The Prevalence of Metabolic Syndrome In Chronic Obstructive Pulmonary Disease: A Systematic Review

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ABSTRACT
Type 2 Diabetes Mellitus (T2DM) and cardiovascular diseases (CVD) are common in patients with chronic obstructive pulmonary disease (COPD). Prevention of these co-morbidities in COPD requires knowledge on their risk factors. Metabolic syndrome (MetS) predisposes to the development of T2DM and CVD but its prevalence in COPD remains unclear. The aim of this review was to assess the prevalence of MetS and its components in COPD patients compared to controls and to investigate the contribution of clinical characteristics to MetS prevalence. We systematically searched PubMed and EMBASE for original studies in COPD that have investigated the prevalence of MetS and its components. In total, 19 studies involving 4208 COPD patients were included. The pooled MetS prevalence was 34%. Compared to controls, the prevalence was higher in COPD (10 studies, 32% and 30%, p = 0.001). The three most prevalent components in both COPD and controls were arterial hypertension (56% and 51%), abdominal obesity (39% and 38%) and hyperglycemia (44% and 47%). Compared to COPD patients without MetS, those with MetS had higher body mass index (BMI) (29.9 and 24.6 kg/m², p < 0.001), higher forced expiratory volume in 1 second (FEV₁) % predicted (54 and 51, p < 0.001) and were more frequently female (31% and 25%, p = 0.011). In conclusion, the prevalence of MetS in COPD patients is high and hypertension, abdominal obesity and hyperglycemia are the most prevalent components. Further studies are needed to evaluate the impact of lifestyle factors and medications on MetS in COPD.

Introduction
Chronic obstructive pulmonary disease (COPD) represents a major cause of morbidity and mortality worldwide and is estimated to become the fourth leading cause of death in 2030 (1). Although COPD is primarily characterized by airflow obstruction and pulmonary inflammation, its effects reach beyond the lungs. Systemic manifestations such as osteoporosis, depression, cardiovascular disease (CVD) and Type 2 Diabetes Mellitus (T2DM) are highly prevalent in these patients and significantly contribute to symptom burden and health status (2, 3). CVD and T2DM are present across all COPD disease stages (2) and increase the risk of hospitalization and mortality (4). In fact, in COPD patients with mild-to-moderate airflow obstruction, CVD is even the leading cause of mortality (5).

Prevention of incident T2DM and CVD in patients with COPD requires a detailed understanding of their risk factors, which could be generic or could reflect an interaction between lifestyle and disease specific determinants. Metabolic syndrome (MetS) is a constellation of metabolic risk factors that increase the risk developing T2DM and CVD. The diagnosis of MetS is based on the presence of central obesity, hypertension, dyslipidemia, and hyperglycemia. Various MetS definitions are available and differ in specific cut points of the components (Table 1). The prevalence of MetS in the general population varies from 21%–31% in Asia (6, 7), to 34% in the USA (8), and increases with increasing age and body mass index (BMI) (9). Predisposing factors associated with MetS development are smoking (10, 11) and a sedentary lifestyle (12, 13), which are well-described features in COPD patients (3). Moreover, specific factors relating to COPD as a primary lung disease, such as relative hypoxaemia and steroid use may also contribute to the MetS (14). Therefore, the prevalence of MetS in COPD is hypothesized to be higher compared to the general population. Furthermore, knowledge on predisposing factors may aid in characterizing the patients with the highest risk of developing MetS and it may give more insight into targets for interventions aiming to reduce MetS prevalence, development of T2DM and eventually CVD mortality in COPD.

