**Modifiable risk factors associated with progression to and extension of multimorbidity in people with COPD: a systematic review**

Andi Orlowski1,2, Jack Ettinger1, Alex Bottle2, Sally Snow1, Rachel Ashton1, and Jennifer K Quint2

1. The Health Economics Unit, London, E14 5EA, UK
2. Department of Primary Care and Public Health, Imperial College London, London, UK

Correspondence to:

Andi Orlowski, The Health Economics Unit, London, E14 5EA, UK

**Abstract**

**Background** Chronic obstructive pulmonary disease (COPD) is a multisystem disease, and many patients have multiple conditions. We performed a systematic review of multimorbidity patterns that might inform intervention planning to reduce health-care costs while preserving quality of life for patients.

**Methods** The literature was searched via Embase Classic and Embase, Ovid MEDLINE, the Healthcare Management Information Consortium, and Web of Science for articles and abstracts published in English up to February, 2022. We included clinical observational or comparative studies of risk factors for multimorbidity in people with COPD, pulmonary emphysema, or chronic bronchitis at baseline. Due the heterogeneity of studies, we were unable to perform a meta-analysis and present descriptive results.

**Findings** Of 4,419 papers initially identified, 29 met the inclusion criteria. Eight studies were cluster and network analyses, five were regression analyses, and 17 (in 16 papers) were other studies of specific conditions, physical activity, and treatment. People with COPD more frequently had multimorbidity and had up to ten times the number of disorders of those without COPD. Disease combinations prominently featured cardiovascular and metabolic diseases, asthma, and musculoskeletal and psychiatric disorders. An important risk factor for multimorbidity was low socioeconomic status. One study showed that many patients were receiving multiple drugs and had increased risk of adverse events, and that 10% of medications prescribed were inappropriate.

**Interpretation** Many patients with COPD have multimorbidity with mainly preventable or modifiable conditions. A proactive multidisciplinary approach to prevention and management could reduce the burden of care.

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* **What is already known on this topic** – Chronic obstructive pulmonary disease (COPD) is a multisystem disease, and many patients have multimorbidity, leading to a complex interplay that worsens symptoms across multiple disorders. This cycle leads to increasing health-care use and worsening quality of life of patients. Predicting which people with COPD will go on to develop or experience worsening of multimorbidity, and planning how to intervene to address modifiable risk factors, could help to improve outcomes.
* **What this study adds** – As far as we are aware, no systematic literature review has been performed of COPD in multimorbidity (ie, no condition is secondary to the others, in contrast to COPD with comorbid disorders). The evidence overall highlights that many people with COPD also frequently have preventable or modifiable chronic disorders, increasing the risk of inappropriate polypharmacy, and that multimorbidity seems to be diagnosed or worsen around the time of COPD diagnosis.
* **How this study might affect research, practice or policy** – Given that people with COPD are likely to have multiple other modifiable or preventable conditions and a high proportion will be smokers, proactive multidisciplinary preventive care and management services that take a holistic approach could lessen health-care burden while improving patients’ quality of life. This should include cross-disease medicines reviews to reduce ‘pill burden’, inappropriate drug-drug and drug-disease interactions, and the risk of adverse events while maximising adherence.

**Key words**

COPD, multimorbidity, holistic care, polypharmacy, treatment adherence

**Introduction**

Multimorbidity is the coexistence of at least two chronic diseases where one is not more central to a person’s health than another.(1) By contrast, the term comorbidity is used to indicate an illness that is seen as secondary to an index disorder, generally in research but also in secondary and tertiary care systems that have traditionally been structured around diseases and/or body systems.(2) These concepts are important in health care, as they may affect whether management of long-term conditions is more or less holistic and how well it reflects the reality for many patients.

Chronic obstructive pulmonary disease (COPD) is a multisystem disease characterised by pulmonary and systemic inflammation.(3) Many people with COPD have more than one long-term chronic condition, particularly those with strong associations with smoking, ageing and anxiety and/or depression.(4) Furthermore, disorders frequently associated with ageing occur earlier in life in people with COPD than in those without.(5) In a large UK study, among 51,928 patients aged 25 years or older (mean age 65 years) with COPD, 86% were multimorbid compared with 51% of 1,220,757 people without COPD, and 22% versus 5% had five or more conditions.(6) Frequently occurring conditions in multimorbid patients with COPD are cardiovascular, musculoskeletal, psychiatric, and metabolic disorders, gastro-oesophageal reflux disease, chronic kidney disease, and cancer.(4,7)

Multimorbidity in people with COPD increases the risk of exacerbations and decreases quality of life and exercise tolerance.(8) Together, these effects increase the use of health-care resources(9) and the likelihood of hospital admission(10,11) and mortality.(12) Iheanacho and colleagues(13) performed a systematic literature review of studies published worldwide and found that the average number of primary care visits per person per year ranged from 2.3 to 13.0 for mild to moderate COPD and from 2.8 to 15.1 for severe COPD. The annual number of COPD hospitalisations per year for patients with moderate and severe disease was between 0 and 0.57 in patients with moderate disease and between 0 and 0.88 for patients with very severe disease. Direct costs increased with disease severity, increasing by 1.3 times for annual per-person costs from mild to severe disease in two UK studies and more than doubling in a study from Italy. The review also found that while the main drivers for hospital admissions in patients with COPD were increasing disease severity, restricted lung function, and higher baseline C-reactive protein concentrations, those for longer hospital stays were many and varied and included multiple factors associated with other conditions.

