HHS Public Access

Author manuscript

Semin Respir Crit Care Med. Author manuscript; available in PMC 2016 August 30.

Published in final edited form as:

Semin Respir Crit Care Med. 2015 August ; 36(4): 575–591. doi:10.1055/s-0035-1556063.

Comorbidities and Chronic Obstructive Pulmonary Disease: Prevalence, Influence on Outcomes, and Management

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Abstract

Comorbidities impact a large proportion of patients with chronic obstructive pulmonary disease (COPD), with over 80% of patients with COPD estimated to have at least one comorbid chronic condition. Guidelines for the treatment of COPD are just now incorporating comorbidities to their management recommendations of COPD, and it is becoming increasingly clear that multimorbidity as well as specific comorbidities have strong associations with mortality and clinical outcomes in COPD, including dyspnea, exercise capacity, quality of life, healthcare utilization, and exacerbation risk. Appropriately, there has been an increased focus upon describing the burden of comorbidity in the COPD population and incorporating this information into existing efforts to better understand the clinical and phenotypic heterogeneity of this group. In this article, we summarize existing knowledge about comorbidity burden and specific comorbidities in COPD, focusing on prevalence estimates, association with outcomes, and existing knowledge about treatment strategies.

Keywords

COPD; comorbidity; clinical outcomes

In the past several years, there has been a growing body of literature attempting to better understand the issue of co-morbidity in patients with chronic obstructive pulmonary disease (COPD). The population with COPD in the developed world consists mainly of former or active cigarette smokers and smoking is also a known risk factor for many nonpulmonary diseases. Though smoking may lead to concomitant comorbidities, it is increasingly recognized that patients with COPD also have a high burden of comorbidities which may be independent of smoking. Additionally, it is becoming clear that these comorbidities contribute to worse patient-centered outcomes and increased health care utilization and mortality.

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It is the goal of this article to review the present knowledge surrounding comorbidities and COPD. We first review the topic of general comorbidity burden and then turn our focus to the overlap of COPD with specific comorbid conditions. We chose to examine several of the most common of these comorbid conditions, describing not only prevalence but also evidence for impacts of these conditions on important outcomes in COPD.

Chronic Obstructive Pulmonary Disease and General Comorbidity

There is a diverse body of literature which has emerged to describe the general overlap of comorbidity burden, or multi-morbidity, in patients with COPD. Some studies describe the prevalence of comorbidities or multimorbidity in COPD; others examine previously developed measures of comorbidity burden or develop COPD-specific indices to describe comorbidity burden; and yet other studies incorporate comorbidities into subphenotyping attempts or clustering models.

The majority of studies clearly demonstrate that comorbidities are a nearly ubiquitous problem in patients with COPD.[1–8] Table 1 displays results from studies from the United States, Europe, Latin America, and Australia which all demonstrate in a wide range of COPD cohorts (defined using spirometry, self-report, or administrative data) that approximately 86 to 98% of individuals with COPD have at least 1 comorbid condition,[2–5,8,9] and that the average number of comorbidities per individual is 1.2 to 4.[3–7] Additionally, it seems clear that the burden of comorbidities is more substantial in individuals with more severe COPD.[3,8] Though a limitation of such studies is the heterogeneity in how information on comorbidities is obtained, varying from medical records, self-report, or medication data, the consistency and strength of this signal throughout the literature is certainly difficult to disregard.

Several of the studies from Table 1 utilized the Charlson comorbidity index[10] to describe comorbidity burden. Some recent studies have questioned the validity of this index in the COPD-specific population, given that it was developed and validated in a general hospital cohort to predict mortality. Almagro et al showed that the Charlson index underestimated the burden of comorbidities in a Spanish population with COPD.[1] Accordingly, there have been a few recent attempts to better quantify comorbidity burden in COPD populations. Divo and colleagues from the BODE (Body mass index, airflow Obstruction, Dyspnea, and Exercise capacity) collaborative group developed the COPD-specific comorbidity test (COTE) index to predict mortality in COPD.[11] They demonstrated that when combined with the BODE index, the COTE index added an important degree of prediction to mortality.[12] Given the importance of clinical outcomes in patients with COPD, Frei et al developed the COMCOLD index, designed to predict health status in COPD patients.[13] Descriptions of these indices can be found in Table 2.

Given the emerging interest to establish subphenotypes of COPD, a few studies have attempted to incorporate comorbidities to establish unique COPD phenotypes.[9,14,15] In a study of 342 individuals with COPD identified 3 months after hospitalization for exacerbation, the authors used a clustering algorithm to identify three separate groups, one of which had a higher prevalence of being overweight, more systemic inflammation as well

as cardiovascular disease, and diabetes. Notably, this comorbidity-rich group had more hospitalizations for cardiovascular complications.[14] Vanfleteren et al performed cluster analysis of 213 COPD patients and established five unique comorbidity clusters: (1) less comorbidity; (2) cardiovascular cluster, having more hypertension and atherosclerosis, (3) cachectic cluster, having lower body mass index (BMI), muscle wasting, osteoporosis, and renal impairment; (4) metabolic cluster, having higher BMI, lipid abnormalities, hypertension, and atherosclerosis; and (5) psychological cluster having not only more anxiety and depression but also a high prevalence of coronary heart disease events. Despite comparable lung function, there were important differences in dyspnea and quality of life in different clusters and higher levels of systemic inflammation in the cardiovascular and metabolic clusters.[9] A recent study by Baty et al utilized administrative data of COPD hospitalizations in Switzerland to describe which comorbidities cluster with defined subphenotypes of COPD. The emphysema subtype was associated with cachexia and pulmonary heart disease; the chronic bronchitis subtype was associated with obesity, diabetes, and hypertension; and the asthma/ COPD overlap phenotype was associated with morbid obesity, alveolar hypoventilation, and sleep apnea.[15] Thomsen et al found that among individuals with COPD in two large Danish cohorts, the presence of elevated inflammatory markers including c-reactive protein, fibrinogen, and white blood cell counts were associated with increased risk of having heart disease (myocardial infarction or heart failure), diabetes, lung malignancy, and pneumonia.[16]