In this review we systematically searched the literature for observational studies that analyzed MetS prevalence in COPD patients and preferentially in control populations as well. Furthermore, we investigated the prevalence of the
### Table 1. Most widely used definitions of metabolic syndrome.

| WHO (1998) (15) | EGIS (16) | NCEP ATP III (2001 and 2005) (17, 18) | AACE (2003) (19) | IDF (20) | Alberti (2009) (21) |
|-----------------|-----------|--------------------------------------|------------------|----------|---------------------|
| **Central obesity** | BMI > 30 kg/m² and/or WHR > 0.90 in men or WHR > 0.85 in women | WC ≥ 94 cm in men and ≥ 80 cm in women | WC ≥ 102 cm in men and ≥ 88 cm in women | BMI > 25 kg/m² | WC ≥ 94 cm for Euroid men and ≥ 80 cm for Euroid women, with ethnicity specific values for other groups |
| **Hyperglycemia** | IGT, IFG, or T2DM or lowered insulin sensitivity | IGT or IFG | ≥ 110 mg/dl<sup>a</sup> | IGT or IFG | ≥ 100 mg/dl<sup>b</sup> |
| **Dyslipidemia** | TG ≥ 150 mg/dl and/or HDL < 35 mg/dl in men or < 39 mg/dl in women | TG ≥ 150 mg/dl and/or HDL < 38 mg/dl in men or < 50 mg/dl in women | TG > 150 mg/dl and HDL < 40 mg/dl in men or < 50 mg/dl in women<sup>c</sup> | TG > 150 mg/dl or specific treatment for this lipid abnormality | TG ≥ 150 mg/dl<sup>f</sup> |
| **Hypertension** | ≥ 160/90 mmHg | ≥ 130/85 mmHg | > 130/85 mmHg | | ≥ 130/85 mmHg |
| **Other** | Microalbuminuria<sup>d</sup> | — | — | Other features of insulin resistance<sup>e</sup> | — |
| **MetS diagnosis** | Hyperglycemia plus any two of the other criteria | Plasma insulin > 75<sup>th</sup> percentile plus any two of the other criteria | Three or more of the five criteria | Hyperglycemia plus any of the other criteria | Central obesity plus any two of the other criteria |

**Abbreviations:** AACE, American Association of Clinical Endocrinologists; BMI, body mass index; EGIS, European Group for Study of Insulin Resistance; HDL, high density lipoprotein; IDF, International Diabetes Foundation; IFG, impaired fasting glucose; IGT, impaired glucose intolerance; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; T2DM, Type 2 Diabetes Mellitus; TG, triglycerides; WC, waist circumference; WHO, World Health Organization; WHR, waist-to-hip ratio.

<sup>a</sup> Ethnic specific cutoffs are: Euroid, Sub-Saharan Africans, Mediterranean and Middle East: male ≥ 94 cm, female ≥ 80 cm; South Asians, Chinese and South and Central Americans: male ≥ 90 cm, female ≥ 80 cm; Japanese: male ≥ 85 cm, female ≥ 90 cm.

<sup>b</sup> In the revised NCEP ATP III definition of 2005 criterion for hyperglycemia was glucose level of ≥ 100 mg/dl.

<sup>c</sup> In the revised NCEP ATP III definition of 2005 and in the definition of Alberti, treatment for elevated glucose, elevated triglycerides, reduced HDL and antihypertensive drug treatment in a patient with a history of hypertension were also positive criteria.

<sup>d</sup> Urinary albumin excretion of ≥ 20 µg/min or albumin-to-creatinine ≥ 30 mg/g.

<sup>e</sup> Includes family history of type 2 diabetes mellitus, hypertension and cardiovascular disease, polycystic ovary syndrome, sedentary lifestyle, advancing age, and ethnic groups susceptible to type 2 Diabetes Mellitus.
individual MetS components and studied associations with general clinical characteristics including age, gender, BMI, disease severity, inflammatory profile, medication use and lifestyle characteristics.

**Methods**

**Data sources and search strategy**

This systematic review was performed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (22). Pubmed and EMBASE databases (through April 2015) were used to find relevant articles. The search strategy consisted of terms on MetS and COPD (see Supplementary information appendix 1 for terms used and search strategies). In addition, reference lists of retrieved articles were scanned for additional publications.