A further important issue associated with multimorbidity in patients with COPD is polypharmacy. The UK National Institute for Health and Care Excellence guidelines on treatment of multimorbidity note “A particular issue for health services and healthcare professionals is that treatment regimens (including non-pharmacological treatments) can easily become very burdensome for people with multimorbidity, and care can become uncoordinated and fragmented. Polypharmacy in people with multimorbidity is often driven by the introduction of multiple medicines intended to prevent future morbidity and mortality. However, the case for using these medicines weakens if life expectancy is reduced by other conditions or frailty. The absolute difference made by each additional medicine may also reduce when people are taking multiple preventive medicines”.(14) Schnell and colleagues(15) found that more than half (52%) of 995 adults aged 45 years or older with COPD in their study were receiving more than four medications compared with 32% of 14,828 without COPD. Hanlon et al(16) found that 52% of 8,317 patients with COPD reported polypharmacy with five or more medications compared with 18% of 494,323 of those without COPD. Furthermore, patients with COPD who experienced adverse drug reactions (falls/fractures, constipation, urinary retention, CNS depression, bleeding, and renal injury) were significantly more likely to be receiving three or more medications than patients without COPD, and the proportions increased with multimorbidity.

Predicting which people with COPD will go on to develop or experience worsening of multimorbidity, and planning how to intervene to address modifiable risk factors, could help to reduce costs and preserve quality of life for patients. This systematic literature review aimed to identify modifiable risk factors for progression to or extension of multimorbidity in people with an existing COPD diagnosis and discusses potential management strategies.

**Methods**

***Literature search and selection of reports***

For the purposes of this review, multimorbidity was defined as development or diagnosis of one or more of the long-term conditions used by Barnett et al(17) (Table 1).

A systematic literature review was carried out to identify all papers published from the start of the database collection up to February 2022. The Ovid search platform was used to search four relevant databases: Embase Classic and Embase, Ovid MEDLINE, the Healthcare Management Information Consortium (HMIC). Web of Science was also searched (Table 2).

Search strategies were built iteratively, with relevant keywords and subject headings for each database being added after review of retrieved publications. The final set of search terms (see Appendix) included synonyms of multimorbidity, including “polymorbidity” and “polypathology”, and terms relating to COPD, including “chronic bronchitis”, “emphysema”, and “obstructive airway disease”. Terms associated with the Charlson Comorbidity Index were included in the final set of search terms for Embase, HMIC, and Ovid MEDLINE (see Appendix).

An exploratory search for papers discussing progression from COPD to the specific chronic conditions of interest was conducted. This search was conducted using Embase Classic and Embase for all papers published prior to 6 August 2021 (Table 2). In this search, the Boolean operator “AND” was used to link words relating to specific chronic disease diagnoses to COPD. Conditions relating to infectious diseases were excluded.

Database search results were exported to the systematic review software Covidence. Two reviewers (JE and SS) independently screened titles and abstracts for relevance and reviewed the full texts of reports that included a population diagnosed with COPD and mentioned risk factors for progression to multimorbidity.

Papers that reported observational or comparative studies of risk factors for multimorbidity in people with COPD, pulmonary emphysema, or chronic bronchitis were included. We excluded reports focusing on diagnosis of COPD, COPD exacerbations, hospitalisation for COPD, or COPD-related mortality. Papers were also excluded if participants did not have a diagnosis of COPD at baseline, they did not discuss risk factors for progression to multimorbidity, even if they reported the prevalence of multimorbidity, or were preclinical, pathophysiology, genetic and biomarker studies. Additional exclusions were made for non-English language publications, editorials, opinion pieces, case reports, narrative reviews, and predictive models. To gain the widest possible evidence base in this field, studies were assessed based on methodological quality (completeness of outcome data, selective reporting, and other sources of bias) but were not excluded on this basis. For reports that were not unanimously included or excluded by the two reviewers, they were discussed with a third reviewer (AO) until a decision was reached.

***Data extraction***

Data extraction was performed by SS and JE. Risk factors for progression to multimorbidity in patients with COPD were extracted into data tables.

***Statistical analysis***

Due to the range of study designs, methodologies, and participant samples, it was judged that meta-analysis would not be statistically meaningful. Therefore, we did a descriptive analysis of progression to or worsening of multimorbidity in patients with COPD.