Beyond establishing the prevalence and clinical phenotypes of comorbidities in COPD, there have been a substantial number of studies which have sought to understand the general contribution of comorbidities to outcomes. There has been a great deal of work surrounding the implication of comorbidities with regard to hospitalization risk, length of stay, and hospital-related mortality. Almagro et al showed in a cohort of older individuals followed up after hospitalization for COPD that comorbidity burden as assessed by the Charlson index was associated with higher risk for mortality (odds ratio [OR]: 1.23, 95% confidence interval [CI]: 1.07–1.40) as well as hospital length of stay and readmissions.[17] Using administrative data of hospitalizations where COPD was primary or secondary as the cause in Switzerland, the presence of many comorbidities was associated with in-hospital death and re-hospitalization.[15] In another analysis of Finnish administrative hospitalization data, among hospitalizations in which COPD was the primary diagnosis, the presence of other diagnoses was associated with significantly longer length of hospitalization.[18] Additionally, one study of Maryland Medicaid claims showed that among individuals with COPD, the presence of comorbidities was associated with significantly higher health expenditures.[19]

With regard to mortality, several studies have demonstrated an increased risk for death in individuals with COPD also having significant comorbidity burden.[11,20–22] Divo et al noted significant increases in risk for death in individuals with higher values of the COTE index (hazard ratio [HR]: 1.13, 95% CI: 1.08–1.18).[11] Comorbidity burden assessed by Charlson and/or COTE indices have also been linked to all-cause and respiratory-specific mortality risk in severe COPD.[20,21] Further, in a large epidemiologic cohort, increasing number of comorbidities was associated with increased mortality, such that one comorbid condition increased odds of death by 74% (OR: 1.74, 95% CI: 1.18–2.56), while four or more

comorbidities increased odds of death by more than 400% (OR: 4.57, full 95% CI not available in manuscript).[22]

There have also been several studies demonstrating the importance of comorbidities in their contribution to quality of life in COPD.[5,7,13,23,24] Koskela et al demonstrated the contribution of multiple comorbidities to poor health-related quality of life in a large cohort of hospital-based patients with COPD, demonstrating the strongest association of mental illness with poor quality of life.[23] The relationship of increasing number of comorbidities with incremental decreases in quality of life has been well demonstrated in four studies, including the National Health and Nutrition Examination Survey (NHANES)[5] and three other large epidemiologic studies of COPD.[7,13,24] It is also interesting that several studies have found differences in either comorbidity burden or impacts based on gender[1,2,11,25] or race,[24] and these findings certainly require further study and development.

Ultimately, the compilation of evidence from studies of comorbidity burden and multimorbidity in COPD have demonstrated that multimorbidity is a nearly ubiquitous problem in patients with COPD, and that there are clear short-term associations with mortality, quality of life, and patient-centered outcomes. It also seems clear that attempts to establish subphenotypes of COPD are enriched by the inclusion of comorbidities, which may provide insight into mechanisms for worse outcomes in specific subgroups.

Overlap of Specific Comorbidities and Chronic Obstructive Pulmonary Disease

In addition to the study of the impact of general comorbidity burden on COPD outcomes, several studies have investigated the impact of specific comorbidities on the burden of COPD. Though many comorbid conditions have been studied in this regard, the next section will highlight the research surrounding the most prevalent of these syndromes (Table 3).

Chronic Obstructive Pulmonary Disease and Neurologic Disease

There have been several recent studies designed to understand the susceptibility to and impact of cognitive dysfunction in patients with COPD. In an analysis of 1,425 participants from the Mayo Clinic Study on Aging, Singh et al prospectively ascertained that individuals with doctor-diagnosed COPD have a higher risk for the development of mild cognitive impairment (MCI). Specifically COPD was associated with al-most double the risk of nonamnestic MCI (HR: 1.83, 95% CI: 1.04–3.23).[26] Though this report relied upon doctor diagnoses of COPD, other studies have demonstrated the risk factors for and consequences of cognitive dysfunction in individuals with spirometry-diagnosed COPD. COPD patients with lower forced expiratory volume in one second(FEV_1) and forced vital capacity (FVC) were more likely to have cognitive decline.[27] Recently, Dodd et al found that after matching patients for disease severity, smoking intensity, risk for cerebrovascular disease, and hypoxemia, individuals with COPD suffering from acute exacerbations requiring hospitalization had significantly worse cognitive function with regard to processing speed measured by a host of neuropsychological testing, and these decrements in cognitive function were associated with negative clinical outcome measures such as St. George’s

Respiratory Questionnaire (SGRQ) and COPD Assessment Test scores, in addition to increased length of hospital stay.[28] Another study of 119 patients with a broad spectrum of COPD disease burden found that patients in Global Initiative for Obstructive Lung Disease (GOLD) 2011 categories C and D (including individuals at higher risk for airflow limitation or hospitalization for exacerbation, having any amount of respiratory symptoms or breathlessness) [29] had lower cognitive scores. They also noted that number of exacerbations was a significant predictor for worse cognitive function.[30] Filipowski et al similarly demonstrated significant decreases in mini mental status exam scores following a COPD exacerbation or spontaneous pneumothorax.[31] The prevalence of cognitive impairment in COPD has been reported to be between 3 and 20%, and varies based on the population and diagnostic criteria used.[28]

A few studies have attempted to better understand possible mechanisms for the findings of increased risk for cognitive dysfunction in individuals with COPD. Dodd and colleagues studied 25 patients with COPD and compared their advanced brain magnetic resonance imaging (MRI) findings with those of 25 control participants and foundno difference in degree of brain atrophy but noted significantly increased white matter lesions, hypothesized to be a result of microvascular damage from cigarette smoking.[32] In the Rotterdam study population, cerebral microbleeds in deep or infratentorial areas of the brain were more prevalent on MRIs in the population with COPD compared with controls, and those with COPD had a higher incidence of development of such lesions over time, which the authors hypothesized could be due to vascular changes resulting from systemic inflammation and hypoxia in patients with COPD.[33]

In addition to the above work regarding cognitive impairment in COPD, a recently published study from a large nation-wide cohort of over 20,000 participants in Taiwan found an increased risk of development of Parkinson disease in patients with COPD, again proposing the etiology as due to chronic hypoxemia and systemic inflammation.[34] Ultimately, there appears to be an emerging body of evidence showing that the population with COPD has a high burden of cognitive impairment. This is an important issue in patients with COPD as such impairment could conceivably contribute to lack of adherence to medication and exercise regimens. There is also some evidence that this impairment is associated with poorer clinical outcomes. Understanding the mechanism driving the coincidence of these chronic diseases is of utmost importance to determine if this subgroup would be amenable to specialized therapy, or if early intervention can lead to prevention.

