPD patients reported increased

dyspnea. Obese patients were almost 5 times as likely as normal weight COPD patients to experience moderate or severe dyspnea (adjusted OR of MRC score $\geq 2 = 4.91$). Obese COPD patients had significantly higher MRC scores throughout any given FEV₁ (Figure 3). Garcia-Rio et al. also compared dyspnea intensity, but in a smaller group of 97 normal weight, 172 overweight and 113 obese COPD patients (31). Obese patients had more severe dyspnea compared with normal weight patients on the mMRC scale (1.92 vs. 1.49; $p < 0.01$). However, it must be mentioned that the groups were not matched for lung function or age. Compared with the normal weight group, the obese group consisted of older patients (mean age 66 years $\pm$ 9 vs. 61 years $\pm$ 9 10; $p < 0.01$). Also, the obese group had a history of significantly more pack-years compared with the normal weight group. Furthermore FEV₁ was slightly lower in the obese group compared with the normal weight group (mean FEV₁ % pred. 79% vs. 85%).

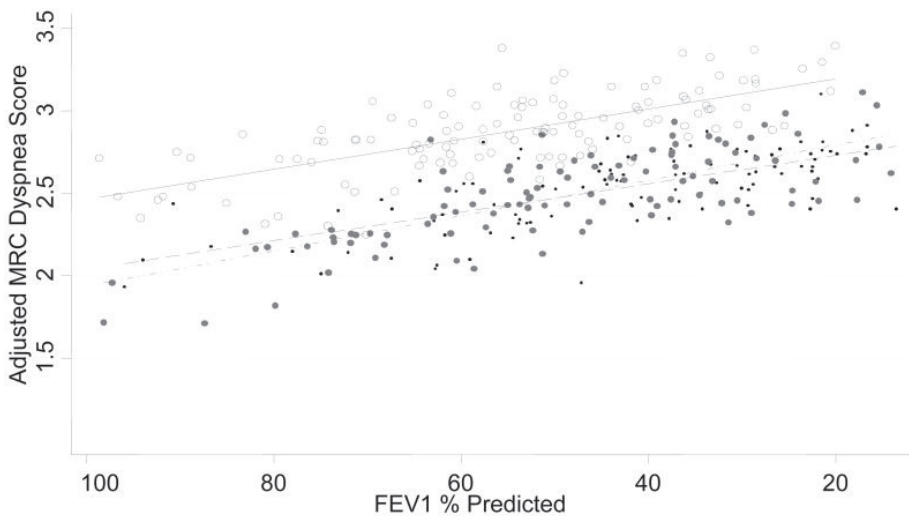


Figure 3. Reproduced from Cecere L, Littman A. Obesity and COPD: associated symptoms, health-related quality of life, and medication use. *COPD* 2011;8(4):275-284. [34]

Reprinted with permission of Taylor & Francis Ltd, <http://www.tandfonline.com>. Copyright © 2017 The adjusted predicted MRC score is given for each subject. For every given severity of airflow obstruction, obese patients are more dyspneic than normal weight patients. Regression lines for each BMI category also shown. (Normal weight: black dots; Overweight: gray dots; Obese: white dots)

What can we conclude?

In conclusion, there is no consensus on the role of obesity on dyspnea in COPD patients. Current data suggests two options:

1. Obese patients, contrary to expectation, do not experience more dyspnea. An explanation for this finding could be that obesity may be beneficial regarding dyspnea due to advantages in respiratory mechanics (less hyperinflation). *See the section about static lung volumes.*
2. Obese patients experience more dyspnea. An explanation could be that bearing more weight in daily life results in more dyspnea due to the increased work of breathing.

Future considerations

The exact role of obesity on dyspnea in COPD still needs to be revealed. It has been hypothesized that a lack of significant increase in dyspnea in obese patients compared to patients with a normal weight, may be due to the fact that most studies use weight-supported exercise (cycling). This could possibly diminish the negative effects of weight on symptom perception. However, this hypothesis is contradicted by a recent study comparing weight-bearing (walking) and weight-supported (cycle) exercise (38). Despite significant differences in physiological responses between the two test modalities, dyspnea intensity was comparable between walking and cycling at any given power output.

Several aspects need to be considered in future studies. One of the main aspects, making it difficult to compare dyspnea between different weight classes, is the heterogeneity of COPD. A true comparison of the net effect of obesity on dyspnea is only possible when cohorts are matched in pathophysiologic phenotypes. This means that not only the level of airflow obstruction (FEV_1), but also the severity of emphysema, need to be comparable in cohorts. Ideally, CT scans should be performed as a measure of emphysema, but measuring DL_{CO} is also acceptable in large cohorts. Although in most of the studies presented above, obese and non-obese groups had comparable degrees of airflow obstruction, it remains unclear whether they also had similar degrees of emphysema. The larger studies lack measurements of static lung volumes and DL_{CO} (6,31,34). Studies which have obtained DL_{CO} are usually small (35,37) or compared groups with significantly different DL_{CO} (32,36). The study performed by Ora et al., is one of the few where DL_{CO} was matched in both groups (37). DL_{CO} in the group with a normal weight was $78 \pm 28\%$ predicted and in the obese group $72 \pm 15\%$ predicted. However, $DL_{CO}/\text{total lung capacity (TLC)}$ was higher in obese subjects compared with the normal weight group. It could have been relevant if the authors had compared the DL_{CO}/VA between the two groups as a measure of emphysema (39). It must be mentioned that some studies suggest that obesity itself leads to higher DL_{CO} ,

probably due to an increase in lung blood volume (10). However, this remains controversial and not all studies support this.

Body composition and adipose tissue distribution should also be taken into account when evaluating the role of obesity on dyspnea. The fat free mass index (FFMI) seems to be an important determinant of COPD outcomes such as mortality and disease severity (2). Furthermore, FFMI may provide additional information beyond BMI regarding dyspnea and must be considered in future studies assessing the role of weight on dyspnea (40). Thus, other measures of body composition (FFMI, central vs. peripheral obesity) need to be evaluated and, more importantly, be equally distributed when comparing cohorts.

Since several other factors such as age, gender and comorbidities also play a role in symptom perception, it is more difficult to deal with these confounders when a study is not performed in prospection with tools like matching (31). Finally, since dyspnea is a subjective symptom, it is also important to keep in mind that we cannot simply compare different scoring scales with each other interchangeably (41). For example, the Borg scale measures the intensity of dyspnea, while the MRC (or mMRC) gives us insight into the limitations of a patient as a result of dyspnea.

Future prospective studies with larger cohorts need to consider the limitations of available data. Obese and normal weight cohorts need proper randomization, minimizing confounders and distributing different phenotypes of COPD equally between the groups (Table 1).

Static lung volumes differ in obese and non-obese COPD patients, but why?

While COPD is characterized by expiratory airflow obstruction, hyperinflation is also often present. Lung hyperinflation in COPD is a result of an increase in lung compliance due to emphysema and effects of expiratory airflow limitation (42). Several definitions for static lung hyperinflation are in use (42–44). However, there is currently no consensus on which to use as a standard. Commonly, hyperinflation is defined by an elevation of the resting functional residual capacity (FRC) above normal (44). Furthermore, an increase of TLC is also considered to be a marker of hyperinflation. However elevated FRC and RV are also often present in the setting of preserved TLC (42). Several ratios, like

RV/TLC, FRC/TLC and IC/TLC are also used to define hyperinflation. The IC/TLC ratio appears to be a good predictor for mortality in patients with COPD (42).

While static lung volumes are often altered in COPD, obesity itself appears to affect static lung volumes as well. The most important effect of increasing BMI is a significant reduction in FRC and expiratory reserve volume (ERV) (29,45–48). As a consequence of obesity, intra-abdominal pressure increases leading to increased intra-thoracic pressure. This mechanism is exaggerated particularly when subjects are in the supine position and results in decreased FRC and ERV (47). Furthermore, obesity leads to reduced lung compliance which seems to be exponentially related to BMI (49). Reduced lung compliance is demonstrated in other studies as well and may be the result of a combination of factors: increased pulmonary blood volume, closure of dependent airways leading to small areas of atelectasis or increased alveolar surface tension due to the reduction in FRC (50). Whether obesity also leads to reduced chest wall compliance is less clear, due to variable results in studies (50). However, in general, it is presumed that as a consequence of obesity both lung and chest wall compliance are altered (51,52). Despite these negative effects, ventilation seems to remain normally distributed in obesity when FRC values are not extremely altered (FRC % pred. >65%) (53). This might be caused by a putative advantage of an increase in lung elastic recoil correlated with increasing BMI.

Eventually, elevated intra-thoracic pressure and the stiffening of the total respiratory system (combination of reduced lung and chest wall compliance) leads to a reduction in FRC and ERV in obesity. Jenkins and Moxham demonstrated that the FRC and ERV are significantly reduced even in mild obesity (54). The relationship between increasing BMI and decreasing static lung volumes is exponential, thus the dramatic changes in FRC and ERV are flattened out with morbid obesity (45). Furthermore, TLC appears to be reduced only with more severe obesity (45,47).

Although BMI is the most used and easiest way to define weight, some suggest that there are better markers to predict pulmonary function. Ochs-Balcom et al. investigated the correlation between various adiposity and body fat distribution markers with forced vital capacity (FVC) (55). In this large cohort of 2,153 individuals from a general population, abdominal adiposity was a better predictor of pulmonary function (FVC) than weight or BMI. However, when looking in more detail with MRI, it seems that the topography of adipose tissue is less important than the cumulative effect of increased chest wall fat (48).

Static lung volumes in obese COPD patients:

The consequences of increasing BMI have also been documented in the presence of COPD. In a large cohort of 2265 COPD patients, O'Donnell studied the impact of BMI on static lung volumes (56). This study showed similar effects of increasing BMI on lung volumes as with the previously mentioned data in subjects without COPD. The 654 obese COPD patients showed significantly lower FRC values compared with COPD patients with a normal weight (mean FRC % pred. 124 ± 32 vs. 147 ± 35 respectively; $p < 0.05$). FRC is a multicomponent value, consisting of ERV and residual volume (RV). In the data presented by O'Donnell, RV decreased exponentially with increasing BMI. However, ERV contributed the most to the decrement of FRC. Mean ERV % predicted dropped dramatically from 91% in normal weight to 54% in the obese group ($p < 0.05$). These effects of BMI on static lung volumes were visible across all GOLD stages (Figure 4). Data from O'Donnell showed that all ratios for lung hyperinflation were in favor of obesity in COPD patients. For example, increasing BMI resulted in significant and linear increase in the IC/TLC ratio (IC/TLC % in obese: 37 ± 10 ; in normal weight: 30 ± 8 ; $p < 0.05$).

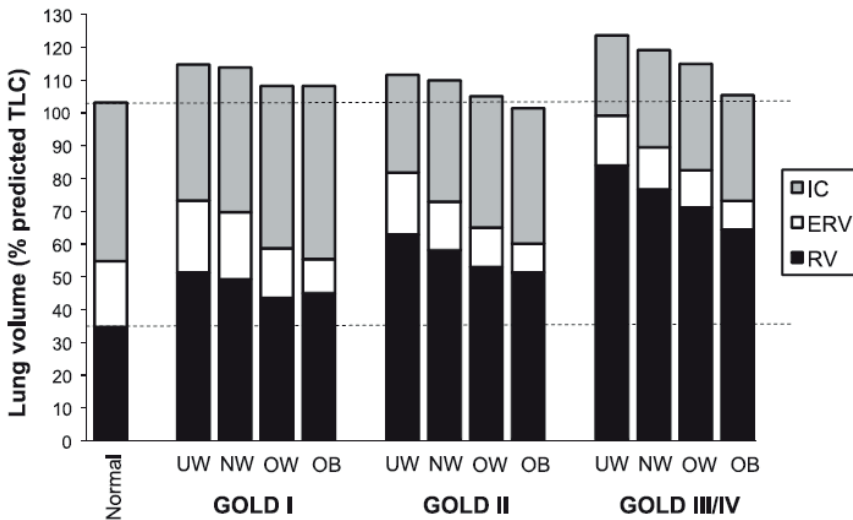


Figure 4. Reproduced from O'Donnell DE, Deesomchok A, Lam YM, et al. Effects of BMI on static lung volumes in patients with airway obstruction. *Chest*. 2011;140 (2):461-8. [56]

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Postbronchodilator lung volume components are shown divided by GOLD stage and BMI. UW = underweight; NW = normal weight; OW = overweight; OB = obese; RV = residual volume; ERV = expiratory reserve volume; IC = inspiratory capacity.

There are other studies as well showing relatively lower static lung volumes in obese COPD patients compared with normal weight COPD patients (35–37,57). Recently published data by Aiello et al. showed a IC/TLC ratio (%) of 36 ± 8 in obese COPD compared to 28 ± 9 in COPD patients with a normal weight ($p < 0.01$) (57). Furthermore, the FRC (% pred.) decreased significantly from $161\% \pm 34\%$ in NW to $137\% \pm 40\%$ in obese ($p < 0.05$).

What can we conclude?

In conclusion, static lung volumes of obese COPD patients are altered. Increasing BMI results in relatively less hyperinflation. Since hyperinflation is a marker of mortality and symptoms, increasing BMI seems to give several advantages in COPD patients. In part, this effect on hyperinflation may explain the better survival of obese COPD patients ('obesity paradox').

Future considerations

Several questions remain. First, is increasing adipose tissue the cause of less hyperinflation or do other factors like FFM and systemic inflammation contribute to this phenomenon? Second, which group of COPD patients benefit the most from extra weight (emphysema vs. obstructive)? Finally, at what cut-off point do the disadvantages of extra weight counterbalance the advantages of less hyperinflation regarding survival and symptoms? When considering survival, a recent meta-analysis indicates that in COPD the lowest risk for mortality is observed with a BMI of 30 kg/m^2 (58). The survival advantage seems to diminish with $\text{BMI} > 32 \text{ kg/m}^2$; however, the authors also state that there is limited evidence to demonstrate a relationship between obesity and mortality and therefore further studies are needed to elucidate this relationship. Future studies need to focus on these questions in order to implement tailored treatment strategies for each individual patient (Table 1).

Exercise testing; does a combination of obesity and COPD lead to reduced exercise capacity?

COPD patients report that they are more inactive in daily life compared to healthy individuals (59). This is also confirmed with quantitative measurements of walking time and movement intensity measured with an activity monitor (60). The 6 minute walk-test (6MWT) or a cycle test is widely used to assess exercise capacity of COPD patients in the diagnostic work up. Whether obesity

influences the exercise capacity of COPD patients, measured with either 6MWT or cycle test, will be discussed in this section.

There is accumulating data indicating a negative effect of obesity on exercise capacity in the daily life of COPD patients (61). This is also demonstrated by studies which used the 6MWT as a tool to assess exercise capacity. Recently, Maatman et al. performed a retrospective analysis on data from 108 obese COPD patients vs. 108 age and FEV₁ matched COPD patients with a normal weight to assess the effects of obesity on exercise testing (62). In this study, the walking distance during 6MWT differed significantly between obese (398 ± 107 m) and normal weight patients (446 ± 109 m, $p < 0.05$). The negative association between BMI and lower functional capacity measured by the 6MWT was also demonstrated in several other studies (6,63–66).

Obesity does not only affect the walking distance measured by the 6MWT but is also associated with exercise induced desaturation (EID). This was demonstrated by a study which included 2,050 COPD patients (mean age: 63.3 ± 7.1 years; FEV₁ % pred.: $48.7\% \pm 15.7\%$) (67). EID, defined by a fall of saturation $\leq 88\%$ during the 6MWT, occurred in 21% of the patients. One of the determinants of EID was a BMI ≥ 30 kg/m² (adjusted OR: 1.57; 95% CI: 1.15–2.14). Moreover, pre walking saturation $\leq 93\%$, emphysema on CT scan and FEV₁ $\leq 44\%$ predicted were stronger determinants of EID.

While the above mentioned studies clearly indicate that obesity has a negative impact on exercise capacity evaluated with 6MWT, it is also interesting that this finding does not seem to apply for weight-supported tests (cycling). In a study performed by Ora et al., obese COPD patients did not experience greater exercise limitation during cycle exercise compared to normal weight COPD patients with similar FEV₁ (both groups 49% pred.) (37). This finding is supported by more recent studies comparing the 6MWT with cycling tests (Figure 5) (62,64). Obesity leads to several physiological changes during exercise which can contribute to reduced exercise capacity. Among these changes are an increased metabolic demand of moving increased weight and the increased work of breathing due to extra weight on the chest wall (68). These changes may be more exaggerated by weight-bearing exercise, thus resulting in worse performance in these tests compared with weight-supported tests.

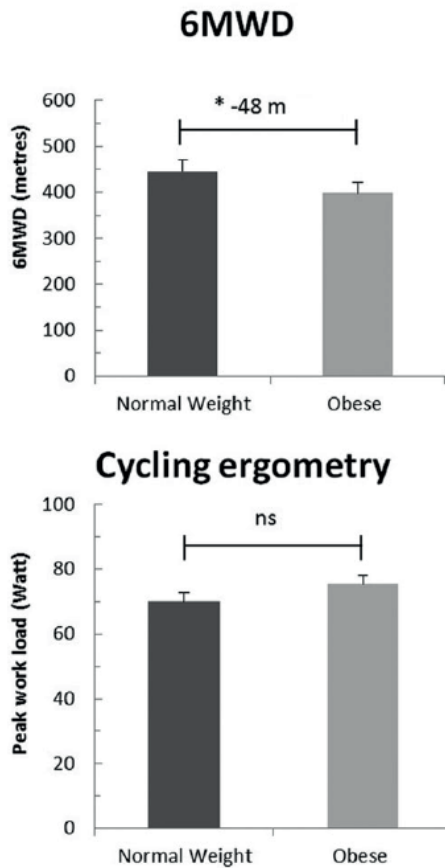


Figure 5. Reproduced from Reproduced from Maatman RC, Spruit MA, van Melick PP, et al. Effects of obesity on weight-bearing versus weight-supported exercise testing in patients with COPD. *Respirology*. 2016; 21 (3):483-8. [62]

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Main outcomes of cycle ergometry and 6-min walk test (6MWD) in normal weight and obese chronic obstructive pulmonary disease (COPD) patients.

What can we conclude?

In summary, despite a beneficial effect on pulmonary function (less hyperinflation), obesity seems to have a negative influence on exercise capacity in COPD, resulting in less walking distance and exercise induced desaturation while walking. This is exposed in studies measuring exercise capacity with weight-bearing tests (activity monitors and the 6MWT). Obesity does not seem to influence outcomes on weight-supported exercise such as cycling.