**Results**

***Selection of studies***

Of 4,419 papers initially identified, 1,335 were deemed unsuitable for review at initial screening and 2,929 were excluded at later assessment stages (Figure 1). Therefore, 153 were used to form the basis of the review, of which 29 were relevant to this report (see Appendix).

***Studies of multimorbidity profiles***

*Cluster and network analyses*

In an investigation of the disease combinations in 11,734 long-term residents in 1,174 nursing homes in the USA, COPD was seen in combination with hypertension in 7% of residents (7% of women and >10% of men).(18) COPD occurred in a three disease combination with hypertension and composite vascular diseases in 4% of residents (3.5% of women and 5.5% of men). Similarly, Shen and colleagues(19) investigated disease combinations by reviewing the electronic health records of 91,453 US patients with COPD. They identified four distinct profiles increasing in morbidity based on the Charlson Comorbidity Index: low morbidity (61%; 1.9 ± 1.4), metabolic-renal (21%; 4.7 ± 1.8), cardiovascular (12%; 4.6 ± 1.9), and multimorbidity (7%; 7.5 ± 1.7). Over a 2-year period of follow-up, the risk of requiring all-cause acute and post-acute care increased significantly without overlap across morbidity levels. Prominent factors in the low morbidity group were younger age (68 vs 74 years, p<0.001), not being a current smoker (20% vs 13%; p<0.001), and engaging in physical activity (51% vs 40%, p <0.001).

A cluster analysis study in Lithuania assessed records of 321,297 patients, 4,834 with COPD and the remainder without, for 32 chronic diseases.(20) Significantly increased prevalence in the COPD group was found for cardiovascular diseases, arrhythmia, heart failure, kidney diseases, and lung cancer (all p<0.0001). The authors also identified disease clusters based on 19 conditions seen in at least 5% of patients. Six disease clusters were identified in men with COPD: cardiovascular diseases, endocrine-metabolic, asthma musculoskeletal, gout-renal, mental disorders, and stroke-cancer-sensory. The most prevalent was cardiovascular diseases (ischaemic heart disease, hypertension, heart failure, and arrhythmias), with 99% of 3,338 men having at least one of these diseases, followed by asthma-musculoskeletal (49%), stroke-cancer-sensory (44%), endocrine-metabolic (diabetes, obesity, and dyslipidaemia; 42%), gout-renal (12%), and mental disorders (8%). Five clusters were identified in women with COPD. Again, the most common contained cardiovascular diseases (100%), followed by the clusters glaucoma-mental disorders-osteoarthritis-back pain-asthma-obesity-dyslipidaemia-diabetes (87%), cancer-osteoporosis-hypothyroidism-hearing loss-cancer (38%), dementia-stroke (14%), and anaemia (5%).

Using network visualisation software, Divo and colleagues(21) compared comorbidity networks for 79 disorders in 1,969 patients with COPD and 316 individuals without COPD. From the 79 disease nodes, the COPD network showed 428 links with p values of ≤0.01. By comparison, the non-COPD network contained only 56 of the disease nodes and had 149 links. Thus, the prevalence, diversity, and degrees of association of comorbidities seems much greater in people with COPD, although the sample size for people without COPD was much smaller. The authors further identified four distinct clusters of anthropometric and clinical characteristics in which nodes were highly interlinked with COPD. One cluster that included 50% of patients had a cardiovascular disease “theme”. Although cardiovascular disease clustering was also seen in the non-COPD group, the prevalence was 30% and the number of links was considerably fewer. Another mode with 50% prevalence in the COPD group centred around individuals with less obstruction, higher BMI, and comorbidities mainly associated with metabolic syndrome. While metabolic syndrome components were present in the non-COPD controls, they were generally seen in older individuals. Two clusters had 30% prevalence in the COPD group. The first included mainly younger currently smoking COPD patients demonstrating high-risk conditions (eg, schizophrenia, anxiety, hepatitis, liver cirrhosis, pancreatitis, and HIV) whereas for non-COPD individuals the cluster contained only anxiety, asthma, and depression and had prevalence of 5%. The theme of the second was gastrointestinal diseases, musculoskeletal diseases, and cancer. While the prevalence in the non-COPD group was also 30%, the cluster contained fewer nodes and links. They authors concluded that COPD patients are affected by larger number of multiple interlinked morbidities, the clustering patterns of which may suggest common pathobiological processes or be utilised for screening and/or therapeutic interventions.

In a separate study, Divo et al(5) investigated whether COPD affected the age at which patients develop multimorbidity. They extracted data from the EpiChron Cohort in Aragón, Spain, for 27,617 people with COPD and 27,617 controls without COPD matched for age, sex, and site, and compared the prevalence of chronic disorders seen mainly in elderly people. In both groups, the number of comorbidities increased with age, but diseases occurred earlier in the COPD group. For instance, in the youngest age group of 40‒55 years, 50% of controls had any of the chronic diseases of interest, compared with 82% of people with COPD. Therefore, age-related diseases were seen 15‒20 years earlier in the COPD group and in the non-COPD control group. Additionally, people with COPD had in this age group had on average two more conditions than controls (p<0.001). Mortality in the COPD group was nearly double that in the control group (19% vs 11%), and age, number of comorbidities, and a diagnosis of COPD were significantly correlated with an increased risk of death in logistic regression (p<0.001).