Chronic Obstructive Pulmonary Disease and Depression

Mental health disorders such as depression and anxiety are extremely common in individuals with COPD, and a subject of much study within the past few decades. One of the earliest characterizations of depression and anxiety in patients with COPD was published by Light et al in 1985, and demonstrated in 45 patients with FEV_1 of less than 1.25 L that 42% had Beck Depression Inventory values consistent with depression.[35] More contemporary characterizations of depression similarly use validated measures of depression such as the Center for Epidemiologic Studies Depression scale (CES-D), the Hospital Anxiety and Depression Scale (HADS), and the Geriatric Depression Scale (GDS) and have described

the prevalence of depression to be between 16.5 and 27.4%.[36–42] Additionally, several studies have demonstrated that the risk for depression is higher in COPD when compared with the general population, even after adjusting for severity of disease,[37,43–46] including a meta-analysis which showed increased risk for depression in six studies, with a pooled RR of 1.69 (95% CI, 1.45–1.96) for the estimate of increased risk in patients with COPD compared with those without.[47]

Not only does the literature support COPD being a risk factor for the development of depression, but depression may also lead to worse outcomes in COPD. The presence of depression has been associated with risk of death in patients with COPD.[41,48–50] A recent meta-analysis based on seven existing studies estimated that the increased risk of death associated with depression in COPD was 83% (RR: 1.83, 95% CI: 1.00–3.36).[47] Depression has also been linked to other outcomes, including worse exercise capacity,[36,40,51] health status and quality of life,[43,44,52–55] rehospitalization,[56] dyspnea,[40,51] exacerbation risk,[39,54] and inability to perform activities of daily living.[44]

As explanation for worse outcomes experienced in individuals with COPD and depression, some have studied levels of inflammatory biomarkers in these individuals, but the signal for this association has been mixed.[57,58] Others have looked at psychosocial stressors and found poor social support,[59] marital status (being divorced, single, or widowed),[40] and low levels of education[40] to be associated with depression in COPD. Another important finding of a few studies was the disproportionate impact of depression on women with COPD.[37,38,53]

Alarmingly, one study found in a population of VA patients with a high prevalence of COPD and depression that only 50.6% of these individuals were adequately treated for their depressive symptoms,[60] while another group provided lower estimates of 27 to 33% of COPD patients receiving treatment of any form for their depression.[61] Though there are few studies that have looked at the impact of pharmacotherapy for depression on outcomes in COPD,[48,62] there have been a few more which have shown that pulmonary rehabilitation programs show some promise in improving depressive symptoms,[51,63–65] dyspnea,[64] quality of life,[66] and exercise capacity[51] in patients with depression and COPD. Regardless, it has been shown that depressive symptoms are a risk factor for nonadherence to maintenance exercise programs in COPD patients,[67] further demonstrating the challenge of treating this population of patients. Given the strong association with COPD and symptoms of depression, future studies should pursue screening and treatment strategies for this subgroup of individuals with a focus on the improvement of not only depression but also patient-reported outcomes such as quality of life, dyspnea, and exercise capacity.

Chronic Obstructive Pulmonary Disease and Anemia

The prevalence of anemia in COPD has been described to be as high as 43.9%,[68] and as low as 7%,[69] but estimates vary widely based on severity of disease, age, and sex. Chambellan et al described an anemia prevalence of 12.6% in men and 8.2% in women in a large cohort of more than 2,500 participants with COPD and noted that a lower hematocrit was associated with worse survival.[70] This association has been reproduced in stable outpatients,[71] inpatients with acute exacerbations of COPD,[72] as well as in the setting of acute respiratory

failure requiring mechanical ventilation.[73] One study demonstrated 4.4 times higher risk (HR: 4.4, 95% CI: 1.96–9.9) for mortality when anemia was present in a cohort of patients hospitalized for COPD exacerbation.[74]

Comorbid anemia has been described not only as a risk factor for death but also as an indicator for health care utilization, with lower hematocrit being a risk for hospitalization, increased duration of hospitalizations,[70,75] and hospital readmission in patients hospitalized for acute COPD exacerbation.[76] Additionally, anemia has been described as a risk factor for long-term oxygen use in patients with COPD.[77] One group of investigators noted a higher risk for dyspnea in COPD patients with concomitant anemia. Additionally, they found alterations in exercise testing measures in these individuals as well as a lower anaerobic threshold, demonstrating lower circulatory efficiency during exercise in COPD patients with anemia.[78] Interestingly, Silverberg et al noted that none of the COPD participants found to have iron deficiency anemia were prescribed iron supplementation. Further, they demonstrated that correction of iron deficiency improved dyspnea scores in their small cohort.[68] It is conceivable that anemia is a risk factor for poor outcomes in COPD because it is a reflection of chronic illness and disease burden. However, the longitudinal associations with mortality in combination with the contribution of anemia to health care utilization and patient-reported outcomes highlight the need for studies of screening and treatment of anemia in patients with COPD, keeping in mind the difficulty of treating the anemia of chronic disease.