**Study selection and data extraction**

A first screening was independently done by two researchers (NCL and RB) based on title and abstract. In case of disagreement, a third person (BB) decided whether to include or exclude the study. Articles were considered for inclusion when they were original studies in patients with COPD, reported on the definition and prevalence of MetS and were written in English. MetS definition, prevalence of MetS and its individual components, age, gender, BMI, forced expiratory volume in 1 second (FEV$_1$), Global initiative for Obstructive Lung Disease (GOLD) stage, information about systemic inflammation, lifestyle characteristics (smoking and physical inactivity), and medication use were extracted. Original authors were contacted in case of missing data. If we were unable to gain information on the MetS definition applied, the study was excluded.

**Statistics**

The overall pooled prevalence was calculated by summing the number of COPD patients with MetS divided by the total number of COPD patients. Means were weighted by sample size to calculate the pooled means. We compared the prevalence of MetS, prevalence of its components and characteristics (i.e., age, gender, BMI and FEV$_1$ %) between COPD patients and controls as well as between COPD patients with and without MetS using Chi-square test for discrete variables and Welch test for continuous variables due to heterogeneity of variance. All analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 22. A $p$-value $< 0.05$ was considered statistically significant.

**Results**

**Study selection**

A flow chart of article selection is presented in Figure 1. The searches in Pubmed and EMBASE yielded 107 and 269 hits, respectively. Of these 376 articles, 69 were duplicates and 278 were excluded based on title and abstract. Of the remaining 29 articles, 6 were excluded because they were not original studies, and 4 were excluded because no prevalence of MetS was mentioned. Finally, 19 observational studies were included, of which 10 included a control group.

![Flow chart of article selection](image-url)
**Table 2. Characteristics of COPD patients in included papers and prevalence of metabolic syndrome and its components.**

| First author | Population (setting) | n   | Age (y) | Sex (%male) | BMI (kg/m²) | FEV₁ %pred | GOLD (%) I / II / III / IV | Definition | Prevalence (%) |
|--------------|----------------------|-----|---------|-------------|-------------|-------------|--------------------------|------------|----------------|
| **North America** | | | | | | | | | |
| Marquis (23) | Patients entering a 12-week rehabilitation program | 38  | 66±7    | 61          | 28±5        | 43±16       | —                        | NCEP-ATP III 2001 | 47           |
| Park (24)    | NHANES subjects with physician-diagnosed emphysema or chronic bronchitis | 223  | 70±9    | 51          | 28.7±7.2    | —           | —                       | Alberti     | 55           |
| Park (25)    | NHANES subjects with physician diagnosed emphysema or chronic bronchitis with FEV₁/FVC < 0.7 | 94   | 62±10   | 45          | 27.0±6.4    | 67±21       | —                       | Alberti     | 58           |
| Poulin (26)  | Patients previously engaged in pulmonary rehabilitation | 28   | 65±5    | 100         | 28.2±3.5²  | 42±16³      | 29/36/36/-              | NCEP ATP III 2005 | 29           |
| **South America** | | | | | | | | | |
| Tanni (27)   | Patients with mild to very severe COPD | 115  | 65±10   | 68          | 25.8±5.7    | 59±25       | 18/38/14/30              | Alberti     | 36           |
| **Europe**   | | | | | | | | | |
| Díez-Manglano (28) | Patients admitted for COPD exacerbation | 375  | 74±9⁴   | 89          | 27.0±4.6⁴  | 43±12⁴      | —/34/54/73               | Alberti⁵    | 48           |
| Minas (29)   | Outpatients with mild to very severe airflow limitation | 114  | 66 (62-71)⁶ | 100        | 25.3±4.6⁴  | 55 (33–66)⁵ | —                       | NCEP-ATP III 2001 | 21           |
| Breyer (30)  | Clinically stable COPD patients from the CIROCOC study | 228  | 64±7    | 59          | 26.2±5.1    | 53±19       | —                       | IDF         | 57           |
| Watz (31)    | Stable outpatients | 170  | 64±4⁴   | 75          | 26.3±5.0⁴  | 56±8⁴       | 20/34/25/21              | IDF         | 47           |
| Fumagalli (32) | Patients referred to pulmonary wards of hospitals | 169  | 74±8    | 73          | 27.3±4.8    | 56±20       | —                       | NCEP ATP III 2005 | 21           |
| Skyba (33)   | Outpatients free from exacerbations for ≥ 8 weeks | 44   | 62±7    | 86          | 26.5±7.1    | 54±23       | —                       | IDF         | 39           |
| **Middle East** | | | | | | | | | |
| Akpinar (34) | Outpatients with stable COPD | 91   | 64±9    | 86          | —           | —           | 14/58/22/7               | NCEP-ATP III 2001 | 45           |
| Küpeli (35)  | Patients reported for regular follow-up at pulmonary department | 106  | 67±9⁴   | 86          | 28.0±5.7⁴  | 63±24⁴      | 27/37/39/6               | NCEP-ATP III 2001 | 27           |
| Ozgen (36)   | Outpatients | 50   | 61±6    | 90          | 27.2±5.0    | 46±17       | —                       | IDF         | 44           |
| Hosny (37)   | Outpatients from the chest unit | 50   | 58±8    | 88          | 27±4        | 54±16       | —                       | NCEP-ATP III 2001 | 40           |
| **East and Northeast Asia** | | | | | | | | | |
| Park (38)    | Newly diagnosed airflow obstruction in KNHANES II | 133  | 61±10⁴ | 75          | 23.5±2.9⁴  | —           | 59/38/4/-                | NCEP-ATP III 2001⁶ | 37           |
| Lam (39)     | Patients with airflow obstruction from the GHHARE | 495  | 64±6⁴   | 26          | —           | —           | —                       | IDF     | 23           |
| Funakoshi (40) | Subjects who underwent a health screening | 645  | 62±9⁴   | 100         | 22.9±2.7⁴  | 80±10³      | 48 GOLD I/54 GOLD II-IV | NCEP-ATP III 2005⁶ | 23           |
| Chung (41)   | KNHANES subjects | 1039 | 65±10⁴ | 73          | 23.4±2.9⁴  | 77±16⁴      | 46/48/6/1               | NCEP-ATP III 2005⁶ | 32           |