Carmona-Pírez and co-workers(22) also drew on data from the EpiChron Cohort to assess multimorbidity in 28,608 patients with COPD, stratified by sex, by the use of network analysis. The findings revealed specific risk factors for psychiatric diseases in women with COPD (behavioural risk disorders) and for cancer in men with COPD (behavioural risk disorders, gastro-oesophageal reflux disease, and obstructive sleep apnoea).

In an exploration of multimorbidity patterns in a population of 12,032 men aged over 50 years, Lluís Zacarías-Pons et al(23) identified four classes of multimorbidity: severely impaired, metabolic, articular-COPD-ulcer, and healthy. The prevalence of the articular-COPD-ulcer prevalence cluster was 19% compared with 51% for the healthy class. The strongest risk factors for being in the articular-COPD-ulcer cluster were current smoking (odds ratio [OR] 3.2, 95% CI 2.4–4.3), former smoking (OR 1.92, 95% CI 1.4–2.4), and age (OR 1.16, 95% CI 1.15–1.18).

Knorst and co-workers(24) assessed the multimorbidity in 470 patients with COPD for whom they could obtain GOLD stage and BMI data. The mean number of comorbidities per patient was 3.1 (SD 1.9), with five or more being found in 22%. A significant correlation was reported between BMI and number of comorbidities, with the average rising to 4.1 per person (*r*=0.32, p<0.001). No correlation was found between the number of comorbidities and severity of COPD. The most common comorbidities were hypertension (44.9%), cardiac disease (20%), diabetes (14.7%), osteoporosis (13.6%), and dyslipidaemia (13%).

*Regression analyses*

In an observational longitudinal study of Medicaid data for 37,151 people with COPD in the USA, Ajmera and colleagues(25) investigated multimorbidity with inflammatory diseases and psychiatric disorders. The overall prevalence of multimorbidity was 79%. Multinomial logistic regression revealed risk of co-existing disorders was increased in women versus men (adjusted OR 1.88, 95% CI 1.75‒2.01) and older adults (55‒64 years) versus younger adults (18‒24 years; adjusted OR 6.14, 95% CI 5.05‒7.04).

Using US household survey data, Miller et al(26) investigated other conditions that were likely to occur in people with self-reported COPD and heart disease (n=968) or no heart disease (n=757). People with COPD and heart disease were most likely to be men and were four times as likely to have diabetes (OR 4.8, 95% CI 3.5‒6.5; p<0.001) and twice as likely to have arthritis (OR 2.2, 95% CI 1.7‒2.8; p<0.001) than people without heart disease. Risks of other conditions (arthritis, sleep apnoea, chronic pain, depression, gastro-oesophageal reflux disease, osteoporosis, and overactive bladder) were also significantly increased, with ORs ranging from 1.5 to 1.8.

As current or former smoking is common among people with COPD, Cunningham and co-workers(27) explored the relationships between smoking, COPD, and ten other conditions (arthritis, asthma, cancer, coronary heart disease, depression, diabetes, high blood pressure, high cholesterol, kidney disease, and stroke). In a cross-sectional study of 405,856 adults in the USA general population who had responded to surveys from the national Behavioral Risk Factor Surveillance System, 33,088 (7%) had COPD. The prevalence of COPD was 14% among current smokers, 7% among former smokers, and 3% among never smokers. Only a quarter of people with COPD (24%) were never smokers, compared with 57% of those without COPD (39% vs 27% were former smokers and 37 vs 16% were current smokers). Ninety-five percent of those with COPD had any of the ten comorbidities of interest, compared with 69% of those without COPD, and the prevalence of all conditions was higher in the COPD group than in the non-COPD group. Significant interactions (p<0.001) were seen between smoking status and COPD and each of the other chronic conditions.

O’Kelly and colleagues(28) investigated multimorbidity in patients with chronic respiratory conditions in Dublin, Ireland. Among 653 patients identified, 393 (60%) had multimorbidity versus 40% with respiratory disease alone. Two hundred and six patients had COPD, with a multimorbidity rate of 43%. Across the whole respiratory disease study sample, which included COPD, asthma, and other chronic respiratory diseases, multimorbidity increased with age, was associated with female sex (OR 1.67, 95% CI 1.01‒2.22; p=0.004) and with lower socioeconomic status (OR 3.18, 95% CI 2.23‒4.56; p<0.0001), and patients had triple the number of general practice visits per year compared with patients who had respiratory disease alone (median 6, range 2‒10 vs median 2, range 0‒5, p<0.0001). The most common comorbidities were depression or anxiety, hypertension, and cardiovascular diseases (all 28%), musculoskeletal disorders (23%), and endocrine disorders (20%).

