Unravelling the mechanisms driving multimorbidity in COPD to develop holistic approaches to patient-centred care

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Shareable abstract (@ERSpublications)
Multimorbidity is common in COPD and is a global health priority. Using novel approaches to understand the complex mechanisms underlying multimorbidity is key to developing targeted, patient-centred management strategies to improve outcomes. https://bit.ly/3fUUkWB

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Abstract

COPD is a major cause of morbidity and mortality worldwide. Multimorbidity is common in COPD patients and a key modifiable factor, which requires timely identification and targeted holistic management strategies to improve outcomes and reduce the burden of disease.

We discuss the use of integrative approaches, such as cluster analysis and network-based theory, to understand the common and novel pathobiological mechanisms underlying COPD and comorbid disease, which are likely to be key to informing new management strategies.

Furthermore, we discuss the current understanding of mechanistic drivers to multimorbidity in COPD, including hypotheses such as multimorbidity as a result of shared common exposure to noxious stimuli (*e.g.* tobacco smoke), or as a consequence of loss of function following the development of pulmonary disease. In addition, we explore the links to pulmonary disease processes such as systemic overspill of pulmonary inflammation, immune cell priming within the inflamed COPD lung and targeted messengers such as extracellular vesicles as a result of local damage as a cause for multimorbidity in COPD.

Finally, we focus on current and new management strategies which may target these underlying mechanisms, with the aim of holistic, patient-centred treatment rather than single disease management.

Overview of multimorbidity in COPD

COPD is a major cause of morbidity and rising mortality worldwide [1, 2]. More than 90% of COPD deaths occur in low- and middle-income countries [3] and COPD mortality is predicted to rise further in these countries despite measures to reduce exposure to risk factors, such as tobacco control policies and declining poverty [4]. Importantly, multimorbidity has been identified as a key modifiable factor, which requires greater recognition, focus and management to improve outcomes and reduce burden of disease in COPD [5].

Whereas comorbidity describes the burden of illness coexisting with a particular disease of interest, multimorbidity is defined as the presence of multiple chronic conditions [6, 7] in an individual. It acknowledges that health conditions may overlap, vary in severity and change in importance over time (figure 1). Multimorbidity is a global health priority [8] and its prevalence increases substantially with age and levels of deprivation [9]. COPD is present in the majority of multimorbid patients [9] and multimorbidity in COPD increases the likelihood of hospital admission [10, 11] and healthcare costs [12], reduces quality of life and exercise tolerance [13] and increases mortality [14]. Studies have shown that patients with COPD are more likely to have comorbid disease compared with the general population, with the most prevalent comorbidities being osteoporosis, hypertension and gastro-oesophageal disease (table 1). Importantly, all these studies recognise that concomitant chronic diseases are often misdiagnosed or undiagnosed in patients with COPD and are thus untreated.

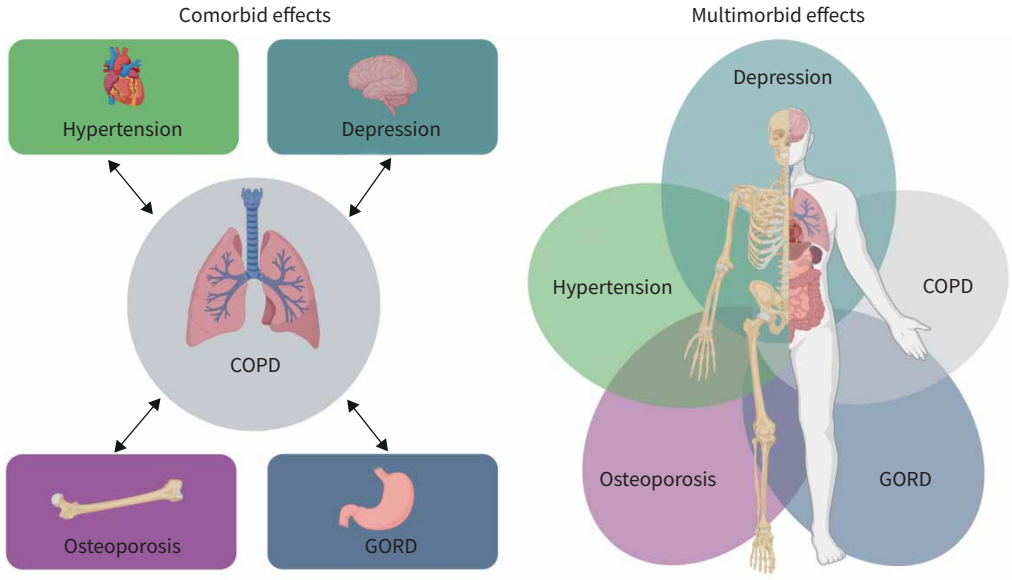

FIGURE 1 Conceptual diagram of comorbidity and multimorbidity in COPD. GORD: gastro-oesophageal reflux disease.

Approaches to understanding complex mechanisms underlying multimorbidity in COPD

Conventionally when studying multimorbidity in COPD, researchers have focused on a single coexistent disease or group of diseases. However, recent evidence supports a more integrative approach, in the hope that this could reveal disease clusters and novel pathobiology mechanisms, leading toward a better understanding and, possibly, integrated co-management of multimorbidity [26–28].

Unsupervised cluster-based analysis uses multivariate techniques to organise information in an unbiased way so that heterogeneous groups of patients can be classified into relatively homogeneous groups or "clusters" [29]. Several studies have used this approach and identified a COPD phenotype with a high prevalence of comorbid disease [30–32] and higher levels of systemic inflammatory markers [31, 32]. Furthermore, Garcia-Aymerich *et al.* [31] showed measures of systemic inflammation did not correlate with bronchial inflammation suggesting that systemic rather than bronchial inflammation may be driving the origins of both COPD and comorbid disease. To investigate the role of systemic inflammation in multimorbidity further, Vanfleteren *et al.* [33] used self-organising maps, an alternative neural network-based nonhierarchical clustering approach, to identify five comorbidity clusters ("less comorbidity", "cardiovascular", "metabolic", "psychologic" and "cachectic" clusters) suggesting that different pathophysiological pathways underlie these clusters.