**Abbreviations:** BG, blood glucose; BMI, body Mass Index; BP, blood pressure; COPD, Chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Obstructive Lung Disease; HDL, high density lipoprotein; IDF, International Diabetes Foundation; n, number of subjects; MetS, metabolic syndrome; NCEP-ATP III 2001, National Cholesterol Education Program Adult Treatment Panel III 2001; NCEP-ATP III 2005, Revised National Cholesterol Education Program Adult Treatment Panel III; TG, triglycerides; WC, waist circumference.

Data are shown as mean±standard deviation unless specified otherwise.

a Pooled mean ± standard deviation.
b Body mass index > 30 kg/m² instead of waist circumference criteria.
c Median (Interquartile range).
d Pooled prevalence of high systolic and diastolic blood pressure.
e Blood glucose ≥ 100 mg/dL instead of ≥ 110 mg/dL.
General characteristics and prevalence of MetS in COPD patients

Characteristics of the COPD patients of the included 19 studies are presented in Table 2. In total, studies reported on 4208 COPD patients. These patients had a pooled mean age of 65 ± 4 years (mean ± standard deviation), a BMI of 25.1 ± 2.0 kg/m² and a FEV₁ % predicted of 66 ± 14% and were mostly men (72%). The overall mean prevalence of MetS was 34% (21–58%) and varied between geographical areas (North America 53%, South America 36%, Europe 41%, Middle East 38% and East and Northeast Asia 28%). Studies differed in the MetS definition used: 6 studies used IDF and 4 studies applied Alberti et al. (21). Five studies used NCEP ATP III 2001, 5 studies used NCEP ATP III 2005, 5 studies used IDF and 4 studies applied Alberti et al. (21).

General characteristics of COPD patients with MetS and without Mets

In total 10 studies compared characteristics of COPD patients with MetS to COPD patients without MetS (24, 25, 27, 29–31, 34–36, 42). Patients with MetS had a higher BMI and had higher FEV₁ % predicted compared to patients without MetS (Table 3). The prevalence of male patients was significantly lower in the MetS group compared to the non-Mets group. Furthermore, four studies reported higher serum C-reactive protein (31, 34–36) and serum interleukin-6 (31) in COPD patients with MetS compared with patients without MetS (data not shown).

