



# Extrapulmonary Comorbidities Associated with Chronic Obstructive Pulmonary Disease: A Review

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**Abstract:** Most patients with chronic obstructive pulmonary disease (COPD) suffer from at least one additional, clinically relevant chronic disease. To a degree, the high global prevalence and mortality rate of COPD is closely related to its extrapulmonary effects. Moreover, the various of comorbidities of COPD and itself interact with each other, resulting in diverse clinical manifestations and individual differences, and thus further influencing the prognosis as well as healthcare burden of COPD patients. This is closely related to the common risk factors of chronic diseases (aging, smoking, inactivity, etc.). Additionally, some pathophysiological mechanisms caused by COPD, including the systemic inflammatory response, hypoxia, oxidative stress, and others, also have an impact on other systems. But comprehensive management and medical interventions have not yet been established. The clinicians should improve their knowledge and skills in diagnosing as well as treating the comorbidities of COPD, and then aim to develop more individualized, efficient diagnostic and therapeutic strategies for different patients to achieve greater clinical benefits. In this article, we will review the risk factors, mechanisms, and treatment strategies for extrapulmonary comorbidities in chronic obstructive pulmonary disease, including cardiovascular diseases, diabetes, anemia, osteoporosis, emotional disorders, and gastroesophageal reflux disease.

**Keywords:** chronic obstructive pulmonary disease, comorbidity, risk factors, therapeutics

## Introduction

Chronic obstructive pulmonary disease (COPD) is a common respiratory disease that can be prevented and treated. It primarily involves various airway and/or alveolar abnormalities caused by excessive exposure to the toxic particles or gases, and can result in persistent and progressively worsening chronic respiratory symptoms and airflow limitations.<sup>1</sup> It is estimated that COPD would become the fourth leading cause of premature death by 2040.<sup>2</sup> Meanwhile, COPD is ranked as sixth leading cause of all-age mortality and years of life loss (YLLs) by 2019, and its rank was proportional to the age.<sup>3</sup>

The enormous financial burden of COPD is closely related to both itself and its multiple comorbidities.<sup>4</sup> In 2011, the 'comorbidities' were included in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and used for the comprehensive evaluation of COPD. In the 2023 GOLD guidelines, the concept of "heterogeneous lung condition" was proposed,<sup>1</sup> emphasizing the diversity and individual differences in clinical manifestations of COPD patients. The reason for this is that various factors, such as hypoxia, oxidative stress (OS), systemic inflammation and other mechanisms, can lead to damage in multiple organs and tissues throughout the body. These include the cardiovascular, endocrine, hematological, locomotor, neuropsychiatric, and digestive system.<sup>5</sup> The risk of comorbidities in COPD patients is also elevated by factors such as smoking history and advanced age.<sup>6</sup> In addition, several extrapulmonary comorbidities of COPD have been found to considerably increase the risk of acute exacerbation, complicate the treatment, and impose a heavy medical burden on COPD patients.<sup>4,7</sup>

Therefore, a comprehensive understanding and early diagnosis of comorbidities are extremely important to optimize the treatment and prognosis of COPD. This review summarizes recent advances in the study of such above extra-pulmonary comorbidities in COPD.

## Method

We conducted a comprehensive search on Medline/PubMed and China national knowledge infrastructure (CNKI) up to December 2023 to identify studies relevant to this review. The combination of the following keywords was used as the potential search terms: “Comorbidities in COPD”, “Relationship”, “Prevalence”, “Risk factors”, “Treatment”, “Management”, “Survival and Quality of Life” and so on. In addition, the reference lists of the retrieved articles were further examined in order to determine their significance to the subject matter of this review.

## COPD and Cardiovascular Diseases (CVD)

A meta-analysis of observational studies found that the probability of cardiovascular events was significantly increased in patients with COPD compared to patients without COPD [OR=2.46; 96% CI; 2.02–3.00; P<0.0001], and the risk of ischemic heart disease (IHD), cardiac dysrhythmia, heart failure, and arterial circulation diseases in COPD patients was two to five times higher than those in the non-COPD population.<sup>8</sup>

COPD and CVD have a significant overlap in risk factors, pathophysiological mechanisms, clinical characteristics, and symptoms, which in turn worsen the prognosis for individuals affected by both conditions.<sup>9,10</sup> Although smoking is a common and significant risk factor for the two diseases mentioned above, an increasing number of studies have indicated that smoking is not the only link between COPD and CVD. Obesity, hypoxia, aging, lifestyle, and genetics may also be common risk factors.<sup>11</sup> In addition, under the stimulation of different factors (eg, inflammation, hypoxia, and OS), in some COPD patients, cardiovascular damage may occur in the early stages.<sup>12</sup> Here, hypoxia can induce stress responses in hemodynamics, leading to an increase in cardiac output index, leading to increased peripheral vascular contraction and OS.<sup>12</sup> Furthermore, increased oxidative stress can further stimulate persistent systemic inflammation, which in turn can effectively alter the vascular structure.<sup>13</sup> The systemic inflammatory response, in turn can significantly enhance cytokine activity, contributing to platelet aggregation and blood coagulation.<sup>14,15</sup> Additionally, OS not only causes extensive damage to the airway epithelium, but can also adversely affect both the function and quantity of endothelial cells. The dysfunction of endothelial cells can disrupt the vascular homeostasis, while excessive endothelial cell apoptosis can effectively reduce their antioxidant, anti-inflammatory, and antithrombotic abilities.<sup>16</sup> This series of reactions can significantly increase the possibility of cardiovascular events.

Clinically, patients with COPD and CVD may sometimes experience exertional dyspnea, and both can increase the patient's fatigue, which can further limit their physical activity and continuously reduce their activity tolerance. Patients with both diseases develop severe symptoms. The most important drugs for COPD currently include bronchodilators (eg,  $\beta$  receptor agonists, anti-cholinergic drugs, and theophyllines), corticosteroids, and other symptomatic therapeutic drugs.<sup>4</sup> It is important to emphasize that recent studies have indicated that the use of dual long-acting bronchodilators can significantly increase the risk of cardiovascular events.<sup>17</sup> However, in the treatment of cardiovascular complications, treatment with  $\beta$  receptor agonist appears to violate the principles of COPD therapy. Interestingly, studies have reported that selective cardiac  $\beta$  receptor agonists exhibit more significant benefits than potential risks in mild to moderate reversible respiratory diseases or coronary artery disease with COPD.<sup>18,19</sup> However, its use in COPD patients combined with heart failure remains controversial.<sup>20</sup> Meanwhile, statins have shown numerous benefits such as antioxidant, anti-inflammatory, antithrombotic, and immunomodulatory properties.<sup>21</sup> These effects prove effective in managing inflammation, reducing the severity of COPD, and lowering CVD-related mortality,<sup>22,23</sup> in addition to reducing the risk of pulmonary hypertension.<sup>24</sup> However, some studies have demonstrated that the beneficial effects of statins may depend on the patient's age and corticosteroid use.<sup>25</sup> Additionally, antiplatelet agents can significantly reduce the risk of ischemic events in patients with COPD.<sup>26</sup> These agents can also contribute to delaying the progression of emphysema,<sup>27</sup> improving dyspnea and quality of life in patients.<sup>28</sup> Furthermore, angiotensin-converting enzyme inhibitor (ACEI) / angiotensin receptor block (ARB) have also been proposed to display a beneficial effect on the risk of cardiovascular events. These drugs may also potentially delay the progression of emphysema while improving the lung function,<sup>29,30</sup>

with dual cardiorespiratory protective properties. In addition, the imbalance between protease and antiprotease is also a major pathogenic mechanism of COPD and CVD. Matrix metalloproteinases (MMPs) play an important role and antiprotease inhibitors are expected to be employed as novel therapeutic targets.<sup>15</sup> Although some MMP inhibitors were found to be safe in cancer trials, their success rate is relatively limited.<sup>31</sup> Therefore, large-scale prospective studies are still needed to further evaluate the safety and effectiveness of MMP inhibitors in COPD patients affected with CVD. It is noteworthy that numerous studies have demonstrated that both COPD and CVD share common mechanisms such as oxidative stress and systemic inflammation. This suggests that antioxidant therapy could provide a novel and effective therapeutic direction for the treatment of COPD and its associated cardiovascular diseases. However, further extensive prospective studies are required to validate this potential therapeutic direction.