TABLE 1 Prevalence of comorbidities in England compared to patients with COPD

	Prevalence in control population[#]	Prevalence in COPD	Reference(s)
Osteoporosis/osteopenia	18–22	50–70	[16, 17]
Hypertension	34–41	40–60	[10, 18]
GORD	33	30–60	[19]
Skeletal muscle dysfunction	9	32	[20]
Depression	7–12	25	[21]
Ischaemic heart disease	15	10–23	[22]
Diabetes	6–10	12–13	[10, 23]
Previous stroke	3	10–14	[18, 23]
Arrhythmia	5–11	11–12	[18]
Congestive heart failure	4	5–19	[18, 24]
Obesity	17–32	18–54	[25]

Data are presented as %. GORD: gastro-oesophageal reflux disease. Adapted from [15]. [#]: control population from the same study(ies) as the COPD comorbidity prevalence reported.

Although clustering approaches have shown promise in identifying COPD subtypes, further work has questioned the reproducibility of these analyses. For example, Castaldi *et al*. [34] demonstrated only modest reproducibility of COPD clustering results across multiple independent cohorts and suggested that COPD heterogeneity is best characterised by continuous disease traits coexisting within the same individual rather than separate identifiable COPD subtypes. More recently, studies have demonstrated that continuous measures of disease (disease axes) were better at predicting emphysema progression [35] and mortality than subtypes alone [36]. In contrast, Burgel *et al*. [37] was able to demonstrate reproducible clustering across cohorts in relation to mortality, with enrichment for multimorbidity in subgroup I. Together, these studies suggest there may be multiple distinct sets of subtypes that depend on a specific clinical outcome of interest.

Mathematical-based network theory demonstrates that disease co-occurrence is not the result of simple chance, but as a result of genetic predisposition in concert with cumulative pathobiological processes in response to biological stressors [28]. For example, Park *et al*. [38] showed that diseases that share genes or involve proteins that interact with each other show elevated comorbidity, demonstrating correlations between the structure of cellular networks and disease patterns in the population. This approach to network analysis maps the molecular and phenotypic interactions that could provide new insights into the pathobiology of multimorbidity in COPD [39]. Using this approach, Grosdidier *et al.* [40] identified several shared genes, proteins and biological pathways common to the most prevalent COPD multimorbidities (such as ischaemic heart disease, diabetes and obesity) suggesting common biological mechanisms. Furthermore, several of these were targets of the tobacco exposome, suggesting a link for the common exposure theory. Divo *et al*. [41] used network analysis to show that the prevalence of comorbidities (number of nodes) and number of simultaneous comorbidities is higher in COPD patients compared with controls. In addition, the COPD comorbidity network was found to have a "scale-free" architecture, indicating the existence of a few, highly connected nodes (diseases) in the network, so-called "hubs" that may play a key pathogenic role [42]. Based on this, they proposed that therapies targeted towards these hubs could result in improvement of outcomes in multiple diseases. Finally, they identified a number of "modules" consisting of coexisting diseases, which are interlinked beyond simple coincidence [41]. For example, they described module 1A comprised of 17 nodes connected by 81 edges around the theme of older COPD individuals with cardiovascular comorbidities (such as hypertension and coronary artery disease) and clinical characteristics known to confer worse prognosis in patients with COPD (forced expiratory volume in 1 s (FEV_1) <50%, modified Medical Research Council score >2, 6-min walk distance <350 m). Interestingly, these were similar to groups described by the cluster analysis studies [31, 32], thus reinforcing the concept that targeting key modules could be important for achieving meaningful outcomes from treatment across conventional single-morbidity strategies.

Towards an understanding of mechanistic drivers to multimorbidity in COPD

Understanding the mechanisms that could be driving these relationships between COPD and coexisting disease is key to developing novel strategies for treating this complex and heterogeneous disease. In this section, we explore the potential relationships between mechanistic drivers and examine the evidence supporting the competing hypotheses of disease genesis.

Current knowledge in the field of mechanisms underlying multimorbidity in COPD is summarised in figure 2.

Multimorbidity in COPD over the life course

Early origins of disease

Since the seminal work of Lange *et al*. [43] on lung function trajectories leading to COPD, there has been increasing interest in lung function development and its early determinants. These analyses and several other studies demonstrated that a low FEV_1 in early adulthood is important in the genesis of COPD; however, an accelerated decline in FEV_1 is not necessary [44, 45].

A normal lung function trajectory throughout life has three phases: a growth phase from birth to early adulthood, a plateau phase from ~20 years and a decline phase resulting from physiological ageing. Although smoking is still a major factor, other environmental, genetic and developmental factors with diverse biological mechanisms and effects can lead to an abnormal lung function trajectory, resulting in respiratory disease in adulthood [46]. In addition to COPD, a lower peak lung function in early adulthood is associated with cardiovascular and metabolic disease as well as premature mortality [44]. Therefore, early-life lung health has important implications for multimorbidity as well as single disease entities and further research is needed to better understand the biological mechanisms underlying these different abnormal lung trajectories.