Differences in prevalence of MetS and its components between COPD patients and controls

In total, 10 studies compared COPD patients (n = 2864) with a control group (n = 24532) (25, 30, 34, 36–41). Characteristics of COPD patients are shown in Table 2, characteristics of the controls are presented in Supplemental Table S1. COPD patients were significantly older, had a significantly lower BMI and were more often males (data not shown). As presented in Figure 2, a higher prevalence of MetS among COPD patients compared to controls was found in 9 out of 10 studies (23, 25, 30, 34, 36–39, 41), and was significant in 5 studies (23, 30, 34, 37, 38). The overall mean prevalence of MetS in COPD patients was 32% (23–58%) versus 30% (17–54%) in controls (p = 0.001). In total, 7 studies reported the prevalence of MetS components in COPD patients (N = 1725) and controls (N = 18380). As shown in Figure 3, the three most prevalent components in both COPD patients and controls were hypertension (56% and 51%), hyperglycemia (44% and 47%) and abdominal obesity (39% and 38%). Prevalence of hypertension and low HDL cholesterol was significantly different between COPD patients and controls while prevalence of other components was comparable between both groups.

Contributing factors of MetS in COPD

Smoking status in MetS and non-MetS patients was reported in 5 studies (24, 28–30, 35). Four studies found no significant difference (24, 28, 30, 35) and one study showed significantly less
smoking in the MetS group expressed by pack-years (29). Physical activity level was assessed in three studies (24, 25, 31) by measuring the physical activity level with an accelerometer or by measuring the sedentary time. One study found no significant difference in sedentary time between the MetS group and non-MetS group (25), however, the other studies showed significantly reduced physical activity levels and lower activity intensity in the COPD patients with MetS compared to the patients without MetS (24, 31). Medication use between MetS and non-MetS patients with COPD was reported in three studies (28, 30, 35). These studies showed more inhaled or oral steroid use, more statin use, more beta-blockers use and more antihypertensives in the MetS group compared to the non-MetS group. No differences were found in use of anti-diabetics, insulin and long term oxygen therapy (28, 30).

**Discussion**

This systematic review of current literature shows that the prevalence of MetS in COPD is significantly higher in COPD patients compared to controls. MetS is more prevalent in overweight and obese patients with less advanced airflow obstruction and seems to occur more frequently in female patients. The three most prevalent MetS components in both COPD patients and controls are hypertension, abdominal obesity and hyperglycemia. Smoking does not seem to be a discriminative factor between patients with and without MetS, while further studies are needed to assess the impact of other lifestyle factors and medications on MetS prevalence.

To our knowledge, this is the first systematic review on the prevalence of MetS and its components in COPD patients. Our findings are strengthened by the large number of included subjects in both the patient and control groups and the review provides some new insights about the risk profile for MetS in COPD.

A high MetS prevalence implies a significant risk for development of T2DM with or without CVD. Previous research has indeed shown that both CVD and T2DM are frequent co-morbidities in COPD (4, 5). Furthermore, COPD patients with CVD, hypertension and T2DM were shown to be at increased risk for hospitalizations and all-cause mortality (4). The high MetS prevalence in lower disease stages coincides with the reported high cardiovascular-related mortality in mild to moderate disease (5). Furthermore, recent studies have identified a so-called “co-morbidity predominant subtype” of COPD patients, which is characterized by a cluster of metabolic co-morbidities, including obesity, CVD and T2DM (43, 44). This seems to coincide with the most prevalent MetS components found in our review.

COPD patients with MetS were more frequently females, had higher BMI and higher FEV₁ compared to COPD patients without MetS. The later was also shown by many studies reporting the highest MetS prevalence in patients with GOLD stage II compared to higher GOLD stages (28, 29, 32, 34, 36). This observation could be due to a relatively higher influence of lifestyle on body composition and metabolic health in less advanced disease compared to COPD induced triggers on the wasting process in advanced disease (45). Secondly, if we assume that MetS in COPD is also related to higher CVD risk, these patients might die earlier of CVD mortality, not reaching end-stage COPD.