In a retrospective study, Le and co-workers(29) investigated the multimorbidity burden in 739,118 Medicare beneficiaries with COPD in the USA aged 65 years or older. The authors calculated the prevalence of multimorbidity at COPD diagnosis and 1 year after diagnosis and estimated the rates of onset per 100 person-years 1 year before versus 1 year after diagnosis. The findings were compared with the same number of Medicare beneficiaries without COPD, matched for age, sex, and race. In the COPD group, the average number of comorbidities was 10 (SD 4.7) compared with only one (SD 3.3) in the non-COPD group. The most frequent comorbidities seen at COPD diagnosis had all increased in prevalence 1 year later: hypertension change from 70.8% to 80.2%; hyperlipidaemia 52.2% to 64.8%; anaemia 42.1% to 52.0%; arthritis 39.8% to 47.7%; and congestive heart failure 31.3% to 38.8%. The rates of new onset before and after COPD diagnosis were hyperlipidaemia (22.8 and 27.6 cases per 100 person-years), anaemia (17.8 and 20.3), and arthritis (12.9 and 13.2), hypertension (39.8 and 32.3), and congestive heart failure (16.2 and 13.2). The odds ratios for all diseases assessed were increased in the COPD group compared with in the non-COPD group.

***Studies of specific conditions***

*Cardiovascular and metabolic diseases*

Nesterovska et al(30) investigated whether risk of atrial fibrillation was increased by the presence of COPD. The study included 86 patients with asthma and COPD overlap syndrome (ACOS) but no cardiovascular disease or thyroid dysfunction. Around half (42 [49%]) had paroxysmal atrial fibrillation. Identified risk factors for atrial fibrillation were reduced FEV1, hypoxaemia, blood pressure, and systemic inflammation.

Asker and colleagues(31) found that among 95 people with COPD and pulmonary hypertension, 68 (72%) had coronary artery disease. The presence of coronary artery disease correlated positively with male sex (*rs*=0.224, p=0.029) and hypertension (*rs*=0.227, p=0.07) but negatively with FEV1/FVC ratio (*rs*=‒0.253, p=0.013) and systolic pulmonary artery pressure (*rs*=‒0.215, p=0.037). No correlation was found between the severity of coronary artery disease and pulmonary hypertension. In a large population study in Copenhagen, Denmark, compared with people who had no respiratory disease, Ingebrigtsen an co-workers(32) found significantly raised risks of coronary heart disease and heart failure in people with COPD (1.3, 95% CI 1.2‒1.5) for coronary heart disease and 1.9, 95% CI 1.6‒2.3 for heart failure) or ACOS (1.3, 95% CI 1.2‒1.5 and 1.9, 95% CI 1.6‒2.3, respectively) when with FEV1­  was lower than 50%.

An analysis by Sklander Hansen et al(33) in Denmark identified that heart disease affects a substantial proportion of people with COPD. Among 70,274 people with a diagnosis of COPD in Danish health registries, hypertension was reported in 48% and heart disease in 16%. These patients tended to be older than 65 years and to have low educational levels.

In the cluster validation study by Triest and colleagues (34), the cachetic cluster contained 39 (19%) of 208 patients with COPD, of whom 80% had each of low muscle mass and underweight. As for the psychological cluster mentioned earlier, this cluster was deemed not relevant to controls. Of note, in the metabolic diseases cluster, although numerically obesity, hyperglycaemia, insulin resistance, and dyslipidaemia values were significantly higher among patients with COPD than controls, the differences in the clusters for both sets of patients had high values and, therefore, this cluster was deemed not specific to COPD.

*Asthma, hypoxaemia, and allergies*

Working on the principle that people with similar comorbidity profiles also often have similar disease severity, use of health care, and clinical outcomes, Sklander Hansen et al(33) aimed to identify comorbidity clusters among 70,274 people with COPD in Danish health registries. Chronic comorbidities were reported in 81% of people. Cluster analysis revealed that 30% of the total cohort had allergies without other comorbidities. These people were generally young (60% aged 35‒54 years) and had lower health-care use than individuals with any kind of comorbidity.

Female sex has been suggested as a predictor of asthma and COPD overlap syndrome (ACOS). Garneau-Picard and co-workers(35) found that in a group of 154 patients (47% men, 53% women) women with ACOS had a lower tobacco exposure (41.9 95% CI 38.1–45.7 vs 36.0 95% CI 32.5–39.5 pack-years, p=0.0278), lower prevalence of severe asthma (64.7% vs 44.9%, p=0.0264), higher FEV1/FVC ratio (65.5 95% CI 64.8–66.2 vs 67.2 95% CI 66.7–67.7%, p=0.0002), and more comorbidities (3.2 95% CI 2.7–3.7 vs 4.6 95% CI 3.9–5.4, p=0.0012).