Chronic Obstructive Pulmonary Disease and Sleep Apnea

Poor sleep quality and daytime sleepiness have been shown to be prevalent issues in patients with COPD, with one case–control study showing a prevalence of 67.9% of COPD cases having poor sleep quality signified by a Pittsburg Sleep Quality Questionnaire (PSQI) score of 5 or greater.[79] One study showed a prevalence of 48.1% of insomnia in patients with COPD in a large telephone survey.[45] Poor sleep quality in patients with COPD has been associated with poor outcomes such as quality of life.[80]

Estimates of prevalence of obstructive sleep apnea (OSA) in populations with COPD vary widely. Three studies showed no increased prevalence of OSA (as measured by sleep study) among individuals with COPD compared with controls.[81–83] The largest of these studies, an analysis of more than 5,000 individuals in the Sleep Heart Health Study, showed no significant difference in prevalence of sleep-disordered breathing in patients with and without obstructive airways disease, though this population mostly had mild obstruction.[83] Despite findings for lack of difference in prevalence of OSA, one of these studies showed that when COPD and OSA were present together, the degree of nocturnal desaturation and time spent in desaturation at night were worse,[82] and the Sleep Heart Health Study also showed a greater degree of desaturation when both diseases were present compared with participants with COPD or OSA alone.[83] A few studies showed COPD is more prevalent in a study population with OSA,[84,85] with the presence of COPD in addition to OSA being associated with more hypoxemia and hypercarbia as well as higher pulmonary artery pressure measurements at rest and with exercise.[85] The highest estimate for prevalence was

in one small study of patients hospitalized for COPD exacerbation which showed a prevalence of 51.4% of OSA defined as apnea hypopnea index ≥ 5.[86]

The presence of OSA and COPD, termed in much of the literature as the "overlap syndrome," has been shown to be associated with several negative outcome measures. Marin et al found the presence of the overlap syndrome was related to increased risk of death (RR: 1.70, 95% CI: 1.21–2.38) and severe exacerbation of COPD requiring hospitalization (RR: 1.70, 95% CI: 1.16–2.77) when compared with individuals with COPD only, and that this risk was mitigated in those with overlap syndrome treated with CPAP.[87] Another study showed an increased economic burden in individuals with overlap syndrome compared with COPD alone, evidenced by a significantly higher number of medical claims and costs incurred in a study of Maryland Medicaid claims.[88] The overlap syndrome has also been recently associated with increased risk for several intermediate cardiovascular outcomes including increased risk for new onset atrial fibrillation,[89] arterial stiffness,[90] and right ventricular remodeling.[91] Such findings further raise suspicions that the impact of OSA and cardiovascular disease on COPD outcomes could be mediated by alterations in inflammatory pathways.[92] These findings for worsened outcomes in individuals with the overlap syndrome emphasize the importance of understanding whether screening and therapeutic strategies should be approached differently in this population.

Chronic Obstructive Pulmonary Disease and Obesity

As the prevalence of obesity rises in the general population,[93] the importance of obesity as a comorbidity in COPD is gaining recognition. The prevalence of obesity in the population with COPD has been estimated between 29.1[94] and 43%,[95] and appears to vary somewhat based on severity of COPD, with higher prevalence in less severe COPD,[94] and also based on the constellation of other comorbidities affecting the patients.[94] The prevalence of obesity in COPD has been shown to be higher than in the general population even after matching for age, sex, and other demographic factors.[94,96]

Obesity has been associated with worse outcomes including health status, quality of life, and dyspnea and higher use of inhaled medications compared with lean patients with COPD independent of degree of airflow obstruction.[96,97] Additionally, the presence of obesity has been shown to be associated with increased health care utilization.[98]

The link between obesity and exercise capacity is less clear. Some studies show an association with reduced exercise capacity,[95,96] while others do not.[99] One group showed that obesity was associated with worse exercise capacity, but when adjusted for the amount of work (related to extra weight in kg), the distance walked was comparable. This group went on to find no difference in physiologic response to exercise in COPD patients based on body habitus.[100] One group surprisingly showed a higher peak oxygen uptake (VO_2) in exercise testing of obese patients with COPD compared with those with normal BMI.[101] It is possible that the discrepant findings with regard to the associations of obesity with exercise capacity could be explained by the impact of body habitus on the various components of exercise physiology. However, further studies are needed to better clarify this relationship.

It is theorized that differences in outcomes in obese patients with COPD could be related to differences in pulmonary mechanics. For example, obesity has been associated with decreased lung volumes and functional residual capacity[101,102] and also with less hyperinflation.[103] Another group described expiratory tracheal collapse as a frequent finding on CT scans of obese patients with COPD.[104] Another possible etiology for the negative impact of obesity is increased systemic inflammation,[96,105–108] which has been posited to contribute to worse outcomes through several mechanisms including a higher burden of cardiovascular disease or impact on the airways itself.

Interestingly, two groups have described the over-diagnosis of obstructive lung disease in obese individuals in some populations using symptoms and patient report for diagnosis, including a large population of Veterans in the United States.[109,110] This research demonstrates the importance of diagnosing COPD with spirometry particularly in obese populations, given the complexity of the possible etiologies for dyspnea. It is clear that obesity is prevalent in COPD and understanding its implications for clinical outcomes is of utmost importance. Ultimately, understanding its impact on outcomes, particularly functional outcomes, is difficult given obesity's seemingly ubiquitous impact on the many aspects of pulmonary and exercise function.

