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Modifiable risk factors that may be addressed in routine care to prevent progression to and extension of multimorbidity in people with COPD: a systematic literature review

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a multisystem disease, and many patients have multiple conditions. We explored multimorbidity patterns that might inform intervention planning to reduce healthcare costs while preserving quality of life for patients. Literature searches up to February 2022 revealed 4419 clinical observational and comparative studies of risk factors for multimorbidity in people with COPD, pulmonary emphysema, or chronic bronchitis at baseline. Of these, 29 met the inclusion criteria for this review. 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, 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. Many patients with COPD have mainly preventable or modifiable multimorbidity. A proactive multidisciplinary approach to prevention and management could reduce the burden of care.

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. It is 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 healthcare, as they may affect whether management of long-term conditions is more or less holistic and how well it reflects reality for 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 diseases that have strong associations with smoking, ageing and anxiety and/or depression.[4] Furthermore, age-related disorders frequently 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% had multimorbidity compared with 51% of 1 220 757 people without COPD, and 22% vs 5% had five or more conditions.[6] Frequently occurring conditions in 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 exacerbation and decreases quality of life and exercise tolerance.[8] Together, these effects increase the use of healthcare resources[9] and the likelihood of hospital admission[10 11] and mortality.[12] Iheanacho *et al*[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 hospital admissions 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 rose with worsening 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 concentrations of C-reactive protein, those for longer hospital stays were many and varied and included multiple factors associated with other conditions.

A further important issue associated with multimorbidity is polypharmacy, which can reduce quality of life, increase burden on patients and raise risks of adverse drug events, morbidity and mortality. Potential fragmentation and reduced coordination of care can increase healthcare use, including unplanned and emergency care.[14] Schnell *et al*[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 8317 patients with COPD reported polypharmacy with five or more medications compared with 18% of 494 323 of those without COPD.

Predicting which people with COPD will go on to develop or experience extension 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 was performed as part of the groundwork for development of an impactibility model[17] and had the objective of exploring the breadth of relevant information in the literature. In this paper, we discuss which modifiable risk factors are most reported in people with COPD and might be possible to address in routine care to prevent progression to or extension of multimorbidity in people with an existing COPD diagnosis. We also discuss potential management strategies.

METHODS

Literature search and selection of reports

For the purposes of this review, multimorbidity was defined as progression from COPD to one or more of the long-term conditions used by Barnett *et al*[18] that could be treated, prevented or changed by routine care (table 1).

A systematic literature review was carried out to identify all papers published from the start of each database's collection up to February 2022. The Ovid search platform was used to search Embase Classic and Embase, Ovid MEDLINE and 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 online supplemental 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 (CCI) were included in the final set of search terms for Embase, Ovid MEDLINE and HMIC (see online supplemental appendix).

An exploratory search for papers discussing progression from COPD to the specific chronic conditions of interest was conducted. This search was performed using Embase Classic and Embase for all papers published prior to 6 August 2021 (table 2). The Boolean operator ‘AND’ was used to link words relating to specific chronic disease diagnoses with "COPD". Conditions relating to infectious diseases were excluded.

Database search results were exported to 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 exacerbation, hospital admission for COPD or COPD-related mortality. Papers were also excluded if participants did not have a diagnosis of COPD at baseline, the report did not discuss risk factors for progression to multimorbidity (even if they reported the prevalence of multimorbidity) or were preclinical, pathophysiology, genetic and/or 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). However, because the aim of this study was to explore what is discussed in the literature and not make clinical recommendations, no formal quality assessment process was applied and no papers were 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. Results were considered by type of study performed and/or by disease being discussed. Thus, some studies might be discussed more than once in the results section depending on the data they contained.