## COPD and Endocrine Diseases

According to statistics, up to 40% of COPD cases are associated with one or more diseases related to metabolic syndrome (MetS), with diabetes being the most common.<sup>32,33</sup> COPD is also regarded as a common comorbidity of diabetes, and they mutually increase the risk of disease and unfavorable prognostic factors.<sup>34,35</sup> It is worth indicating that the severity of diabetes has been strongly related to the deterioration of lung function, which could be related to the limited activity and the reduced quality of life of COPD patients.<sup>36,37</sup> In contrast, hyper glycaemia can also cause a decline in lung function and physical performance.<sup>38</sup> For instance, in a 30-year follow-up study involving more than 27,000 non-smokers, low FEV<sub>1</sub> was found to precede diabetes and has a significant predictive effect on diabetes incidence.<sup>39</sup> Multiple shared risk factors and pathological changes play a vital role in their cooccurrence and interaction, including smoking, obesity, age, hypoxia, oxidative stress, inflammation, and so on.<sup>34</sup>

A sustained systemic inflammatory response and OS are considered as major factors in the progression of these two diseases.<sup>33</sup> The inflammation of airways can cause harm to pancreatic beta cells and obstruct the signaling pathway of insulin, resulting in insulin resistance.<sup>40,41</sup> At the same time, the hyperglycemic state can lead to inflammation and oxidative stress, resulting in damage to the pulmonary blood vessels.<sup>42</sup> Additionally, the damage to the endothelial cells in the pulmonary blood vessels can lead to connective tissue proliferation and subsequently reduce pulmonary compliance.<sup>43</sup> In addition, the advanced glycation end products (AGEs) associated with hyper glycaemia can trigger inflammation and attenuate alveolar retraction, thus exacerbating the patient's ventilatory deficits.<sup>44</sup> At the same time, diabetic autonomic neuropathy can also dysregulate airway diastolic function.<sup>45</sup> Additionally, hypoxia has the potential to impact glucose metabolism and insulin sensitivity,<sup>29</sup> leading to an increased risk of excessive oxidation and oxidative stress. Furthermore, it can disrupt the defense provided by antioxidants as well as antiproteases, and evolve into a potential risk factor for diabetes mellitus.<sup>33</sup> Interestingly, although corticosteroids can also increase the risk of diabetes.<sup>46</sup> For instance, corticosteroids, which are commonly used in COPD patients, some studies have reported that the risk of diabetes was only significantly increased upon treatment with high-doses of corticosteroids.<sup>47,48</sup> However, other studies have suggested that the combined use of inhaled corticosteroids (ICS) and statins could increase the risk of developing new-onset diabetes.<sup>49</sup> Therefore, more long-term observational studies and randomized controlled trials should be conducted in the future to assess the potential safety of drug combinations.

For the treatment of COPD cases combined with diabetes, blood sugar control is essential, as it has been linked to immune dysfunction.<sup>50</sup> Recently, the hypoglycemic drug metformin has received significant attention because of its properties of anti-inflammatory and antioxidant. It effectively improves lung outcomes by reducing the production of pro-inflammatory factors through the activation of AMP-activated protein kinase (AMPK).<sup>51</sup> Furthermore, it promotes the breakdown of inflammatory mediators by stimulating autophagy,<sup>52</sup> with a primary focus on inhibiting the nuclear factor of kappa B (NF- $\kappa$ B) pathway, which is considered to play a crucial role in promoting inflammation.<sup>53,54</sup> In addition, metformin can also attenuate oxidative stress-induced cytotoxicity and inhibit the inflammatory response in macrophages through an AMPK-dependent pathway.<sup>55</sup> However, the use of metformin still remains controversial. Several large-scale cohort studies have demonstrated that metformin can significantly reduce the risk of exacerbation and all-cause mortality in COPD patients.<sup>56,57</sup> However, another retrospective cohort study suggested that metformin failed to improve the blood glucose elevation caused by COPD in non-diabetic patients.<sup>58</sup> Hence, additional clinical trials of metformin with stronger evidence are needed to validate its effectiveness in delaying progression. Among other oral hypoglycemic agents, thiazolidinedione drugs and dipeptidyl peptidase-4 (DPP-4)

inhibitors can substantially attenuate the inflammatory reactions while lowering blood sugar, thereby protecting the lung tissues.<sup>59,60</sup> Sulfonylureas can reduce risk of acute exacerbation of COPD, bacterial pneumonia and cardiovascular events.<sup>61</sup> However, recently, there has been growing attention on glucagon-like peptide 1 (GLP-1) receptor agonist and sodium-glucose cotransporter 2 (SGLT-2) inhibitor. Research suggests that GLP-1 receptor agonists can enhance airway function and reduce the risk of exacerbation of COPD.<sup>62,63</sup> Additionally, SGLT-2 inhibitors have shown a reduced risk of exacerbating obstructive airway disease when compared to DPP-4 inhibitors.<sup>64</sup> In addition to medication, reducing sedentary time, increasing exercise, and implementing individual nutritional interventions can also effectively improve the quality of life and prognosis of COPD patients with diabetes.

## COPD and Hematological Diseases

A number of previous studies have shown that high incidence of hypoxia in COPD patients could lead to a compensatory increase in erythropoietin (EPO), leading to secondary hyperhemoglobinemia. However, recent studies in China and abroad suggest that anemia was also one of the comorbidities of COPD and its incidence rate was even higher than that of hyperhemoglobinemia.<sup>65,66</sup> It was found that compared to hyperhemoglobinemia, anemia has a greater impact on the disease severity and quality of life in COPD patients.<sup>67,68</sup> As shown in a 9-year multicenter clinical study in Korea, anemia (WHO criteria) can serve as an independent risk factor for mortality in COPD.<sup>69</sup> In addition, it has been observed that COPD patients affected with anemia had a higher comorbidity burden, especially CVD and MetS,<sup>70</sup> which further increased their disease burden and risk of death.

Currently, COPD combined with anemia is considered to belong to the anemia of chronic disease (ACD), commonly known as “inflammatory anemia”, which is essentially an immune-driven inflammatory response.<sup>71,72</sup> Prolonged chronic inflammation in COPD patients can significantly weaken the proliferative stimulation response of EPO and shorten the lifespan of red blood cells.<sup>73</sup> In addition, some inflammatory factors can directly inhibit hypoxia-induced activation of EPO, which leads to an increase in OS. These factors also interfere with EPO receptor-mediated signaling pathways, thus inhibiting the production of EPO.<sup>74</sup> During chronic inflammation, phagocytes have been found to inhibit inflammation by depleting iron and affect iron metabolism as well as transport. This is primarily caused by high levels of hepcidin, leading to iron deficiency in the body, which evolves into iron deficiency anemia (IDA).<sup>75,76</sup> Thus, iron deficiency can affect lung function and disease progression in COPD,<sup>77,78</sup> forming a vicious circle. Furthermore, since COPD is a chronic wasting disease with malnutrition, there may be a deficiency of hematopoietic raw materials,<sup>79</sup> resulting in a decrease in red blood cells.

Hemoglobin can transport oxygen to the various tissues and organs. However, the decrease in hemoglobin in anemia patients leads to a reduction in oxygen supply capacity. Although the blood oxygen partial pressure is sometimes within the normal range, the patient may still be in a state of hypoxia. Therefore, patients with anemia are more likely to develop symptoms such as dyspnea, affecting the motor ability and quality of life.<sup>67</sup> Therefore, it is important to actively improve the hemoglobin level. For clinical improvement of anemia, we generally choose direct blood transfusions, EPO injections, and supplementation with hematopoietic raw materials. However, it has been suggested that patients with COPD combined with anemia are resistant to EPO due to the inhibitory effect of inflammatory factors on erythroid progenitor cells.<sup>80</sup> Furthermore, although iron supplementation has been found to be effective in reducing the levels of OS in COPD patients, recent studies have further shown that iron therapy could affect the composition of the microbiota as well as the distribution of fecal metabolites, to a certain extent, which has a potentially detrimental effect on the patients.<sup>81,82</sup> It is worth noting that intravenous iron supplementation can be effective in increasing hemoglobin levels while reducing gastrointestinal adverse effects compared to oral iron supplementation. This is particularly significant as inflammation can impair iron absorption in the gut.<sup>83</sup> In addition, the supplementation of essential nutrients like vitamins and amino acids plays a pivotal role in facilitating the production of hemoglobin and erythropoiesis, underscoring their potential importance. Vitamin C is recognized as a powerful antioxidant, while vitamin D has the potential to exhibit anti-inflammatory effects.<sup>84,85</sup> Although it is currently unclear whether the effectiveness of treating the inflammation response is more effective in the primary disease. There are novel treatment strategies available related to the iron regulatory pathway and hypoxia-inducible factor stabilizers for inflammatory anemia, but their efficacy needs to be further evaluated in clinical trials.<sup>76</sup>

## COPD and Locomotor System Diseases

Skeletal muscle dysfunction and osteoporosis are locomotor system comorbidities found in COPD, and the risk of incidence is 1.9 times higher than in normal individuals.<sup>86</sup> The incidence of reduced muscle mass in COPD patients is about 15.5%-34%,<sup>87</sup> and it is approximately 38.5% in patients affected with osteoporosis.<sup>88</sup> Osteoporosis is a systemic metabolic bone disease characterized by a decrease in bone mass and structural deterioration of bone tissue, leading to an increase in bone fragility and the risk of fractures.<sup>89</sup> In contrast, osteoporosis is mostly asymptomatic in COPD patients and is typically only detected when a fracture takes place. Therefore, special attention should be paid to the early identification of high-risk patients with COPD combined with osteoporosis.