*Sleep apnoea*

Patients who have obstructive sleep apnoea (OSA) and ACOS are known to have lower nocturnal oxygen saturation than those with either disease alone, often leading to severe hypoventilation while sleeping. Ganga and colleagues(36) performed a single-centre study of 2,873 patients older than 65 years with COPD (n=416), OSA and COPD (n=28), or OSA alone (n=60) or neither disorder (n=2,369) to investigate new-onset atrial fibrillation (AF). Non-adjusted incidence was 11%, 21%, 7%, and 5%, respectively. The risk multimorbidity was significantly higher than with a single disease alone (both p<0.05). After adjustment for age, sex, heart failure, chronic kidney disease, and hypertension, the OR for AF in patients with OSA and COPD was 3.66 (95% CI, 1.06‒6.9, p=0.007). Spicuzza and colleagues(37) reported from a retrospective observational study of people with OSA with and without COPD. The risk of cardiovascular diseases, metabolic disorders, and gastro-oesophageal reflux disease was substantially increased by COPD (OR=7.8, 95% CI 4.86‒11.39; p<0.001). Lacedonia et al(38) found similar trends in a retrospective analysis where they compared people with ACOS or OSA alone.

*Psychological disorders*

Anxiety and depression are commonly comorbidities in COPD. Phan and colleagues(39) reported in a cross-sectional study that among 242 people with COPD, 124 (51%) had symptoms of either depression and/or anxiety, and 81 (34%) had symptoms of both. Multiple regression revealed associations with younger age, having a carer, psychological medical history, comorbidities, and reduced quality of life. Silva Júnior and colleagues(40) hypothesised that the presence of COPD would increase the risk of major depression even in people with mild hypoxaemia. They assessed 30 patients with major depression and 30 without depression (controls). A significant association was seen between COPD Assessment Test scores greater than 20 and major depression (OR 7.88; 95% CI 1.96 - 31.7; p = 0.004), making COPD is a predictive factor.

A UK study of depression in 44 patients with COPD and lung cancer attending an outpatient clinic.(41) The relative risk and odds ratios of patients with COPD developing depression were 1.4 and 1.6, respectively. The number of coexisting comorbidities significantly raised the odds ratio to 2.13 (95% CI 1.02‒4.49).

Triest and co-workers(34) performed a validation study of comorbidity clusters previously identified in patients with COPD. They compared the clusters in 208 patients with COPD group and a control group of 200 elderly patients without COPD. The psychological cluster included 40 patients with COPD, of whom 95% had anxiety and 59% had depression. By contrast, very few controls had anxiety and/or depression and, therefore, this cluster was deemed relevant only to COPD.

***Physical activity***

Associations between COPD, level of physical activity, and 31 comorbidities were assessed in 601 adults in Spain.(42) Ninety-four percent of participants had comorbidities. Low levels of physical activity were significantly associated with increased risk of urinary incontinence (OR 2.12, 95% CI 1.21–3.69), chronic constipation (OR 1.97, 95% CI 1.12–3.46), cataracts (1.84, 95% CI 1.07–3.15), chronic anxiety (1.51, 95% CI 1.00–2.27), and chronic lumbar back pain (1.49, 95% CI 1.04–2.13). The authors concluded that recommending increased physical activity could improve the quality of life for patients with COPD.

Yu et al(43) performed a longitudinal study to assess the relationship between physical activity and multimorbidity risk in 409 patients with COPD selected from primary care in the Netherlands and Switzerland. Patients were followed up for 5 years and self-reported physical activity, occurrences of cardiovascular, neurological, endocrine, musculoskeletal, malignant, and infectious diseases, and mental health. Physical activity showed significant associations with reduced anxiety (adjusted hazard ratio 0.89, 95% CI 0.79–1.00; p=0.045) and depression (adjusted hazard ratio 0.85, 0.75–0.95; p=0.005). For other disorders, likelihood of occurrence was reduced with physical activity, but not significantly so.

***Polypharmacy***

One study addressed polypharmacy (taking five or more drugs per day) along with multimorbidity. Among 245 patients with COPD in Crete, Greece, Ierodiakonou et al(44) found that 77% of patients had multimorbidity, which increased to 84% in those with age 65 years or older. More than half (55%) of patients were receiving multiple drugs, but 10% of medications were found to be inappropriate. Polypharmacy was associated with COPD Assessment Test scores of 10 or greater, multimorbidity, several cardiometabolic diseases, cancer, depression and anxiety, and prostate disorders. Coadministration of medications increased the cumulative risk of falls in 22%, constipation in 17%, and cardiovascular events in 13% of patients. The authors concluded that polypharmacy increases the risk of worse health outcomes in patients with COPD.