Future considerations

These results give an interesting insight into the effects of obesity and COPD on functional capacity, but also raise some questions that needs to be explored. The 6MWT is a simple test to perform in daily practice and is widely used to assess exercise capacity, but should this test be also applied on obese COPD patients when we only want to measure the effects of COPD on functional status? How can the decreased walking distance by obese patients be interpreted when we evaluate prognosis and disease progression, especially considering the beneficial role of obesity on mortality? Furthermore, since exercise is one of the cornerstones in the non-pharmacologic management of COPD, should obese COPD patients be advised to use different exercise modalities (more weight-supporting exercise)? These questions needs to be addressed in translational studies which give guidance for daily practice.

COPD exacerbations; is obesity a risk- or protective factor?

In a large retrospective patient chart review of 313,233 patients admitted to the hospital with a COPD exacerbation in Spain, the association of weight with both mortality and the risk of readmission within 30 days was assessed (69). Compared to patients with a normal weight, obese patients showed a lower in-hospital mortality risk (OR 0.52; 95% CI 0.49–0.55) and lower early re- admittance risk for the same diagnosis (COPD) (OR 0.87; 95% CI 0.85–0.92). Compared to normal weight patients, the risk of readmission after discharge was 13% lower in obese patients and 29% higher if malnutrition was documented in the medical chart. Unfortunately the diagnoses were all based on ICD-9 coding, therefore weight, height and thus BMI could not be given. Higher BMI, particularly overweight to mild obesity, also proved to be protective for survival in a retrospective study with a median follow up of 3.26 years after hospitalization due to acute exacerbation of COPD (70). Furthermore, obesity was also associated with decreased mortality after a severe exacerbation of COPD (HR 0.76; 95% CI 0.70–0.82) in a large cohort of Veterans Affairs (71).

While the data presented indicate a beneficial role for obesity regarding survival after COPD exacerbation and a lower risk of 30-day readmission, it still remains debatable whether obesity affects the risk of exacerbation itself. Several studies indicate that obesity plays neither a beneficial nor

a disadvantageous role on exacerbation risk in COPD (18,34). However, interestingly a recent study including 3,631 COPD patients, showed increased odds of self-reported severe exacerbation in the past year for obese patients (6). Furthermore, the odds of severe exacerbation increased with increasing obesity class ($p=0.005$). This latter finding is supported by Danish data, indicating an association between genetically determined high BMI, defined through the BMI allele score, with an increased risk of recurrent exacerbations (72). Contrary to expectations, a measured high BMI (using weight and height) was not associated with exacerbations of COPD in this study, thus making it difficult to translate these results for clinical practice.

What can we conclude?

Obesity is associated with better survival and a lower risk of early readmission after hospitalization due to COPD exacerbation in some studies. However, there are also indications that obese COPD patients experience more severe exacerbations. The exact role of obesity on the risk of COPD exacerbation remains disputable.

Future considerations

Our current view is based on variable data from retrospective analyses, self-reported variables, diagnosis based on ICD coding and at best basic spirometry without additional information on static lung volumes or DL_{CO} . Prospective studies with clear definitions for obesity, COPD and exacerbation with proper follow-up are indispensable in the future in order to enhance our understanding of this issue (Table 1).

Conclusions

COPD and obesity are both major health problems. While the global prevalence of obesity is rapidly increasing, prevalence rates of obesity among COPD patients are variable (ranging from 18% to 54%). Obesity seems to be more prevalent in COPD patients compared to those without COPD; however, not all data are consistent with this finding. Study methodology, cohort selection, genetic and sociodemographic differences, are confounding factors that contribute to the variability in prevalence rates. Future studies have to focus on minimizing confounders, in order to give a realistic view of the prevalence of obesity in COPD. Furthermore, to date, it is not clear whether COPD plays a role in the development of obesity or vice versa. Longitudinal studies with a long period of follow-up may identify possible causal links in the future.

Dyspnea is one of the main symptoms in COPD, however there is no consensus on how dyspnea is influenced by obesity in COPD patients. It is hypothesized that obese COPD patients might benefit, from favorable respiratory mechanics (less lung hyperinflation) and thus experience relatively less dyspnea. However, data are also emerging indicating worse outcomes, including dyspnea, in obese COPD patients. Several factors, including the heterogeneity of COPD, looking beyond BMI, and matching study populations in terms of confounding factors need to be considered when studying this issue. Future studies with larger cohorts in a prospective setting may lead to definite conclusions regarding this subject.

When comparing pulmonary function, COPD patients tend to have a reduction of FRC (especially the ERV) with increasing BMI. This leads to relatively lower levels of lung hyperinflation and could contribute to better survival (obesity paradox) and less symptoms. Other details, including correlations with other components of obesity (fat distribution, inflammation etc.) are unclear.

Data indicate that obese COPD patients have deteriorated functional capacity measured by the 6MWT and activity monitors. Obesity also seems to be one of the determinants of exercise induced desaturation during these tests. However, weight-supported testing (cycling) does not seem to be negatively influenced by obesity. These results need further exploration in translational studies which give guidance on how to apply these findings for daily practice in the management of COPD patients in different weight categories.

Finally, obesity seems to be associated with lower mortality and lower risk of early readmission after hospitalization with COPD exacerbation. However, whether obesity reduces the risk of exacerbations remains unclear.

By reviewing the prevalence of obesity in COPD patients and the impact of obesity on dyspnea, pulmonary function, exercise capacity, and COPD exacerbations, we can conclude that there are still important knowledge gaps and unrevealed issues. Despite emerging data, our understanding of the complex interaction between obesity and COPD is still limited. To date, conclusive guidelines for daily practice regarding the management of obese COPD patients are lacking. More research in this area is encouraged in order to enhance our knowledge and develop guidelines for the management of obese COPD patients.

Conflict of interest

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Chapter 3

Obesity in COPD: Comorbidities with Practical Consequences?

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Abstract

COPD and Obesity often coexist and there is a complex interaction between them. Our aim was to evaluate the prevalence of obesity in a secondary care COPD population. Furthermore, the presence of comorbidities in obese (COPD_{OB}) and non-obese COPD (COPD_{NO}) individuals was studied. In 1654 COPD patients (aged ≥ 18 years) who visited a pulmonologist between January 2015 and December 2015, patient characteristics, pulmonary function tests and comorbidities were obtained from the medical records. Subjects were categorized according their BMI as underweight ($< 18.5 \text{ kg/m}^2$), normal weight ($18.5\text{--}24.9 \text{ kg/m}^2$), overweight ($25.0\text{--}29.9 \text{ kg/m}^2$) or obese ($\text{BMI} \geq 30.0 \text{ kg/m}^2$). The Charlson comorbidity index and COTE index were used to quantify comorbidities. The prevalence of obesity was 21.8% in our COPD population. Obesity was significantly less common in GOLD stage IV (10.1%) compared to GOLD I (20.5%), II (27.8%) and III (18.9%). COPD_{OB} had different comorbidities compared with COPD_{NO}. Hypertension, diabetes mellitus, atrial fibrillation and congestive heart failure were significantly more prevalent in COPD_{OB} compared with COPD_{NO}. Osteoporosis and lung cancer were significantly more common in COPD_{NO} compared with COPD_{OB}. Obesity is common in patients with COPD and is most prevalent in COPD GOLD I-II and least prevalent in COPD GOLD IV. Obese COPD patients have different comorbidities than non-obese COPD patients. Cardiovascular and metabolic comorbidities, especially hypertension and diabetes mellitus, are highly prevalent in obese COPD patients. Active screening for these conditions should be a priority for physicians treating obese COPD patients.

Introduction

Obesity and Chronic Obstructive Pulmonary Disease (COPD) frequently coexist.(1–4) In 2014, 13% of the global adult population met the criteria for obesity (Body Mass Index (BMI) $>30 \text{ kg/m}^2$). (5) Also, in the Netherlands the prevalence of obesity was 13.7% in 2015. (6) Existing data show a great variation in prevalence rates of COPD due to differences in demography, diagnostic criteria and survey methods.(7) Estimations vary from 210 to 600 million people having COPD worldwide. (8) In a systematic review the global prevalence of COPD was estimated to be 9–10%. (9) The prevalence of both conditions is projected to increase in the future.(7,10)

The prevalence of obesity in COPD has been studied in several countries but the results are inconsistent and ranges between 18–54%. (11–18) Most studies suggest a higher prevalence of obesity in COPD patients compared to non-COPD individuals.(11,12,14) In these studies the prevalence of obesity in the COPD cohorts exceeds the prevalence of obesity in the studied general populations which varies between 10–24%. However, epidemiological data from a Latin American study demonstrated a lower prevalence of obesity in COPD compared with non-COPD subjects (23% VS 31% respectively). (13)

Factors that may explain the variability in data regarding the prevalence of obesity in COPD are the study method, degree of airflow limitation, sex, genetic and socio-demographic differences. Most of these studies relied on self-reported data and could not include objective information like: pulmonary function, anthropometric measurements and/or physician made diagnosis. (12,13,15,16) Other limitations are small number of subjects ($n=213 - 355$) or having an age limit for inclusion or excluding severe comorbidities. (11,14,18)

There is increasing evidence indicating different patterns of comorbidities in COPD patients compared to non-COPD individuals. (19,20) It is known that cardiovascular, metabolic and cognitive comorbidities are relatively common in COPD.(21–29) Most of these comorbidities lead to higher hospitalization rates and in-hospital mortality. (30) However, it is relatively unknown which role the co-existence of obesity plays on the occurrence of comorbidities in COPD.

The primary aim of this study was to evaluate the prevalence of obesity in a well-defined, large COPD population from a secondary care clinic.

Furthermore, the presence of comorbidities in obese (COPD_{OB}) and non-obese COPD (COPD_{NO}) groups was studied. Additionally, we compared the prevalence of obesity and the coexistence of comorbidities between GOLD stages.

Methods

Study Design and Patients

This study was performed in the outpatient clinic of Rijnstate hospital, a large teaching hospital in the Netherlands. The study was approved by Rijnstate Hospital institutional review board and the local ethics committee (LTC number: 2015-0686). Medical records of individuals (aged ≥ 18 years) registered with the ICD-10 diagnose of COPD between January 2015 and December 2015 were evaluated retrospectively. Data was extracted from the electronic database which is used as part of usual medical care in our hospital. The electronic records contain documentation of in- and outpatient contacts from all specialties within the hospital, data on all examinations (lab, pulmonary function, radiology etc.), medication use and referral letters from the general practitioners.

Patients were only selected when a pulmonologist had diagnosed them with COPD. The indicated diagnosis of COPD was checked and verified by evaluating the most recent Pulmonary Function Test (PFT) using the post bronchodilator values. The European Community for Coal and Steel reference equations were used to calculate predicted values. (31) Obstructive disease was confirmed if the ratio of Forced Expiratory Volume in one second (FEV₁) to Vital Capacity (VC) was below the 5th percentile of the predicted value (Lower Limit of Normal (LLN)).(32)

Patients with a history of asthma, asthma-COPD overlap syndrome (ACOS), solely restrictive lung disease and those with FEV₁/VC $\geq$ LLN were excluded. Furthermore, patients with diagnose of COPD but without available PFT were also excluded from analysis.

When all the above mentioned criteria of inclusion were met, medical records were reviewed thoroughly, including documentation of all in - and outpatient contacts from other medical specialist in order to gain information on comorbidities.

Variables of Interest

Patient characteristics like sex, age, height, weight, BMI, diagnosis of COPD by a pulmonologist, comorbidities, use of inhalers and smoking status as well as pulmonary function tests parameters were obtained from the medical records

Height, weight and BMI were obtained from the most recent PFT reports. Patients were categorized to weight classes according to WHO criteria (33): underweight (UW) defined as BMI < 18.5 kg/m², normal-weight (NW) defined as BMI 18.5–24.99 kg/m², overweight (OW) defined as BMI 25.0–29.99 kg/m² and obese (OB) defined as BMI ≥ 30.0 kg/m². The severity of COPD was classified according to GOLD guidelines. (7)

We chose to review the medical records on comorbidities used in the Charlson comorbidity index, COTE index and three most common comorbidities in COPD not listed in the mentioned indexes (hypertension, depression and osteoporosis). (18,34–36) Comorbidities were scored on physician based diagnoses which were retrieved from the documentation of specialists and general practitioners.

Statistics

Descriptive statistics were used to characterize the study population at baseline. Continuous variables are expressed as mean $\pm$ SD while discrete variables are shown as percentages. A two-tailed *p* value < 0.05 was considered statistically significant. Between-group comparisons were made using the independent t-test (for 2 groups) or the ANOVA (for > 2 groups). Post hoc analysis using Bonferroni or Games-Howell (depending on homogeneity of variance according to Levene's test) were used to correct for multiple comparisons. The Chi-squared test was used to assess the differences in prevalence rates between GOLD stages. Post hoc analysis using Bonferroni were used to correct for multiple comparisons. For comparisons of comorbidities between obese and non-obese, binary logistic regression was used and the models were adjusted for age, sex, smoking status and FEV₁ % predicted. Analyses were performed with SPSS 21.0 for Windows (SPSS, IBM, USA).

Results

Description of the Cohort

A total of 2249 medical records were reviewed retrospectively. 595 cases did not meet the inclusion criteria. Most patients were excluded because they appeared to have a diagnosis of Asthma or ACOS (n=307). For the final analysis we included 1654 cases, who had met the inclusion criteria (Figure 1).

Baseline characteristics

Baseline characteristics of the 1654 included subjects with a diagnosis of COPD are presented in Table 1. The proportion of male and female subjects was in balance (52% and 48% respectively). The mean age of our COPD population was 68.5 ± 10.5 years. According to the Gold classification, 7.4% of the study population was classified as GOLD I, 43.7% as GOLD II, 36.9 % as GOLD III and 12.0% as GOLD IV.

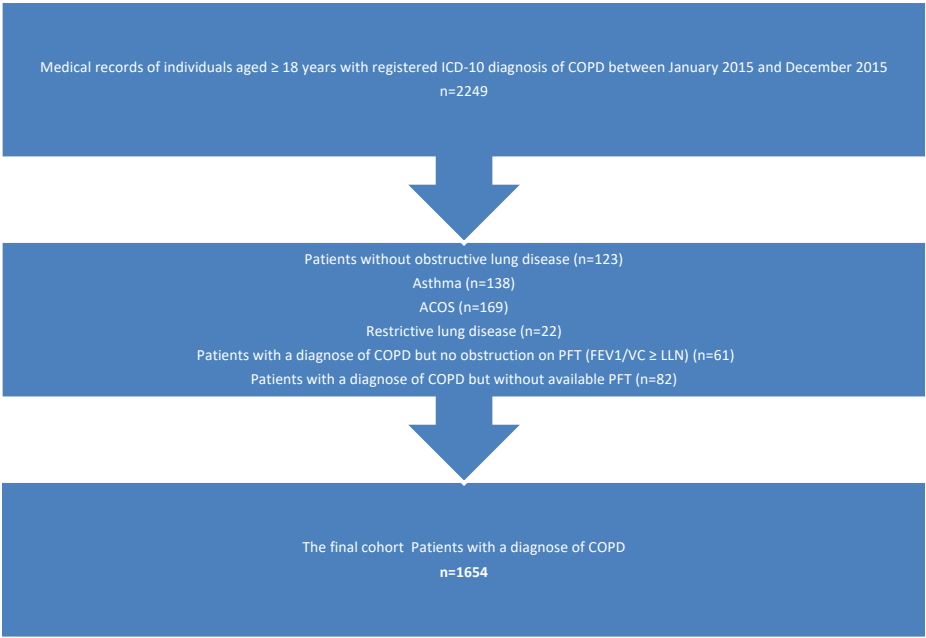


Figure 1. Cohort formation.

Table 1. Patient's characteristics categorized by GOLD stage (I-IV).

GOLD	I	II	III	IV	Total
N (%)	122 (7.4)	723 (43.7)	610 (36.9)	199 (12.0)	1654 (100)
Male/Female (%)	46.7/53.3	51.3/48.7	50.8/49.3	59.3/40.7	51.7/48.3
Age, years	69.1 ± 12.2	69.8 ± 10.8 * (III-IV)	68.2 ± 9.9	64.5 ± 8.8* (I-III)	68.5 ± 10.5
Height, m	168.7 ± 10.3	168.7 ± 9.2	168.3 ± 8.9	170.5 ± 9.6* (III)	168.8 ± 9.2
Weight, kg	75.6 ± 16.2	77.9 ± 18.9 * (III-IV)	73.2 ± 17.6	69.0 ± 16.7* (I-III)	74.9 ± 18.2
BMI, kg/m ²	26.5 ± 4.6	27.3 ± 5.9 * (III-IV)	25.8 ± 5.6	23.7 ± 5.5* (I-III)	26.3 ± 5.8
FEV ₁ , L	2.3 ± 0.7 ^a	1.6 ± 0.5 ^a	1.0 ± 0.3 ^a	0.7 ± 0.2 ^a	1.3 ± 0.6
FEV ₁ , % predicted	90.0 ± 7.9 ^a	62.2 ± 8.2 ^a	40.3 ± 5.7 ^a	24.7 ± 3.5 ^a	51.7 ± 18.4
VC, L	4.0 ± 1.2 ^a	3.4 ± 1.0 ^a	3.0 ± 0.9 ^s	2.8 ± 0.9 ^a	3.2 ± 1.0
VC, % predicted	122.0 ± 15.7 ^a	101.9 ± 17.3 ^a	89.0 ± 17.3 ^a	75.2 ± 15.4 ^a	95.4 ± 20.5
FEV ₁ /VC MAX, %	56.6 ± 6.2 ^a	47.6 ± 8.5 ^a	35.9 ± 8.2 ^a	26.3 ± 6.0 ^a	41.4 ± 11.6
FEV ₁ /FVC, %	59.4 ± 7.6 ^a	51.2 ± 9.4 ^a	39.6 ± 9.6 ^a	30.1 ± 7.6 ^a	45.0 ± 12.4
DL _{CO} (mmol/min/Kpa) predicted (n=658) [®]	63.0 ± 20.0	57.9 ± 17.2	48.1 ± 15.1* (I-II,IV)	38.7 ± 11.8* (I-III)	53.1 ± 17.8
DL _{CO} /VA predicted (n=658) [®]	66.5 ± 20.7	69.3 ± 21.9	62.8 ± 21.3* (II)	54.8 ± 19.6* (I-III)	65.3 ± 21.8
Smoking status, %					
Current smoker	47.1	36.7	32.8	36.2	35.9
Ex-smoker	47.9	60.7	64.2	62.3	61.3
Never smoked	5.0	2.3	2.0	1.5	2.3
Unknown	0.0	0.3	1.0	0.0	0.5

Data presented as mean ± SD unless otherwise stated. * p < 0.05 compared with the GOLD classes mentioned within brackets. a p < 0.05 compared with all other groups. [®] From 1654 patients the DLCO and DLCO/VA of 658 patients were available in our database. Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; GOLD, the global initiative for chronic obstructive lung disease; L, liter; Max, maximal; FEV₁, forced expiratory volume in 1 second; FEV₁ % predicted, % of predicted value of forced expiratory volume in 1 second; VC, vital capacity; VC % predicted, % of predicted value of vital capacity; DLCO, diffusing capacity of the Lungs for carbon monoxide; VA, alveolar volume; SD, standard deviation.