Smoking is an established risk factor for COPD and has been associated with increased MetS prevalence and increased CVD risk (11). It would thus be expected that the prevalence of smokers is higher in COPD patients with MetS compared to patients without MetS. Furthermore, physical inactivity and sedentary activity are also associated with MetS (12, 13) and typical for COPD patients (3). However, limited studies reported smoking prevalence and physical activity level and future studies addressing MetS in COPD should include detailed assessment of lifestyle factors including smoking behavior and physical activity level as well as dietary quality which was recently shown to be poor in these patients (46).

Medications can directly influence the prevalence of MetS. Accordingly, the NCEP ATP III and IDF definitions of MetS include medication use for dyslipidemia, hypertension or diabetes as fulfillment of the selected criteria (Figure 1). However, not all studies clearly reported use of medications as a positive criterion for MetS. This inconsistency may explain the vast differences in the prevalence of hyperglycemia and dyslipidemia among studies. Furthermore, oral glucocorticoids can increase blood glucose levels, HDL levels and appetite, and cause muscle atrophy and abdominal obesity (47). Indeed, of the four studies in COPD reporting medication use, two found a significantly higher use of steroids in the group with MetS (28, 31). Other common medications in COPD, such as anti-depressants can cause impaired glucose tolerance (48), further contributing to MetS. Medications can thus influence MetS prevalence in COPD and need to be considered in future studies.

MetS and components were prevalent in COPD patients, but the prevalence varied greatly among studies, which could be due to differences in study design and setting. As MetS is a predictor for CVD and DM, existing co-morbidities can greatly affect its' prevalence. Minas et al., which excluded COPD patients with DM and CVD with the exception of hypertension, reported the lowest MetS prevalence (22%), whereas Diez-Manglano et al. and Breyer et al. found the highest MetS prevalence in COPD patients with more co-morbidities (28, 30). Furthermore, included studies used different MetS definitions (Table 1), which are similar, but apply slightly different criteria for diagnosing MetS. Moreover, the average prevalence of MetS differed in different regions, with a lower MetS prevalence in the Asian studies (28%) compared to European (41%) and American studies (53%). This is consistent with findings from population studies, which found lower prevalence in Asia (21% in China (6) and 31% in Korea (7)) compared to USA (34%) (8). Furthermore, the difference in MetS prevalence between COPD patients and controls was small. This could be explained by the fact that the control group included subjects without COPD, but with other co-morbidities. Altogether, the study diversity has probably contributed to the broad range of reported MetS prevalence and components prevalence observed in our review and should be considered when interpreting the results.

The concept of MetS has received criticism on its applicability in scientific research and it has been questioned whether it better predicts cardiometabolic risk compared to its individual components (49). Studies assessing individual MetS components or insulin resistance as the cornerstone of MetS might...
help unveil the background of increased cardiometabolic risk in COPD patients and allow us to specifically target these factors. While the relative influence of lifestyle versus disease specific determinants and medication is still unclear, we know that exercise training may improve MetS in other risk populations (50). Pulmonary rehabilitation is an established intervention in COPD focusing on exercise training but the effects on modification of MetS is surprisingly not yet investigated in detail. Studies assessing the effect of such interventions on the cardiometabolic risk in COPD patients would contribute importantly to the understanding of MetS and to reducing disease burden for both patients and the healthcare system.

Conclusion
The prevalence of MetS is higher in COPD patients compared to controls. Its most prevalent components are abdominal obesity, hypertension and hyperglycemia. MetS is more prevalent in female patients, patients with less severe COPD and high BMI. Smoking does not seem to be discriminative for MetS in COPD. Data is lacking on the contribution of physical activity and medications to MetS prevalence in COPD. Future longitudinal and interventional studies are needed to unveil the relation of lifestyle and disease to MetS prevalence as well as the best management possibilities.

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Authors Lipovec and Beijers contributed equally to this work.

Declaration of interest
The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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