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

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

Condition	Criteria for identification
Hypertension	Read code ever recorded
Depression	Read code recorded in past 12 months OR ≥4 antidepressant prescriptions (excluding low-dose tricyclics) in past 12 months
Painful condition	≥4 prescription-only medicine analgesic prescriptions in past 12 months OR ≥4 specified antiepileptics in the absence of an epilepsy Read code in past 12 months
Asthma (currently treated)	Read code ever recorded AND any prescription in past 12 months
Coronary heart disease	Read code ever recorded
Treated dyspepsia	≥4 prescriptions in BNF section 1.3 in past 12 months 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 and systematic connective tissue disorders	Read code ever recorded
Hearing loss	Read code ever recorded
Anxiety and other neurotic, stress-related and somatoform disorders	Read code in past 12 months OR ≥4 anxiolytic/hypnotic prescriptions in past 12 months OR ≥4 10/25 mg amitriptyline in past 12 months and do not meet criteria for 'pain'
Irritable bowel syndrome	Read code ever recorded OR ≥4 prescription-only medicine antispasmodic prescriptions in past 12 months
New diagnosis of cancer in past 5 years	Read code first recorded in past 5 years
Alcohol problems	Read code ever recorded
Other psychoactive substance misuse	Read code ever recorded
Treated constipation	≥4 laxative prescriptions in past year
Stroke and 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 past 12 months
Dementia	Read code ever recorded
Schizophrenia (and related non-organic psychosis) or bipolar disorder	Read code ever recorded/recorded in past 12 months (code dependent) OR lithium prescribed in past 168 days
Psoriasis or eczema	Read code ever recorded AND ≥4 related prescriptions in past 12 months (excluding simple emollients)
Inflammatory bowel disease	Read code ever recorded
Migraine	≥4 prescription-only medicine antimigraine prescriptions in past year
Blindness and 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

Continued

Table 1 Continued

Condition	Criteria for identification
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*.[18] One or more long-term conditions could have developed or been diagnosed after the diagnosis of COPD.
BNF, British National Formulary; NSAIDs, non-steroidal anti-inflammatory drugs.

provide a descriptive analysis of progression to or extension of multimorbidity in patients with COPD.

RESULTS

Selection of studies

Of 4418 studies (in 4419 papers) initially identified, 1335 were deemed unsuitable for review at initial screening and 3053 were excluded at later assessment stages (figure 1). Therefore, 29 studies were deemed to be relevant to this report.

Multimorbidity prevalence and characteristics

Shen *et al*[19] performed a cluster analysis to investigate disease combinations in 91 453 US patients with COPD. They reviewed electronic health records and identified four distinct profiles: low morbidity (based on CCI; 61%; mean CCI score 1.9 SD±1.4), metabolic–renal (21%; 4.7±1.8), cardiovascular (12%; 4.6±1.9) and multimorbidity (7%; 7.5±1.7).

A cluster analysis study in Lithuania assessed records of 321 297 patients for 32 chronic diseases.[20] In this cohort, 4834 had COPD, which was associated with significantly increased prevalence of cardiovascular diseases, arrhythmia, heart failure, kidney diseases and lung cancer (all p<0.0001). They further assessed the 19 conditions seen in at least 5% of patients (n=3338) and revealed six disease clusters in men with COPD: cardiovascular diseases (99% had at least one), asthma–musculoskeletal (49%), stroke–cancer–sensory (44%), endocrine–metabolic (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 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 *et al*[21] compared comorbidity networks for 79 disorders in 1969 patients with COPD and 316 individuals without COPD. From the 79 disease nodes, the COPD network showed 428 links with significance of p≤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 seem much greater in people with COPD. Nevertheless, 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 node with 50% prevalence in the COPD group centred around individuals with less obstruction, higher body mass index (BMI) and comorbidities mainly associated with metabolic syndrome. Metabolic syndrome components were present in the non-COPD controls but they were seen mostly in older individuals. Two clusters had 30% prevalence in the COPD group. The first included mainly younger current smokers with psychiatric disorders and diseases associated with high-risk bevaviours (eg, schizophrenia, anxiety, hepatitis, liver cirrhosis,

Table 2 Databases searched with dates

Search number	Database	Search end date(s)*
1	Embase Classic+Embase	26 July 2021 and 10 February 2022
2	Ovid MEDLINE ALL	10 February 2022
3	Health Management Information Consortium	November 30 2021
4	Web of Science	11 February 2022
5	Embase Classic+Embase (specific conditions of interest)	6 August 2021

*All databases were searched from inception.