Subjects in GOLD II did have a higher BMI compared to GOLD III/IV. DL_{CO} decreased with the GOLD stage. When looking at smoking status, 36% of the study population was currently smoking. There were relatively more current smokers in COPD GOLD I, while the prevalence of ex-smokers was highest in GOLD III.

Prevalence of obesity

In the entire COPD population, the prevalence of obesity was 21.8%. Only 5.1% of the population was underweight (Figure 2). Most of the COPD patients were normal weight (40.7%) or overweight (32.4%).

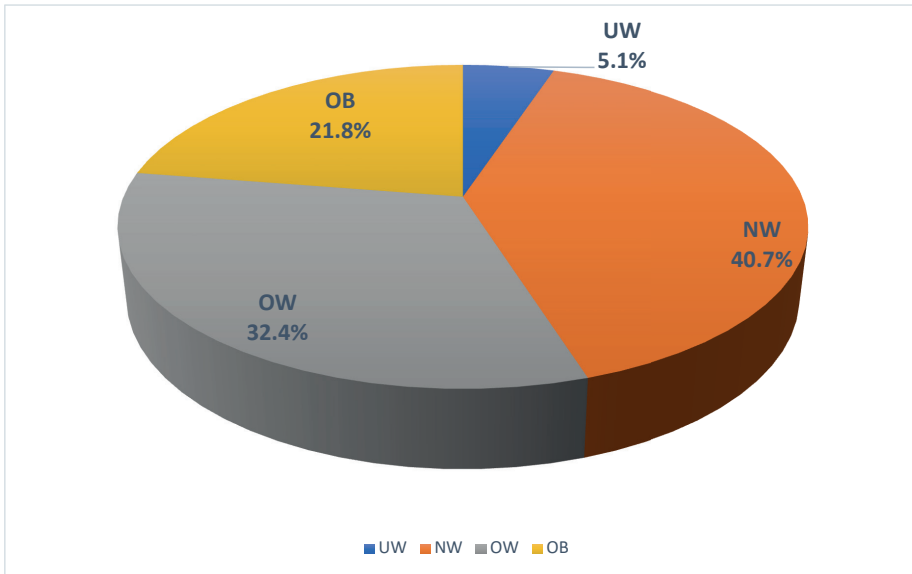


Figure 2. Distribution of weight classes in the COPD population. The prevalence (in percentages) of each weight class is provided in the pie-chart. Abbreviations: UW, under-weight; NW, normal weight; OW, overweight; OB, obese.

In figure 3 the prevalence of both extremes in weight classes (obesity and underweight) are presented for each GOLD stage. Obesity was significantly more prevalent in GOLD stages I (20.5%), II (27.8%) and III (18.9%) than in GOLD IV (10.1%). When looking at UW, the prevalence was significantly higher in patients with COPD GOLD IV (11.1%) compared with GOLD I (1.6%) and II (3.5%) ($p < 0.05$).

There was no significant difference in the prevalence of OB between males and females (19.9% vs 23.9% respectively; $p = 0.06$). OW was more prevalent in male subjects in comparison to females (38.4% vs 26.0%; $p < 0.01$). Overall

there was no significant difference in mean BMI between females and males (mean BMI females: 26.3 ± 6.4 ; males: 26.3 ± 5.1 respectively; $p = 0.84$). Both UW and NW were more common in females in comparison with males, but only with UW the difference was significant (UW: 7.3% vs 3.0% $p < 0.01$; NW: 42.8% vs 38.7% $p = 0.09$).

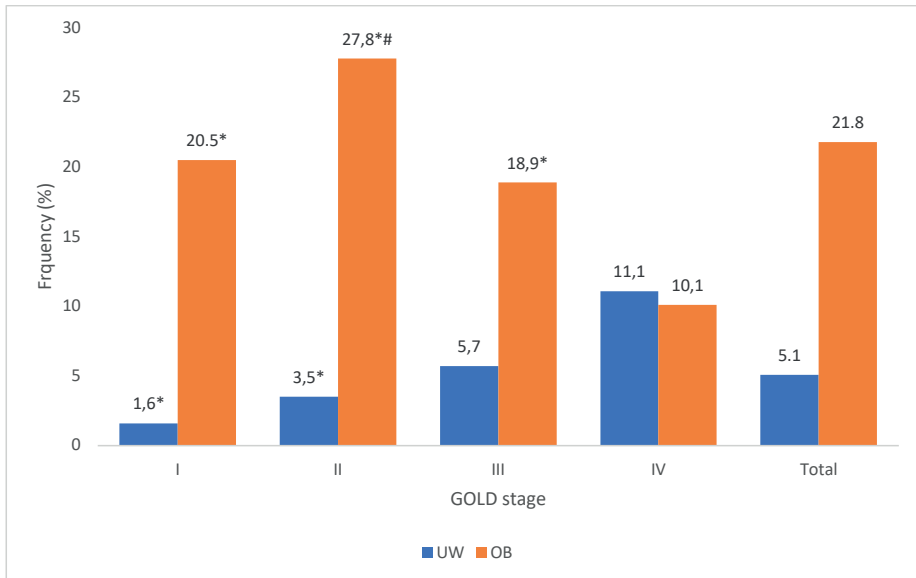


Figure 3. Prevalence (%) of obese (OB) and under-weight (UW) patients in different GOLD stages (I-IV). * $p < 0.05$ compared to GOLD class IV of the same weight class, # $p < 0.05$ compared to GOLD class III of the same weight class.

Comorbidities

The prevalence of comorbidities within our study population is listed in Table 2. Medical records were screened for 29 comorbidities and all of these were present in our COPD population. The prevalence of the described comorbidities ranged from 0.1% to 46%. Hypertension (45.5%), cancer (23.4%), coronary artery disease (18.5%) and diabetes mellitus (17.5%) were the most prevalent comorbidities. Figure 4 shows the proportion of COPD_{OB} and COPD_{NO} individuals with a certain number of comorbidities. The number of comorbidities for each patient ranged from 0 to 9. Within the COPD_{OB} group 72% had two or more comorbidities, in comparison 54% of COPD_{NO} patients had two or more comorbidities ($p < 0.01$).

Table 2. Prevalence of comorbidities (%) in the COPD population

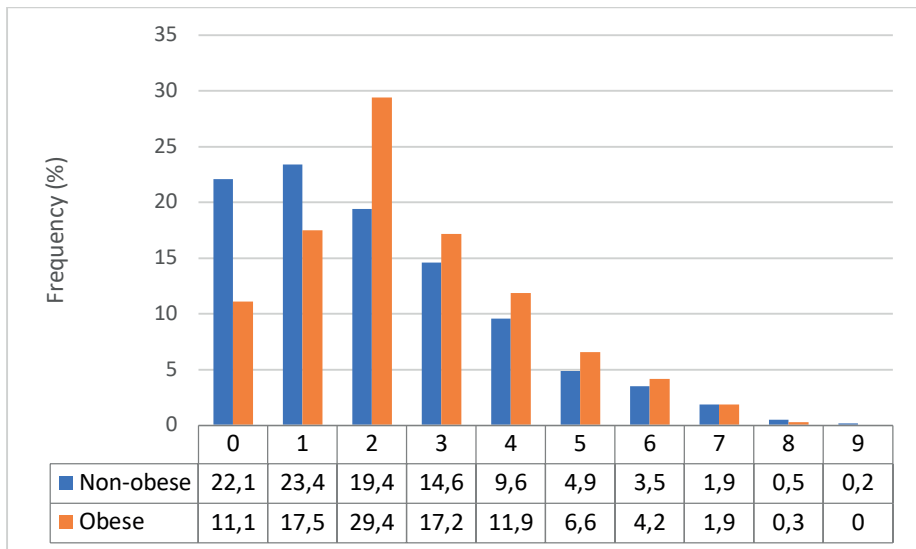
Prevalence of comorbidities (%) in the COPD population	
Cardiovascular	45.5
• Hypertension	18.5
• Coronary artery disease	15.2
• Congestive heart failure	15.9
• Atrial fibrillation or flutter	12.7
• Peripheral vascular disease	8.4
• Myocardial infarction	
Metabolic syndrome	17.5
• Diabetes mellitus	15.5
– Diabetes mellitus uncomplicated	2.1
– Diabetes with end organ damage	
Gastrointestinal and liver disease	3.1
• Peptic ulcer disease	1.9
– Chronic liver disease	0.7
– Moderate or severe liver disease	
Malignancy	23.4
• All types of cancer	4.8
– Lung carcinoma	2.3
– Breast carcinoma	1.4
– Carcinoma with metastasis	0.6
– Lymphoma	0.3
– Esophageal carcinoma	0.3
– Leukemia	0.1
– Pancreatic carcinoma	13.6
– All other cancer types	
Psychological status	13.2
• Depression	7.5
• Anxiety	1.6
• Dementia	
Skeletal disease	12.8
• Osteoporosis	
Neurological disorder	5.7
• Cerebrovascular disease	1.0
• Hemiplegia	
Others	10.2
• Moderate to severe chronic kidney disease	1.7
• Pulmonary fibrosis	0.2
• Connective tissue disease	0.2
• AIDS	

Table 3. Comorbidities which are significantly more prevalent in obese or non-obese COPD patients.

	Prevalence (%)	OR	95% CI	P value
Obese				
DM	34	3.74	2.81 - 4.99	<0.01
HT	63	2.68	2.08 - 3.47	<0.01
CHF	19	1.74	1.25 - 2.42	<0.01
AF	20	1.53	1.11 - 2.12	0.01
Non obese				
LUC	5	2.01	1.04 - 4.01	0.04
OS	14	1.73	1.15 - 2.61	<0.01

The odds are adjusted for age, sex, smoking status and FEV1 % predicted. Abbreviations: DM, diabetes mellitus; HT, hypertension; CHF, congestive heart failure; AF, atrial fibrillation or flutter; LUC, lung cancer; OS, osteoporosis.

In Figure 5, comorbidities with a prevalence of $\geq 5\%$ are presented and compared between COPD_{OB} and COPD_{NO}. In Table 3, the adjusted odds ratio of comorbidities which were significantly more prevalent in obese vs. non obese and vice versa are presented. Hypertension (63.4%) and diabetes mellitus (34.1%) were the most prevalent comorbidities in COPD_{OB}. The prevalence of hypertension was significantly higher in COPD_{OB} compared to COPD_{NO} (63.4% versus 40.5% respectively; $p < 0.01$). Also the prevalence of diabetes mellitus was significantly higher in COPD_{OB} compared to COPD_{NO} (34.1% versus 12.9% respectively; $p < 0.01$).

**Figure 4.** Number of comorbidities (%) in the obese and non-obese individuals.

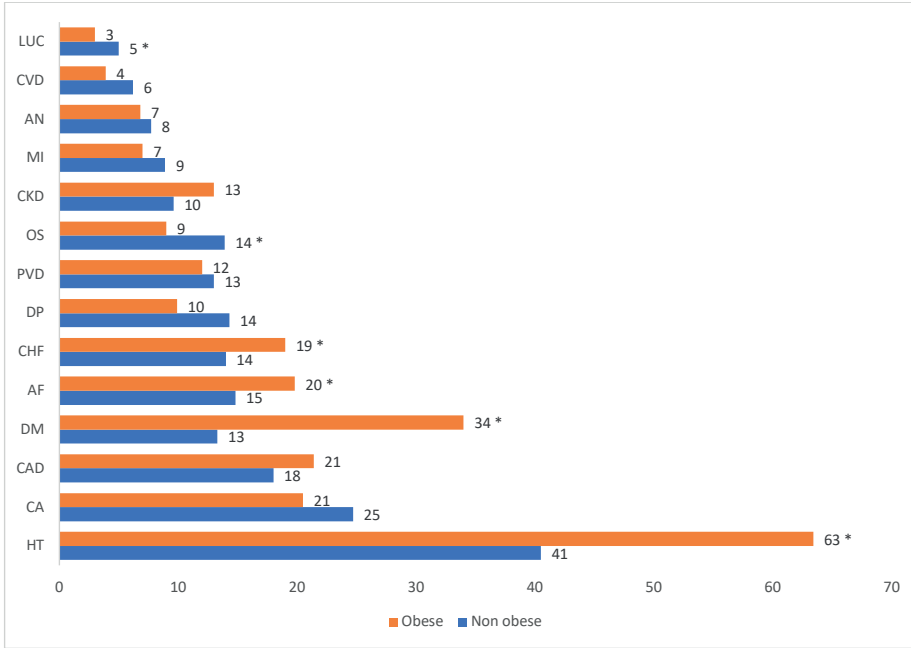


Figure 5. Prevalence of comorbidities (%) in obese and non-obese COPD patients. Abbreviations: HT, hypertension; CA, carcinoma; CAD, coronary artery disease; DM, diabetes mellitus; AF, atrial fibrillation or flutter; CHF, congestive heart failure; DP, depression; PVD, peripheral vascular disease; OS, osteoporosis; CKD, moderate to severe chronic kidney disease; MI, myocardial infarction; AN, anxiety; CVD, cerebrovascular disease; LUC, lung cancer. * Comorbidity is significantly more prevalent comparing to the other group ($p < 0.05$).

When looking at other cardiovascular diseases, congestive heart failure (COPD_{OB} 19.4%; COPD_{NO} 14.0%; $p = 0.01$) and atrial fibrillation/flutter (COPD_{OB} 19.9%; COPD_{NO} 14.8%; $p = 0.02$) were more prevalent in obese patients as well. There were no statistically significant differences in the prevalence of myocardial infarction, coronary artery disease and peripheral vascular disease between COPD_{OB} and COPD_{NO} . We also found significant differences between COPD_{OB} and COPD_{NO} when comparing the prevalence rates of osteoporosis (8.9% vs 13.8%) and lung cancer (2.8% vs 5.4%). These conditions were significantly more common in COPD_{NO} compared with COPD_{OB} ($p < 0.05$).

Discussion

Prevalence of obesity in COPD

The prevalence of obesity in our COPD population was 21.8%. This exceeded the prevalence of underweight (5.1%) by more than 4 times. Obesity was most prevalent in patients with COPD GOLD I and II (20.5% and 27.8% respectively) and least prevalent in patients with COPD GOLD IV (10.1%).

The prevalence of obesity in our study is comparable with results from Vanfleteren et al (18) (213 COPD patients with a mean FEV₁% predicted of 51%; from a rehabilitation clinic; prevalence of COPD_{OB} 23%), the PLATINO study (13) (759 COPD patients recruited from a population-based epidemiological study; prevalence of COPD_{OB} 23%) and a Canadian study (12) (self-reported data of 3470 COPD patients from the Canadian National Health Survey; prevalence of COPD_{OB} 24.6%). However it is not consistent with data from an earlier Dutch study in a primary care population of 317 COPD patients (14) (prevalence of COPD_{OB} 18%), a study with 355 COPD patients from Northern California recruited from a database of primary-to-tertiary care (prevalence of COPD_{OB} 54%) (11), a survey from Middle East and North Africa where 996 self-reported COPD patients from the general population were recruited (prevalence of COPD_{OB} 30%) (15) and a cohort of 2265 individuals referred to a tertiary care pulmonary function laboratory (prevalence of COPD_{OB} 30%). (17) In our study, obesity was most prevalent in patients with COPD GOLD I and II (20.5% and 27.8% respectively) and least prevalent in patients with COPD GOLD IV (10.1%). This later finding is in line with the study of Steuten et al. (14)

Some factors may explain the variability in prevalence between the studies. First, it is important to use a correct definition for "having COPD" or "being obese". Studies with a relatively large sample size have used self-reported diagnosis, weight and length to define COPD and obesity. (12,15,16) Utilization of self-reported data is a popular methodology in studies, however it is proved to be less reliable. (37-41) Our study population was diagnosed with COPD by a pulmonologist. Furthermore, we used data from the most recently performed PFT's to confirm the diagnosis. Anthropometric measurements like weight and height are measured during each PFT in our hospital, so these data were extracted from the PFT reports to calculate the BMI. This method reduced the chance of incorrect information regarding the diagnosis and other used variables (BMI, COPD Gold stage etc.).

Second, use of FEV_1/FVC ratio to diagnose obstructive disease is very common. This parameter was also used in most of the studies which confirmed the diagnosis of COPD with PFT. (11,13,14,18) Measuring FVC is a practical way to estimate the 'actual' vital capacity (VC). However FEV_1/FVC ratio seems to be less reliable comparing with $FEV_1/(\text{slow}) VC$ ratio to diagnose obstructive disease (42–44). FVC is dependent on flow and for example, in case of air-trapping, FVC is smaller than VC.

Third, the prevalence of obesity is correlated with the severity of airflow obstruction. An explanation for this might be that COPD subjects with obesity die in earlier stage of COPD and therefore not reach severe stages of COPD. Nevertheless, the higher prevalence of obesity in milder COPD makes it assumable that selection of a study population strongly influences the prevalence rates. In general, COPD patients from a primary care population have milder disease stage (GOLD I and II) compared to patients at secondary care clinics. Hence one would expect that the prevalence of obesity would be higher in primary care than in secondary care. Contrary to our expectation, the prevalence of obesity was lower in a Dutch primary care population. (14) Despite having relatively more subjects with COPD GOLD I and II (78%), obesity was less common in this population comparing to ours (18% vs 21.8% respectively). Although it must be mentioned that this primary care study included a relatively small number of COPD patients ($n=317$). Also surprisingly our secondary care population, consisting mostly of patients with COPD GOLD II and III, did not differ in the prevalence of obesity with patients from a rehabilitation clinic in the Netherlands (18). When evaluating the data in more detail, the mean $FEV_1\%$ predicted of our population matched with the rehabilitation clinic population ($52 \pm 18\%$ predicted vs $51 \pm 17\%$ predicted respectively). This might explain similarity in our prevalence rates. Furthermore, patients with severe comorbidities (like active malignancy) were not included in the study performed at the rehabilitation clinic. It is assumable that inclusion of such patients would lead to lower prevalence rates of obesity.