Chronic Obstructive Pulmonary Disease and Metabolic Syndrome

Metabolic syndrome affects anywhere from 21 to 57%[111–116] of patients with COPD and many studies show a higher prevalence of metabolic syndrome in individuals with COPD compared with controls,[113,116] even after accounting for other risk factors.[112,116] Interestingly, some have found the prevalence of metabolic syndrome in COPD to be higher in those with better lung function[117,118] or less severe stages of COPD.[111,119] Sarcopenia[120] and low levels of physical activity[115,119] have been identified as risk factors for metabolic syndrome in patients with COPD.[119] In addition, individuals with COPD and the metabolic syndrome were noted to be younger and with less severe airflow impairment, but had higher amounts of insulin resistance and leptin to adiponec-tin imbalance signifying a greater degree of metabolic derangement and inflammation.[121]

There is less information regarding the impact of metabolic syndrome on functional outcomes in COPD. Several groups have shown an increase in the prevalence of other comorbidities in patients with metabolic syndrome and COPD,[116,118] as well as hospitalizations for non-COPD causes.[118] Metabolic syndrome has also been shown to be associated with COPD exacerbation frequency and duration,[122] as well as increased use of inhaled corticosteroids (ICS),[118] though the temporality of these findings is unclear given cross-sectional study designs. Though an association with better lung function was described, as noted above in a few studies, one group demonstrated in a very large study an association of metabolic syndrome in COPD with more lung function impairment.[123] Upon further examination, there is some suggestion that the pattern of this impairment could be restrictive given that the risk for decrement in FVC appears to be higher than that of FEV_1, and such findings would be consistent with those of others who noted a higher degree of restriction on pulmonary function tests (PFTs) in individuals with COPD and metabolic syndrome,[120] which could be due to the obesity component of metabolic syndrome.

Those with metabolic syndrome and COPD[113,119,122,124] have also been shown to have a higher degree of systemic inflammation. One study identified a higher degree of aortic inflammation by positron emission tomography-computed tomography (PET-CT) in individuals with COPD also having visceral fat metabolic activity, suggesting a mechanism for the higher risk for other comorbidities such as cardiovascular disease in patients having COPD and metabolic syndrome.[125] The literature regarding COPD and metabolic syndrome suggests a risk for worse outcomes that needs further examination with large-scale longitudinal studies before determinations about the value of screening and treatment can be made.

Chronic Obstructive Pulmonary Disease and Diabetes

Diabetes is a common chronic medical condition in the general population and it is increasingly clear that diabetes is more prevalent in those with COPD than in the general population. Mannino and colleagues studied more than 20,000 participants in both the Cardiovascular Health Study (CHS) and Atherosclerosis Risk in Communities (ARIC) cohorts and found that diabetes was present in 10.1% of GOLD 1 participants, 12.6% of GOLD 2 participants, and 14.5% of GOLD 3–4 participants. There was a higher risk for diabetes in those with GOLD 3–4 COPD compared with those without (OR: 1.5, 95% CI: 1.1–1.9), and this risk was independent of BMI, smoking, and other confounding factors.[126] Another group found a prevalence of diabetes of 18.7% in a population of COPD patients associated with a university hospital in Italy, with a higher risk for the presence of diabetes in obese participants, those with more comorbidities, and those with more severe COPD.[127] A large study of the Taiwanese National Health Insurance Research Database found a higher incidence of developing diabetes in individuals with COPD compared with age and gender-matched controls, and noted that this risk was independent of many confounding factors, though the study was limited by its lack of data on smoking.[128] The Nurses' Health Study also showed a higher risk for the development of diabetes in women with self-reported COPD compared with those without (RR: 1.8, 95% CI: 1.1–2.8).[129] The prevalence of diabetes was also noted to be as high as 23% in a population of patients hospitalized for acute exacerbation of COPD.[130]

The presence of diabetes among those with COPD has been shown to be associated with worse outcomes, such as mortality and hospitalization.[126] Though there are studies,[131,132] including a meta-analysis,[46] showing an association of lower lung function with diabetes in the general population, it is not as clear what, if any, impact diabetes has on lung function in individuals with established diabetes. Kinney et al studied this issue in the large COPDGene cohort and found that though diabetes was associated with worse lung function in former and current smokers without established COPD, this association was not significant in participants with established COPD. However, they noted lower exercise capacity among individuals with COPD also having diabetes compared with those without diabetes.[133] Whether the use of oral or ICS contributes to the heightened risk for diabetes and resulting outcomes has also been of interest. Though one general population study found an association with use of ICS and the development of diabetes,[134] a second study of more than 8,000 participants in COPD clinical trials of ICS found no increased incidence of diabetes in

those treated with ICS compared with placebo and also noted no significant change in random glucose levels over the course of these studies.[135]

Some have explored potential mechanisms for the increased risks of diabetes in COPD. Bolton et al demonstrated that though glucose levels were similar in a group of COPD patients when compared with a group of healthy controls, levels of insulin resistance as estimated by the homeostasis model assessment index were found to be higher in COPD patients compared with controls, despite minimal differences in fat-free mass and BMI. The same group had higher levels of inflammatory mediators, including interleukin-6 and tumor necrosis factor-α receptors.[136] Such studies suggest strongly that the heightened risk of diabetes is related to heightened systemic inflammation in COPD, and could also contribute to the higher risk for mortality and hospitalizations that result, but further studies on the subject are needed to better elucidate the mechanism.

Chronic Obstructive Pulmonary Disease and Cardiovascular Disease

Several large population-based, longitudinal studies have demonstrated that individuals with COPD have a high risk of concomitant cardiovascular disease.[137–141] In two separate cohorts (ARIC and CHS), Mannino et al showed that the risk for developing cardiovascular disease was more than two times higher in individuals with airflow obstruction (GOLD 3–4) compared with those without (OR: 2.4, 95% CI: 1.9–3.0).[126] Two large studies of administrative datasets have estimated the prevalence of coronary heart disease among patients with COPD to be 22 to 33.6%, and the prevalence of congestive heart failure to be 13.5 to 24.4%.[142,143] A recent systematic review noted significant variability in estimates of cardiovascular disease prevalence, but found the prevalence of coronary heart disease ranged from 4.7 to 60%, the prevalence of congestive heart failure ranged from 7.1 to 31.3%, and the prevalence of unspecified cardiovascular disease ranged from 29 to 70%.[144] Epidemiologic studies have also demonstrated a high incidence of death from cardiovascular causes in patients with COPD,[138,145–150] further demonstrating the high burden of concomitant cardiovascular disease in the COPD population. For example, 27% of deaths in the TORCH (Toward a Revolution in COPD Health) study were attributed to cardiovascular causes.[145]