It has been found that most pathogenic factors can simultaneously affect muscle strength and bone strength in COPD patients. In addition to the patient's low body mass index, malnutrition and decreased exercise tolerance, systemic inflammatory responses, OS, hypoxia, intake of hormone drugs and vitamin D deficiency are all considered as potential risk factors, increasing bone loss and even leading to fragility fractures.<sup>90,91</sup> Furthermore, fractures associated with osteoporosis could further increase the poor prognosis of COPD due to lack of exercise and prolonged bed rest, such as deterioration of the lung function, poor quality of life, as well as increased hospitalization and mortality rates.<sup>92</sup> This can potentially create a vicious cycle of these two diseases and places a heavy burden on patients. Under the normal circumstances, bone resorption by osteoclasts and bone formation by osteoblasts alternate in bone tissues to maintain the balance of bone mass.<sup>93</sup> However, both the hypoxic state and systemic inflammation in COPD patients could effectively stimulate the proliferation and differentiation of osteoclasts, thus affecting the bone metabolism.<sup>94,95</sup> In addition, in patients who smoke, nicotine not only stimulates osteoclast activity, but also triggers apoptosis in osteoblasts, thereby further contributing to osteoporosis.<sup>96,97</sup> It is important not to overlook that COPD patients may suffer from deficiency of Vitamin D due to limited activity, reduced sunlight exposure, malnutrition, and the promotion of Vitamin D metabolism by corticosteroids. This deficiency can potentially lead to bone loss as a result of the inability to maintain calcium homeostasis.<sup>98</sup>

In terms of pharmacological treatment, corticosteroid is an effective treatment for COPD, however, the potential development of secondary osteoporosis due to prolonged usage should not be ignored.<sup>99</sup> Although oral administration has been reported to cause apoptosis of bone cells and loss of bone strength,<sup>100</sup> there is still controversy regarding the impact of inhaled corticosteroids (ICS) on bone strength.<sup>91,101</sup> Currently, the GOLD does not explicitly state that using ICS could lead to significant negative impacts associated with osteoporosis. However, numerous studies have indicated that the use of ICS raises the risk of osteoporosis regardless of the duration of exposure.<sup>102</sup> In general, except in patients with COPD in the acute exacerbation stage, systemic application of corticosteroids should be avoided to reduce the risk of bone related adverse effects. In the treatment of osteoporosis, bisphosphonates have been shown to be effective in the treatment of hormone-related bone loss, and are usually combined with calcium and vitamin D.<sup>103</sup> In addition, some novel drugs, including denosumab and teriparatide, have been found to have more potent effects in improving the bone density, preventing fractures, and have higher safety.<sup>104–106</sup> Hence, these are expected to become a first-line medication for the treatment of osteoporosis-related corticosteroids.<sup>107</sup> It has also been suggested that romosozumab, a sclerostin inhibitor that both induces bone formation and inhibits bone resorption, could possibly reduce the risk of fracture to a greater extent in comparison to alendronate.<sup>108</sup> Additionally, the use of some antioxidants is considered as a new potential therapeutic direction to prevent and reduce the negative effects of OS on bone remodeling and osteoblastic cells.<sup>109</sup> However, additional research is necessary in order to thoroughly investigate the potential risks associated with them.

## COPD and Mental Disorders

The combined nervous system diseases associated with COPD mainly include emotional disorders, cognitive impairments, pulmonary encephalopathy and consciousness disorders. Emotional disorders (eg, anxiety and depression) are the most common and easily misdiagnosed. Interestingly, a systematic retrospective study found that the incidence of COPD patients developing emotional disorders was approximately three times higher in comparison to the control group.<sup>110</sup> However, the incidence of COPD combined with anxiety and depression has been shown to be between 19.5%–50% in China, and the incidence varies between different studies due to various factors, such as sample size, diagnostic tools, and disease severity.<sup>111,112</sup>

Patients with COPD often find themselves in a vicious cycle of “dyspnea- decreased activity- increased mental symptoms - dyspnea exacerbation”.<sup>113</sup> However, a variety of factors such as behavior, societal influence, and the illness itself contribute to the development of anxiety and depression. In addition, COPD patients suffer from recurrent illness and reduced social engagement that perpetuates anxiety/depression, which in turn can increase the risk of acute exacerbation of COPD. In addition, to the emotional disorders caused by reduced social participation primarily induced by the degradation of body function, this phenomenon could also be related to the influences of hypoxemia and hypercapnia on areas of the brain areas involved in regulation of both ventilation and defensive behaviors.<sup>114,115</sup> For chronic smokers, long-term inhalation of nicotine stimulates the body’s inflammatory response and can cause damage to the glial cells. Consequently, this leads to brain damage and the development of mood disorders,<sup>116</sup> and potential impact of cigarette smoke on the regulation of neurohormonal secretion rhythms can also contribute to mood disorders in patients.<sup>117</sup> Moreover, the chronic inflammatory response in COPD can also have a direct impact on the central nervous system, including an increase in negative emotions.<sup>118</sup> In addition, imbalance of inflammatory factors can also increase risk of mood disorders in COPD patients<sup>119</sup>. Recently, the potential relationship between imbalance in immune system response and emotional disorders has also been suggested.<sup>120</sup> However, the relationship between COPD combined with emotional disorders and immunological mechanisms is complex, and further research is still needed for more in-depth exploration.

COPD catalyzes the development of emotional disorders, and emotional disorders can influence both the occurrence and development of COPD. Therefore, early intervention should be carried out in patients with COPD, focusing on the impact of psychological changes on the development and prognosis of the physical diseases. Currently, the main treatment includes pharmacological therapy and non-pharmacological therapy, while non-pharmacological therapy also includes various treatment methods, such as comprehensive pulmonary rehabilitation therapy, psychological therapy and collaborative nursing mode.<sup>121</sup> Although pulmonary rehabilitation is known to improve mood and provide several other benefits to COPD patients, studies have found that it has inconsistent rates of continuation and completion, with only half of participants continuing in a rehabilitation center and merely 30% completing the full duration of their treatment.<sup>122</sup> Therefore, it is imperative to conduct further studies on pulmonary rehabilitation programs aimed at providing adequate support and ensuring participants’ successful completion. Additionally, it is crucial to discover viable alternative interventions for patients who are unable to participate in routine pulmonary rehabilitation. It is worth noticing that there could be potential interactions between drugs for COPD and those for anxiety/depression. Tricyclic antidepressants (TCA) may potentiate other adverse effects of beta-2 adrenergic agonists and anticholinergic bronchodilators, but tricyclic antidepressants are not considered absolutely contraindicated for use in patients with COPD because of the above mentioned interactions.<sup>123,124</sup> Therefore, both the efficacy and safety of anxiolytic/depressant medications for the treatment of COPD-associated mood disorders still needs to be confirmed by more clinical trials. Additionally, considering the potential influence of inflammatory cytokines on depression, the emergence of cytokine modulators as a potential treatment for depression in individuals with chronic inflammation chronic inflammation<sup>125</sup> should be explored. However, it is crucial to conduct more extensive randomized controlled trials with robust evidence to thoroughly assess this field. Overall, to minimize the adverse effects of emotional disorders and improve quality of life, comprehensive interventions including medication, psychology and rehabilitation are required.