Finally, other factors like genetic, socio-demographic differences and sex may also play a role in prevalence rates of obesity in COPD. Several studies indicate that obesity is more prevalent in women. (12,13,45) However, our data did not show any difference between mean BMI of males and females.

An interesting finding is the significantly higher prevalence of obesity in our COPD population compared to the prevalence of obesity in general (Dutch)

population; 21.8% and 13.7% respectively ($p < 0.01$). (6) We did not have a control group of non-COPD individuals to compare the rates, nevertheless our finding confirms the results of some earlier studies.(11–14,18) When evaluating prevalence rates it is possible that we relatively find more obese individuals in a COPD population, simply because they live longer than non-obese COPD patients. Whether COPD is a risk factor for developing obesity or that obese patients are more prone for developing COPD remains unclear and needs to be studied prospectively.

Comorbidities in obese and non-obese COPD

Hypertension, cancer, diabetes mellitus and coronary artery disease were the most common comorbidities in our COPD cohort. This is in line with previous data. (18,25,46–48). COPD_{OB} had significantly more comorbidities compared to COPD_{NO}. Also the pattern of comorbidities differed between obese and non-obese COPD patients.

In COPD_{OB} hypertension and diabetes mellitus were the most prevalent comorbidities. The prevalence of both diseases was significantly higher in COPD_{OB} compared with COPD_{NO}. Also other cardiovascular comorbidities like atrial fibrillation/flutter and congestive heart failure were significantly more prevalent in COPD_{OB}. Surprisingly, coronary artery disease (CAD) was not more common in COPD_{OB} compared to COPD_{NO} (21.3% vs 17.7% respectively; $p = 0.13$). However in further analyses we found that CAD was significantly more prevalent in patients with BMI ≥ 25.0 kg/m² compared with patients with BMI < 25.0 kg/m² (21.1% VS 15.5% respectively; $p < 0.01$). Various studies have demonstrated that cardiovascular comorbidities, including hypertension, often co-exist with COPD and are associated with increasing BMI, age and smoking. (49–53) Inflammation might play a role in the development of cardiovascular diseases amongst COPD patients, however the exact mechanism remains unclear. Factors which might contribute in the development of diabetes mellitus in COPD patients are systemic inflammation and use of corticosteroids, especially systemic corticosteroids.(54,55) However in this study we found no differences in the use of inhaled corticosteroids (ICS) between COPD_{OB} and COPD_{NO} (% of patients using ICS: COPD_{OB} 63.4%; COPD_{NO} 65.6; $p = 0.5$). Osteoporosis and lung cancer were significantly less prevalent in COPD_{OB} compared to COPD_{NO}.

In daily practice, underweight is one of the main focus points in COPD care. In part, this is due to the clear negative effects on important endpoints like

mortality. Our study indicates that obesity is much more common in COPD than underweight. Therefore, physicians should be more aware of the common coexistence of COPD and obesity. Furthermore obese COPD patients seem to have more and different comorbidities compared to non-obese COPD. Hypertension and diabetes mellitus are the most common comorbidities in obese COPD patients. These treatable conditions can be easily diagnosed. Thus diagnosing these conditions should be a point of focus. Early referral for diagnosing the most common comorbidities may benefit the quality of life and reduce mortality. Whether, and if so, how to treat obesity in COPD patients remains a question that needs to be evaluated in the future.

Limitations and future studies

Some limitations of our study need to be addressed. We evaluated data from a single center. In order to generalize these prevalence rates, a multicenter study is more appropriate. Due to the cross-sectional nature of this study, potential causal links cannot be established. Future prospective studies with follow up of patients are needed to investigate causal links. Furthermore, the prevalence rate of obesity and comorbidities seems to be strongly depending on the demographic characteristics of the population. These figures might differ in other parts of the world and cannot be generalized to all COPD patients. Also it must be kept in mind that our COPD population represented a sample of patients being treated at a secondary care hospital. We did not have a control group of non-COPD individuals to compare the rates, nevertheless our finding confirms the results of some earlier studies. Obesity was only assessed by BMI in this study. Other adiposity measures may have added value, however BMI seems to be a measure which is as clinically important and accurate compared to other measures. (56,57) The severity of COPD was based on the latest PFT. Although it is the policy within our department to only perform a PFT when patients are stable (have no exacerbation), we cannot rule out that some PFT's were performed during an exacerbation, thus overestimating the severity of COPD.

Conclusion

Obesity is common in patients with COPD and is most prevalent in COPD GOLD I-II and least prevalent in COPD GOLD IV. Obese COPD patients have different comorbidities than non-obese COPD patients. Cardiovascular and metabolic comorbidities, especially hypertension and diabetes mellitus, are more

prevalent in obese COPD patients. Recognition and active screening of these comorbidities, should be a priority for clinicians treating obese COPD patients.

Conflict of interest statement

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Chapter 4

Adiposity increases weight-bearing exercise-induced dyspnea despite favoring resting lung hyperinflation in COPD

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Abstract

Objectives: Our aim was to study the associations between resting lung hyperinflation, weight-bearing exercise-induced dyspnea and adipose distribution in obese and normal-weight COPD patients.

Methods: We performed a comparison between 80 obese COPD patients (COPD_{OB}) with 80 age- and FEV₁ matched normal-weight COPD patients (COPD_{NW}). Dyspnea was assessed by the mMRC scale and the Borg dyspnea score before and after a 6 minute walk test. Further characterization included spirometry, body plethysmography, and metronome paced tachypnea (MPT) to estimate dynamic hyperinflation. Body composition was assessed with bioelectrical impedance analysis. Associations between dyspnea scores and BMI and body composition groups were studied using logistic regression models.

Results: COPD_{OB} patients had attenuated increases in TLC, FRC and RV compared to COPD_{NW} patients ($p < 0.01$). The groups had comparable 6 minute walking distance and Δ FRC upon MPT ($p > 0.05$). Compared to COPD_{NW}, COPD_{OB} patients reported more often a mMRC ≥ 2 (65 vs. 46%; $p = 0.02$; OR 3.0, 95% CI 1.4-6.2, $p < 0.01$) and had higher Δ Borg upon 6MWT: 2.0 (SEM 0.20) vs. 1.4 (SEM 0.16), $p = 0.01$; OR for Δ Borg ≥ 2 : 2.4, 95% CI 1.1-5.2, $p = 0.03$. Additional logistic regression analyses on the associations between body composition and dyspnea indicated that increased body fat percentage, fat mass index and waist-to-hip ratio were associated with higher ORs for mMRC ≥ 2 and Δ Borg upon 6MWT ≥ 2 .

Conclusion: Despite its beneficial effect on resting lung hyperinflation, adiposity is associated with increased weight-bearing exercise-induced dyspnea in COPD.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) and obesity are major health problems and the prevalence of both disorders is increasing.(1,2) Dyspnea, particularly exercise-induced, is one of the predominant and most disturbing symptoms in patients with COPD (3), and is considered an even more important risk factor for mortality than the degree of airflow limitation.(4) Dyspnea has been defined as a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity, and many physiological and psychological factors can have an influence on dyspnea.(5)

Most COPD patients have some degree of resting lung hyperinflation. (6) Hyperinflation is one of the mechanisms leading to dyspnea in COPD by causing mechanical limitation to increase tidal volumes, increasing elastic recoil and affecting airway stretch receptors. (7) Obesity in itself also affects dyspnea through various mechanisms. (8–10) Focusing primarily on the pulmonary function, it is believed that pulmonary function in otherwise healthy obese subjects is affected by several factors including a mass effect of extra-thoracic adipose tissue and increased intra-abdominal pressure by local abdominal adiposity. (11–13) This can result in excess bibasal airway collabs, increased small airway resistance, local airtrapping and diffuse microatelectasis. This, in turn will increase static lung elastic recoil pressure leading to lower end-expiratory lung volumes (EELV) and lower functional residual capacity (FRC). (9,12) Collectively, the net result is an increase in the work of breathing being associated with increased sense of shortness of breath. (10,14) There is a complex interaction between COPD and obesity in terms of effects on pulmonary function.(15,16) When combined, it has been consistently observed that obese COPD patients tend to have attenuated increased resting lung hyperinflation compared to non-obese COPD patients, even when controlled for degree of airflow limitation.(17)

In the study of exercise-induced dyspnea in obese COPD, it is important to note that inconsistencies between studies appear to be related to a difference between weight-supported and weight-bearing exercise protocols. For example, studies examining lung function dynamics and dyspnea during weight-supported symptom-limited cycling tests have shown that obesity has no negative influence on dyspnea. (18–20) In these studies dyspnea measured by Borg dyspnea scores were comparable between normal weight and obese COPD patients. More conflicting results have been produced by studies

assessing weight-bearing exercise-induced dyspnea in obese COPD patients. Some studies indicate that dyspnea levels, measured with different tools (Borg scores during 6MWT and/or mMRC), are comparable between obese and normal weight COPD. (21–25) However, there is also accumulating data reporting increased dyspnea in obese COPD patients. (22,26–28)

In a cross-sectional comparison between age- and FEV₁-matched obese and normal-weight COPD patients, we investigated the association between resting lung hyperinflation and weight-bearing exercise-induced dyspnea and explored the effects of body fat distribution on these associations. We hypothesized that markers of adiposity are associated with increased weight-bearing exercise-induced dyspnea in COPD, independent of the degree of resting lung hyperinflation.

Methods

Subjects

We studied COPD patients, defined according to the GOLD definition (29), who were either obese (BMI ≥ 30 kg/m²) or normal-weight (BMI 18.5 to 25 kg/m²). There were no restrictions with regard to sex or the severity of airflow limitation. Subjects were clinically stable (ie. no history of exacerbation in the previous 2 months) and were >18 years of age. Exclusion criteria were recent acute cardiovascular events, unstable cardiac arrhythmia, neuromuscular disorders and respiratory comorbidity other than COPD, such as asthma and lung diseases causing restriction (interstitial lung diseases) to minimize confounding. Furthermore patients who were unable to perform pulmonary function tests (PFT), 6MWT or fill out the questionnaires were excluded.

Study Design

This study was performed at a teaching hospital in The Netherlands. The study was approved by the regional committee and local ethics committee (reference 1026/160614). Consecutive obese COPD patients (COPD_{OB}) visiting the pulmonary outpatient clinic who met the inclusion criteria were asked to participate. For each COPD_{OB} participant, one age-matched (± 5 years) and FEV₁-matched (± 5 %predicted; based on the most recent PFT) normal-weight COPD patient (COPD_{NW}) was asked to participate. Of the 394 eligible COPD patients, a total of 160 were willing to participate. All subjects completed two visits to perform the tests. We obtained informed consent from all subjects.

Procedures

During the first visit, the modified Medical Research Council (mMRC) dyspnea scale (30) and the Saint George Respiratory Questionnaire (SGRQ) (31,32) were assessed. Subjects were asked about their tobacco exposure and smoked pack years were calculated. During this visit anthropometric measurements (weight, height, waist circumference and hip circumference) were obtained. Body composition was measured with bioelectrical impedance analysis (Bodystat 1500; Bodystat, UK). Fat-free mass index (FFMI) was calculated as the ratio of FFM to height in meters squared. Known comorbidities were retrieved from hospital files.

During the second visit spirometry, body plethysmography and 6MWT were performed. The walk work during 6 MWT (6MWW) was calculated as a product of distance x body weight). The European Community for Coal and Steel reference equations were used to calculate predicted values. (33) The Borg dyspnea score was assessed at rest and at the end of 6MWT. Furthermore, Metronome Paced Tachypnea (MPT) was performed for detection of dynamic hyperinflation. During the MPT test a respiratory rate twice the baseline rate for 20s is achieved in patients, which is immediately followed by sequential measurement of inspiratory capacity. (34) Trained staff performed these tests in accordance with American Thoracic Society/European Respiratory Society guidelines (35) and were not aware of the study goals.

After completion of the PFT, 3 subjects in the COPD_{OB} were excluded because they had a TLC<80% predicted. As a consequence, we also excluded their 3 matched COPD_{NW} peers for analyses. Consequently, 80 COPD_{OB} and 80 COPD_{NW} subjects were included in the analyses. Diffusion capacity could not be measured in 2 COPD_{OB} and 2 COPD_{NW} subjects (technical reasons); body box measurements could not be measured in 1 COPD_{NW} because of claustrophobia; 6MWT results were missing for 2 COPD_{OB} (not able to walk at the day of the test because of hip problem and fractured leg) and 1 COPD_{NW} (technical reason); dynamic hyperinflation results were missing in 1 COPD_{OB} (technical reason).

Statistics

Descriptive statistics were used to characterize the study population. Continuous variables are expressed as mean (SD) and discrete variables are shown as percentages. Comparisons of means for continuous variables were conducted by using t-tests (two-tailed). Proportions of categorical variables were compared by Chi-squared test (two-tailed). Additional hypothesis-

generating post hoc analysis were also performed to better understand the role of obesity and measures of body composition on dyspnea. Binary logistic regression models were used to study independent associations between COPD subgroups, body composition measures and dyspnea. A p -value <0.05 was considered to be statistically significant. Analyses were performed using SPSS version 20.0 (IBM, USA).

Results

Table 1 shows the comparisons of demographics, anthropometry, body composition, comorbidities and QoL between the groups. The groups were comparable in terms of sex distribution, pack years smoked and smoking status. None of the patients used long-term oxygen therapy. Although SGRQ scores tended to be higher in the COPD_{OB} patients, these difference were not significant.

Pulmonary function and 6-minute walk test

Pulmonary function parameters and 6MWT results are presented in Table 2. By design, FEV₁ was matched between COPD_{OB} and COPD_{NW} patients and averaged 1.47 L (SD 0.62) corresponding to 55.4 (SD 17.9) % predicted for the study population as a whole. While both groups were characterized by increased static lung volumes, COPD_{OB} patients showed significantly attenuated increases in TLC, FRC and RV compared to COPD_{NW} patients. Mean ERV % predicted was decreased by 24.6% (SD 3.8%) in the COPD_{OB} patients, while it was increased with 25.9% (SD 5.0 %) in the COPD_{NW} patients ($p < 0.01$). The loss of diffusing capacity of the lungs for carbon monoxide (DL_{CO}) was also attenuated in COPD_{OB} patients compared to COPD_{NW} patients.

The 6MWD was comparable between both groups, however the COPD_{OB} had significantly higher walk work (6MWW) as expected. While both groups showed on average significant desaturation, the magnitude of desaturation was similar. Resting peripheral oxygen saturation was comparable between the groups. Finally, despite the observed differences in resting lung hyperinflation, both groups showed similar absolute levels of dynamic hyperinflation upon the MPT test.

Table 1. Characteristics of the study participants. Data are presented as mean (SD) unless otherwise stated.

	COPD_{OB}	COPD_{NW}	P value
N	80	80	
Age, years	64.5 (8.3)	65.1 (8.3)	0.63
Male, %	52.5	43.8	0.27
Pack years	36.6 (23.9)	36.8 (18.7)	0.97
Current smokers, %	23.8	36.2	0.21
Height, cm	170 (10)	168 (10)	0.29
Weight, kg	99.5 (15.4)	65.3 (7.7)	<0.01
BMI, kg/m ²	34.5 (4.0)	23.0 (1.4)	<0.01
Waist circumference, cm	119 (10)	91 (8)	<0.01
Hip circumference, cm	111 (8)	96 (5)	<0.01
Waist/Hip ratio	1.08 (0.08)	0.95 (0.09)	<0.01
Fat, %	40.0 (8.8)	32.1 (6.7)	<0.01
FFMI, kg/m ²	20.5 (2.5)	15.6 (1.5)	<0.01
FMI, kg/m ²	13.9 (4.3)	7.4 (1.8)	<0.01
Use of inhalers, %			
SABA	38.8	48.8	0.20
SAMA	16.2	8.8	0.15
LABA	90.0	86.2	0.46
LAMA	82.5	86.2	0.66
ICS	67.5	65.0	0.74
Known comorbidities, %			
Diabetes mellitus	18.8	1.2	<0.01
Hypertension	45.0	27.5	0.02
Atrial fibrillation	2.5	3.8	0.65
Myocardial infarction	12.5	7.5	0.29
Heart failure	0.0	3.8	0.08
SGRQ mean score			
Symptoms	50.7	49.9	0.84
Impacts	32.2	28.8	0.25
Activity	64.7	57.7	0.06
Total	45.1	41.2	0.16

Abbreviations: BMI, body mass index; FFMI, free fat mass index; FMI, fat mass index; SABA, short-acting beta agonist; SAMA, short-acting muscarinic antagonist; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; ICS, inhaled corticosteroid, SGRQ, St. George's Respiratory Questionnaire.

Table 2. Pulmonary function and 6MWT. Data are presented as mean (SD) unless otherwise stated.