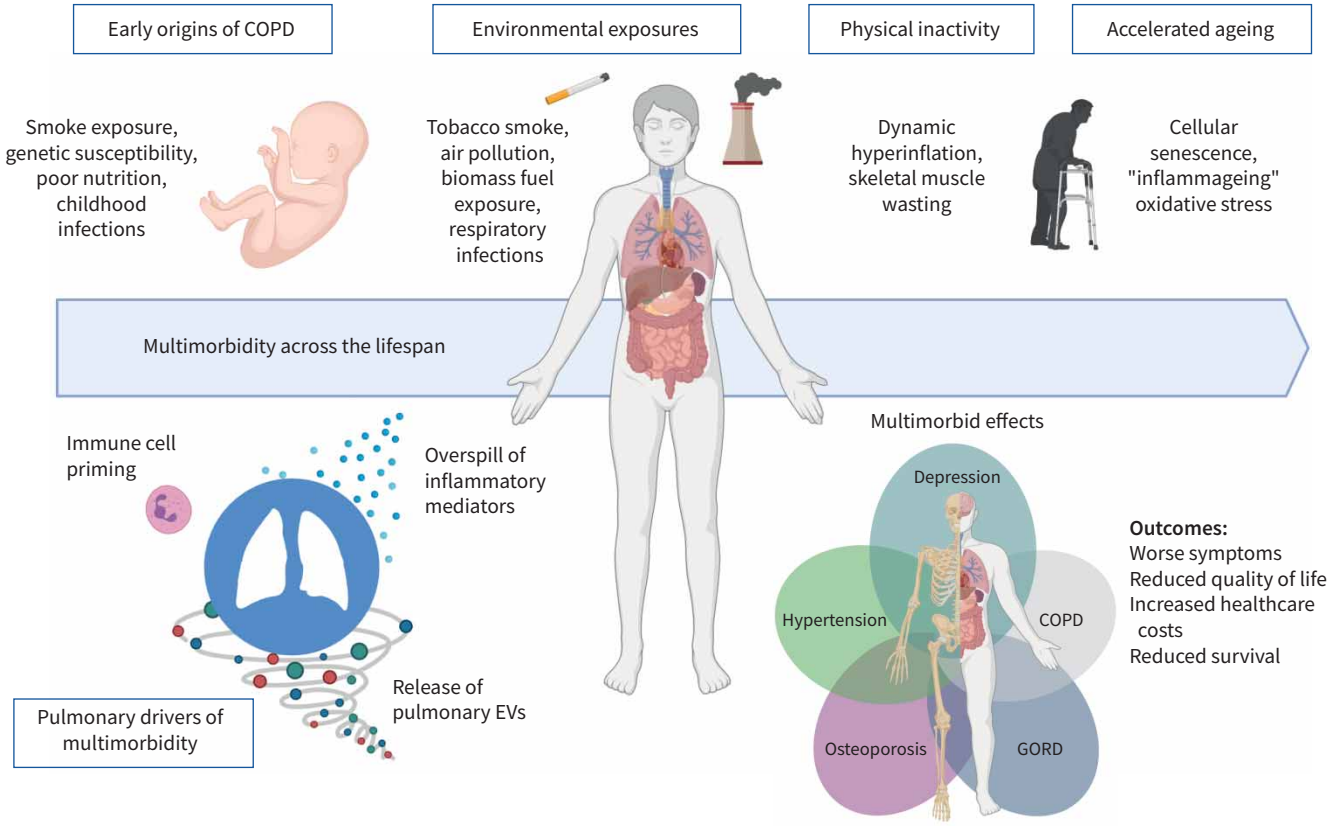

FIGURE 2 Drivers, mechanisms and outcomes for multimorbidity in COPD. EVs: extracellular vesicles; GORD: gastro-oesophageal reflux disease.

Recently, Kachroo *et al*. [47] used network approaches to investigate the epigenetic modifications caused by *in utero* smoke exposure, which may link to risk for COPD in adulthood. They identified several putative disease pathways supportive of exposure-related and age-associated developmental origins of COPD.

COPD and many of its comorbidities are often recognised and diagnosed too late, and therefore investigating these biological mechanisms underlying different abnormal lung function trajectories is key to impacting on early diagnosis and informing new therapeutic and preventative interventions including vaccinations [48, 49].

Environmental exposures and risk factors

Multimorbidity can arise as a consequence of environmental exposures, such as cigarette smoke, biomass fuel and physical inactivity, leading to multiple organ damage and disease.

Smoking

Tobacco smoke exposure is considered the primary risk factor for COPD, and is estimated to account for up to 80–90% of cases in the developed world. Furthermore, smoking is an important risk factor for other comorbid conditions such as lung cancer [50], cardiovascular disease [51] and osteoporosis [52]. Several studies have tried to unpick the complex relationship between common exposure and/or risk factors and presence of comorbid disease in COPD.

Large prospective cohort studies have demonstrated that the association between lung function impairment and cardiovascular disease was largely due to common risk factors such as age, sex, race, smoking, hypertension, diabetes, cholesterol and fibrinogen levels [53]. This was further supported by Van Remoortel *et al*. [54] who found prevalence of premorbid risk factors (*e.g.* obesity and hypertension) and comorbid diseases (*e.g.* heart disease, diabetes, skeletal muscle dysfunction and osteoporosis) was comparable in patients with COPD and in smokers, but was higher than in healthy nonsmokers. Importantly, physical activity and smoking were more strongly associated with multimorbidity than airflow

limitation. Furthermore, these findings were in accordance with Thomsen *et al*. [55], who reported that the risks of cardiovascular comorbidities and all-cause mortality were increased in former and current smokers with COPD, but not in never-smokers with COPD (Copenhagen General Population Study).

Together, these studies provide evidence that exposure to shared risk factors (such as tobacco smoke) may contribute to the multimorbid burden in COPD, even in early and pre-clinical disease. This underlines the importance of treating modifiable risk factors (such as smoking cessation) early to improve multimorbid ill-health.