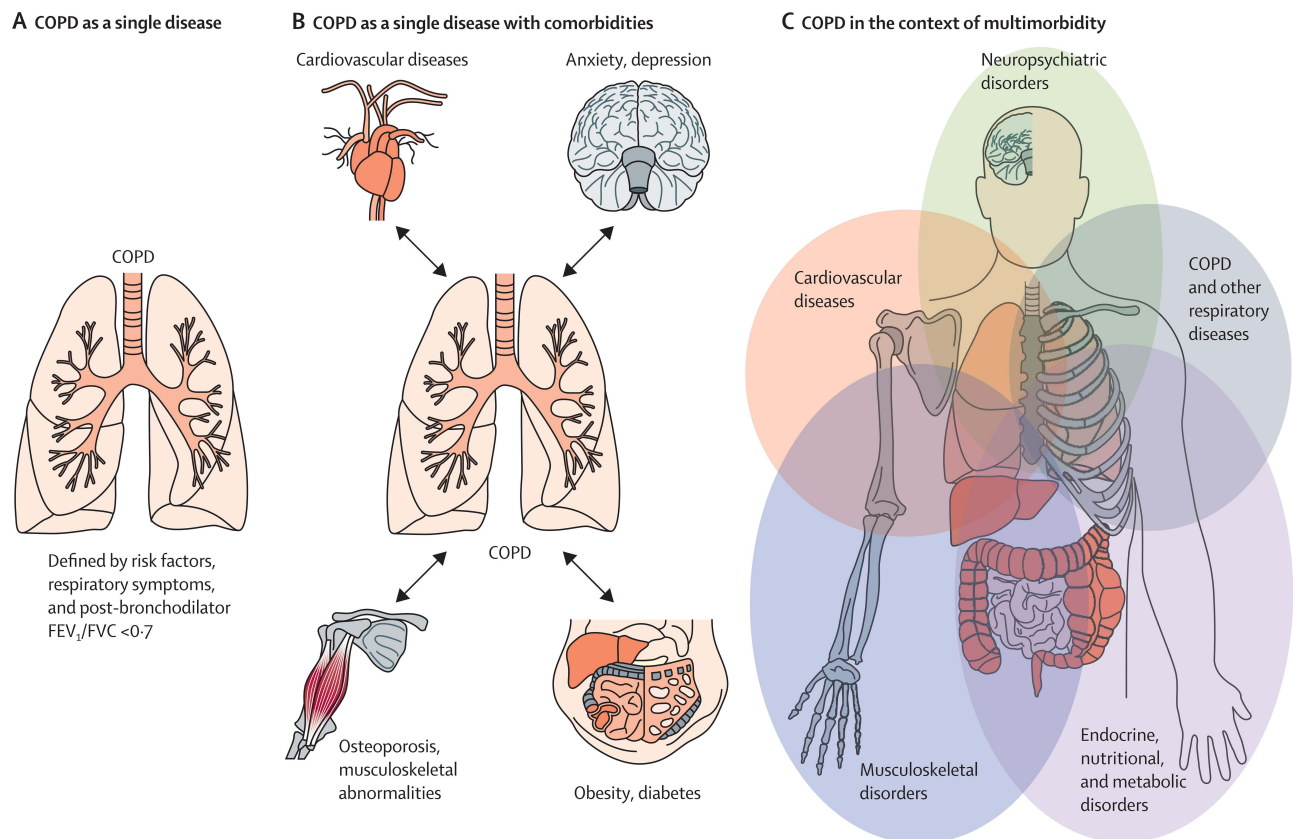
## COPD and Digestive System Diseases

Common digestive system comorbidities associated with COPD include gastroesophageal reflux, chronic gastritis, peptic ulcer, irritable bowel syndrome and inflammatory bowel disease. Among these, gastroesophageal reflux disease (GERD) is a common but frequently overlooked condition, which can markedly increase the frequency of acute exacerbation of COPD. This primarily results because of airway irritation and damage from reflux of acidic gastric contents, bronchoconstriction due to the cough reflex triggered by vagal stimulation, bacterial reflux and even bacterial colonization due to aspiration.<sup>126–128</sup> Similarly, changes in chest pressure due to COPD may increase the risk of GERD. Additionally, recurrent coughing in COPD patients can also exacerbate reflux, and the use of receptor agonists commonly prescribed for COPD have a diastolic effect on the esophageal sphincter while dilating the bronchial tubes, potentially increasing the likelihood of the development of gastroesophageal reflux.<sup>129–131</sup> Thus, GERD and COPD can interact with each other. However, there remains a lack of comprehensive knowledge regarding the exact causal relationship between them.

At present, there is a lack of sufficient information on the impact of anti-reflux therapy on COPD, and there is ongoing controversy regarding the appropriateness of using acid-inhibitory drugs, specifically proton pump inhibitors (PPIs). Several studies have indicated that PPI treatment could potentially exacerbate COPD,<sup>132</sup> yet others have suggested that the risk of pneumonia was not increased by PPI treatment.<sup>133</sup> In addition, some studies have demonstrated that acid-suppressing therapy could improve the scores of lung symptom,<sup>134</sup> but paradoxically, the lung function of the majority of patients does not show significant improvement.<sup>135,136</sup> In addition, use of azithromycin has been found to be noteworthy as it can promote cholinergic activity to accelerate gastric emptying.<sup>137</sup> For the moment, the efficacy and safety of PPIs in patients with chronic obstructive pulmonary disease (COPD), as well as the relationship between increased gastric acidity and progression of COPD, still need to be studied on a larger scale.

## Conclusions

COPD is usually accompanied by one or more comorbidities that interact with each other. Chronic inflammation, oxidative stress, hypoxia, and smoking serve as mutual links connecting COPD and comorbidities. Although the mechanisms remain elusive and the current guidelines recommend a management according to the principle of single-disease guideline-directed medical treatment,<sup>1</sup> it's appropriate to treat them as a whole (Figure 1).<sup>138</sup> For almost every patient with COPD, the clinical reality is that the disease is a component of multimorbidity. Therefore, we need to find integrated multimorbidity management, considering both pharmacological and nonpharmacological strategies. It's important for every clinician to realize that an



**Figure 1** COPD and multimorbidity. This conceptual framework represents the most important change in disease concept since the Review<sup>139</sup> by Decramer and Janssens on COPD and comorbidities was published in the first volume of *The Lancet Respiratory Medicine*, and demands a shift in the management paradigm from an approach that focuses on COPD as a single disease of the respiratory system with comorbidities, to one in which COPD is viewed as a component of multimorbidity. **(A)** Previously COPD was seen as a single disease. **(B)** COPD and different comorbidities have generally gained attention because of the progress in understanding, but they were still viewed separately. **(C)** Patients with COPD and comorbidities should be considered as suffering from a multimorbid state, which should be treated as a whole. COPD=chronic obstructive pulmonary disease. FVC=forced vital capacity.

**Note:** Reprinted from *The Lancet Respiratory Medicine*, 11/11, Leonardo M Fabbri, Bartolome R Celli, Alvar Agustí, Gerard J Criner, Mark T Dransfield, Miguel Divo, Jamuna K Krishnan, Lies Lahousse, Maria Montes de Oca, Sundeep S Salvi, Daiana Stolz, Lowie E G W Vanfleteren, Claus F Vogelmeier, COPD and multimorbidity: recognising and addressing a syndemic occurrence, 1020-1034, Copyright 2023, with permission from Elsevier.<sup>138</sup>

effective patient-centered management approach is a more efficient treatment option. So, multi-disciplinary, multi-level, and effective research is necessary to thoroughly investigate and develop targeted treatment strategies that are more appropriate for COPD and its comorbidities. This strategy can provide strong theoretical support for the management and prevention of these conditions. Moreover, the clinicians should also improve their cognitive and diagnostic abilities in management of COPD-related comorbidities. They should develop personalized and effective diagnosis and treatment approaches for individual patients to optimize their clinical outcomes.

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## Disclosure

The authors declare that they have no conflicts of interest in this work.