	COPD _{OB}	COPD _{NW}	P value
Pulmonary function			
FEV1, % predicted	56.2 (17.7)	54.6 (18.1)	0.57
FEV1, L	1.54 (0.65)	1.40 (0.58)	0.14
VC, % predicted	95.1 (17.4)	103.5 (23.0)	0.01
VC, L	3.36 (1.01)	3.41 (1.03)	0.73
FVC, % predicted	89.0 (18.0)	99.2 (21.2)	<0.01
FVC, L	3.06 (0.97)	3.17 (1.01)	0.49
TLC, % predicted	113.9 (16.6)	124.6 (17.6)	<0.01
TLC, L	6.82 (1.55)	7.18 (1.55)	0.15
FRC, % predicted	139.1 (30.5)	164.5 (33.0)	<0.01
FRC, L	4.42 (1.21)	5.08 (1.27)	<0.01
IC, % predicted	102.2 (23.4)	94.7 (24.0)	0.04
IC, L	2.64 (0.85)	2.29 (0.70)	<0.01
ERV, % predicted	75.4 (34.0)	125.9 (45.0)	<0.01
ERV, L	0.71 (0.39)	1.12 (0.52)	<0.01
RV, % predicted	155.6 (37.7)	175.1 (49.2)	<0.01
RV, L	3.46 (0.94)	3.81 (1.25)	0.04
RV/TLC ratio, %	51.2 (8.3)	52.9 (11.4)	0.28
FRC/TLC ratio, %	64.7 (8.1)	70.7 (7.5)	<0.01
DLCO SB, % predicted	68.7 (17.8)	51.5 (15.1)	<0.01
DLCO/VA, % predicted	84.3 (22.1)	61.0 (19.1)	<0.01
6MWT			
6MWT, % predicted	81.8 (15.6)	76.6 (19.0)	0.06
6MWT, m	386 (80)	403 (103)	0.26
6MWW, kg/m	38542 (9535)	26508 (8141)	<0.01
SpO2 at rest, %	94 (3)	95 (3)	0.05
6MWT-induced drop in SpO2, %	4.4 (5.2)	4.7 (5.1)	0.67
MPT			
FRC increase upon MPT, %	20.2 (10.1)	19.5 (13.7)	0.71
delta FRC, L	0.51 (0.26)	0.42 (0.52)	0.09

Abbreviations: FEV1, forced expiratory volume in 1 second; VC, vital capacity; FVC, forced vital capacity; TLC, total lung capacity; FRC, functional residual capacity; ERV, expiratory reserve volume; RV, residual volume; DLCO, diffusing capacity of the lungs for carbon monoxide; VA, alveolar volume; 6MWT, 6 min walk test; 6MWD, 6 min walking distance; 6MWW, walk work (6MWD x weight); SpO2, peripheral oxygen saturation; MPT, metronome paced tachypnea. Remark: due to missing values DLCO: n=78 in both COPDOB and COPDNW; TLC, RV: n=79 in COPDNW; 6MWT: n=78 in COPDOB, n=79 in COPDNW; MPT: n=79 in COPDOB.

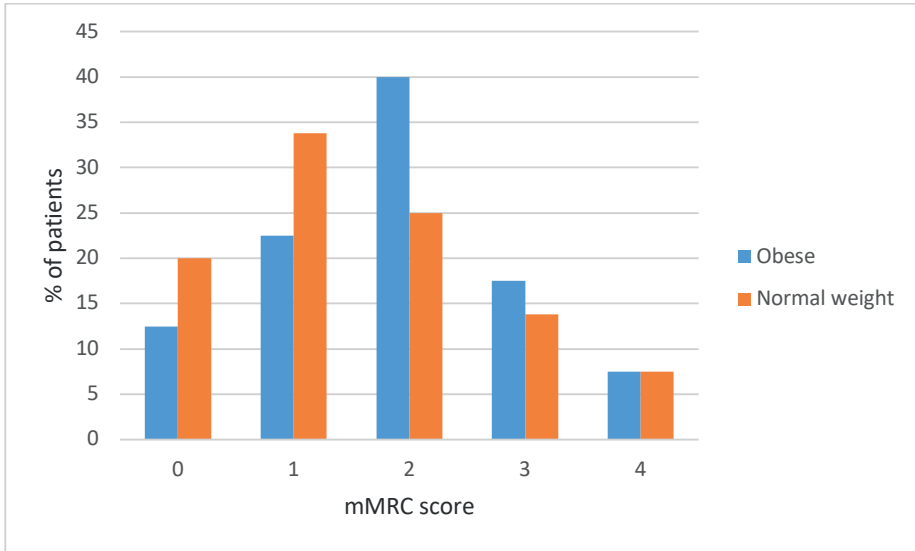


Figure 1. Modified Medical Research Council Dyspnea Scale. Percentage of COPD_{OB} and COPD_{NW} with certain mMRC score. Abbreviations: mMRC, modified medical research council dyspnea scale.

Dyspnea assessed by mMRC

mMRC dyspnea scores for COPD_{OB} and COPD_{NW} patients are presented in Figure 1. The proportion of patients with mMRC $\geq$ 2 was 65.0% in COPD_{OB} and 46.2% in COPD_{NW} ($p=0.02$). The unadjusted OR of mMRC $\geq$ 2 was 2.2 (95% CI 1.1 – 4.1; $p = 0.02$) for COPD_{OB} compared to COPD_{NW}. The adjusted logistic regression models for the association of BMI group with mMRC $\geq$ 2 are presented in Table 3. Addition of resting lung hyperinflation marker FRC to the model increased the OR of obesity for mMRC $\geq$ 2.

Dyspnea by Borg scores at 6MWT

Dyspnea was also measured at the start of 6MWT and at the end of the test with the Borg scale. The Borg dyspnea scores in COPD_{OB} group increased from 2.0 at rest to 4.0 at the end of 6MWT. In COPD_{NW} the Borg score increased from 1.8 at rest to 3.2 at the end of 6MWT. The Δ Borg upon 6MWT was significantly higher in COPD_{OB} compared to COPD_{NW} (2.0 vs. 1.4; $p = 0.01$). In COPD_{OB} 39 (50%) patients had an increase of ≥ 2 in Borg score at the end of 6MWT, while in COPD_{NW} 27 (34%) showed such an increase ($p=0.04$). Adjusted logistic regression models for the association between BMI group and Δ Borg scores during the 6MWT are presented in Table 3.

Table 3. Independent associations of BMI group (obese versus normal weight) with mMRC ≥ 2 and Δ Borg ≥ 2 during the 6MWT by different models of logistic regression. Model 1: adjusted for age, sex, smoking status, smoking pack years, known comorbidities and 6MWD % pred. (for Δ Borg ≥ 2 only). Model 2: as model 1 with additional adjustment for FRC, % pred. Model 3: as model 2 but with adjustment for 6MWW (walk work) instead of 6MWD % pred.

	Model 1		Model 2		Model 3	
mMRC ≥ 2	OR (95 %CI)	p	OR (95 %CI)	p	OR (95 %CI)	P
BMI group						
COPD _{NW}	Reference	-	Reference	-	-	
COPD _{OB}	3.0 (1.4 - 6.2)	< 0.01	4.5 (2.0 - 10.2)	<0.01	-	
Δ Borg ≥ 2						
BMI group						
COPD _{NW}	Reference	-	Reference	-	Reference	-
COPD _{OB}	2.4 (1.1 - 5.2)	0.03	2.9 (1.3 - 6.7)	0.01	4.19 (1.6 - 10.7)	<0.01

Abbreviations: FRC, functional residual capacity.

Associations between measures of body composition and dyspnea

To provide more insight into the relation of body composition with mMRC (Supplement Table 1) and Δ Borg upon 6MWT (Supplement Table 2), we performed additional hypothesis generating post hoc analyses. For this, we determined the sex-specific median values for each body composition parameter within the COPD_{NW} and COPD_{OB} groups separately, and subsequently divided COPD_{NW} and COPD_{OB} patients into “low” and “high” with respect to their sex- and group-specific medians. The COPD_{NW} “low” group was taken as the reference in logistic regression analyses. The results in Supplement Tables 1 and 2 show that whereas overall the COPD_{OB} low subgroups already had increased odds of having mMRC ≥ 2 and Δ Borg ≥ 2 , these odds were even further increased considerably in the COPD_{OB} subgroups with the highest sex-specific BMI, WC, WHR, %fat, FFMI and FMI.

Discussion

In this study we compared pulmonary function and measures of weight-bearing exercise-induced dyspnea between FEV₁- and age-matched obese and normal-weight COPD patients. COPD_{OB} patients had less resting lung hyperinflation, yet they reported higher mMRC and higher Borg scores at the end of the 6MWT. Furthermore, markers of (abdominal) adiposity appeared to significantly affect mMRC and Δ Borg upon 6MWT in our cohort of COPD patients.

Previous studies assessing dyspnea during weight-bearing exercise or using (m)MRC showed conflicting results. For example, a study by Rodríguez *et al.* indicated similar mMRC and Borg dyspnea scores at end of 6MWT between obese and normal weight COPD groups. (21) This is supported by other studies, where Δ Borg scores during 6MWT (22), Borg scores during domestic ADL's like washing dishes and sweeping the floor (23) and mMRC (24,25) were comparable between obese and normal weight COPD. To the contrary, others reported increased dyspnea in obese COPD patients. (22,26,27) We designed our study by taking the confounders and limitations of these studies into account. As age and severity of airflow obstruction are determinants of symptom perception (5), we excluded the effects of these variables by matching the groups for age and FEV₁. We did not include patients with comorbidities such as asthma, OSAS, recent acute cardiovascular event, atrial fibrillation at time of inclusion and lung diseases causing restriction such as interstitial lung diseases to minimize confounding.

Our results suggest that obesity in COPD is associated with increased weight-bearing exercise-induced dyspnea. Several factors seem to influence dyspnea ratings in obese COPD patients. Generally, lung hyperinflation is one of the determinants of increased dyspnea and poor QoL in COPD. (7,36,37) In our study the degree of dynamic lung hyperinflation, as measured with MPT, was comparable between COPD_{OB} and COPD_{NW} and thus was non relevant in the difference in dyspnea between the groups. However, the static lung volumes of COPD_{OB} were lower than COPD_{NW}. This is in line with earlier reports, including comparable obese groups (mean BMI 32-35 kg/m²). (17-19) Like these earlier studies, obesity was associated with lower FRC values with ERV being the most affected compartment. However, despite less resting lung hyperinflation, our COPD_{OB} patients had higher dyspnea ratings than their normal-weight counterparts. Our data suggest that this may at least partly be due to the negative effects of increased adiposity. Indeed, while COPD_{OB} patients have higher odds for mMRC ≥ 2 compared to COPD_{NW}, these odds ratios are even greater when we adjust the models for resting lung hyperinflation. Our data suggest that the positive effects of obesity on pulmonary function protect obese patients to some degree of excess dyspnea. However, the positive effects of obesity in COPD, i.e. less hyperinflation and better DL_{CO} apparently do not outweigh the negative effects of excess weight.

In concordance with the mMRC ratings, COPD_{OB} patients reported significantly higher increase in dyspnea during weight-bearing exertion. This is supported

by earlier reports indicating that with obesity particularly weight-bearing exercise capacity is affected, probably due to increased work of breathing due to carrying excess weight. (38,39) However, definite proof of this hypothesis is lacking and future studies with matched groups need to address this issue. The significantly higher walk work (6MWW) in COPD_{OB} appeared not to be a determinant of increased dyspnea during the 6MWT in our analyses. As with the mMRC, adjusting the models for resting lung hyperinflation resulted in increased odds for dyspnea during exertion, suggesting a protective role for obesity. Although the differences in dyspnea were statistically significant, the question remains whether these small differences (0.6 as measured with Δ Borg in disadvantage of obese) are clinically relevant. Either way, as also shown with adjusting the models for resting hyperinflation, the lower resting hyperinflation as a consequence obesity seems to clearly protect obese COPD patients from increased dyspnea.

In this study we also analyzed the role of different anthropometric and body composition measures on dyspnea. These analyses indicate that patients with central obesity are more likely to experience worse dyspnea as demonstrated by the strong association between increased WHR and dyspnea. Furthermore, the amount of fat as measured by FMI and Fat % seems to be stronger associated with higher dyspnea ratings (both mMRC and Δ Borg during 6MWT) than BMI or FFMI. This suggests that primarily the amount of fat, and perhaps its location (central), are determinants of worse dyspnea with increasing weight in COPD patients. This finding, combined with accumulating data indicating abdominal adiposity as a risk factor for developing COPD (40), is important for future studies to develop treatment strategies specifically targeting subjects with central adiposity. Because FFMI was significantly higher in the obese group we cannot fully rule out that the excess weight in this group might be due to a training effect and that this might had a beneficial effect on dyspnea and QoL. Future studies measuring muscle strength and cardiorespiratory fitness may provide more insight in this complex trade-off.

Our study has some limitations. This was a single center study conducted in a secondary care hospital with COPD patients who had on average moderate airflow limitation. Those with milder disease as well as those with very severe COPD may be underrepresented. Therefore our findings may not be generalizable to the whole COPD population. Furthermore, while our results indicate that obese COPD patients experience more weight-bearing exercise-induced dyspnea, we do not know whether this is associated with sedentary

behavior since we did not perform accelerometry to objectively assess daily physical activity. It is plausible that patients who experience more weight-bearing exercise-induced dyspnea perform less of those activities in daily living (41). Also we did not measure parameters of ventilation and gas exchange during exertion. Therefore we could not compare or match for cardio-respiratory fitness. It should also be mentioned that this study was not designed to assess physiological mechanisms leading to dyspnea. Therefore this study cannot provide in a thorough mechanistic explanation for the results. Future studies are needed in order to unravel these mechanisms.

In conclusion, our study indicates that despite its beneficial effect on resting lung hyperinflation, adiposity is associated with increased weight-bearing exercise-induced dyspnea in COPD.

Conflict of interest statement

This work was supported by an unrestricted grant from GlaxoSmithKline. The funding agency had no involvement in study design, data collection, data analysis, interpretation of data, or writing of the report. The Authors declare that there is no conflict of interest.

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Supplemental Tables

Supplement Table 1. Association between anthropometric and body composition measures and mMRC ≥ 2 .

	Model 1		Model 2	
	OR (95% CI)	P	OR (95% CI)	P
BMI classes				
NW low	Reference		Reference	
NW high	1.16 (0.46 - 2.96)	0.75	1.80 (0.66 - 4.93)	0.26
OB low	2.21 (0.82 - 5.93)	0.12	4.28 (1.40 - 13.11)	0.01
OB high	3.96 (1.46 - 10.71)	<0.01	8.47 (2.26 - 27.33)	<0.01
WC classes				
NW low	Reference		Reference	
NW high	1.05 (0.41 - 2.68)	0.93	1.25 (0.47 - 3.36)	0.65
OB low	2.05 (0.77 - 5.43)	0.15	3.31 (1.15 - 9.54)	0.03
OB high	4.32 (1.48 - 12.68)	<0.01	8.16 (2.47 - 26.97)	<0.01
Waist-to-hip ratio classes				
NW low	Reference		Reference	
NW high	1.53 (0.59 - 3.96)	0.38	1.61 (0.61 - 4.49)	0.32
OB low	1.92 (0.72 - 5.11)	0.19	2.95 (1.03 - 8.45)	0.04
OB high	7.39 (2.43 - 22.53)	<0.01	12.81 (3.80 - 43.22)	<0.01
FFMI classes				
NW low	1.43 (0.55 - 3.68)	0.46	1.15 (0.43 - 3.07)	0.78
NW high	Reference		Reference	
OB low	2.98 (1.11 - 8.01)	0.03	4.15 (1.46 - 11.79)	<0.01
OB high	3.68 (1.35 - 10.09)	0.01	4.87 (1.69 - 14.00)	<0.01
FMI classes				
NW low	Reference		Reference	
NW high	1.97 (0.72 - 5.39)	0.19	2.62 (0.90 - 7.64)	0.08
OB low	2.37 (0.87 - 6.46)	0.09	4.20 (1.38 - 12.76)	0.01
OB high	7.02 (2.37 - 20.83)	<0.01	14.56 (4.19 - 50.58)	<0.01
Fat % classes				
NW low	Reference		Reference	
NW high	2.18 (0.77 - 6.14)	0.14	2.50 (0.84 - 7.38)	0.10
OB low	2.86 (1.04 - 7.91)	0.04	4.41 (1.47 - 13.23)	<0.01
OB high	6.57 (2.17 - 19.92)	<0.01	13.43 (3.80 - 47.48)	<0.01

Abbreviations: mMRC, modified medical research council dyspnea scale; BMI, body mass index; WC, waist circumference; FFMI, fat free mass index; FMI, fat mass index; FRC, functional residual capacity. For each variable the sex specific median for obese and normal weight groups were calculated. Obese subjects with values $\geq$ sex specific median were marked as 'OB high', while normal weight subjects were marked as 'NW high'. The OR of scoring mMRC ≥ 2 are presented for each variable. Model 1: adjusted for age, smoking status, smoking packyears, known comorbidities Model 2: as model 1 with additional adjustment for FRC, % pred.

Supplement Table 2. Association between anthropometric and body composition measures and Δ Borg score during 6MWT.

	Model 1		Model 2	
	OR (95% CI)	P	OR (95% CI)	P
BMI classes				
NW low	Reference		Reference	
NW high	1.28 (0.49 - 3.35)	0.61	1.82 (0.65 - 5.06)	0.25
OB low	1.82 (0.67 - 4.94)	0.24	3.04 (1.01 - 9.16)	0.05
OB high	2.15 (0.83 - 5.59)	0.12	3.66 (1.24 - 10.80)	0.02
WC classes				
NW low	Reference		Reference	
NW high	1.14 (0.43 - 2.98)	0.80	1.35 (0.50 - 3.66)	0.55
OB low	2.05 (0.78 - 5.44)	0.15	2.98 (1.05 - 8.46)	0.04
OB high	1.70 (0.62 - 4.66)	0.30	2.62 (0.87 - 7.82)	0.09
Waist-to-hip ratio classes				
NW low	Reference		Reference	
NW high	1.45 (0.55 - 3.86)	0.46	1.63 (0.59 - 4.51)	0.35
OB low	1.22 (0.45 - 3.34)	0.70	1.74 (0.60 - 5.06)	0.31
OB high	3.80 (1.36 - 10.56)	0.01	5.87 (1.92 - 17.91)	<0.01
FFMI classes				
NW low	0.79 (0.30-2.10)	0.64	0.62 (0.22 - 1.72)	0.36
NW high	Reference		Reference	
OB low	1.69 (0.65 - 4.39)	0.28	2.18 (0.80 - 5.94)	0.13
OB high	1.44 (0.54 - 3.81)	0.46	1.69 (0.62 - 4.61)	0.31
FMI classes				
NW low	Reference		Reference	
NW high	3.97 (1.35 - 11.66)	0.01	4.87 (1.58 - 15.05)	<0.01
OB low	3.43 (1.18 - 10.00)	0.02	5.33 (1.68 - 16.96)	<0.01
OB high	4.27 (1.46 - 12.50)	<0.01	7.17 (2.17 - 23.76)	<0.01
Fat % classes				
NW low	Reference		Reference	
NW high	4.40 (1.44 - 13.43)	0.01	4.78 (1.51 - 15.11)	<0.01
OB low	3.26 (1.10 - 9.62)	0.03	4.40 (1.41 - 13.73)	0.01
OB high	5.21 (1.71 - 15.93)	<0.01	8.63 (2.48 - 30.03)	<0.01

For each variable the sex specific median for obese and normal weight groups were calculated. Obese subjects with values $\geq$ sex specific median were marked as 'OB high', while normal weight subjects were marked as 'NW high'. The OR of Δ Borg score ≥ 2 during 6MWT are presented for each variable. Model 1: adjusted for age, smoking status, smoking packyears, known comorbidities Model 2: as model 1 with additional adjustment for FRC, % pred.