Although it is clear that there are associations between shared risk factors and multimorbidity in COPD, other studies suggest that airflow limitation itself has a super-added risk on presence and outcome of multimorbidity. A large (>20 000 subjects), population-based study in the United States showed that airflow obstruction was associated with greater comorbidity, independent of shared risk factors such as age, sex, race, smoking status and body mass index (BMI). In addition, those with respiratory impairment and comorbid disease were at significantly higher risk of death and hospitalisation [10]. This was in line with data from Sin *et al.* [56], which showed a striking relationship between reduced FEV_1 and mortality from ischaemic heart disease independent of smoking. Where even a modest decline of FEV_1 (from mean 109% predicted to 88% predicted), was associated with a five-fold increase in death from ischaemic heart disease, independent of baseline smoking status and other potential confounding factors such as age, gender, blood pressure, BMI and diabetes. This relationship was not only shown in cross-sectional data, but also prospectively in the Lung Health Study of nearly 6000 subjects, where decline in FEV_1 predicted death from cardiovascular disease, independent of smoking ($p=0.002$) [57].

Based on these studies, one well-described link for this association of cardiovascular disease with COPD, independent of common risk factors, is the role of low-grade chronic systemic inflammation present in both diseases, which could potentially be driving both pathologies. This is further discussed later.

Physical inactivity

Inactivity is prevalent in patients with COPD and is a major risk factor for many systemic manifestations of COPD [54]. Patients with COPD become less active early in the disease course [58] and this becomes more marked during exacerbations [59]. Furthermore, inactivity in COPD is associated with increased exacerbations and early mortality [60, 61]. Inactivity may lead to systemic consequences in COPD by several different mechanisms.

Although the relationship between inactivity and COPD is multifactorial, collective evidence suggests that dynamic hyperinflation plays a major role in exercise limitation [62]. Additionally, hyperinflation is directly associated with worse patient-centred outcomes such as progressive breathlessness, anxiety and lower quality-of-life scores, all of which impact on comorbid disease [63]. However, treatment of hyperinflation with pulmonary rehabilitation, bronchodilators and lung volume reduction interventions does not fully reverse the effects of inactivity, suggesting that there are other factors at play.

Skeletal muscle wasting is an important consequence of inactivity in patients with COPD. Furthermore, skeletal muscle wasting may lead to a "downward disease spiral", whereby quadriceps myopathy and anaerobic metabolism at low exercise intensity leads to a further reduction in exercise capacity [64]. Inactivity results in protein catabolism within skeletal muscle, leading to muscle atrophy and sarcopenia. Specifically, deconditioning in COPD is associated with reduced oxidative capacity [65], fibre atrophy and reduced skeletal muscle cross-sectional area [66]. Spruit *et al.* [67] suggest that skeletal muscle weakness during exacerbations may be because of circulating cytokines. In addition, even at low doses, long-term corticosteroid use contributes to myopathy in COPD [68]. Conversely, treatment with antioxidants may improve skeletal muscle endurance, by ameliorating the effects of oxidative stress [69].

In addition to skeletal muscle wasting, inactivity may lead to other systemic sequelae. Studies have shown that inactivity is an independent risk factor for osteoporosis [70], type 2 diabetes, cardiovascular disease [71] and depression [72]. There is some evidence suggesting that low-grade systemic inflammation may be a unifying mechanism. Epidemiological studies have shown that physical inactivity is associated with higher levels of systemic inflammatory markers [73, 74]. Furthermore, the Women's Health Study (>27 000 participants) showed that physical activity could reduce cardiovascular risk, mediated mostly by a reduction in inflammatory markers (C-reactive protein (CRP), fibrinogen and intercellular adhesion molecule (ICAM)-1) [75]. However, most studies investigating the effect of training interventions did not show a reduction in circulating inflammation markers [76, 77].

Accelerated ageing

With a given genetic background, chronic diseases may develop and progress (at different speeds and in various combinations) in response to common risk factors, such as those listed earlier [78]. Accelerated ageing as a result of these environmental factors may be a unifying mechanism for this [79]. In support of this, cellular senescence with telomere shortening, a surrogate marker for accelerated ageing, was reported in circulating leukocytes in several comorbid diseases such as COPD [80], myocardial infarction, stroke and diabetes [81].

Furthermore, ageing is characterised by low-grade chronic inflammation ("inflammageing") and with this, important age-related perturbations in the gut microbiota have been recognised as a potential source [82]. Interventions directed at the composition of gut microbiota might be important in controlling this imflammageing process and be another key component of multimorbidity management.

Oxidative stress

Increased oxidative stress in the major mechanism that drives accelerated ageing through its damaging effect on DNA, activation of mammalian target of rapamycin (mTOR) signalling and shortening of telomeres. Oxidative stress is implicated in several pathological mechanisms (including NF-κB and phosphoinositide 3-kinase (PI3K)) in COPD, and these have resulted in targets for potential treatments [83]. Furthermore, it is likely that oxidative stress is also a mechanism driving multimorbidity in COPD, with increased levels of serum 8-hydroxy-2′ -deoxyguanosine (a product of DNA damage) in patients with coronary artery disease [84] and diabetes [85].

Pulmonary components of multimorbidity

Systemic inflammation from the COPD lung

Pulmonary inflammation is a hallmark of COPD pathogenesis [86, 87]. The inflammatory profile is characterised by increased numbers of innate and adaptive immune cells and cytotoxic mediators within the airways [88, 89], which have been suggested to "spill over" into the systemic circulation [90]. There is evidence that systemic inflammation is common in patients with clinically stable COPD [91–93] and is implicated in several comorbid conditions [94], including accelerated ageing [95]. However, patterns of inflammation are heterogeneous [96] and quantifying systemic inflammation in COPD is difficult, where many of the studies use cross-sectional data from small sample sizes and it may not be a persistent phenomenon [97]. Agustí *et al.* [98] showed that although the majority of COPD patients (~70%) demonstrate a degree of systemic inflammation (defined as elevated levels of one of CRP, interleukin (IL)-6, IL-8, fibrinogen, tumour necrosis factor (TNF)-α or leukocytes), only 16% of COPD patients had persistent inflammation. Importantly, those with persistent inflammation (despite having relatively similar lung function impairment) had significantly increased mortality and exacerbation frequency. Furthermore, this persistence of a systemic inflammatory phenotype is linked to atherosclerosis, ischaemic heart disease, stroke and cardiovascular mortality, independent of COPD [99], and specifically increased systemic TNF-α has been implicated as a mechanism for cachexia and skeletal muscle wasting in COPD [100].