## References

1. GOLD Report. Global initiative for chronic obstructive lung disease; 2023. Available from: <https://goldcopd.org/2023-gold-report-2/>. Accessed February 24, 2024.
2. Foreman KJ, Marquez N, Dolgert A, et al. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016–40 for 195 countries and territories. *Lancet*. 2018;392(10159):2052–2090. doi:10.1016/S0140-6736(18)31694-5
3. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. 2020;396(10258):1204–1222. doi:10.1016/S0140-6736(20)30925-9
4. Chen YH. Interpretation of global strategy for the diagnosis, treatment, management and prevention of chronic obstructive pulmonary disease 2022 report. *Chinese General Practice*. 2022;25(11):1294–1304+1308.
5. Huang YL, Min J, Li GH, et al. The clinical study of comorbidities and systemic inflammation in COPD. *J Sichuan Univ*. 2019;50(1):88–92.
6. Divo MJ, Celli BR, Poblador-Plou B, et al. Chronic Obstructive Pulmonary Disease (COPD) as a disease of early aging: evidence from the EpiChron Cohort. *PLoS One*. 2018;13(2):e0193143. doi:10.1371/journal.pone.0193143
7. Agustí A, Celli BR, Criner GJ, et al. Global initiative for chronic obstructive lung disease 2023 report: gold executive summary. *Am J Res Crit Care Med*. 2023;207(7):819–837.
8. Chen W, Thomas J, Sadatsafavi M, et al. Risk of cardiovascular comorbidity in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Lancet Respir Med*. 2015;3(8):631–639. doi:10.1016/S2213-2600(15)00241-6
9. André S, Conde B, Fragoso E, et al. COPD and Cardiovascular Disease. *Pulmonology*. 2019;25(3):168–176. doi:10.1016/j.pulmoe.2018.09.006
10. Kunisaki KM, Dransfield MT, Anderson JA, et al. Exacerbations of chronic obstructive pulmonary disease and cardiac events. A post hoc cohort analysis from the submit randomized clinical trial. *Am J Respir Crit Care Med*. 2018;198(1):51–57.
11. Shi Y, Zhang J, Huang Y. Prediction of cardiovascular risk in patients with chronic obstructive pulmonary disease: a study of the national health and nutrition examination survey database. *BMC Cardiovascul Disord*. 2021;21(1):417. doi:10.1186/s12872-021-02225-w
12. Maclay JD, MacNee W. Cardiovascular disease in COPD: mechanisms. *Chest*. 2013;143(3):798–807. doi:10.1378/chest.12-0938
13. Brassington K, Selemidis S, Bozinovski S, et al. New frontiers in the treatment of comorbid cardiovascular disease in chronic obstructive pulmonary disease. *Clin Sci*. 2019;133(7):885–904. doi:10.1042/CS20180316
14. Sin DD, Man SFP. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease. *Circulation*. 2003;107(11):1514–1519. doi:10.1161/01.CIR.0000056767.69054.B3
15. Brassington K, Selemidis S, Bozinovski S, et al. Chronic obstructive pulmonary disease and atherosclerosis: common mechanisms and novel therapeutics. *Clin Sci*. 2022;136(6):405–423. doi:10.1042/CS20210835
16. Karoli NA, Rebrov AP. Endothelial dysfunction in patients with chronic obstructive pulmonary disease in combination with coronary heart disease. *Terapevticheski Arkhiv*. 2019;91(3):22–26. doi:10.26442/00403660.2019.03.000061
17. Parkin L, Williams S, Sharples K, et al. Dual versus single long-acting bronchodilator use could raise acute coronary syndrome risk by over 50%: a population-based nested case-control study. *J Intern Med*. 2021;290(5):1028–1038. doi:10.1111/joim.13348
18. Yang YL, Xiang ZJ, Yang JH, et al. Association of  $\beta$ -blocker use with survival and pulmonary function in patients with chronic obstructive pulmonary and cardiovascular disease: a systematic review and meta-analysis. *Eur Heart J*. 2020;41(46):4415–4422. doi:10.1093/eurheartj/ehaa793
19. Gulea C, Zakeri R, Alderman V, et al. Beta-blocker therapy in patients with COPD: a systematic literature review and meta-analysis with multiple treatment comparison. *Respir Res*. 2021;22(1):64. doi:10.1186/s12931-021-01661-8
20. Hawkins NM, Petrie MC, Macdonald MR, et al. Heart failure and chronic obstructive pulmonary disease the quandary of beta-blockers and beta-agonists. *J Am Coll Cardiol*. 2011;57(21):2127–2138. doi:10.1016/j.jacc.2011.02.020
21. Zhang W, Li CW, Yang L, et al. Advances in the use of statins in chronic obstructive pulmonary disease and its comorbidities. *Chin J Lung Dis*. 2021;14(01):114–116.
22. Lu Y, Chang R, Yao J, et al. Effectiveness of long-term using statins in COPD - a network meta-analysis. *Respir Res*. 2019;20(1):17. doi:10.1186/s12931-019-0984-3
23. Ingebrigtsen TS, Marott JL, Nordestgaard BG, et al. Statin use and exacerbations in individuals with chronic obstructive pulmonary disease. *Thorax*. 2015;70(1):33–40. doi:10.1136/thoraxjnl-2014-205795