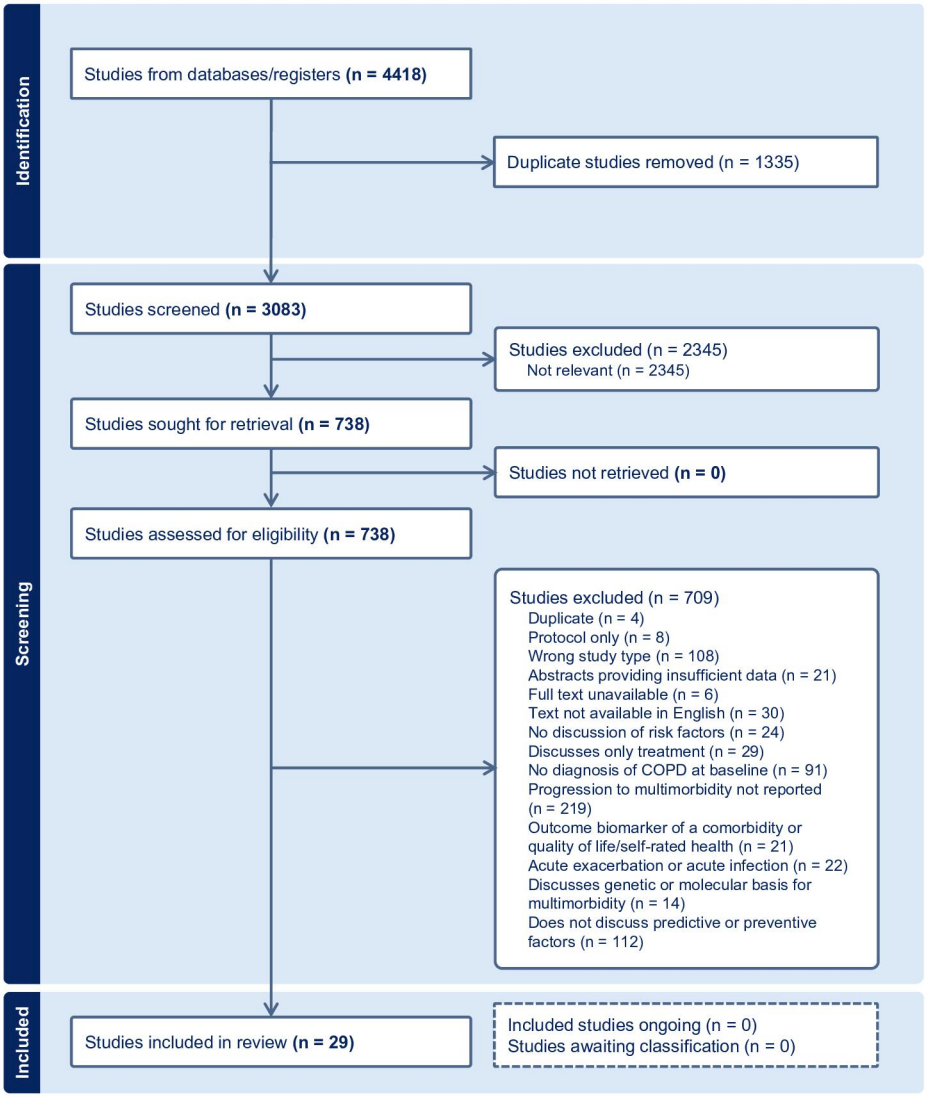

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram. COPD, chronic obstructive pulmonary disease.

pancreatitis and HIV), whereas for individuals without COPD, 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. The authors concluded that patients with COPD are affected by larger numbers of interlinked morbidities, the clustering patterns of which may suggest common pathobiological processes that might be useful for screening and/or therapeutic interventions. In another study, Divo *et al*[5] also showed that COPD affects the timing of 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. Patients were separated into incremental age groups (40–55, 56–65, 66–75, 76–85 and ≥85 years) and the prevalence of chronic disorders seen mainly in elderly people was compared between the two groups. The number of comorbidities increased with age in both but occurred earlier in the COPD group. For instance, in the youngest age group of 40–55 years, 50% of controls had any disease of interest compared with 82% of people with COPD (p<0.001). Furthermore, multimorbidity with two or more disorders were seen 10–15 years earlier among patients with COPD at baseline than among controls.

Carmona-Pírez *et al*[22] also performed a network analysis based on data from the EpiChron Cohort to assess multimorbidity in 28 608 patients with COPD. The findings revealed several clusters of diseases that were specifically associated with COPD, such as behavioural risk disorders. These clusters featured psychiatric multimorbidity in women and cancer multimorbidity in men with COPD. Risks of gastro-oesophageal reflux disease and obstructive sleep apnoea were also raised in men.