**Discussion**

Of conditions seen in multimorbid people with COPD, cardiovascular disorders, metabolic disorders, and anxiety/depression are extremely common, all are potentially modifiable, and, importantly, prevalence increases after COPD is diagnosed. Additionally, multimorbidity with conditions that are often age related in the general population occur earlier in people with COPD. Therefore, there is an accompanying risk of long-term polypharmacy with more medications than in people without COPD. Cardiovascular diseases are the most frequent disorders seen in multimorbid men and women with COPD, particularly coronary artery disease. Among the other most common disorders, men more frequently have cancer and gastro-oesophageal disorders, whereas psychiatric and musculoskeletal disorders affect women more.

Most patients with COPD have complex disease profiles, experiencing multiple other chronic conditions and a much-heightened risk of developing or extending multimorbidity. Our findings highlighted the associations between COPD, multimorbidity, and high-risk conditions and behaviours, such as smoking, obesity, low physical activity, and low socioeconomic status. Additionally, Le and colleagues reported increased prevalence of many chronic conditions after the diagnosis of COPD in elderly participants. That study was not designed to assess causality, but Alter and colleagues suggest that some increases are due to worsening of COPD and some are age related.(45) However, this area is not well researched, and other reasons, such as increased investigations for associated disorders and/or lack of testing for or modification of other risk factors, should be explore further. Finally, compared with knowledge of other disorders, patients’ understanding of COPD symptoms, treatment, and long-term disease course, including multimorbidity, is poor and can lead to undertreatment.(46) Care for COPD should, therefore, consider preventive measures at the national or regional level plus measures at the population/individual level addressing risk in patients with diseases frequently seen in multimorbidity; holistic approaches that involve primary and secondary care teams; creation of educational materials and opportunities (eg, to address and maintain lifestyle changes); development of individualised care plans that support self-management, as recommended by the Global Initiative for Chronic Obstructive Lung Disease(47) and national guidelines, such as those of the National Institute for Health and Care Excellence(48); and multidisciplinary management with health-care professionals in other specialties.(49)

An important aspect of COPD and multimorbidity care is self-management. Ansari et al(50) found in a survey that multimorbid patients with COPD gave less priority to COPD, particularly mild or moderate disease, than to other coexisting disorders because they did not recognise its importance in terms of long-term health implications. Later, these authors considered self-management among multimorbid patients with COPD and found that an education programme significantly changed patients’ perspectives of its role in multimorbidity.(51) As well as considering the education of patients, Cravo and colleagues(52) made six key recommendations to health-care professionals to improve the development of self-management plans: better education for on disease management and consultation skills; new targets and priorities for patient-focused outcomes; skills-gap audits to identify barriers to self-management; sharing of best practices within primary care networks and ongoing professional development; enhanced initial consultations to establish optimal self-management from the outset; and negotiation and sharing of self-management plans at the point of diagnosis.

Jassem and colleagues(53) proposed an integrated care model for patients with advanced COPD in Poland. Long-term maintenance care involved planned visits to primary care (GPs and community and specialty nurses), secondary care (pneumonologists), and other professional or volunteer carers and social workers. As the disease or the patient’s health worsened, they recommended spiritual, psychological, and palliative care support. Information on health status after exacerbations, including multimorbidity, would be shared and managed as appropriate during or in addition to planned visits. This model could be well adapted for earlier stage disease with the addition of other specialties as appropriate.

Only one study assessing polypharmacy met our selection criteria, but the increased risk of adverse drug reactions, overtreatment with redundant drugs, and drug-drug and/or drug-disease interactions(16) make this an important factor in the care of patients with COPD and progression multimorbidity. Furthermore, use of high numbers of drugs can contribute to reduced adherence across therapies, and, in COPD, increased disease severity and risk of exacerbations. Regular medicines reviews that include clinical and pharmacy health care professionals should be considered as part of an integrated care pathway for people with COPD.

This review has some limitations. The papers included showed substantial heterogeneity, and it was not possible to perform a meta-analysis or account for bias in studies. Therefore, we present a descriptive analysis of the findings. More papers might have been found if more databases had been searched. However, by the time the last search was done, no further publications were identified. Due to the nature of what is being investigated, many of the studies published are observational. We cannot, therefore, cite causal links between COPD and multimorbidity. However, our findings reveal positive associations between COPD and the development or worsening of multimorbidity that occurs in reasonably consistent, predictable patterns. Only one study was found that dealt with polypharmacy. This area warrants more investigation to maximise the effectiveness of treatment without overly high pill burden on patients. Study designs that focus on these aspects and/or more long-term epidemiological data would be beneficial in this area.