24. Wu WT, Chen CY. Protective effect of statins on pulmonary hypertension in chronic obstructive pulmonary disease patients: a nationwide retrospective, matched cohort study. *Sci Rep.* 2020;10(1):3104. doi:10.1038/s41598-020-59828-0
25. Huang YJ, Kao S, Kao LT, et al. Association between statin use and exacerbation of chronic obstructive pulmonary disease among patients receiving corticosteroids. *Int J Chronic Obstr.* 2021;16:591–602. doi:10.2147/COPD.S292026
26. Andell P, James SK, Cannon CP, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes and chronic obstructive pulmonary disease: an analysis from the platelet inhibition and patient outcomes (PLATO) trial. *J Am Heart Assoc.* 2015;4(10):e002490. doi:10.1161/JAHA.115.002490
27. Aaron CP, Schwartz JE, Hoffman EA, et al. A longitudinal cohort study of aspirin use and progression of emphysema-like lung characteristics on CT imaging: the mesa lung study. *Chest.* 2018;154(1):41–50. doi:10.1016/j.chest.2017.11.031
28. Fawzy A, Putcha N, Aaron CP, et al. Aspirin use and respiratory morbidity in COPD: a propensity score-matched analysis in subpopulations and intermediate outcome measures in COPD study. *Chest.* 2019;155(3):519–527. doi:10.1016/j.chest.2018.11.028
29. Vasileiadis IE, Goudis CA, Giannakopoulou PT, et al. Angiotensin converting enzyme inhibitors and angiotensin receptor blockers: a promising medication for chronic obstructive pulmonary disease? *COPD.* 2018;15(2):148–156. doi:10.1080/15412555.2018.1432034
30. Tejwani V, Fawzy A, Putcha N, et al. Emphysema progression and lung function decline among angiotensin converting enzyme inhibitors and angiotensin-receptor blockade users in the copdgene cohort. *Chest.* 2021;160(4):1245–1254. doi:10.1016/j.chest.2021.05.007
31. Almutairi S, Kalloush HM, Manoon NA, et al. Matrix metalloproteinases inhibitors in cancer treatment: an updated review (2013–2023). *Molecules.* 2023;28(14):5567. doi:10.3390/molecules28145567
32. Cebron Lipovec N, Beijers RJ, van den Borst B, Doehner W, Lainscak M, Schols AM. The prevalence of metabolic syndrome in chronic obstructive pulmonary disease: a systematic review. *COPD.* 2016;13(3):399–406. doi:10.3109/15412555.2016.1140732
33. Chan SMH, Selemidis S, Bozinovski S, et al. Pathobiological mechanisms underlying metabolic syndrome (MetS) in chronic obstructive pulmonary disease (COPD): clinical significance and therapeutic strategies. *Pharmacol Ther.* 2019;198:160–188.
34. Cazzola M, Rogliani P, Calzetta L, et al. Targeting mechanisms linking COPD to type 2 diabetes mellitus. *Trends Pharmacol Sci.* 2017;38(10):940–951. doi:10.1016/j.tips.2017.07.003
35. Frizzelli A, Aiello M, Calzetta L, et al. The interplay between diabetes mellitus and chronic obstructive pulmonary disease. *Minerva Med.* 2023;114(1):68–73. doi:10.23736/S0026-4806.22.07742-4
36. Kinney GL, Black-Shinn JL, Wan ES, et al. Pulmonary function reduction in diabetes with and without chronic obstructive pulmonary disease. *Diabetes Care.* 2014;37(2):389–395. doi:10.2337/dc13-1435
37. Mekov EV, Slavova YG, Genova MP, et al. Diabetes mellitus type 2 in hospitalized COPD patients: impact on quality of life and lung function. *Folia Medica.* 2016;58(1):36–41. doi:10.1515/foimed-2016-0005
38. Liu J, Song X, Zheng S, et al. A prospective study on physical performance of Chinese chronic obstructive pulmonary disease males with type 2 diabetes. *Medicine.* 2021;100:35.
39. Zaigham S, Nilsson PM, Wollmer P, et al. The temporal relationship between poor lung function and the risk of diabetes. *BMC Pulm Med.* 2016;16(1):75. doi:10.1186/s12890-016-0227-z
40. Cyphert TJ, Morris RT, House LM, et al. NF- $\kappa$ B-dependent airway inflammation triggers systemic insulin resistance. *Am J Physiol Regulatory Integr Comp Physiol.* 2015;309(9):R1144–1152. doi:10.1152/ajpregu.00442.2014
41. Xu M. The changes of the inflammatory profiles and oxidative stress for insulin resistance in AECOPD patients with T2DM. *Anhui Medical University.* 2018;2018:1.
42. Khateeb J, Fuchs E, Khamaisi M. Diabetes and lung disease: a neglected relationship. *Rev Diabet Stud.* 2019;15:1–15. doi:10.1900/RDS.2019.15.1
43. Mauricio D, Gratacòs M, Franch-Nadal J. Diabetic microvascular disease in non-classical beds: the hidden impact beyond the retina, the kidney, and the peripheral nerves. *Cardiovasc Diabetol.* 2023;22(1):314. doi:10.1186/s12933-023-02056-3
44. Dai Y, Zhou S, Qiao L, et al. Non-apoptotic programmed cell deaths in diabetic pulmonary dysfunction: the new side of advanced glycation end products. *Front Endocrinol.* 2023;14:1126661. doi:10.3389/fendo.2023.1126661
45. Klein OL, Krishnan JA, Glick S, et al. Systematic review of the association between lung function and Type 2 diabetes mellitus. *Diabet Med.* 2010;27(9):977–987. doi:10.1111/j.1464-5491.2010.03073.x
46. Price DB, Russell R, Mares R, et al. Metabolic effects associated with ICS in patients with COPD and comorbid type 2 diabetes: a historical matched cohort study. *PLoS One.* 2016;11(9):e0162903. doi:10.1371/journal.pone.0162903
47. Miravittles M, Auladell-Rispau A, Monteagudo M, et al. Systematic review on long-term adverse effects of inhaled corticosteroids in the treatment of COPD. *Eur Respir Rev.* 2021;30(160):210075. doi:10.1183/16000617.0075-2021
48. Liu X. Effect of Corticosteroid use in chronic obstructive pulmonary disease with diabetes on diabetic complications. *Genom Appl Biol.* 2019;38(11):5204–5208.
49. Ajmera M, Shen C, Sambamoorthi U. Concomitant medication use and new-onset diabetes among Medicaid beneficiaries with chronic obstructive pulmonary disease. *Popul Health Manag.* 2017;20(3):224–232. doi:10.1089/pop.2016.0047
50. Jin Y, Liu A. The Changes and significance of immune function in chronic obstructive pulmonary disease patients with diabetes mellitus. *J Clin Pulm Med.* 2012;17(2):267–268.
51. Deng HB, Long M, Jia KL. Experimental study of the effects of AMP-dependent protein kinase metformin on emphysema in aged rats. *Chin J Mult Organ Dis Elderly.* 2019;18(11):864–868.
52. Saber S, El-Kader EMA. Novel complementary coloprotective effects of metformin and MCC950 by modulating HSP90/NLRP3 interaction and inducing autophagy in rats. *Inflam-mopharmacology.* 2021;29(1):237–251. doi:10.1007/s10787-020-00730-6
53. Peng Q. Effects and mechanism of metformin on inflammatory and oxidative stress in COPD rats. *Zheng Univ.* 2019;2019:1.
54. Zhang Y, Zhang H, Li S, et al. Metformin alleviates LPS-induced acute lung injury by regulating the SIRT1/NF- $\kappa$ B/NLRP3 pathway and inhibiting endothelial cell pyroptosis. *Front Pharmacol.* 2022;13:801337. doi:10.3389/fphar.2022.801337
55. Cheng D, Xu Q, Wang Y, et al. Metformin attenuates silica-induced pulmonary fibrosis via AMPK signaling. *J Transl Med.* 2021;19(1):349. doi:10.1186/s12967-021-03036-5
56. Tseng CH. Metformin and risk of chronic obstructive pulmonary disease in diabetes patients. *Diabetes Metabolism.* 2019;45(2):184–190. doi:10.1016/j.diabet.2018.05.001