The association of cardiovascular disease with other important COPD outcomes has also been established. Cardiovascular disease was shown to be associated with worse quality of life and health status,[139,151,152] dyspnea,[152] and exercise capacity[151,152] in patients with COPD. Cardiovascular disease has also been associated with COPD-related hospitalization[153] as well as health care utilization and costs.[139,153] Aside from shared environmental risk factors such as smoking and pollution, there have been several mechanisms proposed for the increased risk of poor outcomes in COPD patients with cardiovascular disease, including systemic and vascular inflammation, genetic predisposition, and physical inactivity. Future work should not only consider mechanisms but also move forward with testing treatment strategies for this subgroup, particularly in light of the early evidence that patients with COPD and cardiovascular disease may benefit greatly from rehabilitation.[154]

Chronic Obstructive Pulmonary Disease and Gastroesophageal Reflux Disease

Estimates of the prevalence of gastroesophageal reflux disease (GERD) in COPD vary widely based on the diagnostic criteria applied and COPD severity. Studies using a case definition of GERD based on validated questionnaires or medical records and coding estimate the prevalence to be in the range of 7.7 to 37% in patients across a wide range of COPD severity.[155–159] Studies using more rigorous methods such as 24-hour esophageal pH probe monitoring estimate the prevalence to be even higher: 37 to 78%,[160–163] with very high prevalence estimates (57–62%) in studies of more severe COPD.[160,163] Interestingly, two of these studies demonstrated the presence of GERD by esophageal pH probe in patients with no reported reflux symptoms, including one in which 8 out of 12 asymptomatic patients with severe COPD had reflux demonstrated on esophageal pH probe testing.[161] A few of these studies have compared the prevalence to a matched cohort of individuals without COPD and have found the risk for presence of GERD to be higher,[156,162] though the evidence regarding COPD as a risk factor for GERD is mixed.[155,164]

Some studies have suggested higher BMI and lower inspiratory capacity to be risk factors for the presence of GERD in patients with COPD.[163,165] Subsequently, the presence of GERD symptoms and doctor-diagnosed GERD have been associated with worse quality of life,[166,167] chronic bronchitis[167] symptoms, and higher health care expenditures in patients with COPD.[168]

The most well-studied outcome has been the association of GERD with exacerbation risk and health care utilization, and was even the subject of a recent meta-analysis.[169] Four studies defining GERD based on either questionnaires or doctor diagnosis showed GERD to be associated with a significantly higher risk for COPD exacerbation.[157,159,167,170] Another study found GERD to be a risk factor for exacerbation but also confirmed the presence of GERD with lower esophageal pH probe testing.[171] Table 4 displays results from these studies. The natural next question is whether treatment of individuals with COPD with acid reduction medications such as proton pump inhibitors (PPI) is beneficial. One study randomized 100 COPD patients to low-dose lansoprazole versus usual care to determine if such treatment would reduce risk for exacerbations in any individual with COPD regardless of whether one had an existing diagnosis of GERD, and as such they excluded people with a known diagnosis of ulcer or GERD. They found a lower risk for exacerbation in the group treated with PPI (OR: 0.28, $p = 0.048$).[172] However, another small study randomized 36 patients with asthma and COPD with reflux symptoms to twice daily omeprazole versus placebo and found no change in airway hyperresponsiveness, peak expiratory flow variability, symptom scores, or medication use.[173]

Though the existing research about the prevalence of GERD in COPD varies based on the population and diagnostic strategy, GERD appears to be a relatively prevalent condition in patients with COPD, and seems to have a reasonably strong association in mostly cross-sectional, observational studies with exacerbation risk. What remains to be seen is whether a strategy of early diagnosis and treatment of GERD can modify the course of disease and frequency of exacerbations.

Chronic Obstructive Pulmonary Disease and Osteoporosis

Osteoporosis has been described in 21 to 66% of the COPD population, with estimates varying based on the severity of disease and other population characteristics.[66,174–180] Understanding the risk factors for osteoporosis in COPD has been complex due to the use of systemic glucocorticoids in patients with exacerbations or severe disease. Despite this, some risk factors have been described, the most common of which is low BMI.[181–183] Additionally, worse COPD severity,[178] as measured by FEV_1, residual volume/total lung capacity ratio,[182] diffusing capacity for carbon monoxide,[183] and CT measures including percentage emphysema[180] have been associated with higher prevalence of osteoporosis. Additionally, COPD patients with osteoporosis have been shown to have a higher prevalence of exacerbations,[178,184] though only one of the studies describing this association adjusted for steroid dose and usage.[178] Despite limitations in our understanding of risk factors for the development of osteoporosis in COPD, there is a suggestion that the risk of osteoporosis is independent of treatment with glucocorticoids. Furthermore, osteoporosis is associated with a specific phenotype of COPD[9] and may be linked to alterations in systemic and vascular inflammation, and arterial stiffness measured by pulse wave velocity.[185]

Chronic Obstructive Pulmonary Disease and Allergic Disease

The overlap of allergic disease and atopy has been recognized as a significant contributor to morbidity in asthma, but has been less well studied in the population with COPD. A few recent studies have highlighted not only that allergic disease is a prevalent problem in COPD (present in 18–29% of COPD) but also the importance of allergic disease in determining COPD disease severity. In the first of these recent studies, Fattahi et al demonstrated that atopy, defined as a positive Phadiatop test, was present in 18.3% of their population of 1,277 actively smoking COPD patients. They showed that atopy was associated with increased cough and chest tightness. Further, they noted that individuals with atopy were more likely to have remission of cough when treated with ICS.[186] Jamieson et al found a prevalence of 25% in the NHANES III population of allergic disease, and 29% with atopy in a population of 77 former smokers with COPD in the Baltimore–Washington area. These estimates were in comparison to 30.3% with allergic disease in the general population from NHANES III estimated in the same study. Jamieson et al also found significantly higher risk for respiratory symptoms of chronic cough, phlegm, wheezing, and health care utilization in the individuals with allergic symptoms in the NHANES survey, while in the Baltimore cohort they found significantly higher risk for wheezing, emergency department (ED) visits, antibiotic use, and nocturnal cough in atopics with COPD. Additionally, they found a higher risk for wheezing, nocturnal symptoms, and ED visits with an increasing number of allergic sensitizations, demonstrating a “dose–response” relationship of allergic disease and COPD outcomes.[187] Caillaud et al noted a prevalence of 42% of chronic nasal symptoms in a group of 274 patients with COPD which were associated with both the presence of hay fever and atopic dermatitis diagnoses.[188] These individuals were found to have worse quality of life and more dyspnea than COPD participants without nasal symptoms. Ultimately, better understanding the subgroup of patients with COPD and allergic disease could lead to efforts to develop specialized therapeutic strategies for this subgroup of COPD.