Understanding the drivers of systemic inflammation in COPD is important, as it is likely to be fundamental to the pathogenesis of COPD. Studies have shown that systemic inflammation persists despite smoking cessation [101] and increases during exacerbations [102–104]. In addition, it seems to be an important determinant for patient outcome, with associations with accelerated decline in lung function [105] and exacerbations [106], as well as a two- to four-fold risk of cardiovascular disease, diabetes, lung cancer and pneumonia [107]. Furthermore, systemic inflammation is linked to psychological comorbidity with evidence it is key to the development of depression [108], anxiety and cognitive impairment [109]. The origin of systemic inflammation in COPD is much debated and Sinden and Stockley [90] reviewed the evidence for pulmonary "overspill" in 2010.

A lack of correlation between inflammatory markers in the sputum and blood of COPD patients has provided some evidence against the overspill theory [110–113]. In addition, several other drivers to systemic inflammation are reported including smoking, lung hyperinflation (discussed earlier), tissue hypoxia, skeletal muscle wasting and bone marrow stimulation [114]. Therefore, the origin of systemic inflammation in COPD is complex and likely to be multifactorial.

Immune cell priming in the COPD lung

Despite the lack of direct evidence supporting the overspill theory, other studies suggest that immune cell activation or "priming" occurs within the COPD lung in both stable disease and at exacerbation, leading to systemic inflammation [115, 116]. Leukocyte priming results in enhanced migratory and cytotoxic responses [117, 118], which may contribute to systemic inflammation and comorbid disease. Studies have

shown that cytokine priming of neutrophils occurs in response to cigarette smoke exposure [119, 120]. NOGUERA *et al.* [116] showed an increase in expression of the endothelial adhesion molecules and production of reactive oxygen species (ROS) in circulating neutrophils in patients with COPD compared with smokers with normal lung function. This demonstrates an important disease effect on neutrophil priming and implicates their role in systemic endothelial dysfunction. Furthermore, monocytes also accumulate in the lungs of smokers in response to cigarette smoke [121] and it is likely that smoke-activated macrophages release monocytic chemokines (*e.g.* monocyte chemoattractant protein-1) into the peripheral blood [122]. Besides stimulating recruitment of cells to the lungs, in response to smoking these chemokines can also prime circulating monocytes, which increases adhesion to the endothelium and provides a possible mechanism for atherosclerosis [123, 124]. Furthermore, TNF-α is increased in the blood [125, 126] and sputum of COPD patients [127], and increased production of TNF-α in response to cigarette smoke may contribute to the priming of circulating inflammatory cells [119].

Overall, these experimental data suggest that local cytokine release in the periphery, whether in response to acute cigarette smoke exposure, or in the context of COPD, prime immune cells to coordinate a systemic inflammatory response and possible contribute to the burden of multimorbidity.

Although much of the focus has been on the role of macrophage- and neutrophil-driven inflammation in COPD, the importance of eosinophilic inflammation has been highlighted in several studies, showing that eosinophilic COPD patients have more frequent exacerbations [128–130], and are more responsive to corticosteroid treatment [131]. Less is known about their role in comorbid disease, although it has been demonstrated that eosinophils play a pivotal role in metabolic homeostasis [132, 133], and have been found to be associated with coronary artery disease [134, 135] and thrombus formation [136]. More recently, blood eosinophils have been found to correlate with the presence of hypertension in older patients with COPD [137]. It might not be surprising that in COPD patients, different comorbidities may be associated with eosinophil increase, where blood eosinophils could be the result of immune cell priming within the bone marrow.

Pulmonary extracellular vesicles as mediators of local and systemic inflammation

Purposeful, direct intercellular communication is key to inducing and resolving inflammation. Extracellular vesicles (EVs) are intercellular messengers present in all body fluids, transporting proteins, lipids and RNA [138]. They are involved in immunomodulation [138, 139], implicated in inflammatory lung disorders, including COPD [140–142], and may be a universal disseminator of inflammation [143]. EVs can originate from the endosomal compartment (exosomes) or be shed from the cell surface (microvesicles (MVs)). The following section reviews how pulmonary EVs support inflammation in the lungs and how they may exit the lungs and contribute to dissemination of inflammation and therefore multimorbidity.

EVs in the airways

EVs were first identified in the healthy human bronchoalveolar lavage fluid (BALF) in 2003, and found to express CD86, ICAM-1 and major histocompatibility complex class I and II [144]. Pulmonary EVs are likely to originate from different cell sources depending on health and disease; however, bronchial epithelial cells have been suggested as the main source of lung EVs [145]. Epithelial cell injury secondary to cigarette smoke is known to stimulate release of EVs, which are pro-inflammatory (induce IL-8 and vascular endothelial growth factor release) [146] and profibrotic (promote fibroblast differentiation) [147]. Furthermore, epithelial-derived EVs could also have a role in innate defence, whereby when enriched for mucins (glycoproteins vital for maintaining mucus barriers), EVs can bind to and neutralise influenza virus [148]. In addition, EVs are released by alveolar macrophages and are implicated in regulation of several inflammatory processes in response to cigarette smoke and airway pathogens [149–154]. Taken together, these studies suggest a role for pulmonary EVs in regulating pulmonary inflammation in response to noxious stimuli, and further work has suggested these may be driven in part by EV shuttling of microRNA [155, 156].