57. Yen FS, Chen W, Wei JCC, et al. Effects of metformin use on total mortality in patients with type 2 diabetes and chronic obstructive pulmonary disease: a matched-subject design. *PLoS One*. 2018;13(10):e0204859. doi:10.1371/journal.pone.0204859
58. Ho TW, Huang CT, Tsai YJ, et al. Metformin use mitigates the adverse prognostic effect of diabetes mellitus in chronic obstructive pulmonary disease. *Respir Res*. 2019;20(1):69. doi:10.1186/s12931-019-1035-9
59. Wang MT, Lai JH, Huang Y-L, et al. Use of antidiabetic medications and risk of chronic obstructive pulmonary disease exacerbation requiring hospitalization: a disease risk score-matched nested case-control study. *Respir Res*. 2020;21(1):319. doi:10.1186/s12931-020-01547-1
60. Chen KY, Wu SM, Tseng CH, et al. Combination therapies with thiazolidinediones are associated with a lower risk of acute exacerbations in new-onset COPD patients with advanced diabetic mellitus: a cohort-based case-control study. *BMC Pulm Med*. 2021;21(1):141. doi:10.1186/s12890-021-01505-7
61. Yen FS, Wei JC, Yu TS, et al. Sulfonylurea use in patients with type 2 diabetes and COPD: a nationwide population-based cohort study. *Int J Environ Res Public Health*. 2022;19(22):15013. doi:10.3390/ijerph192215013
62. Rogliani P, Matera MG, Calzetta L, et al. Long-term observational study on the impact of GLP-1R agonists on lung function in diabetic patients. *Respir Med*. 2019;154:86–92. doi:10.1016/j.rmed.2019.06.015
63. Pradhan R, Lu S, Yin H, et al. Novel antihyperglycaemic drugs and prevention of chronic obstructive pulmonary disease exacerbations among patients with type 2 diabetes: population based cohort study. *BMJ*. 2022;379:e071380.
64. PCM A, Tan KCB, Lam DCL, et al. Association of sodium-glucose cotransporter 2 inhibitor vs dipeptidyl peptidase-4 inhibitor use with risk of incident obstructive airway disease and exacerbation events among patients with type 2 diabetes in Hong Kong. *JAMA Network Open*. 2023;6(1):e2251177. doi:10.1001/jamanetworkopen.2022.51177
65. Cote C, Zilberberg MD, Mody SH, et al. Haemoglobin level and its clinical impact in a cohort of patients with COPD. *Europ resp J*. 2007;29(5):923–929. doi:10.1183/09031936.00137106
66. Sarkar M, Rajta PN, Khatana J. Anemia in Chronic obstructive pulmonary disease: prevalence, pathogenesis, and potential impact. *Lung India*. 2015;32(2):142–151. doi:10.4103/0970-2113.152626
67. Ferrari M, Manea L, Anton K, et al. Anemia and hemoglobin serum levels are associated with exercise capacity and quality of life in chronic obstructive pulmonary disease. *BMC Pulm Med*. 2015;15:58. doi:10.1186/s12890-015-0050-y
68. Xu Y, Hu T, Ding H, et al. Effects of anemia on the survival of patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Expert Rev Respir Med*. 2020;14(12):1267–1277. doi:10.1080/17476348.2020.1816468
69. Oh YM, Park JH, Kim EK, et al. Anemia as a clinical marker of stable chronic obstructive pulmonary disease in the Korean obstructive lung disease cohort. *J Thorac Dis*. 2017;9(12):5008–5016. doi:10.21037/jtd.2017.10.140
70. Putcha N, Fawzy A, Paul GG, et al. Anemia and adverse outcomes in a chronic obstructive pulmonary disease population with a high burden of comorbidities. An Analysis from SPIROMICS. *Ann Am Thoracic Soc*. 2018;15(6):710–717. doi:10.1513/AnnalsATS.201708-687OC
71. Chen H, Deng J, Feng YL. Anaemia associated with chronic obstructive pulmonary disease. *Chin J Respir Crit Care Med*. 2009;8(6):606–608.
72. Lin HR, Deng C, Liu H, et al. Correlation analysis of incidences of anemia and hypoproteinemia and age and sex in patients with chronic obstructive pulmonary disease. *Chin J Lung Dis*. 2019;12(3):311–314.
73. de Hoepers ATC, Menezes MM, Fröde TS. Systematic review of anaemia and inflammatory markers in chronic obstructive pulmonary disease. *Clin Exp Pharmacol Physiol*. 2015;42(3):231–239. doi:10.1111/1440-1681.12357
74. Kuhrt D, Wojchowski DM. Emerging EPO and EPO receptor regulators and signal transducers. *Blood*. 2015;125(23):3536–3541. doi:10.1182/blood-2014-11-575357
75. Lin SN, Wang FH, Shi HF, et al. Study on the mechanism of iron homeostasis disorder in mediating anemia in COPD patients with type II respiratory failure. *Chin J Diffic and Compl Cas*. 2021;20(10):1012–1016.
76. Lanser L, Fuchs D, Kurz K, et al. Physiology and inflammation driven pathophysiology of iron homeostasis-mechanistic insights into anemia of inflammation and its treatment. *Nutrients*. 2021;13(11):3732. doi:10.3390/nu13113732
77. Kim MH, Kim YH, Lee DC. Relationships of serum iron parameters and hemoglobin with forced expiratory volume in 1 second in patients with chronic obstructive pulmonary disease. *Korean J Fam Med*. 2018;39(2):85–89.
78. Sato K, Inoue S, Igarashi A, et al. Effect of iron deficiency on a murine model of smoke-induced emphysema. *Am J Respir Cell Mol Biol*. 2020;62(5):588–597. doi:10.1165/rcmb.2018-0239OC
79. Shi QF, Sheng Y, Wang SY. Progress in the study of the effect of anaemia on patients with chronic obstructive pulmonary disease. *J Clin Pulm Med*. 2019;24(1):144–147.
80. Sharma RK, Chakrabarti S. Anaemia secondary to erythropoietin resistance: important predictor of adverse outcomes in chronic obstructive pulmonary disease. *Postgrad Med J*. 2016;92(1093):636–639. doi:10.1136/postgradmedj-2015-133814
81. Pérez-Peiró M, Martín-Ontiyuelo C, Rodó-Pi A, et al. Iron replacement and redox balance in non-anemic and mildly anemic iron deficiency COPD Patients: insights from a clinical trial. *Biomedicines*. 2021;9(9):1191. doi:10.3390/biomedicines9091191
82. Loveikyte R, Bourgonje AR, van Goor H, et al. The effect of iron therapy on oxidative stress and intestinal microbiota in inflammatory bowel diseases: a review on the conundrum. *Redox Biol*. 2023;68:102950. doi:10.1016/j.redox.2023.102950
83. Bonovas S, Fiorino G, Allocca M, et al. Intravenous versus oral iron for the treatment of anemia in inflammatory bowel disease: a systematic review and meta-analysis of randomized controlled trials. *Medicine*. 2016;95(2):e2308. doi:10.1097/MD.0000000000002308
84. Lei T, Lu T, Yu H, et al. Efficacy of Vitamin C supplementation on chronic obstructive pulmonary disease (COPD): a systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis*. 2022;17:2201–2216. doi:10.2147/COPD.S368645
85. Fletcher J, Cooper SC, Ghosh S, et al. The role of vitamin D in inflammatory bowel disease: mechanism to management. *Nutrients*. 2019;11(5):1019. doi:10.3390/nu11051019
86. Schnell K, Weiss CO, Lee T, et al. The prevalence of clinically-relevant comorbid conditions in patients with physician-diagnosed COPD: a cross-sectional study using data from NHANES 1999–2008. *BMC Pulm Med*. 2012;12:26. doi:10.1186/1471-2466-12-26
87. Sepúlveda-Loyola W, Osadnik C, Phu S, et al. Diagnosis, prevalence, and clinical impact of sarcopenia in COPD: a systematic review and meta-analysis. *J Cach Sarcop Muscle*. 2020;11(5):1164–1176. doi:10.1002/jcsm.12600
88. Chen YW, Ramsook AH, Coxson HO, et al. Prevalence and risk factors for osteoporosis in individuals with COPD: a systematic review and meta-analysis. *Chest*. 2019;156(6):1092–1110. doi:10.1016/j.chest.2019.06.036
89. Sözen T, Özışık L, Başaran NÇ. An overview and management of osteoporosis. *Eur J Rheumatol*. 2017;4(1):46–56. doi:10.5152/eurjrheum.2016.048