Chronic Obstructive Pulmonary Disease and HIV/AIDS

The increased susceptibility to pulmonary disease among human immunodeficiency virus (HIV)-infected individuals has been described almost since the first description of HIV and acquired immune deficiency syndrome (AIDS). As outlined in a recent comprehensive review,[189] the epidemiology of lung disease in HIV patients is best viewed in the framework of the pre- and post-antiretroviral therapy eras. Prior to the widespread availability of antiretroviral therapy, pulmonary complications of HIV were considered to be mostly of infectious etiology, though there was an emerging recognition of radiographic and lung function abnormalities which may be related to HIV itself.[190–192]

As HIV becomes a chronic disease, it is becoming increasingly clear that it coexists commonly with COPD, with estimates suggesting that 10 to 16%[193,194] of HIV/AIDS patients have COPD. Studies have demonstrated that individuals with HIV appear to have higher risk for COPD.[193,195,196] Additionally, several large-scale studies have found that HIV appears to be an independent risk factor for the development of COPD after adjustment for traditional COPD risk factors, including smoking, injection drug use, and socioeconomic status.[194,195]

Lending further weight to the association of HIV with COPD risk, one study showed the risk for COPD rose with increasing viral load.[197] As well, worse markers of HIV disease control are associated with more rapid FEV_1 decline.[198] In addition, in patients with COPD, HIV was associated with worse quality of life, independent of smoking status.[199] It has also been recognized that HIV is associated with a higher risk of primary lung cancer,[200–202] but whether the presence of COPD further increases this risk is not clear.

Early detection and treatment of COPD among individuals with HIV could have important ramifications for outcomes including lung function and quality of life. This is doubly important given the emerging evidence for serious interactions between some antiretroviral agents and some types of ICS.[203,204]

Chronic Obstructive Pulmonary Disease and Lung Cancer

Though shared risk factors such as smoking or air pollution could be implicated for the overlap of COPD and lung cancer, there have been several studies in the past decade which have established COPD as an independent risk factor for lung cancer,[205–209] including a study conducted in never smokers with COPD.[207] The prevalence of COPD in lung cancer patients is estimated at 50%,[209] while the estimates of lung cancer prevalence in COPD patients varies based on the population and the severity of COPD but is estimated to be between 3.8 and 8.0%.[206,208] The risk of lung cancer is estimated to be more than 2 times higher in individuals with airway obstruction,[205,206,208] and between 50% and 3.5 times higher in individuals with emphysema.[205,207,208]

Large epidemiologic studies show that lung cancer is a major cause of death in the COPD population.[126,147,210] A third of deaths in the Lung Health Study (LHS), which included patients with mild to moderate COPD at baseline and followed over 14.5 years, were attributed to lung cancer[210] and 23.9 to 25.4% of patients in GOLD categories 2–4 died of

lung cancer in the ARIC study.[147] There are limited studies which have investigated the impact of lung malignancy on quality of life or patient-reported outcomes in COPD. However, a few studies have suggested that the presence of COPD or emphysema in lung cancer patients is associated with increased recurrence after resection, even in early stage disease.[211,212]

There are several potential mechanisms for increased risk for and mortality from lung cancer in COPD. There is evidence from genome-wide association studies for shared genetic loci for the development of lung cancer and COPD.[213,214] There are some studies which also suggest that common exposures such as tobacco smoke or air pollution could lead to epigenetic modification of bronchial cells and increase risk for the development of either COPD or lung cancer by similar mechanisms.[215,216] Another possible mechanism is that the inflammation that is present systemically and in the airways of individuals with COPD could predispose to the development of lung cancer. Regardless of the mechanism, the high prevalence of comorbid lung disease in patients with COPD has already inspired trials aimed at studying enhanced lung cancer screening in this population.[217]

Conclusion

Based on multiple studies of multimorbidity in COPD, it is clear that the presence of comorbidities is a nearly ubiquitous problem in patients with COPD, and their presence is associated with significant risk for mortality as well as worse patient-centered outcomes. Accordingly, several studies have attempted to develop tools for the description of comorbidity burden in COPD specifically, and others have attempted to incorporate comorbidities into novel phenotyping techniques as we attempt to better understand the heterogeneity of COPD. In addition, the high prevalence and impact of specific comorbidities on COPD and COPD outcomes should not be underappreciated.

The growing body of research in this area continues to point to the importance of incorporating the complexity of multimorbidity with regard to decision making in patients with COPD. Moving forward, investigation should begin to focus upon understanding the value of screening for comorbid conditions in COPD, and also the value of specialized treatment strategies including pharmacotherapy, rehabilitation and exercise programs, and measures to consolidate care in this complex population. Additionally, better understanding the true impact of comorbidities on outcomes in COPD will require longitudinal data to help better establish causality. Without this, associations noted in cross-sectional studies can be questioned given possible associations of comorbidities with severity of disease and exacerbation events. Based on our review of this literature, it also seems likely that there are gender and racial disparities with regard to the prevalence and impact of comorbidities in COPD, and further research in this area should attempt to better elucidate these interactions and their mechanisms. Challenges in comorbidities research that must be considered moving forward include the importance of finding accurate and valid methods to diagnose comorbidities in research, while also incorporating information on the degree of severity of these comorbid diseases. As we better confront these challenges, we can begin to impact the treatment of patients with COPD.