In an exploration of multimorbidity patterns in a population of 12 032 men aged over 50 years, Zacarías-Pons *et al*[23] identified that the strongest risk factors for multimorbidy among men with COPD were social deprivation (OR 3.3, 95% CI 2.3 to 4.7), current smoking (OR 3.2, 95% CI 2.4 to 4.3), former smoking (OR 1.9, 95% CI 1.4 to 2.4), obesity (OR 1.7, 95% CI 1.3 to 2.4), being separated or single (OR 1.7, 95% CI 1.3 to 2.4) and age (OR 1.16, 95% CI 1.15 to 1.18). They found also that COPD was clustered with osteoarthritis, rheumatoid arthritis, ulcer and cataracts.

Knorst *et al*[24] assessed multimorbidity in 470 patients with COPD for whom they could obtain Global Initiative for Chronic Obstructive Lung Disease stage and BMI data. The mean number of comorbidities per patient was 3.1 (SD 1.9), rising to 4.1 in patients with obesity, indicating a significant correlation with BMI (r=0.32, p<0.001). Five or more multimorbid disorders were present in 105 (22%). No correlation was found between the number of comorbidities and severity of COPD. The most common comorbidities were hypertension (45%), cardiac disease (20%), diabetes (15%), osteoporosis (14%) and dyslipidaemia (13%).

In an observational longitudinal study of Medicaid data for 37 151 people with COPD in the USA, Ajmera *et al*[25] investigated multimorbidity with inflammatory diseases (arthritis, cardiovascular diseases, diabetes, hypertension, hyperlipidaemia and osteoporosis) and psychiatric disorders (anxiety, bipolar disorder, depression and schizophrenia). The overall prevalence of multimorbidity was 79%. Multinomial logistic regression revealed that the risk of coexisting disorders was increased in women versus men (adjusted OR 1.88, 95% CI 1.75 to 2.01) and older adults (age 55–64 years) versus younger adults (age 18–24 years; adjusted OR 6.14, 95% CI 5.05 to 7.04).

Cardiovascular and metabolic diseases

Heart diseases are seen in a substantial proportion of people with COPD. In an analysis by Hansen *et al*[26] of 70 274 people with a diagnosis of COPD in Danish health registries, hypertension was reported in 48% and heart disease in 16%. In an investigation of disease combinations in 11 734 long-term residents in 1174 nursing homes in the USA, COPD was seen in combination with hypertension in 7% of residents (7% of women and >10% of men).[27] COPD was noted in a three-disease combination with hypertension and composite vascular diseases in 4% of residents (3.5% of women and 5.5% of men). Jurevičienė *et al*[20] found that among 4834 patients with COPD, rates of cardiovascular diseases, arrhythmia and heart failure were significantly increased (all p<0.0001). At least one cardiovascular disease was seen in nearly all men (98.7% of 3338) and women (99.5% of 1496) with COPD.

Nesterovska *et al*[28] investigated whether risk of atrial fibrillation was increased by the presence of COPD. The study included 86 patients with coexisting asthma and COPD but no cardiovascular disease or thyroid dysfunction. Around half (42 (49%)) had paroxysmal atrial fibrillation.

Asker *et al*[29] 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 the ration of forced expiratory volume in 1 s forced vital capacity (FEV_1:FVC) (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, Ingebrigtsen *et al*[30] compared the risks of coronary heart disease and heart failure in people with varying phenotypes of COPD and/or coexisting asthma and COPD (n=11 988) or no respiratory disease (n=42 058). Risks of coronary heart disease and heart failure were greatest in the presence of COPD with FEV_1 <50% of predicted (HRs 1.8, 95% CI 1.4 to 2.3 p<0.001 and 2.9, 2.2 to 3.9, p<0.001, respectively) and COPD with late-onset asthma with FEV_1 <50% of predicted (HRs 2.2, 95% CI 1.6 to 3.0, p<0.001 and 2.9, 2.0 to 4.3, p<0.001, respectively).

Miller *et al*[31] found that heart disease in people with COPD increases the risk of further disorders. They used US household survey data for 968 people with self-reported COPD and heart disease and 767 with COPD and no heart disease. Those with heart disease were most likely to be men and were nearly five times as likely to have diabetes (OR 4.8, 95% CI 3.5 to 6.5; p<0.001) and more than twice as likely to have arthritis (OR 2.2, 95% CI 1.7 to 2.8; p<0.001) as 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.