90. Xiao YJ, Wang SP. Progress in the study of factors and mechanisms associated with skeletal muscle dysfunction in chronic obstructive pulmonary disease. *J Clin Pulm Med*. 2016;21(2):340–343.
91. Song ZH, Song HP, Wang ZQ. Research progress on the effect of chronic obstructive pulmonary disease on bone strength. *Chin J Osteoporos*. 2022;28(4):613–618.
92. Lehouck A, Boonen S, Decramer M, et al. COPD, bone metabolism, and osteoporosis. *Chest*. 2011;139(3):648–657. doi:10.1378/chest.10-1427
93. Compston JE, McClung MR, Leslie WD. Osteoporosis. *Lancet*. 2019;393(10169):364–376. doi:10.1016/S0140-6736(18)32112-3
94. Gorissen B, de Bruin A, Miranda-Bedate A, et al. Hypoxia negatively affects senescence in osteoclasts and delays osteoclastogenesis. *J Cell Physiol*. 2018;234(1):414–426. doi:10.1002/jcp.26511
95. Liang B, Feng Y. The association of low bone mineral density with systemic inflammation in clinically stable COPD. *Endocrine*. 2012;42(1):190–195. doi:10.1007/s12020-011-9583-x
96. Lu Y, Di YP, Chang M, et al. Cigarette smoke-associated inflammation impairs bone remodeling through NFκB activation. *J Transl Med*. 2021;19(1):163. doi:10.1186/s12967-021-02836-z
97. Marinucci L, Balloni S, Fettucciari K, et al. Nicotine induces apoptosis in human osteoblasts via a novel mechanism driven by H<sub>2</sub>O<sub>2</sub> and entailing Glyoxalase 1-dependent MG-H1 accumulation leading to TG2-mediated NF-κB desensitization: implication for smokers-related osteoporosis. *Free Radic Biol Med*. 2018;117:6–17. doi:10.1016/j.freeradbiomed.2018.01.017
98. Kokturk N, Baha A, Oh YM, et al. Vitamin D deficiency: what does it mean for chronic obstructive pulmonary disease (COPD)? A comprehensive review for pulmonologists. *Clin Respir J*. 2018;12(2):382–397. doi:10.1111/crj.12588
99. Compston J. Glucocorticoid-induced osteoporosis: an update. *Endocrine*. 2018;61(1):7–16. doi:10.1007/s12020-018-1588-2
100. Chotiyarnwong P, McCloskey EV. Pathogenesis of corticosteroids-induced osteoporosis and options for treatment. *Nat Rev Endocrinol*. 2020;16(8):437–447. doi:10.1038/s41574-020-0341-0
101. Gonçalves PA, Dos Santos Neves R, Neto LV, et al. Inhaled glucocorticoids are associated with vertebral fractures in COPD patients. *J Bone Mineral Metab*. 2018;36(4):454–461. doi:10.1007/s00774-017-0854-3
102. Chiu KL, Lee CC, Chen CY. Evaluating the association of osteoporosis with inhaled corticosteroid use in chronic obstructive pulmonary disease in Taiwan. *Sci Rep*. 2021;11(1):724. doi:10.1038/s41598-020-80815-y
103. Allen CS, Yeung JH, Vandermeer B, et al. Bisphosphonates for steroid-induced osteoporosis. *Cochrane Database Syst Rev*. 2016;10(10):CD001347. doi:10.1002/14651858.CD001347.pub2
104. Lewiecki EM. New and emerging concepts in the use of denosumab for the treatment of osteoporosis. *Therapeutic Advan Musculosk Dis*. 2018;10(11):209–223. doi:10.1177/1759720X18805759
105. Saag KG, Wagman RB, Geusens P, et al. Denosumab versus risedronate in corticosteroids-induced osteoporosis: a multicentre, randomised, double-blind, active-controlled, double-dummy, non-inferiority study. *Lancet Diabetes Endocrinol*. 2018;6(6):445–454. doi:10.1016/S2213-8587(18)30075-5
106. Ding L, Hu J, Wang D, et al. Efficacy and safety of first- and second-line drugs to prevent glucocorticoid-induced fractures. *J Clin Endocrinol Metab*. 2020;105(1):dgz023. doi:10.1210/clinem/dgz023
107. Yuan C, Liang Y, Zhu K, et al. Clinical efficacy of denosumab, teriparatide, and oral bisphosphonates in the prevention of corticosteroids-induced osteoporosis: a systematic review and meta-analysis. *J Orthopaedic Surg Res*. 2023;18(1):447. doi:10.1186/s13018-023-03920-4
108. Anagnostis P, Gkekakos NK, Potoupnis M, et al. New therapeutic targets for osteoporosis. *Maturitas*. 2019;120:1–6. doi:10.1016/j.maturitas.2018.11.010
109. Marcucci G, Domazetovic V, Nediani C, et al. Oxidative stress and natural antioxidants in osteoporosis: novel preventive and therapeutic approaches. *Antioxidants*. 2023;12(2):373. doi:10.3390/antiox12020373
110. Zareifopoulos N, Bellou A, Spiropoulou A, et al. Prevalence, contribution to disease burden and management of comorbid depression and anxiety in chronic obstructive pulmonary disease: a narrative review. *COPD*. 2019;16(5–6):406–417. doi:10.1080/15412555.2019.1679102
111. Huang J, Bian Y, Zhao Y, et al. The impact of depression and anxiety on chronic obstructive pulmonary disease acute exacerbations: a prospective cohort study. *J Affective Disorders*. 2021;281:147–152. doi:10.1016/j.jad.2020.12.030
112. Liu YJ, Tian XL, Guo XH, et al. Prevalence of anxiety and depression in chronic obstructive pulmonary disease. *Chin J Respir Crit Care Med*. 2020;19(5):425–429.
113. Montserrat-Capdevila J, Godoy P, Marsal JR, et al. Overview of the impact of depression and anxiety in chronic obstructive pulmonary disease. *Lung*. 2017;195(1):77–85. doi:10.1007/s00408-016-9966-0
114. Riske L, Thomas RK, Baker GB, et al. Lactate in the brain: an update on its relevance to brain energy, neurons, glia and panic disorder. *Therap Advan Psychopharmacol*. 2017;7(2):85–89. doi:10.1177/2045125316675579
115. Freire RC, Perna G, Nardi AE. Panic disorder respiratory subtype: psychopathology, laboratory challenge tests, and response to treatment. *Harvard Rev Psych*. 2010;18(4):220–229. doi:10.3109/10673229.2010.493744
116. De Luca SN, Chan SMH, Dobric A, et al. Cigarette smoke-induced pulmonary impairment is associated with social recognition memory impairments and alterations in microglial profiles within the suprachiasmatic nucleus of the hypothalamus. *Brain Behav Immun*. 2023;109:292–307. doi:10.1016/j.bbi.2023.02.005
117. Sundar IK, Yao H, Huang Y, et al. Serotonin and corticosterone rhythms in mice exposed to cigarette smoke and in patients with COPD: implication for COPD-associated neuropathogenesis. *PLoS One*. 2014;9(2):e87999. doi:10.1371/journal.pone.0087999
118. Pelgrim CE, Peterson JD, Gosker HR, et al. Psychological co-morbidities in COPD: targeting systemic inflammation, a benefit for both? *Eur J Pharmacol*. 2019;842:99–110. doi:10.1016/j.ejphar.2018.10.001
119. Zhang T, Wang G, Li Q, et al. Relationship between serum Th1/Th2 imbalance and depression in elderly patients with COPD and its clinical implications. *Technol Health Care*. 2023;31(6):2047–2058. doi:10.3233/THC-230665
120. Foley ÉM, Parkinson JT, Mitchell RE, et al. Peripheral blood cellular immunophenotype in depression: a systematic review and meta-analysis. *Mol Psychiatry*. 2023;28(3):1004–1019. doi:10.1038/s41380-022-01919-7
121. Recio Iglesias J, Díez-Manglano J, López García F, et al. Management of the COPD patient with comorbidities: an experts recommendation document. *Int J Chronic Obstr*. 2020;15:1015–1037. doi:10.2147/COPD.S242009
122. Taylor SJC, Sohanpal R, Steed L, et al. Tailored psychological intervention for anxiety or depression in COPD (TANDEM): a randomised controlled trial. *Eur Respir J*. 2023;62(5):2300432. doi:10.1183/13993003.00432-2023

123. Yohannes AM, Alexopoulos GS. Pharmacological treatment of depression in older patients with chronic obstructive pulmonary disease: impact on the course of the disease and health outcomes. *Drugs Aging*. 2014;31(7):483–492. doi:10.1007/s40266-014-0186-0
124. Pollok J, van Agteren JE, Carson-Chahhoud KV. Pharmacological interventions for the treatment of depression in chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2018;12(12):CD012346. doi:10.1002/14651858.CD012346.pub2
125. Kappelmann N, Lewis G, Dantzer R, et al. Antidepressant activity of anti-cytokine treatment: a systematic review and meta-analysis of clinical trials of chronic inflammatory conditions. *Mol Psychiatry*. 2018;23(2):335–343. doi:10.1038/mp.2016.167
126. Huang C, Liu Y, Shi G. A systematic review with meta-analysis of gastroesophageal reflux disease and exacerbations of chronic obstructive pulmonary disease. *BMC Pulm Med*. 2020;20(1):2. doi:10.1186/s12890-019-1027-z
127. Harding SM, Allen JE, Blumin JH, et al. Respiratory manifestations of gastroesophageal reflux disease. *Ann N Y Acad Sci*. 2013;1300:43–52. doi:10.1111/nyas.12231
128. Lee AS, Lee JS, He Z, et al. Reflux-aspiration in chronic lung disease. *Ann Am Thorac Soc*. 2020;17(2):155–164. doi:10.1513/AnnalsATS.201906-427CME
129. Broers C, Tack J, Pauwels A. Review article: gastro-oesophageal reflux disease in asthma and chronic obstructive pulmonary disease. *Aliment Pharmacol Ther*. 2018;47(2):176–191. doi:10.1111/apt.14416
130. Lee AL, Goldstein RS. Gastroesophageal reflux disease in COPD: links and risks. *Int J Chronic Obstr*. 2015;10:1935–1949. doi:10.2147/COPD.S77562
131. Zou M, Zhang W, Xu Y, et al. Relationship between COPD and GERD: a bibliometrics analysis. *Int J Chronic Obstr*. 2022;17:3045–3059. doi:10.2147/COPD.S391878
132. Lee SW, Lien HC, Chang CS, et al. The impact of acid-suppressing drugs to the patients with chronic obstructive pulmonary disease: a nationwide, population-based, cohort study. *J Res Med Sci*. 2015;20(3):263–267. doi:10.4103/1735-1995.156174
133. Kang J, Lee R, Lee SW. Effects of gastroesophageal reflux disease treatment with proton pump inhibitors on the risk of acute exacerbation and pneumonia in patients with COPD. *Respir Res*. 2023;24(1):75. doi:10.1186/s12931-023-02345-1
134. Liu H. Assessment of anti-reflux treatment on pulmonary ventilation function and inflammatory cytokines in patients with stable chronic obstructive pulmonary disease combined with gastroesophageal reflux. *Exp Ther Med*. 2018;15(6):5528–5536. doi:10.3892/etm.2018.6077
135. Kikuchi S, Imai H, Tani Y, et al. Proton pump inhibitors for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2020;8(8):CD013113. doi:10.1002/14651858.CD013113.pub2
136. Yu F, Huang Q, Ye Y, et al. Effectiveness of proton-pump inhibitors in chronic obstructive pulmonary disease: a meta-analysis of randomized controlled trials. *Front Med Lausanne*. 2022;9:841155. doi:10.3389/fmed.2022.841155
137. Broad J, Sanger GJ. The antibiotic azithromycin is a motilin receptor agonist in human stomach: comparison with erythromycin. *Br J Pharmacol*. 2013;168(8):1859–1867. doi:10.1111/bph.12077
138. Fabbri LM, Celli BR, Agustí A, et al. COPD and multimorbidity: recognising and addressing a syndemic occurrence. *Lancet Respir Med*. 2023;11(11):1020–1034. doi:10.1016/S2213-2600(23)00261-8
139. Decramer M, Janssens W. Chronic obstructive pulmonary disease and comorbidities. *Lancet Respir Med*. 2013;1(1):73–83. doi:10.1016/S2213-2600(12)70060-7

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