Abbreviations: mMRC, modified medical research council dyspnea scale; BMI, body mass index; WC, waist circumference; FFMI, fat free mass index; FMI, fat mass index; FRC, functional residual capacity.



Chapter 5

Sleep hypoventilation is common in diurnal normocapnic COPD patients with severe or very severe obstruction and is not associated with body mass index

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Abstract

Sleep hypoventilation (SH) is common in COPD patients with diurnal hypercapnia, however there are little data on the presence of SH in COPD patients with diurnal normocapnia. In this study the prevalence of SH in stable normocapnic COPD patients with severe or very severe obstruction (GOLD stages III and IV) was evaluated across body mass index (BMI) classes and associations between SH and body composition measures were explored.

A total of 56 diurnal normocapnic COPD patients, of whom 17 normal-weight (COPD_{NW}), 18 overweight (COPD_{OW}) and 21 obese (COPD_{OB}), underwent polysomnography to objectify SH and bioelectrical impedance analysis to assess body composition. The overall prevalence of SH was 66.1% and was not different across BMI classes. Logistic regression models indicated that SH was not associated with waist-to-hip ratio, body fat percentage and fat-free mass index.

Our data indicate that SH is common in diurnal normocapnic COPD patients with severe or very severe obstruction and is not associated with BMI or body composition.

Introduction

During sleep, COPD patients may have impairments in gas exchange (hypoxemia with or without hypercapnia). Nocturnal gas exchange impairments in COPD have been associated with adverse effects, such as arrhythmias during sleep, pulmonary hypertension, exacerbation frequency and mortality (1,2). Nocturnal hypoxemia in COPD patients is well investigated (3,4), but data on sleep hypoventilation (SH) is limited. Even though non-invasive ventilation for (daytime) chronic hypercapnic respiratory failure in COPD usually takes effect by alleviating hypercapnia during sleep (5), there is no clarity on the prevalence of SH in patients with COPD. This applies particularly to patients with hypoventilation only during sleep while displaying normocapnia during wakefulness (6). Identification of the latter seems important, as SH is believed to precede daytime hypercapnia and chronic hypercapnic respiratory failure (7,8).

Sleep hypoventilation has been defined by the American Association of Sleep Medicine (AASM) as an increase in PaCO_2 (or surrogate) to a value >55 mmHg (7.3 kPa) for ≥ 10 minutes, or an increase in $\text{PaCO}_2 \geq 10$ mmHg (1.3 kPa) above the awake supine value to a value exceeding 50 mmHg (6.7 kPa) for ≥ 10 minutes (9). Whereas hypoxemia in COPD may be a result of pulmonary failure only, (sleep) hypoventilation results from failure of the respiratory pump and thus ventilatory failure (10). Sleep itself leads to a reduction of alveolar ventilation: the loss of the wakefulness drive, increased airway resistance and diminished chemosensitivity during non-Rapid Eye Movement (REM) sleep result in a mild increase of PaCO_2 and decrease of PaO_2 (11). During REM sleep these changes are further enhanced by rapid shallow breathing and reduced activity of accessory respiratory muscles (12). In contrast to healthy subjects, in whom these changes are mild, several factors may contribute to increased work of breathing (and subsequently ventilatory failure) in patients with COPD, including increased upper airway resistance and mechanical disadvantages imposed by hyperinflation, as well as respiratory muscle dysfunction and ventilation-perfusion mismatch (7,13).

Obesity, which on its own may lead to alveolar hypoventilation, may add to the respiratory load and further aggravate alveolar hypoventilation in patients with COPD. In fact, studies in COPD patients with diurnal hypercapnia indicate that SH is common and correlates with higher BMI (14,15).

Studies on the prevalence of SH in COPD patients with diurnal normocapnia are more scarce. Nevertheless, some data are available suggesting the presence of SH in COPD patients with diurnal normocapnia (16,17). Data from COPD and obstructive sleep apnea (OSA) studies indicate a higher BMI as one of the risk factors of developing SH, but this was not found in a study including normocapnic COPD patients (17). However, the median BMI in the latter study was 25 kg/m² with only 13% of the study population presenting with a BMI of ≥ 30 kg/m². It is thus unclear, whether obesity is a risk factor for SH in patients with diurnal normocapnic COPD. Also, it is unknown whether body composition, independent of BMI, is associated with SH in these patients.

The primary objective in this study was to evaluate the association between BMI and prevalence of SH in stable normocapnic COPD patients with severe or very severe obstruction (GOLD stages III and IV). Our secondary objective was to explore associations between SH and body composition measures. We hypothesized that higher BMI and higher measures of adiposity were associated with SH.

Methods

Study Design

This was an observational study performed at Rijnstate Hospital, Arnhem, The Netherlands. Patients were recruited between February and December 2016. The study was approved by the regional ethics committee (CMO Arnhem-Nijmegen) and Rijnstate Hospital local ethics committee (2015-1750). COPD patients who met the inclusion criteria were invited to participate by their pulmonologist. All subjects signed informed consent and spent one night at the hospital for polysomnography (PSG).

Subjects

We included normal-weight (COPD_{NW}), overweight (COPD_{OW}) and obese (COPD_{OB}) patients with COPD. All patients had a diagnosis of severe to very severe COPD, defined as an obstructive lung function with forced expiratory volume in 1 second/forced vital capacity (FEV₁/FVC) < lower limit of normal and FEV₁ < 50% predicted (COPD stages GOLD III and IV) according to the GOLD report [18]. Normal weight was defined as BMI 18.5-24.99 kg/m², overweight as BMI 25.00-29.99 kg/m², and obese as BMI ≥ 30 kg/m². All patients were

clinically stable, had no exacerbation history in the preceding 4 weeks, and included men and women between 18-80 years of age.

Exclusion criteria were 1) presence of significant comorbidity potentially interfering with outcomes of interest (i.e. cardiovascular, neuromuscular or other respiratory diseases); 2) inability to perform pulmonary function tests or fill in questionnaires; 3) previous diagnosis of moderate to severe obstructive sleep apnea either previously or during study PSG (apnea hypopnea index (AHI) ≥ 15 events/hour) and/or active positive airway pressure treatment; 4) daytime hypercapnia, defined by awake capillary $p\text{CO}_2 > 48$ mmHg (6,4 kPa) during a stable phase of disease.

Measurements

Information on demographics, medication use, smoking habits, known comorbidities, and anthropometric measurements (weight, height, waist and hip circumference) were obtained. Body composition was measured with bioelectrical impedance analysis (Bodystat 1500, Bodystat, UK) yielding body fat percentage and fat-free mass (FFM) from which fat-free mass index (FFMI) was calculated as $\text{FFM}/\text{height}^2$. Spirometry and body plethysmography data were either collected from medical records if assessed < 1 year prior to inclusion, or were assessed as part of study measurements according to international standards (19). Daytime capillary blood gasses were taken in all subjects. PSG set-up and PSG analysis was performed according to the 2012 AASM specifications (Smart-PSG, Cidelec, France) (9). Sleep scoring was performed manually by an experienced sleep technologist.

Transcutaneous $p\text{CO}_2$ ($P_{\text{tc}}\text{CO}_2$, Tosca, Radiometer, Australia) was attached to the earlobe between 9:00-9:30 p.m. Tosca was calibrated with CO_2 -gas at the beginning and at the end of the night to correct for overnight $p\text{CO}_2$ -drift. At 10:00 p.m. PSG measurements were started. All PSG data (total sleep time, sleep efficiency, duration of REM and NREM sleep and sleep apnea/hypopneas), O_2 -saturation and $P_{\text{tc}}\text{CO}_2$ were stored and analyzed using Cidelec software. SH was defined according to AASM criteria: an increase in PaCO_2 (or surrogate) to a value > 55 mm Hg for ≥ 10 minutes, or an increase in $\text{PaCO}_2 \geq 10$ mmHg above the awake supine value to a value exceeding 50 mmHg for ≥ 10 minutes (9). The severity of SH was assessed by comparing the highest $P_{\text{tc}}\text{CO}_2$ during sleep, mean $P_{\text{tc}}\text{CO}_2$ during sleep, change in $P_{\text{tc}}\text{CO}_2$ between awake to the level of mean $P_{\text{tc}}\text{CO}_2$ during sleep ($\Delta P_{\text{tc}}\text{CO}_2$ MEAN) and change in $P_{\text{tc}}\text{CO}_2$ between awake to the highest $P_{\text{tc}}\text{CO}_2$ during sleep ($\Delta P_{\text{tc}}\text{CO}_2$ Max) in

the different weight groups. Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) (20).

Statistics

Descriptive statistics were used to characterize the study population. Continuous variables were expressed as mean $\pm$ SD while discrete variables were shown as percentages. A two-tailed *p* value < 0.05 was considered statistically significant. For between-group comparisons, the independent t-test (for 2 groups) or the ANOVA (for >2 groups) were utilized. Post hoc analyses were performed with Bonferroni or Games-Howell (depending on homogeneity of variance according to Levene's test) to correct for multiple comparisons. Proportions of categorical variables were compared by Chi-squared test (two-tailed). Binary logistic regression models were used to assess the associations between SH and its potential determinants (pulmonary function, anthropometric measures etc.). Analyses were performed with SPSS version 21.0 (IBM, USA).

Results

A total of 75 eligible patients completed PSG. Five patients were excluded from further analyses because of newly diagnosed OSA and another 14 because of technical failures (8 failures for transcutaneous PCO_2 -measurement, 6 PSG failures). Finally, 17 COPD_{NW} , 18 COPD_{OW} and 21 COPD_{OB} were included in the analyses.

The characteristics of the study participants are presented in Table 1. There were no statistically significant differences in age, sex, pulmonary medication use or comorbidities between BMI classes. There were significantly less current smokers in COPD_{OB} compared to the COPD_{OW} and COPD_{NW} while smoked pack years were comparable. As expected, weight, hip and waist circumference, body fat percentage and fat-free mass index gradually increased with increasing BMI class. Pulmonary function parameters are presented in Table 2. COPD_{OB} had significantly higher FEV_1 values compared to COPD_{NW} . FRC and residual volume (RV) decreased and inspiratory capacity (IC) increased with increasing BMI class. Diffusion capacity of the lungs for carbon monoxide (DLCO) was comparable between BMI classes. Mean diurnal capillary pCO_2 was not significantly different between BMI classes, and averaged at 41.0 mmHg for the group as a whole.

Table 1. Characteristics of the study participants. Data are presented as mean (SD) unless otherwise stated.

	NW	OW	OB	Total group	P between groups	PNW vs OW	PNW vs OB	POW vs OB
N	17	18	21	56	-	-	-	-
Age, mean	63.1 (9.6)	68.4 (5.5)	67.0 (8.0)	66.3 (8.0)	0.13	-	-	-
Sex, % males	47	61	43	50	0.50	-	-	-
Weight, kg	64.6 (7.6)	79.1 (9.0)	90.6 (10.9)	79.0 (14.2)	<0.01	<0.01	<0.01	<0.01
Height, cm	170 (8)	168 (7)	167 (10)	168 (9)	0.45	-	-	-
BMI	22.3 (1.7)	28.0 (1.3)	32.5 (1.2)	28.0 (4.5)	<0.01	<0.01	<0.01	<0.01
Hip circumference, cm	92 (5)	100 (7)	108 (11)	101 (11)	<0.01	<0.01	<0.01	0.02
Waist circumference, cm	90 (6)	105 (9)	114 (9)	104 (13)	<0.01	<0.01	<0.01	<0.01
Waist/hip ratio	0.98 (0.08)	1.06 (0.12)	1.07 (0.13)	1.04 (0.11)	0.05	-	-	-
Fat, %	31 (8)	36 (7)	42 (7)	37 (9)	<0.01	0.12	<0.01	0.10
FFMI, kg/m2	15.3 (2.3)	17.8 (2.4)	19.0 (2.3)	17.5	<0.01	<0.01	<0.01	0.40
Smoked pack years	37 (23)	41 (30)	33 (16)	37 (23)	0.57	-	-	-
Smoking status								
% current smokers	41	28	5	23	0.02	0.40	0.01	0.08
Use of inhalers								
% using SABA	71	61	61	64	0.80	-	-	-
% using SAMA	6	17	10	11	0.58	-	-	-
% using LABA	100	94	95	96	0.47	-	-	-
% using LAMA	100	83	86	89	0.10	-	-	-
% using ICS	82	78	76	79	0.89	-	-	-

Table 1. Continued.

	NW	OW	OB	Total group	P between groups	P NW vs OW	P NW vs OB	P OW vs OB
Comorbidities								
% Diabetes	0	22	14	13	0.05	-	-	-
% Hypertension	18	50	48	39	0.09	-	-	-
%Atrial fibrillation	12	6	5	7	0.69	-	-	-
% Myocardial infarction	0	17	10	9	0.12	-	-	-
% Congestive heart failure	0	0	0	0	-	-	-	-

Abbreviations: BMI, body mass index; FFMI, free fat mass index; SABA, short-acting beta agonist; SAMA, short-acting muscarinic antagonist; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; ICS, inhaled corticosteroid.

Table 2. Pulmonary function tests. Data are presented as mean (SD) unless otherwise stated.

	NW	OW	OB	Total group	P between groups	PNW vs OW	PNW vs OB	OW vs OB
FEV1, % pred	32.2 (8.5)	38.1 (6.6)	43.9 (9.5)	38.5 (9.5)	<0.01	0.13	<0.01	0.10
FEV1, L	0.90 (0.35)	0.96 (0.20)	1.08 (0.35)	0.99 (0.31)	0.21	-	-	-
VC, % pred	88.5 (18.6)	93.4 (15.2)	94.6 (17.8)	92.4 (17.1)	0.53	-	-	-
VC, L	3.15 (0.99)	3.14 (0.84)	3.02 (0.92)	3.10 (0.90)	0.89	-	-	-
IC, % pred	81.9 (18.9)	88.9 (13.1)	98.0 (19.8)	90.2 (18.6)	0.03	0.74	0.02	0.35
IC, L	2.14 (0.67)	2.19 (0.52)	2.30 (0.73)	2.22 (0.64)	0.72	-	-	-
FRC, % pred	191.6 (29.1)	162.9 (28.7)	155.3 (21.3)	168.3 (30.0)	<0.01	<0.01	<0.01	1.00
FRC, L	6.05 (1.16)	5.16 (1.08)	4.74 (1.04)	5.26 (1.20)	<0.01	0.06	<0.01	0.70
ERV, % pred	107.7 (33.4)	106.7 (39.9)	87.1 (39.6)	99.7 (38.5)	0.17	-	-	-
ERV, L	1.02 (0.42)	0.94 (0.44)	0.72 (0.35)	0.88 (0.41)	0.06	-	-	-
RV, % pred	227.9 (42.6)	203.2 (45.3)	185.3 (31.0)	203.1 (42.4)	0.01	0.24	<0.01	0.49
RV, L	5.11 (1.03)	4.61 (0.90)	4.04 (0.67)	4.53 (0.95)	<0.01	0.30	<0.01	0.13
TLC, % pred	130.9 (15.5)	121.6 (17.9)	120.3 (13.8)	123.8 (16.1)	0.11	-	-	-
TLC, L	7.82 (1.38)	7.09 (1.29)	6.77 (1.41)	7.18 (1.41)	0.07	-	-	-
RV/TLC, %	65.9 (11.7)	65.6 (10.0)	60.7 (7.9)	63.8 (9.9)	0.19	-	-	-
DLCO SB, % pred	46.5 (12.1)	53.7 (15.2)	55.7 (11.4)	52.3 (13.3)	0.10	-	-	-
DLCO/VA, % pred	56.6 (14.7)	64.4 (18.3)	71.6 (20.9)	64.8 (19.1)	0.06	-	-	-
PcCO2, mmHg	40.3 (3.2)	41.4 (3.9)	41.3 (4.5)	41.0 (3.9)	0.67	-	-	-

Abbreviations: FEV1, forced expiratory volume in 1 second; VC, vital capacity; TLC, total lung capacity; FRC, functional residual capacity; ERV, expiratory reserve volume; RV, residual volume; DLCO, diffusing capacity for carbon monoxide; VA, alveolar volume; PcCO2, capillary pCO2.

Table 3. Polysomnography and sleep hypoventilation. Data are presented as mean (SD) unless otherwise stated.

	NW	OW	OB	Total group	P between groups
TST, min	369 (87)	380 (56)	391 (62)	381 (68)	0.63
Sleep efficiency, % TST/PST	64.5 (13.5)	66.3 (8.3)	69.3 (8.7)	66.9 (10.3)	0.36
% REM of TST	15.3 (7.6)	16.9 (6.4)	17.2 (7.6)	16.6 (7.1)	0.69
AI, events/hour, mean	0.65 (1.6)	0.67 (1.3)	0.81 (1.1)	0.71 (1.3)	0.92
AHI, events/hour, mean	10.2 (5.4)	9.9 (5.4)	11.1 (6.6)	10.4 (5.8)	0.81
MeanSpO2 during sleep	90.3 (2.1)	89.6 (2.2)	88.8 (3.1)	89.5 (2.6)	0.21
Lowest SpO2 during sleep	81.5 (5.2)	79.6 (7.1)	81.1 (5.5)	80.8 (5.9)	0.58
Mean sleep P _{tc} CO ₂ , mmHg	53.4 (4.9)	54.6 (5.8)	54.9 (6.4)	54.3 (5.7)	0.70
Highest P _{tc} CO ₂ , mmHg	58.5 (6.4)	60.3 (6.0)	60.5 (7.7)	59.8 (6.8)	0.62
Highest P _{tc} CO ₂ REM, mmHg	59.9 (6.5)	60.1 (6.3)	60.5 (7.8)	60.2 (6.8)	0.96
ΔP _{tc} CO ₂ MEAN, mmHg	5.4 (2.9)	6.8 (4.0)	6.5 (3.7)	6.3 (3.6)	0.49
ΔP _{tc} CO ₂ MAX, mmHg	10.5 (4.3)	12.5 (4.2)	12.1 (4.8)	11.8 (4.5)	0.40
Sleep hypoventilation, %	64.7	66.7	66.7	66.1	0.99

Abbreviations: TST, total sleep time; REM, rapid eye movement sleep; AI, arousal index; AHI, apnea/hypopnea index; SpO2, oxygen saturation; PtcCO2, transcutaneous pCO2; Δ PtcCO2 MEAN, delta PtcCO2 between awake and mean PtcCO2 during sleep; Δ PtcCO2 Max, delta PtcCO2 between awake and highest PtcCO2 during sleep.