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Table 1

Studies describing comorbidity burden in patients with COPD

	Population	Measure of comorbidity burden
Almagro et al 2012[17] Spain	*N* = 606 Observational study Mean FEV_1 69% predicted	Mean (SD) Charlson score 3.1 (2)
Anecchino et al 2007[2] Italy	*N* = 126,283 Administrative dataset Unknown COPD severity	98% of patients received prescriptions for at least 1 nonpulmonary medication
Areias et al 2014[3] Brazil	*N* = 89 Clinic-based cohort Mean FEV_1 38% predicted	86% had at least 1 comorbidity Mean (SD) number of comorbidities 3.9 (2.4) Mean (SD) Charlson score of 4 (1.4)
Fumagalli et al 2013[4] Italy	*N* = 169 Clinic-based cohort Mean FEV_1 56.3% predicted	94.1% had at least 1 comorbidity Mean (SD) Charlson score 4.88 (2.07)
Putcha et al 2013[5] USA	NHANES survey 2001–2008 Self-reported COPD	95.7% with at least 1 comorbidity Mean number of comorbidities 3
Putcha et al 2014[24] USA	*N* = 3,690 Observational study Mean FEV_1 50.2% predicted	Mean (SD) number of comorbidities 3.3 (2.3)
García-Olmos et al 2013[6] Spain	*N* = 3,124 Administrative data set Age > 40 y	Mean (SD) number of comorbidities 4 (2)
López Varela et al 2013[7] Latin America	*N* = 759 Observational study Unknown COPD severity	Mean (SD) number of comorbidities 1.2 (0.04)
Noteboom et al 2014[8] Australia	*N* = 70 Recruited from pulmonary rehab Mean FEV_1 38% predicted	96% had at least 1 comorbidity 29% had 5 or more comorbidities
Vanfleteren et al 2013[9] The Netherlands	*N* = 213 Observational study Mean FEV_1 51.2% predicted	97.7% had at least 1 comorbidity 53.5% had 4 or more comorbidities

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second; SD, standard deviation.

Table 2

Description of COPD comorbidity indices

Study	Outcome predicted	Score formulation
Divo et al[11] "COTE index"	Mortality	6 points each: lung, esophageal pancreatic, breast cancer, anxiety (women only) 2 points each: all other cancers, liver cirrhosis, atrial fibrillation/flutter, diabetes with neuropathy, pulmonary fibrosis 1 point each: congestive heart failure, gastric/duodenal ulcers, coronary heart disease
Frei et al[13] "COMCOLD index"	Health status (feeling thermometer)	6 points for depression 4 points for anxiety 3 points each for peripheral artery disease, cerebrovascular disease, symptomatic heart disease (CHF or CHD)

Abbreviations: CHD, coronary heart disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease.

Table 3

Prevalence estimates of major comorbidities in COPD and associations with outcomes

Comorbidity	Prevalence	Associations with outcomes
Allergic disease	18–42%[186–188]	Cough, phlegm, wheezing Health care utilization
Anemia	7–43.9%[68–70]	Mortality Hospitalization, length of stay, readmission risk Dyspnea
Cardiovascular	29–70% (general CVD) 4.7–60% (CHF) 7.1–31.3% (CHD)[142,144,218]	Mortality Quality of life, health status Dyspnea, exercise capacity Hospitalization Health care utilization and expenditures
Cognitive impairment	2–20%[28]	Quality of life, health status Length of hospital stay
Depression	16.5–42%[35–42]	Mortality Dyspnea, exercise capacity Quality of life, health status Rehospitalization risk Exacerbation risk Inability to perform ADLs
Diabetes	10.1–23%[126,127,130]	Mortality Hospitalization Exercise capacity
GERD	37–78%[160–163]	Quality of life Chronic bronchitis symptoms Health care expenditures Exacerbation risk
HIV/AIDS	10–16% of HIV/AIDS patients with COPD[193,194]	Quality of life
Lung cancer	3.8–8.0%[206,208]	Mortality Recurrence of malignancy
Metabolic syndrome	21–57%[111–116]	Other comorbid disease Hospitalizations Exacerbation risk
Obesity	29.1–43%[94–96]	Quality of life, health status Dyspnea, exercise capacity Health care utilization
Osteoporosis	21–66%[66,174–176,178–180,182]	
Sleep apnea	22.3–51.4%[83–86]	Mortality Exacerbation risk Health care expenditures Cardiovascular outcomes

Abbreviations: GERD, gastroesophageal reflux disease; HIV/AIDS, human immunodeficiency virus/acquired immune deficiency syndrome; CHF, congestive heart failure; CVD, cardiovascular disease; CHD, coronary heart disease; ADLs, activities of daily living; COPD, chronic obstructive pulmonary disease.

Table 4

Studies of GERD as risk factor for COPD exacerbations

Study	Population and GERD definition	Hospitalizations	ED visits	COPD exacerbations
Kim et al 2013[157]	*N* = 141,057	OR 1.54	OR 1.55;	
	Administrative data GERD and COPD diagnoses in medical records	95% CI (1.50–1.58)	95% CI (1.48–1.62)	
Martinez et al 2014[167]	*N* = 4,438 COPDGene study GERD doctor diagnosis			OR 1.17 95% CI (1.05–1.31)
Rascon-Aguilar 2006[159]	*N* = 86 Clinic cohort GERD diagnosed by questionnaire			1.56 more exacerbations per year (SD 0.44–2.69)
Takada et al 2011[170]	*N* = 221 Clinic cohort GERD diagnosed by questionnaire	OR 4.34 95% CI (1.72–10.94)		OR 12.599 95% CI (3.13, 50.70)
Terada et al 2008[171]	*N* = 80 Clinic cohort GERD diagnosed by symptoms and pH probe Moderate to severe COPD			RR 6.55 95% CI (1.86–23.11)

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; ED, emergency department; GERD, gastroesophageal reflux disease; OR, odds ratio; RR, relative risk; SD, standard deviation.