Triest *et al*[32] identified a cachetic disease cluster in 39 (19%) of 208 patients with COPD that was characterised particularly by low muscle mass and underweight (both 80%), hyperglycaemia (54%), arterial stiffness (29%) and hypertension (28%). This cluster of disorders was not relevant in the control group without COPD. A metabolic diseases cluster was also identified among patients with COPD, which featured obesity, hyperglycaemia, insulin resistance, dyslipidaemia and cardiovascular disorders. However, it was also present in the control group and did not have specificity for COPD.

Respiratory disease

O'Kelly *et al*[33] performed a multivariable analysis to assess risk of multimorbidity in patients with chronic respiratory conditions in Dublin, Ireland. The authors separated respiratory disease into asthma (n=432), COPD (n=206) or other (n=15). Among all 653 patients, 393 (60%) had multimorbidity. While asthma

was the most frequently reported disease, the rate of multimorbidity was lower than that for COPD (213 (54%) of 432 vs 169 (82%) of 206). In multivariable analysis, only a diagnosis of COPD was associated with increased rates of multimorbidity. The most common comorbidities in the whole cohort were depression or anxiety, hypertension and cardiovascular diseases (all 28%), musculoskeletal disorders (23%) and endocrine disorders (20%).

Nesterovska *et al*[28] assessed 86 patients with asthma and COPD overlap syndrome (ACOS). The respiratory effects of this condition in people who developed paroxysmal atrial fibrillation were a reduction in FEV_1 by 36.5% and an increase in hypoxaemia by 12.3%. These changes correlated significantly with the development of atrial fibrillation when seen alongside increased blood pressure and systemic inflammation.

Ganga *et al*[34] performed a single-centre study to investigate new-onset atrial fibrillation in 2873 patients older than 65 years with obstructive sleep apnoea alone (n=60), COPD alone (n=416), both (n=28) or neither (n=2369). Non-adjusted incidence of atrial fibrillation was 7%, 11%, 21% and 5%, respectively. The risk of multimorbid atrial fibrillation was significantly increased in the COPD subgroup (OR 1.79, 95% CI 0.190 to 0.962, p=0.003) and notably more so in the subgroup of patients with both obstructive sleep apnoea and COPD (3.66, 95% CI 1.06 to 6.9, p=0.007). By contrast, obstructive sleep apnoea alone and neither disease were not predictive.

Spicuzza *et al*[35] reported a retrospective observational study of people with obstructive sleep apnoea 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 to 11.39; p<0.001). Lacedonia *et al*[36] found similar trends in a retrospective analysis where they compared people with coexisting asthma and COPD or obstructive sleep apnoea alone.

Psychological disorders

Anxiety and depression are common comorbidities in COPD. Phan *et al*[37] reported in a cross-sectional study that among 242 people with COPD, 124 (51%) had symptoms of 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 *et al*[38] 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 controls without depression. A significant association was seen between COPD Assessment Test scores greater than 20 and major depression (OR 7.88; 95% CI 1.96 to 31.7; p=0.004), making COPD a predictive factor.

A UK study used questionnaires in 44 patients with COPD and lung cancer who were attending an outpatient clinic to assess the risk of depression.[39] The relative risk and ORs of patients with COPD developing depression were 1.4 and 1.6, respectively. The number of coexisting comorbidities significantly raised the OR to 2.13 (95% CI 1.02 to 4.49).

Triest *et al*[32] performed a validation study of comorbidity clusters previously identified in patients with COPD. They compared the clusters in 208 patients with COPD 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 and 31 comorbidities and how these were affected by level of physical activity were assessed in 601 adults in Spain.[40] 94% 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 to 3.69), chronic constipation (OR 1.97, 95% CI 1.12 to 3.46), cataracts (OR 1.84, 95% CI 1.07 to 3.15), chronic anxiety (OR 1.51, 95% CI 1.00 to 2.27) and chronic lumbar back pain (OR 1.49, 95% CI 1.04 to 2.13). The authors concluded that recommending increased physical activity could improve the quality of life for patients with COPD.

Yu *et al*[41] 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 HR 0.89, 95% CI 0.79 to 1.00; p=0.045) and depression (adjusted HR 0.85, 0.75 to 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 (defined by the authors as taking five or more drugs per day) along with multimorbidity. Among 245 patients with COPD in Crete, Greece, Ierodiakonou *et al*[42] 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. Co-administration 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.