PSG and nocturnal transcutaneous CO_2 data are shown in Table 3. Overall SH prevalence was 66.1%. SH prevalence was similar across BMI classes. There was no significant difference between the mean BMI in the group with SH ($28.1 \pm 4.5 \text{ kg/m}^2$) compared to the group without SH ($27.7 \pm 4.4 \text{ kg/m}^2$; $p=0.75$). In patients with SH, the highest $\text{P}_{\text{tc}}\text{CO}_2$ occurred in almost all (36 of 37 patients) during REM-sleep, while the remaining patient did not present REM-sleep during the sleep study. All the measures which assessed the severity of SH (highest $\text{P}_{\text{tc}}\text{CO}_2$ during sleep, mean $\text{P}_{\text{tc}}\text{CO}_2$ during sleep, $\Delta \text{P}_{\text{tc}}\text{CO}_2$ MEAN and $\Delta \text{P}_{\text{tc}}\text{CO}_2$ Max) were slightly higher in the overweight and obese group compared to the normal-weight, but these differences were statistically not significant. Furthermore, explorative logistic regression models performed in the whole study population, showed no statistically significant associations between SH with waist circumference, hip circumference, waist-to-hip ratio, body fat percentage, FFMI, pulmonary function parameters, smoking status, class of inhalers, mean and lowest SpO_2 during sleep, capillary pCO_2 during wakefulness or AHI (data not shown).

In the group as a whole, PSQI data indicated that overall sleep quality was poor (global score >5). There were no differences between BMI classes in the total score and in subdomains of the questionnaire in the unadjusted analysis. Also in further analysis, considering adjustments for potential cofounders (*age, sex, smoking status, packyears, comorbidities, FEV1% predicted, FRC% predicted and DLCO*), by using one-way analysis of covariance (ANCOVA), there were no significant differences between BMI classes.

Discussion

In this study we demonstrated that SH as defined by AASM criteria, is a common finding in stable COPD patients (GOLD stages III-IV) with normocapnia during wakefulness. In our study population 66% of the COPD patients complied with the AASM definition of SH. Furthermore, we observed that the BMI did not influence the prevalence of SH.

Only few studies have evaluated the prevalence of nocturnal hypercapnia in COPD patients with diurnal normocapnia. Similar to our results, Kitajima et al. found a high prevalence (48%) of nocturnal episodic hypercapnia in COPD patients (16). They used a mild definition of nocturnal hypercapnia namely an episodic increase of $\geq 5 \text{ mmHg}$ from baseline $\text{P}_{\text{tc}}\text{CO}_2$ accompanied by an

episodic oxygen desaturation of $< 90\%$ for ≥ 5 minutes continuously, at least once during the night. Furthermore, no evaluation of an association with weight or BMI was performed by Kitajima et al.

Another study by Holmedahl et al. did apply the AASM SH criteria in normocapnic COPD patients and found that only 6 out of the 76 normocapnic patients (8%) studied appeared to have SH (17). The mean BMI of their study population was lower (25.5 kg/m^2) compared to the present study (28.0 kg/m^2), while the mean FEV_1 predicted was higher (43% vs. 38.5%). These differences might (partially) explain the lower prevalence of SH reported by Holmedahl et al. This assumption is supported by the following: Firstly, the severity of airflow obstruction in COPD has been associated with a higher risk for hypoventilation/hypercapnia (21). In our study, mean FEV_1 was considerably lower, especially in our NW (32 %) and OW (38%) group compared to the group of Holmedahl et al., providing a possible explanation for the higher prevalence in our study. Secondly, previous studies evaluating COPD patients with diurnal hypercapnia, indicate that the prevalence and severity of SH is correlated with higher BMI values (14,15). Also, studies in patients with OSA without COPD indicate that obesity is an independent risk factor for hypoventilation (22-24). Hence, even though we did not find an association between BMI classes and SH, the higher overall BMI in our study population may have played a role in the higher overall prevalence of SH. It is also important to mention that differences in results with Kitajima et al. and Holmedahl et al. might be due to the use of different devices for $\text{P}_{\text{tc}}\text{CO}_2$ measurement (Kitajima: SenTec; Holmedahl: Radiometer) and placement of the transcutaneous electrodes, while we have placed this to the earlobe it is unknown at which site the electrodes were placed in the other studies.

In our study we found no association between BMI class and (severity of) SH. Also, parameters of sleep quantity and sleep quality as measured by PSG and PSQI, were comparable between BMI groups. Although this result is in line with a previous study in normocapnic COPD patients (17), indicating no negative association between increasing weight and SH, it is in contrast with data from hypercapnic COPD patients (14,15), where higher BMI was correlated with nocturnal hypoventilation. A potential explanation might be that the NW group had more airflow obstruction compared to the OB group, thus masking the negative effect of higher BMI on SH prevalence. However, we could not find a correlation between the prevalence of SH and BMI or FEV_1 . Similarly, no correlation was found between the presence of SH and body fat distribution or

body composition markers. This lack of correlations may be due to the bias of only including patients with severe or very severe COPD (GOLD stages III-IV) in combination with relatively small sample sizes in the various BMI groups due to a relatively high number of excluded patients. More studies, including COPD patients of all GOLD stages and larger study populations are needed in the future to address these issues.

Our data indicate that a large portion of COPD patients with diurnal normocapnia have SH as defined by the AASM. In COPD, lung hyperinflation may be protective against certain sleep-related breathing disorders such as obstructive sleep apnea. However, by diminishing the efficacy of diaphragm and in conjunction with disturbed ventilation-perfusion, worsening airflow obstruction during sleep and decreased skeletal muscle contraction, it contributes to disturbed gas exchange during sleep (7). Earlier reports indicate that nocturnal gas exchange impairments are associated with arrhythmias during sleep, pulmonary hypertension, higher risk of COPD exacerbation and worse survival (1,2,16). A recent study in patients with COPD GOLD stages III-IV, indicated reduced hospital admissions, improved symptoms and quality of life measures by using low pressure domiciliary non-invasive ventilation in this group (25). Interestingly, all these benefits were not only seen in patients with diurnal hypercapnia, but also in normocapnic patients. This study did not assess SH in their subjects as a possible explanation of this finding. One could hypothesize that the relative high prevalence of SH in the normocapnic group, as shown in our study, might have played a role. Taking all this into consideration, our findings emphasize the urgency of further studies dealing with early identification of patients with SH to explore the potential of treating SH.

To our best knowledge, this is the first study assessing the prevalence and correlation of SH with obesity as a primary objective in stable normocapnic COPD patients using the AASM criteria for SH. However, this study has some limitations: The final study sample included less patients than initially anticipated, as more than 25% of patients had to be excluded from analysis, mainly because of technical PSG failures. The airflow limitation was unexpectedly significantly better in COPD_{OB}. Theoretically, this might partially explain why SH was not more prevalent in this group. However, also after adjustment for this confounder we could not find a negative correlation between obesity and SH. It should be noted that our results are not generalizable for the whole COPD population, since only patients with severe or very severe COPD were included. We did not assess bicarbonate levels with

arterial blood gasses during wakefulness. High levels of bicarbonate can be suggestive for SH and it would be interesting to correlate this with the more direct measurement of transcutaneous PCO_2 during sleep. Furthermore, while the AASM definition is usually used to define SH, some could argue the clinical relevance of this definition because this only discriminates between having SH and not having SH and does not provide insight into the severity of SH. Finally, this was a single center study with no control group of healthy individuals to compare for the occurrence and severity of SH.

In conclusion, we observed that SH was common in our sample of stable COPD Gold III and IV patients with daytime normocapnia and was not associated with BMI or body composition.

Conflict of interest statement

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Chapter 6

General discussion

Both COPD and obesity are common, and their prevalence is projected to increase in the future (1–4). Individually, both obesity (5) and COPD (6) are associated with increased mortality. However, when both conditions collide, their impact on outcomes is not consistently detrimental as might be presumed. The present thesis explores several aspects of the complex interplay between obesity and COPD.

Prevalence of obesity in COPD and its impact on other comorbidities: a significant concern?

Prevalence

Knowledge regarding the prevalence of obesity in COPD provides the basis for better understanding the complex interaction between these two conditions, developing targeted interventions, and optimizing healthcare resources. However, current data show great variability in the prevalence rates ranging from 13% to 54% (7–15). This thesis includes a study (**Chapter 3**) that explored the prevalence of obesity in a cohort of patients with COPD attending an outpatient pulmonology clinic and reports a prevalence of 22%.

The variability observed in the prevalence rates of obesity in COPD is influenced by various factors. Given the use of different databases, such as primary care, secondary care, rehabilitation clinic and general population in studies including patients with varying severity of COPD, it is important to consider the setting which is used for data retrieval when comparing results. Furthermore, global and cross-cultural variability is a major cause of variation in prevalence rates (2). Gender distribution may also influence the results, as some studies propose that obesity rates are higher in female patients with COPD (9,10). This could be one of the contributing factors resulting in higher prevalence rates of obesity in COPD (8). However, the influence of gender on prevalence rates of obesity was not evidenced in the study presented in **Chapter 3**. (8) Genetic factors may also contribute to the variability in data as genetics have been shown to account for at least 50% of the interindividual variance of BMI (16). As it is unclear to what extent these genetic factors contribute to the co-occurrence of obesity and COPD, they could potentially impact obesity prevalence in COPD. Furthermore, a significant inverse correlation has been observed between the degree of airflow limitation and prevalence of obesity in patients with COPD (11). Data from this thesis aligns with that finding, showing significantly lower prevalence of obesity

in patients with COPD GOLD IV compared to GOLD I and II. The accuracy of utilized data in studies can also affect the reported prevalence of obesity in COPD. To ensure accuracy, it is preferred to use objective measures such as spirometry for COPD diagnosis and measurement of weight and height for BMI assessment. However, self-reported data is commonly used in studies due to its convenience and ability to include larger study populations, even though it is a less reliable study methodology (17–19). Finally, the parameters used to define airflow obstruction impacts prevalence figures as well. As the use of FEV1/FVC ratio to diagnose obstructive disease is very common, particularly in primary care setting where handheld spirometry is often used, it has proven to be less reliable comparing with FEV1/(slow) VC ratio to diagnose obstructive disease (20–22).

Certain factors influencing the prevalence rates of obesity in COPD, such as socio-demographic differences, gender distribution and genetic factors cannot be modified. These should be documented as much as possible in publications for accurate interpretation of the results. Contrary, other factors such as the degree of airflow limitation (selection of severity of COPD in the study population), use of objective measurements and appropriate parameters from the pulmonary function can be considered in study design to minimize bias. In **Chapter 3** we tried to minimize bias by taking these factors into account. Despite some limitations, our data suggest a substantial prevalence of obesity among COPD patients. Whether obesity is more or less common in patients with COPD compared to non-COPD subjects remains unclear. Until 2008 studies suggested a higher prevalence of obesity in COPD patients than in general population (23), which is consistent with our findings. However, this finding was mainly based on indirect comparisons. More recent studies making a direct comparison between COPD and non-COPD show conflicting results, with some indicating higher prevalence in COPD patients (9), others showing comparable rates (24), and some even observing lower obesity rates (10,25). Future research, including meta-analysis of studies that consider the aforementioned biases, is necessary to clarify this issue.

Impact of obesity on comorbidities in COPD

Compared to non-COPD individuals, patients with COPD show distinct comorbidity patterns, including higher rates of cardiovascular, metabolic, and cognitive disorders (26–35). In **Chapter 3** we demonstrated that within a secondary care outpatient COPD cohort, those with obesity had more comorbidities compared to their non-obese counterparts. Furthermore, while

diabetes mellitus, hypertension, congestive heart failure and atrial fibrillation were significantly more common in obese patients with COPD, lung cancer and osteoporosis were more prevalent in non-obese patients with COPD. Thus, comorbidity profiles seem to be different across BMI classes in COPD.

To date, the exact pathophysiological mechanisms that link cardiovascular and metabolic diseases to COPD are largely unknown. Multiple factors, including visceral fat accumulation, loss of peripheral skeletal muscle, reduced activity of oxidative enzymes and systemic inflammation may play a role (36). However, a study identifying five clusters of comorbidities in COPD, including cardiovascular and metabolic clusters, revealed that low-grade systemic inflammation was mostly comparable across comorbidity clusters (14). This implies that the association between systemic inflammation and comorbidities in patients with COPD is not indisputable or straightforward. Furthermore, it has been suggested that the use of corticosteroids may be associated with the coexistence of diabetes mellitus in COPD patients, as demonstrated not only with systemic corticosteroids (37,38) but also with inhaled corticosteroids (39,40). However, concerning the latter, we did not observe a difference in the use of inhaled corticosteroids between obese and non-obese COPD.

In general, the presence of increasing number of comorbidities in COPD is associated with impaired health status, higher readmission rates following exacerbation and higher mortality (41,42). Therefore, obesity seems a significant concern in COPD. As COPD, obesity and many of their mutual comorbidities are influenced by lifestyle; interventions targeting tobacco use, physical activity and healthy nutrition are essential in management of these patients. Also pharmacological interventions seem promising as recently some preliminary studies indicate that glucagon-like-peptide-1 receptor agonists may achieve improvements in pulmonary function alongside with weight loss in obese COPD patients (45,46). These pharmacological interventions targeting both obesity and COPD need confirmation in larger cohorts. The awareness that obese COPD patients have more and distinct comorbidities compared to non-obese COPD patients can aid in risk stratification and early screening of prevalent comorbidities. Early diagnosis and management of these treatable conditions might benefit quality of life and mortality risk in obese COPD patients.

In order to eventually make tailored guidelines for the management of obese COPD patients, some important knowledge gaps need to be addressed in the

future. While lifestyle is involved in the development of both COPD and obesity, it remains unclear whether also COPD is a risk factor for developing obesity or that obese patients are more prone for developing COPD. Can one condition be influenced or even prevented by targeting the other? Furthermore, the effect of screening for particularly cardiovascular and metabolic risk factors and comorbidities in obese COPD patients needs to be evaluated prospectively. Finally, studies indicating that obesity itself is associated with a *decreased* risk of exacerbation (43) and *better* long-term outcomes after hospitalization when compared to non-obese COPD (44), emphasize that probably not a "one size fits all" approach is appropriate in the management of obese COPD patients. In the future it should be determined which intervention suites best for each obese COPD patient based on their (disease) characteristics.

Impact of obesity on pulmonary function and dyspnea in COPD patients; is excess body weight solely detrimental?

6

Lung hyperinflation is usually present in COPD due to loss of elastic recoil and parenchymal destruction (47). Obesity, however, is associated with reduced lung hyperinflation (48–51) as a result of increased intra-thoracic pressure caused by increased intra-abdominal pressure due to excessive fat and reduced lung and chest wall compliance (50,52–55). Contrasting effects are also observed with diffusion capacity of the lungs for carbon monoxide (DL_{CO}). While COPD typically leads to reduced DL_{CO} as a result of emphysema, obesity is associated with elevated DL_{CO} as a result of increased lung blood volume, basal lung perfusion and cardiac output (53,56).

The combined effect of obesity and COPD on hyperinflation was assessed in **chapter 4**, where a beneficial effect of obesity on hyperinflation was demonstrated in patients with COPD. Consistent with previous reports, FRC and particularly ERV were significantly lower in obese COPD compared to non-obese COPD (13,57–60). Additionally, DL_{CO} in obese COPD patients was significantly preserved compared to non-obese COPD patients.

The consequences of this relatively favourable pulmonary function in obese COPD on dyspnea and quality of life (QoL) were also assessed in **chapter 4**. Previous studies using weight-supported exercise protocols reported no negative influence of obesity on dyspnea in COPD patients (58–60). However,

earlier reports showed conflicting results concerning dyspnea during weight-bearing exercise and perceived dyspnea in daily life (69–76). The study presented in **chapter 4**, aimed to evaluate the net effects of obesity on weight-bearing induced dyspnea and QoL in patients with COPD. While many confounders, including age and severity of airflow limitation can influence dyspnea (65), the subjects were matched for FEV₁ and age. The results indicate that obesity in COPD is associated with increased weight-bearing exercise-induced dyspnea. However, it was also demonstrated that the reduced lung hyperinflation protected the obese COPD patients from more pronounced dyspnea. Furthermore, this study also highlights that location of adipose tissue (central) and other body composition measures (Fat Mass Index and Fat %) are more important than BMI, as these factors were more strongly associated with dyspnea than BMI. The QoL was comparable in obese-COPD and non-obese COPD patients.

The aforementioned results implies that the impact of obesity on pulmonary function and dyspnea in patients with COPD are not solely detrimental. While in general the obese cohort had increased weight-bearing exercise-induced dyspnea, it is presumable that some subgroups of COPD patients might not experience detrimental outcomes with increasing weight. In order to understand the precise impact of increasing weight on clinical outcomes in patients with COPD, it is important to assess other disease characteristics beyond airway obstruction. As shown in this thesis, at least markers of hyperinflation and DL_{co} needs to be taken into consideration. These markers do not only influence symptoms but seem also important for overall survival. Indeed, hyperinflation is associated with increased mortality in COPD (47). Therefore obesity may also contribute to better prognosis in COPD as it reduces hyperinflation. The better DL_{co} in obese COPD patients may be due to a lesser extent of emphysema in these patients. As the extent of emphysema is associated with higher all cause- and COPD related mortality, it could partly explain the better survival rates (78,79). However, whether obesity directly contributed to less emphysema is unknown. Furthermore, the extent to which the preserved DL_{co} in obese COPD patients reflects lower-grade emphysema, favourable influences of obesity, or a combination of these factors remains uncertain. Future studies using imaging, such as CT scans to quantify emphysema could help to shed light on this question.

Another important finding which needs consideration in future studies is to focus on other body compositions markers beyond BMI. As the association

between dyspnea and central obesity (elevated waist-to-hip-ratio), fat mass Index and fat % were more stronger compared to BMI it is important to assess these markers. Earlier reports also emphasize the importance of high lean muscle mass/Fat Free Mass (FFM), which is associated with better cardiorespiratory fitness (85). While cardiorespiratory fitness is associated with improved survival (86), earlier studies have indicated that FFM is a predictor of mortality independent of the amount of fat mass in COPD (87). The obese population included in **chapter 4** had a significantly higher FFMI compared to the non-obese group, as such it seems that in general the obese population under treatment for COPD might have a better cardiorespiratory fitness, which can explain the (relative) better outcomes. Together with data which suggest that waist circumference might be a better predictor of mortality, independent of BMI (88), this highlights the importance of considering other body composition measures of obesity beyond the BMI in future studies.