Circulating EVs

Aberrant release of endothelial MVs occurs in lung disease as a consequence of damage the lung capillary bed [157, 158]. Circulating pulmonary endothelial-derived MVs are increased in smokers with signs of early emphysema [159]. COPD patients have elevated circulating endothelial-derived MVs, which are further elevated during exacerbations. These MVs had markers indicating pulmonary capillary origin, suggesting that their release is associated with pulmonary capillary endothelial damage [160].

Evidence for EVs exiting the lung

Rather than just “overspill” from the lung into the systemic circulation, there is evidence to suggest that pulmonary EVs undergo targeted release into the circulation as a result of increased pulmonary vascular

permeability in response to acute and chronic inflammation [161]. This will affect the exchange of EVs between the blood and the epithelial lining, with the possibility of pulmonary EVs reaching systemic circulation and potentially distant organs. For example, EVs from pulmonary endothelial cells carry α_1-antitrypsin (A1AT) and may be involved in shuttling A1AT across the alveolar membrane to recipient epithelial cells [162], possibly to prevent excessive pulmonary inflammation. Furthermore, proteomic characterisation of BALF exosomes from sarcoid patients showed proteins associated with inflammation, cellular migration and complement components [163]. In addition, vitamin D-binding protein (a potent chemoattractant for leukocytes) was significantly increased in both BALF and serum EVs, which may be a result of pulmonary exosomes exiting into systemic circulation.

EVs, systemic inflammation and comorbidities

EVs are implicated in the pathogenesis of several other inflammatory disorders. Several studies have demonstrated the presence of pro-inflammatory EVs in rheumatoid arthritis [164], multiple sclerosis (MS) [165] and inflammatory bowel disease [166]. Specifically, pro-inflammatory EVs have been identified both in the synovial fluid of patients with rheumatoid arthritis where active joint inflammation occurs and in the circulation [164, 167, 168], suggesting a role for EVs in mediating systemic inflammation. MS patients have increased levels of circulating platelet MVs, which correlate with disease subtype and increase during active inflammation [169]. In addition, EVs from MS patients have been implicated in disease progression *via* endothelial barrier disruption [165], degradation of the blood–brain barrier and promotion of neural inflammation [170].

Further to EVs driving systemic inflammation and progression of inflammatory disease, several studies have suggested a role for EVs, particularly endothelial-derived microparticles, in vascular comorbidities [171]. Increased levels of endothelial microparticles have been found in patients with hypertension [172], atrial fibrillation [173], obesity [174] and type 2 diabetes [175]. These microparticles can promote clotting, oxidative stress and endothelial dysfunction, all contributing to the pathogenesis of disease. Therefore, by targeting the production of these microparticles or altering their structure, several risk factors for cardiovascular disease could be modified simultaneously, thereby treating comorbidity in these patients using a unified therapy.

Treatment approaches for multimorbidity in COPD

Management of patients with multimorbidity is now the most important task facing the medical community and presents a fundamental challenge to the single-disease focus that pervades medicine [176]. Self-management approaches to improve knowledge, confidence and skills of patients may prove an important approach in these patients [177, 178]. Recent guidelines suggest that management of multimorbidity should involve personalised assessment and tailored treatment plans. The aim of treatment should be to improve length and quality of life by consolidating management, whereby treatment based on single-disease guidelines is no longer an acceptable approach [179]. Current and future treatment strategies are summarised in table 2 and discussed in detail in the next section.

Current treatment strategies

Smoking cessation

Smoking is a key risk factor for multimorbidity in COPD [54]. Consequently, smoking cessation may represent a key target for primary and/or secondary prevention of multimorbidity. Effective tobacco control policies (*i.e.* smoking ban legislation) have been shown to reduce smoking, with rapid improvement in the risks of chronic diseases such as cardiovascular disease and lung cancer [211]. Therefore, although difficult to achieve, smoking cessation should remain an important part of multimorbidity management.

Exercise and pulmonary rehabilitation

Pulmonary rehabilitation has been shown to reduce breathlessness, increase exercise capacity and improve quality of life in COPD patients [212, 213]. Physical activity and regular exercise are both recommended and are beneficial not only for patients with COPD, but also for patients with cardiovascular disease, musculoskeletal disease, obesity, diabetes mellitus and most other chronic medical conditions [182, 214]. Furthermore, a systematic review and meta-analysis including six randomised controlled trials showed that comprehensive pulmonary rehabilitation programmes, (including exercise training, education and psychosocial support) can effectively reduce anxiety and depression [181]. Although traditionally used to bronchospasm, there is evidence to suggest that various β_2-agonists increase skeletal muscle mass and strength and prevent fatigue [215]. This suggests that optimal use of inhaled therapy could minimise symptoms and improve compliance with exercise programmes.

TABLE 2 Summary of current and future treatment strategies for multimorbidity in COPD