Smoking

Garneau-Picard *et al*[43] investigated the influence of smoking on multimorbidity in people with ACOS. In a group of 154 patients with irreversible airway obstruction (47% men, 53% women; 100 smokers with ACOS and 54 with irreversible airway obstruction not related to smoking), a sex-specific symptom pattern was found that suggested greater susceptibility of women to smoke. Woman had lower prevalence of severe asthma (44.9% vs 64.7%, p=0.0264) but had higher FEV_1:FVC values (67.2, 95% CI 66.7 to 67.7 vs 65.5, 95% CI 64.8 to 66.2, p=0.0002) and more comorbidities (4.6, 95% CI 3.9 to 5.4 vs 3.2, 95% CI 2.7 to 3.7, p=0.0012) than men, despite having lower tobacco exposure (36.0 pack-years, 95% CI 32.5 to 39.5 vs 41.9 pack-years, 95% CI 38.1 to 45.7, p=0.0278). Furthermore, compared with female non-smokers with airway obstruction, more women with ACOS had severe asthma, used more medication and had a worse FEV_1:FVC, whereas men showed no significant differences from other men with ACOS or men or women with non-smoking-related disease.

Cunningham *et al*[44] explored the relationships between smoking, COPD and 10 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 US 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). 95% of those with COPD had any of the 10 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. Zacarías-Pons *et al*[23] calculated ORs of 3.2 (95% CI 2.4 to 4.3) for current smoking and 1.92 (95% CI 1.4 to 2.4) for former smoking in a disease cluster that included COPD.

In a retrospective study, Le *et al*[45] 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 1 (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 changed from 70.8% to 80.2%; hyperlipidaemia from 52.2% to 64.8%; anaemia from 42.1% to 52.0%; arthritis from 39.8% to 47.7%; and congestive heart failure from 31.3% to 38.8%. The rates of new onset 1 year before and after COPD diagnosis were hyperlipidaemia (22.8 and 27.6 cases per 100 person-years, respectively), anaemia (17.8 and 20.3), arthritis (12.9 and 13.2), hypertension (39.8 and 32.3) and congestive heart failure (16.2 and 13.2). The ORs for all diseases assessed were increased in the COPD group compared with those in the non-COPD group.

DISCUSSION

This systematic literature review indicated high prevalence of multimorbid cardiovascular disorders, metabolic disorders and anxiety and depression in people with COPD, and disease profiles were frequently complex. Multimorbid age-related diseases occur earlier in people with COPD than those in the general population. Therefore, there is an accompanying risk of long-term increased healthcare needs and increased risks of polypharmacy, adverse drug-related events, morbidity and mortality. Differences between the sexes in preventable or modifiable diseases that should be noted are the increased likelihood of gastro-oesophageal disorders in men and psychiatric and musculoskeletal disorders in women.

Most patients with COPD have complex disease profiles, and have 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 *et al* 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 *et al* suggest that the increased prevalence of some multimorbid diseases are due to worsening of COPD whereas some are age related.[46] 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 explored 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.[47] Care for COPD should, therefore, consider preventive measures at population, national, regional and individual levels to address risk of frequently seen multimorbid diseases . Such measures might be 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 underscore the importance of COPD in relation to other diseases and support self-management (eg, exercise, diet, etc), as recommended by the Global Initiative for Chronic Obstructive Lung Disease[48] and national guidelines, such as those of the National Institute for Health and Care Excellence[49]; and multidisciplinary management with healthcare professionals in other specialties.[50]

Jassem *et al*[51] proposed an integrated care model for patients with advanced COPD in Poland. Long-term maintenance care involved planned visits to healthcare providers in primary care (general practitioners and community and specialty nurses) and 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 exacerbation, 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 risk of multimorbidity among patients with COPD. Furthermore, use of high numbers of drugs can contribute to reduced adherence across therapies, and, in COPD, increased disease severity and risk of exacerbation. Regular medicine reviews that include clinical and pharmacy healthcare 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. Furthermore, we chose to include abstracts providing clear data where studies were relevant but full reports were not available. This decision was made to ensure wide exploration of the literature and include poorly represented areas of research. However, these factors meant that it was not possible to perform a meta-analysis or account for bias in studies and that descriptive analysis of the findings was more appropriate. 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 and to reduce the risk of drug-related unplanned and emergency care. 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 considered preventable and/or modifiable. Patients seen in general practice with cardiovascular, metabolic and musculoskeletal disorders, particularly arthritis or osteoporosis and 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 healthcare 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 diagnosis of other diseases seems to increase quickly around the time of COPD diagnosis, and the risks associated with polypharmacy.

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