In the discussion on whether in some cases obesity eventually may be even beneficial in patients with COPD, it is important to mention several confounding factors that must be considered when evaluating this relationship. First, some suggest the possibility of "reversed causality" bias, where weight loss may be a consequence of illness, rather than obesity being protective (87). This might explain the lower mortality rates in severe COPD, a phenomena called the "obesity paradox". Second, as some data indicate that obesity itself is associated with increased symptoms, it is possible that obese individuals seek medical attention earlier and thus present in earlier stages of disease, which might benefit their prognosis (91). Third, in some cardiovascular disease studies, the obese group were less likely to smoke compared to non-obese groups, which has been proposed as a possible explanation of favorable outcomes in the obese (92,93), however this is not often seen in COPD studies including studies performed in this thesis.

It is evident that in obese COPD patients solely using weight as a determinant of clinical outcomes is an oversimplification of the reality. While in general it is clear that obesity harms health, it has become more clear that obesity has paradoxical effects in COPD. As it is increasingly recognized that COPD is a heterogeneous disease with distinct pathophysiologic differences and specific disease types (94), it is time to shift to more detailed evaluation of obese COPD patients. Future studies need to focus on these specific disease types in order to identify which of these patients are harmed, unaffected or even benefited by increasing BMI. In the future interventions targeting specific variables

of obesity in specific COPD subtypes seem more appropriate, rather than interventions simply based on the generalized measure of “weight”, tied solely to “GOLD classification”. Subsequent studies are warranted to eventually develop more tailored guidance for COPD patients regarding their individual optimal weight/body composition based on their disease characteristics.

Sleep hypoventilation in COPD; is obesity a risk factor?

COPD does affect breathing during sleep and as a consequence it can result to sleep hypoventilation (SH) (95). While existing studies on COPD patients with diurnal hypercapnia have suggested a possible association between increased BMI and the occurrence of SH (96,97), limited data are available on patients with diurnal normocapnia (98,99). The findings presented in **chapter 5**, indicate that SH is prevalent in diurnal normocapnic COPD patients with severe or very severe obstruction (COPD Gold III and IV), with an overall prevalence of 66%. Notably, unlike previous studies on COPD patients with diurnal hypercapnia, no association was observed between increasing BMI and SH in this patient population.

While both COPD (100,101) and obesity (102) are associated with increased risk for alveolar hypoventilation, it is surprising that we could not find an association between increasing BMI and SH. One possible explanation for this finding is that increase in BMI may have a positive effect on neural respiratory drive during sleep in patients with COPD. This hypothesis is derived from studies that have demonstrated that neural respiratory drive during sleep decreased in COPD, while it increased in OSA, and it remained similar to the wake drive (did not decrease) in overlap syndrome (103,104). In these studies the COPD group had the lowest BMI, the OSA group the highest BMI and the BMI in the overlap group was in between. Therefore, it is possible that increasing BMI may benefit respiratory neural drive during sleep in COPD and consequently not lead to more sleep hypoventilation in COPD. However, this hypothesis needs further exploration in obese COPD patients without OSA, as other mechanisms linked to OSA rather than to increasing BMI may cause this effect. Furthermore, as lung hyperinflation in COPD may reduce ventilation, amongst others due to its negative effect on efficacy of diaphragmatic contraction (101), the lower hyperinflation associated with obesity in patients with COPD may have a protective role. Alternatively, it is possible

that increasing BMI may have a negative role in SH, but only in cases of severe obesity or advanced COPD, as this association has only been observed in COPD patients with diurnal hypercapnia. As the obese group in **chapter 5** had an average BMI of 32.5 kg/m², the potential detrimental effect of severe or morbid obesity on SH cannot be ruled out by these results. Finally, a negative effect of BMI may not have been detected in **chapter 5** due to the relatively small cohort size and inclusion of only patients with COPD Gold III/IV.

It is important to acknowledge that determining a potential causal relationship between obesity and SH poses challenges, as some propose that reverse causality might also contribute to this association. Specifically, sleep disturbance may lead to the onset of hormonal and metabolic patterns that promote increased food intake and unhealthy consumption, potentially contributing to the development of obesity (105). As such, the relationship between obesity and SH may be bidirectional, rather than simply unidirectional. To date only few studies, including the study presented in **chapter 5**, have evaluated the prevalence of SH in stable normocapnic COPD patients. While these studies have reported varying prevalence rates, they suggest that a significant proportion of these patients may be affected by SH. SH is believed to be precursor of diurnal hypercapnia/chronic hypercapnic respiratory failure. Furthermore, gas exchange impairments during sleep are associated with poor outcomes, including arrhythmias during sleep, pulmonary hypertension, higher risk of COPD exacerbation and worse survival (101,106,107). Therefore, it is important to identify patients at risk for SH. Future prospective studies are needed to clarify the clinical consequences of isolated nocturnal SH and identify individuals who may progress to chronic respiratory failure.

Conclusions

In this thesis, it is demonstrated that obesity is a prevalent condition in COPD and that obese COPD patients have more and distinct comorbidities compared to non-obese COPD patients. Interestingly, obesity is associated with beneficial effects on pulmonary function, with lower lung hyperinflation and higher diffusion capacity. These advantages associated with obesity likely contribute to the observation that obese patients with COPD, despite experiencing increased weight-bearing exercise-induced dyspnea, are relatively protected against higher levels of dyspnea. Also, it may partially explain the notion that they do not have reduced quality of life and do not show

increased risk for sleep hypoventilation compared to their non-obese peers. Furthermore, it is suggested that other body composition measures and the location of adipose tissue may be more important than BMI in association with outcomes such as dyspnea.

The results of this thesis contribute to knowledge of the complex and sometimes paradoxical interplay between COPD and obesity, particularly concerning the prevalence of obesity in COPD, and the impact of obesity on the co-occurrence of other comorbidities, pulmonary function, dyspnea and sleep hypoventilation in patients with COPD. However, it is important to acknowledge that most of our current understanding in this field is based on associations derived from retrospective observational data. Future studies that unravel causal links and elucidate the exact mechanism at play are essential. Considering that COPD is a heterogeneous disease with distinct pathophysiologic differences and specific disease types, and in the obese population not only weight but also other body composition measures are linked to clinical outcomes, our research focus needs to expand beyond the GOLD classification and BMI. This expansion is necessary to determine the ideal body composition for each individual patient.

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Chapter 7

Summaries

Summary

Chronic Obstructive Pulmonary Disease (COPD) is a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, sputum production) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction. COPD is a prevalent chronic disease with a significant disease burden. Obesity, defined by a body mass index (BMI) $\geq 30.0 \text{ kg/m}^2$, is also a prevalent condition affecting many people around the world. This thesis explores several aspects of the interaction between COPD and obesity when they co-occur.

Chapter 2 provides an overview of the impact of obesity on COPD. This narrative review describes the current knowledge on the prevalence of obesity in patients with COPD. Furthermore, the effect of obesity on pulmonary function, dyspnea, exercise capacity and exacerbation risk is described. While the prevalence rates are variable in studies, important factors causing this variability are discussed. Amongst others, physician made diagnosis by at least performing spirometry and measuring weight and length is encouraged instead of self-reported diagnosis. While obesity is associated with less lung hyperinflation in patients with COPD, previous studies show conflicting results concerning how this affects dyspnea. This review describes several confounding factors in studies. Furthermore, the importance of taking the heterogeneity of COPD and other body composition markers aside of BMI into account are discussed.

The prevalence of obesity in a population of COPD patients attending the outpatient clinic was assessed in **Chapter 3**. This study showed that obesity is common (prevalence of 22%) in this group of COPD patients. Obesity was significantly less common in very severe COPD (GOLD IV) compared to mild to severe groups (GOLD I-III). Obese COPD patients had more comorbidities compared to non-obese COPD patients. Furthermore, cardiovascular and metabolic comorbidities were more common in obese COPD patients.

The impact of obesity on pulmonary function and dyspnea was studied in **Chapter 4**. To minimize confounding the obese and non-obese COPD cohorts were matched for age and severity of airflow obstruction (FEV_1). Obese COPD patients had favourable lung function with less lung hyperinflation and better diffusing capacity of the lung. Despite this advantage, obese COPD patients

described increased weight-bearing exercise-induced dyspnea. However, it was also shown that the lower hyperinflation protected the obese from more pronounced dyspnea. Also the quality of life did not differ between obese and non-obese COPD patients. Finally, this study demonstrated that the amount of fat, as measured by fat% and fat mass index, and location of fat tissue (central) were more strongly associated with dyspnea compared to BMI.

Only few studies had previously assessed the prevalence of sleep hypoventilation (SH) in COPD patients with normocapnia during wakefulness. The study in **Chapter 5** showed that SH was highly prevalent in patients with severe to very severe COPD (GOLD III-IV), as 66% of them met the criteria of SH. SH is believed to be a risk factor for developing chronic respiratory failure. As such, the high prevalence of SH in **Chapter 5** underscores the need for prospective studies identifying patients at risk for SH and chronic respiratory failure. Contrary to expectations, no correlation were found between increasing BMI and prevalence of SH. Whether the lack of correlation is due to protective mechanisms attributed to obesity or limitations of the study remains unknown.

This thesis highlights the complex and sometimes paradoxical interplay between COPD and obesity. Obesity is a prevalent condition in patients with COPD and affects several clinical outcomes. Whether obesity is detrimental or beneficial for certain outcomes depends on many factors. For sure, characterizing obesity by solely using BMI and COPD by solely using airflow obstruction (GOLD class) is too simplistic and can't pave the way to personalized management. Future research, focussing on different subtypes of COPD as well as taking the heterogeneity of obesity into consideration is needed in order to determine the ideal body composition for each individual patient.

Nederlandse samenvatting

Chronic Obstructive Pulmonary Disease (COPD) is heterogene longaandoening gekenmerkt door chronische respiratoire symptomen (kortademigheid, hoest, sputumproductie) als gevolg van afwijkingen aan de luchtwegen (bronchitis, bronchiolitis) en/of longblaasjes (emfyseem) die aanhoudende, vaak progressieve, luchtstroomobstructie veroorzaken. COPD is een veelvoorkomende chronische ziekte met een aanzienlijke ziektelast. Obesitas, gedefinieerd als een body mass index (BMI) $\geq 30,0$ kg/m², is ook een veelvoorkomende aandoening die veel mensen wereldwijd treft. Dit proefschrift beschrijft verschillende aspecten van de interactie tussen COPD en obesitas wanneer ze samen voorkomen.

Hoofdstuk 2 geeft een overzicht van de impact van obesitas op COPD. Deze review beschrijft de huidige kennis over de prevalentie van obesitas bij patiënten met COPD. Bovendien wordt het effect van obesitas op longfunctie, kortademigheid, inspanning en risico op exacerbatie beschreven. De prevalentie van obesitas bij COPD toont grote mate van variabiliteit in verschillende studies. Belangrijke factoren die deze variabiliteit mogelijk kunnen verklaren worden besproken. Voor een beter beeld is het o.a. van belang om door een arts gestelde diagnose van COPD (ten minste uitvoeren van spirometrie) en werkelijk gemeten gewicht en lengte te gebruiken in studies in plaats van door patiënten zelf gerapporteerde data. Hoewel obesitas bij patiënten met COPD geassocieerd is met minder hyperinflatie van de longen, tonen eerdere studies tegenstrijdige resultaten over hoe dit kortademigheid beïnvloedt. Tot slot is het belangrijk om rekening te houden met de heterogeniteit van COPD en andere variabelen van lichaamssamenstelling naast BMI.

De prevalentie van obesitas in een populatie van poliklinische COPD-patiënten werd bestudeerd in **Hoofdstuk 3**. Deze studie toonde aan dat obesitas veel voorkomt (prevalentie van 22%) in deze groep. Obesitas kwam significant minder vaak voor bij zeer ernstige COPD (GOLD IV) in vergelijking met milde tot ernstige groepen (GOLD I-III). Obese COPD-patiënten hadden meer comorbiditeiten vergeleken met niet-obese COPD-patiënten. Bovendien kwamen cardiovasculaire en metabole comorbiditeiten vaker voor bij obese COPD-patiënten.

De impact van obesitas op longfunctie en kortademigheid werd bestudeerd in **Hoofdstuk 4**. De obese en niet-obese COPD-cohorten werden gematcht

voor leeftijd en ernst van luchtwegobstructie (FEV1). Obese COPD-patiënten hadden gunstige longfunctie met minder longhyperinflatie en een betere diffusiecapaciteit van de longen. Ondanks dit voordeel beschreven obese COPD-patiënten een toegenomen kortademigheid bij gewicht-dragende inspanning. Er werd echter ook aangetoond dat de lagere hyperinflatie de obese patiënten weldegelijk beschermt tegen meer uitgesproken kortademigheid. Verder was de kwaliteit van leven vergelijkbaar tussen obese en niet-obese COPD-patiënten. Ten slotte toonde deze studie aan dat de hoeveelheid vet, gemeten als vetpercentage en vetmassa index; en de locatie van vetweefsel (centraal) sterker geassocieerd waren met kortademigheid vergeleken met BMI.

Weinig studies hadden eerder de prevalentie van slaaphypoventilatie (SH) beoordeeld bij COPD-patiënten die overdag normocapnisch zijn. In **Hoofdstuk 5** werd aangetoond dat SH zeer vaak voorkomt bij patiënten met ernstige tot zeer ernstige COPD (GOLD III-IV). Ruim 66% van hen voldeed aan de criteria van SH. SH wordt beschouwd als een risicofactor voor het ontwikkelen van chronisch respiratoir falen. Als zodanig benadrukt de hoge prevalentie van SH in **Hoofdstuk 5** de noodzaak van prospectieve studies die patiënten identificeren wie risico lopen op SH en chronisch respiratoir falen. Buiten de verwachtingen werden geen correlaties gevonden tussen toenemende BMI en de prevalentie van SH. Het blijft nog onbekend of deze gebrek aan correlatie te wijten is aan beschermende mechanismen die aan obesitas worden toegeschreven of aan beperkingen van de studie.

Deze proefschrift benadrukt het complexe en soms paradoxale samenspel tussen COPD en obesitas. Obesitas is een veelvoorkomende aandoening bij patiënten met COPD en beïnvloedt verschillende klinische uitkomsten. Het hangt van vele factoren af of obesitas nadelig of gunstig is voor bepaalde uitkomsten. Het karakteriseren van obesitas door alleen BMI te gebruiken enerzijds en COPD door alleen luchtwegobstructie (GOLD-klasse) te gebruiken anderzijds, is in ieder geval te simplistisch. Toekomstig onderzoek, gericht op verschillende subtypes van COPD, evenals het rekening houden met de heterogeniteit van obesitas, is nodig om zorg op maat te kunnen bieden.



Appendices

List of publications

Research Data Management

Curriculum vitae

Word of gratitude (dankwoord)

List of publications

1. 1. Zewari S, Vos P, van den Elshout F, Dekhuijzen R, Heijdra Y. Obesity in COPD: Revealed and Unrevealed Issues. *COPD: Journal of Chronic Obstructive Pulmonary Disease*. 2017;14(6): 663–673. <https://doi.org/10.1080/15412555.2017.1383978>.
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3. 3. Zewari S, van den Borst B, van den Elshout FJ, Vercoulen JH, Dekhuijzen PN, Heijdra YF, et al. Adiposity increases weight-bearing exercise-induced dyspnea despite favoring resting lung hyperinflation in COPD. *Chronic Respiratory Disease*. 2022;19: 1–8. <https://doi.org/10.1177/14799731211052305>.
4. 4. Zewari S, van den Borst B, van den Heuvel M, van den Elshout F, Sastry M, Vos P. Sleep Hypoventilation is Common in Diurnal Normocapnic COPD Patients with Severe or Very Severe Obstruction and is Not Associated with Body Mass Index. *COPD*. 2023;20(1): 210–215. <https://doi.org/10.1080/15412555.2023.2215324>.

Research Data Management

This thesis is based upon findings from human studies conducted in accordance with the principles of the Declaration of Helsinki. Where applicable, ethical approval was obtained from the regional ethics committee (CMO Arnhem-Nijmegen), or the committee confirmed that the Medical Research Involving Human Subjects Act (WMO) did not apply.

The data for chapter 3 were extracted from the electronic health records system 'Ezis/HiX, Chipsoft'. To ensure privacy, patient data were pseudonymised using a secure, password-protected environment. Patient data were analysed using SPSS. The SPSS dataset was stored separately from the pseudonymisation code to maintain confidentiality. In the analysis dataset all identifiers except the pseudonymisation code were removed. Data will be stored for 15 years according to good clinical practice (GCP) guidelines.

Chapter 4 and 5 included questionnaires, pulmonary function tests and sleep study. The original data were stored in a secured environment which was only accessible by the principal investigator at the department of pulmonary medicine at Rijnstate hospital. These data were stored separately from pseudonymised files which were used for statistical analyses. The datasets utilized during these studies are available from the corresponding author on reasonable request.



Curriculum Vitae



Safir Zewari was born on 18 March 1988 in Kabul (Afghanistan). After completing secondary school (VWO) at Elde College in Schijndel in 2006, he began studying medicine at Radboud University Nijmegen where he obtained his medical degree in 2012. During his studies, he was introduced to scientific research through an internship at Griffith University in Gold Coast, Australia, where he conducted research in the Department of Physiology on contributing factors to the sensation of dyspnea.

After earning his medical degree, he began his PhD research at Rijnstate Hospital in Arnhem in the Department of Pulmonary Medicine, in collaboration with Radboudumc. His research focused on the effects of obesity in patients with COPD. The PhD program was initially supervised by Prof. Dr. P.N.R. Dekhuijzen and Prof. Dr. Y.F. Heijdra, and later by Prof. Dr. M. van den Heuvel as promotor. Day-to-day supervision was provided by co-promoters Dr. P.J. Vos and Dr. F.J.J. van den Elshout, pulmonologists at Rijnstate, and later also by Dr. B. van den Borst, pulmonologist at Radboudumc. The findings of this research are presented in this dissertation.

Safir completed his residency in pulmonary medicine in 2024 at St. Antonius hospital in Nieuwegein and Utrecht under supervision of Dr. F.M.N.H. Schramel. In the final phase of his residency, Safir primarily concentrated his training on thoracic oncology. After completing his residency, he began working as a pulmonologist at Antoni van Leeuwenhoek hospital in Amsterdam. Safir will start his new position as a pulmonologist-thoracic oncologist at Spaarne Gasthuis hospital in 2025.

Safir lives in Nieuwegein with his wife Shabnam and their children Rehan, Damin and Noah.

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