	Pulmonary effects	Multimorbid effects
Current strategies		
Smoking cessation	Reduction in airway inflammation Improves respiratory symptoms and bronchial hyperresponsiveness Prevents accelerated lung decline	Reduction of risk of cardiovascular disease and lung cancer [180]
Exercise and pulmonary rehabilitation	Delays dynamic hyperinflation Reduces functional breathlessness	Increases exercise capacity Improves quality of life Reduces anxiety and depression [181] Increases BMI, skeletal muscle mass and improves osteoporosis [182]
Inhaled corticosteroids	Limited reduction in airway inflammation: decrease in $CD8^+$ T-lymphocytes in airway biopsies [183] Reduction in exacerbations, especially in eosinophilic COPD [131] Increased risk of pneumonia, especially in severe disease [184]	Possible reduction in cardiovascular mortality [185] Possible reduction in systemic inflammation (CRP, TNF-α) [86] Improvement in quality of life (in combination with bronchodilator)
Theophylline	Possible increased inspiratory muscle strength [186] Reduction in neutrophilic inflammation [187]	Not known
PDE4 inhibitors, *e.g.* roflumilast	Reduction in exacerbations and improvement in lung function in patients with chronic bronchitis, FEV_1 <50% and history of frequent exacerbations	Prevention of bone loss and increase in skeletal muscle mass (in a murine model) [188]
Cardiovascular-targeted treatments		
Statins	May reduce exacerbations [189]	Reduction in cardiovascular risk [190] Reduction in oxidative stress and inflammation [191]
ACE inhibitors/ARB	Reduction in exacerbations [192] Decrease in hyperinflation [193]	May improve survival (in those with cardiovascular risk)
β-Blockers	Reduction in exacerbations [194]	Reduction in mortality after myocardial infarction [195] and in heart failure [196] Reduction in oxidative stress [197] Improved exercise capacity [198]
Future strategies		
Metformin (targeting PI3K-AKT-mTOR pathway)	May improve respiratory symptoms and reduce hospitalisations [199]	Possible reduction in mortality in COPD patients with diabetes [200]
Resveratrol (plant-based antioxidant)	Anti-inflammatory in lung epithelial cells [201]	Possible cardioprotective effects [202]
Losmapimod (p38 MAPK inhibitor)	No effect on respiratory symptoms or lung function, but a trend towards reduction in exacerbations [203]	Not yet determined; possible effect on arterial inflammation
NF-κB inhibitors, *e.g.* IκB kinase inhibitors	Not yet determined; possible effects on exacerbations given role in activating inflammatory signalling in the COPD lung [204]	Not yet determined; possible effects on skeletal muscle wasting [205], cardiovascular disease, lung cancer, osteoporosis and diabetes [206]
Antioxidants, *e.g.* Nrf2 activators, NOX4 inhibitors	Not yet determined; possible reduction in inflammation and reversal of corticosteroid resistance	Not yet determined; issues with side-effect profile
Mesenchymal stem cell EVs	Not yet determined; initial trials failed to show benefit [207]	Not yet determined; possibly neuroprotective [208], cardioprotective [209] and anti-inflammatory [210]

PDE4: phosphodiesterase-4; ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blockers; PI3K: phosphatidylinositol 3-kinase; AKT: also known as protein kinase B; mTOR: mechanistic target of rapamycin; MAPK: p38 mitogen-activated protein kinase; IκB: inhibitor of NF-κB; Nrf2: nuclear factor erythroid 2-related factor 2; NOX: NADPH oxidase; EVs: extracellular vesicles; BMI: body mass index; CRP: C-reactive protein; TNF: tumour necrosis factor; FEV_1: forced expiratory volume in 1 s.

Inhaled corticosteroids

Evidence suggests that targeting treatment towards suppressing pulmonary and/or systemic inflammation may benefit multimorbidity in COPD. Although inhaled corticosteroids are a mainstay of COPD therapy, studies show that they may fail to suppress airway inflammation in the COPD [216, 217], and may impair immune cell function in response to common pathogens [218]. Despite this, inhaled corticosteroids have been shown to reduce systemic inflammation [86] and cardiovascular mortality [185]. However, prospective work showed minimal benefit of inhaled corticosteroids on all-cause mortality [219] and no reduction in systemic markers of inflammation [220], suggesting an unlikely beneficial effect on multimorbidity.

Targeting cardiovascular comorbidity in COPD

Observational studies suggest that treatment of cardiovascular disease may have some unexpected benefit on COPD. For example, statins reduce cholesterol and thus cardiovascular risk, but also have pleiotropic effects involving a reduction in oxidative stress and inflammation [221, 222]. Observational studies have shown that statins may reduce exacerbations [189] and cardiovascular mortality in patients with COPD [190]. However, a subsequent systematic review found although statins were associated with a significant reduction in inflammation (CRP and IL-6), this did not translate into improvement in exacerbations, mortality, functional capacity, quality of life, or lung function [191].

Angiotensin-converting enzyme (ACE) inhibitors are widely used to treat hypertension and heart failure, and have been shown to reduce exacerbations and mortality in COPD patients [192]. Both activation of renin–angiotensin system [223, 224] and polymorphisms of the ACE gene have been linked to skeletal muscle wasting in COPD [225]. However, although angiotensin II receptor antagonists reduced hyperinflation in COPD, they had no effect on respiratory or skeletal muscle strength [193]. Furthermore, Curtis *et al.* [226] showed that ACE inhibitors in combination with pulmonary rehabilitation actually reduced exercise capacity in COPD patients. Therefore, current evidence suggests using this therapy in COPD only in the context of coexisting hypertension or heart failure.

Finally, β-blockers reduce mortality in patients after myocardial infarction [195] and those with heart failure [196]. Despite evidence showing that β-blockers benefit patients with COPD, with reductions in exacerbations and mortality [194], prescribers are often reluctant to use them due to concerns about precipitating bronchospasm [227]. Importantly, similar to statins, cardioselective β-blockers such as carvedilol may exert pleiotropic effects including reducing oxidative stress [197] and skeletal muscle adaptation, resulting in improved exercise capacity [198]. However, the recent BLOCK trial by Dransfield *et al.* [228] showed that patients with moderate or severe COPD did not benefit from β-blocker (metoprolol) therapy. In fact, hospitalisation for COPD exacerbation was more common in the treatment group. The trial population did not have any overt cardiovascular disease and therefore no therapeutic indication for treatment with a β-blocker. Physicians should continue to use cardioselective β-blockers in patients with COPD who have coexisting cardiovascular disease [229].

Future treatment strategies for multimorbidity in COPD

Anti-ageing molecules

Accelerated ageing is implicated in both multimorbidity and COPD progression and a better understanding of senescence pathways has identified several potential therapeutic targets [230]. The PI3K–protein kinase B (AKT)–mTOR pathway plays a key role in cellular senescence and inhibition of autophagy. Metformin is widely used to treat type 2 diabetes and indirectly inhibits AMP-activated protein kinase, resulting in inhibition of mTOR and extension of lifespan in mice, probably through increasing nuclear factor erythroid 2-related factor 2 (Nrf2)-induced antioxidant gene expression [231, 232]. Observational data have shown reduced mortality in patients with COPD and diabetes taking metformin compared to non-metformin users [200]. However, earlier evidence showed that metformin did not reduce levels of inflammation or improve clinical outcomes in patients admitted with severe COPD exacerbation [233].