***Conclusions***

Multimorbidity is an extremely common and important feature of COPD. People experience a wide range of disorders, but the most common are generally considering preventable and/or modifiable. Patients seen in general practice with cardiovascular, metabolic, and musculoskeletal disorders, particularly arthritis or osteoporosis who are current or former smokers, should be considered for education about the risks of COPD and new or worsening multimorbidity. A proactive holistic approach to management involving primary and secondary care health-care professionals that includes regular review of all aspects of health, treatment, and lifestyle factors could reduce the burden of care even for patients with several severe long-term conditions. Important areas for future research are to assess changes in multimorbidity over time, as prevalence of multimorbidity seems to progress quickly around the time of COPD diagnosis, and the risks associated with polypharmacy.

**Author contributions**

AO devised the study, AO, JE, SS and JQ performed the literature search and reviewed the papers for inclusion. AO, SS, JE, RA, AB and JQ interpreted the data. RA and AO drafted the article. All authors reviewed the article and approved the final version for publication.

**Competing interests**

The authors declare no competing interests.

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**Data availability statement**

No additional are data available.

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**Figure 1: PRISMA flow diagram**

**Table 1: Disorders of interest included in exploratory analysis of multimorbid conditions**

|  |  |
| --- | --- |
| **Condition** | **Criterion for identification** |
| Hypertension  | Read code ever recorded |
| Depression | Read code recorded in last 12 months OR ≥4 anti-depressant prescriptions (excluding low dose tricyclics) in last 12 months |
| Painful condition | ≥4 prescription only medicine analgesic prescriptions in last 12 months OR ≥4 specified anti-epileptics in the absence of an epilepsy Read code in last 12 months |
| Asthma (currently treated) | Read code ever recorded AND any prescription in last 12 months |
| Coronary heart disease | Read code ever recorded |
| Treated dyspepsia | ≥4 prescriptions in previous 12 months BNF 0103% excluding antacids AND NOT (≥4 NSAIDS OR ≥4 aspirin/clopidogrel) |
| Diabetes | Read code ever recorded |
| Thyroid disorders | Read code ever recorded |
| Rheumatoid arthritis, other inflammatory polyarthropathies & systematic connective tissue disorders | Read code ever recorded |
| Hearing loss | Read code ever recorded |
| Anxiety & other neurotic, stress related & somatoform disorders | Read code in last 12 months OR ≥ 4 anxiolytic/hypnotic prescriptions in last 12 months OR ≥ 4 10/25mg amitriptyline in last 12 months & do not meet the criteria for ‘Pain’ |
| Irritable bowel syndrome | Read code ever recorded OR ≥ 4 prescription only medicine antispasmodic prescription in last 12 months |
| New diagnosis of cancer in last five years | Read code first recorded in last 5 years |
| Alcohol problems | Read code ever recorded |
| Other psychoactive substance misuse | Read code ever recorded |
| Treated constipation  | ≥4 laxative prescriptions in last year |
| Stroke & transient ischaemic attack | Read code ever recorded |
| Chronic kidney disease | Read code ever recorded |
| Diverticular disease of intestine | Read code ever recorded |
| Atrial fibrillation | Read code ever recorded |
| Peripheral vascular disease | Read code ever recorded |
| Heart failure | Read code ever recorded |
| Prostate disorders | Read code ever recorded |
| Glaucoma | Read code ever recorded |
| Epilepsy (currently treated) | Read code ever recorded AND antiepileptic prescription in previous 12 months  |
| Dementia | Read code ever recorded |
| Schizophrenia (and related non-organic psychosis) or bipolar disorder | Read code ever recorded/recorded in last 12 months (code dependent) OR Lithium prescribed in last 168 days |
| Psoriasis or eczema | Read code ever recorded AND ≥ 4 related prescriptions in last 12 months (excluding simple emollients) |
| Inflammatory bowel disease | Read code ever recorded |
| Migraine | ≥4 prescription-only medicine anti-migraine prescriptions in last year |
| Blindness & low vision | Read code ever recorded |
| Chronic sinusitis | Read code ever recorded |
| Learning disability | Read code ever recorded |
| Anorexia or bulimia | Read code ever recorded |
| Bronchiectasis | Read code ever recorded |
| Parkinson’s disease | Read code ever recorded |
| Multiple sclerosis | Read code ever recorded |
| Viral hepatitis | Read code ever recorded |
| Chronic liver disease | Read code ever recorded |

Disorders are defined by Read code or prescribing information, as described by Barnett et al.(17) One or more long-term conditions could have developed or been diagnosed after the diagnosis of COPD. Abbreviations: BNF British National Formulary, NSAID non-steroidal anti-inflammatory drug, POM prescription-only medicine.

**Table 2: Databases searched with dates**

|  |  |  |
| --- | --- | --- |
| **Search number** | **Database** | **Search date range** |
| 1 | Embase Classic+Embase | 1947 to 26 July 2021, updated 10 February 2022 |
| 2 | Ovid MEDLINE ALL | 1946 to 10 February 2022 |
| 3 | Health Management Information Consortium | 1979 to November 2021 |
| 4 | Web of Science | 11 Feb 2022 |
| 5 | Embase Classic+Embase (specific conditions of interest) | 1947 to 6 August 2021 |