PI3K is upregulated in the peripheral lung of COPD and is involved in corticosteroid resistance [234]. Low-dose theophylline may increase sensitivity to inhaled corticosteroids in patients with COPD, by inhibiting oxidant-activated PI3K and restoring histone deacetylase 2 activity (a known anti-ageing molecule) [234]. However, clinical trials of low-dose theophylline have so far had disappointing results [235]. Although these two current therapies have failed to show significant benefits, a newer molecule, resveratrol (a plant-based polyphenol found in grapes, peanuts and red wine), has been shown to extend lifespan by activating Sirtuin-1 [236]. Reports suggest that resveratrol is a powerful antioxidant [237], a PI3K inhibitor [238] and it has been shown to have anti-inflammatory effects in lung epithelial cells [201]. Recent clinical studies in non-COPD patients show improved mitochondrial oxidative metabolism after resveratrol treatment, which could be beneficial for both lung and skeletal muscle impairment in COPD. Moreover, pre-clinical studies suggest that it has cardioprotective effects [202]. Therefore, future treatments for multimorbidity may include novel targets that reduce cellular senescence pathways, thereby reducing accelerated ageing associated with COPD and other comorbid disease.

Targeting inflammation and oxidative stress

Phosphodiesterase (PDE)4 inhibitors are the most developed of the novel anti-inflammatory treatments for COPD. Roflumilast, a selective PDE4 inhibitor, is currently used as an anti-inflammatory treatment in severe COPD to prevent exacerbations in the context of chronic bronchitis. However, the drug's narrow therapeutic window has limited its use [239]. PDE4 inhibition appears to mediate the anti-inflammatory

effects of theophylline, and selective PDE4 inhibitors have a wide spectrum of anti-inflammatory effects in the lung and are more effective against neutrophilic inflammation than corticosteroids [240, 241]. Furthermore, in rats a PDE4 inhibitor prevented bone loss and increased skeletal muscle mass, suggesting that PDE4 inhibitors have the potential to prevent osteoporosis and skeletal muscle wasting in COPD [188].

Oxidative stress is present in the lungs of COPD patients and is a major contributor to accelerated ageing and several COPD comorbidities, including atherosclerosis and diabetes [83]. Existing antioxidants, such as N-acetylcysteine and carbocisteine, have proved disappointing in reducing progression of lung function and exacerbations in COPD [242]. The transcription factor Nrf2 regulates many antioxidant genes and is impaired in COPD [243]. However, current Nrf2 activators (*e.g.* sulforaphane and bardoxolone methyl) are poorly selective, leading to toxicity [244]. ROS may be generated by NADPH oxidases (NOX) in activated inflammatory cells in the airways, and selective NOX4 inhibitors are now in clinical development for various diseases [245]. Furthermore, mitochondria are a major source of ROS in COPD, and selective mitochondria-targeted antioxidants (*e.g.* mitoquinone) are now in clinical studies [246].

Multiple kinases are involved in driving lung inflammation and remodelling in COPD [247], and kinase inhibitors have trialled in the treatment of COPD [248]. Although promising in animal studies, the oral p38 mitogen-activated protein kinase inhibitor (losmapimod) had no significant effects on symptoms or lung function, but a trend toward reduced exacerbations [203]. Furthermore, a recent phase II trial showed that losmapimod had no effect on arterial inflammation and endothelial function, and so does not support kinase inhibitors as an effective treatment for cardiovascular morbidity COPD [249].

Finally, NF-κB regulates the expression of inflammatory cytokines and chemokines (TNF-α and matrix metalloproteinase-9) and is activated in macrophages and epithelial cells of COPD patients, particularly during exacerbations [204]. NF-κB activation is implicated in mediating systemic inflammation and may be involved in several COPD comorbid diseases including skeletal muscle wasting [205], cardiovascular disease, lung cancer, osteoporosis and diabetes [206]. Inhibitors of NF-κB kinases (IKKs) are essential in NF-κB signalling, and several small-molecule inhibitors of IKK are in development as a promising treatment for COPD [250]. However, there are safety concerns regarding profound immunosuppression and impaired host defences as a consequence of targeting ubiquitously expressed NF-κB. Therefore, there are currently no human trials of these molecules.

Targeted therapy with mesenchymal stem cell derived EVs

Stem cell exhaustion has been implicated in ageing [251] and several chronic diseases including COPD [252]. Mesenchymal stem cells (MSCs) are a proposed regenerative therapy, given their ability to differentiate into a variety of cell types and their ability to migrate and engraft into target tissues [253]. However, more recently their biological effects have been attributed to their secreted EVs which have been shown to be neuroprotective [208], cardioprotective [209] and anti-inflammatory [210]. Although pre-clinical studies have demonstrated immunomodulatory and regenerative potential of MSC-based therapy, clinical studies have failed to demonstrate a proven benefit in COPD [207]. Furthermore, work needs to be done to tackle issues in production, safety, characterisation and delivery.

Conclusions

COPD is a multisystem disease characterised by continued poor outcomes despite current therapeutic strategies targeting the lung. While COPD is associated with both pulmonary and systemic inflammation driven by local responses to toxic stimuli, accelerated ageing, inactivity and other lifestyle factors, the synergistic mechanisms by which multimorbidity is driven remains incompletely described. Understanding this complexity is key to discovering the molecular mechanisms driving inflammation and in doing so will lead to new, holistic therapeutic approaches, treating the patient and not the single disease.

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