Original Research
Polypharmacy in Patients With COPD: A Scoping Review

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Abstract:

Chronic Obstructive Pulmonary Disease (COPD) is a global health challenge. Increasing numbers of patients with COPD are prescribed multiple medications (both for COPD and non-COPD disorders). This increases the risk of polypharmacy in these patients which can be linked with patient harm. However, the definition of polypharmacy is varied across literature (ranging from use of ≥3 to ≥20 medications).

This review aims to report the prevalence of polypharmacy, report the varying definitions of polypharmacy, and report medication related harms amongst patients with COPD.

We identified 28 studies reporting polypharmacy rates in COPD populations. 13 studies (46.3%) defined polypharmacy as the use of ≥5 medications; however, the remaining studies had different definitions of polypharmacy. The available studies include multiple different countries and settings (primary care, secondary care, and community-based surveys). Polypharmacy and hyper polypharmacy (use of ≥10 medications) rates varied from 3.9% to 81.4% and 6.6% to 74.6% respectively.

Polypharmacy in patients with COPD is common but poorly understood due to difficulty in comparing previous literature with differences in methodologies, patient populations, and definitions of polypharmacy. The multimorbid COPD population is likely at higher risk of the effects of polypharmacy through poor adherence, adverse drug reactions, and drug-drug interactions. Clinicians should be mindful of the patient's age, comorbidities, and drug-drug interactions while prescribing medications in the COPD clinic.

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Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a global health challenge.[1] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) report recommends a combination of pharmacological and non-pharmacological therapies to manage COPD.[2] The focus for current pharmacological therapy is based on symptoms and disease severity markers such as pulmonary exacerbations, with more recent guidance also linked with blood eosinophil levels. Pharmacotherapy includes inhaled bronchodilators and corticosteroids depending on the above-mentioned factors. COPD medications are often administered through various inhaler devices, which have the potential to cause issues with inhaler technique, adherence, and treatment burden.[2] In addition to inhaled regimens, more severe COPD may require additional treatments such as roflumilast and/or prophylactic antibiotics. Therefore, COPD management, even in isolation, can be associated with polypharmacy. Those patients on multiple medications have a high risk of suffering from adverse drug reactions (ADRs).[2]

Polypharmacy has various definitions in literature, depending on the number of medications prescribed. A systematic review of definitions done by Masnoon *et. al.*, explored various terms used in existing literature. This review included 110 studies, out of which 57 studies (51.8%) defined polypharmacy or major polypharmacy as the use of ≥5 drugs, minor polypharmacy as use of 0 to 4 drugs [8 studies (7.3%)], and moderate polypharmacy as the use of 4 to 5 drugs [1 study (0.9%)]. The use of ≥10 drugs was defined as hyper polypharmacy [1 study (0.9%)], excessive polypharmacy [7 study (6.4%)] or severe polypharmacy [1 study (0.9%)].[3]

Multimorbidity in the general population is associated with polypharmacy and specifically a diagnosis of COPD is associated with an increased risk of polypharmacy.[4] Multimorbidity is defined as the coexistence of two or more (multiple) long-term conditions (MLTCs), without reference to a primary condition, that may overlap, vary in severity, and change in terms of health burden over time.[4,5] COPD is associated with multimorbidity with higher rates of cardiovascular diseases (congestive heart failure, ischemic heart disease, arrhythmias, peripheral vascular disease, hypertension, and atrial fibrillation) as well as bronchiectasis, sleep apnea, anemia, secondary polycythemia, lung cancer, diabetes, osteoporosis, anxiety/depression, and gastroesophageal disease.[2] These may significantly impact the patient's clinical condition and prognosis. These conditions can also mimic the symptoms of COPD, limit lung function or complicate the management of COPD.[2]

Patients with COPD are therefore more likely to have MLTC, polypharmacy, risks of ADRs, hospital re-admissions, and premature mortality.[2,4,5]

Aim:

This review aims to report the prevalence of polypharmacy, the varying definitions of polypharmacy used within COPD populations, factors associated with polypharmacy and medication-related harms in COPD patients.

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Methods

Overview:

A scoping review was selected to consolidate knowledge on polypharmacy in COPD populations. We identified that evidence in this topic required investigation, and a scoping review enables key findings to be quickly summarized and disseminated. The review followed the PRISMA guidelines for scoping reviews: 1) identify objectives; 2) identify relevant studies; 3) analyze the literature for relevance; 4) extract key data; and 5) review and report results. A prespecified protocol was used to guide data synthesis. The protocol was registered through OSF (https://doi.org/10.17605/OSF.IO/KMD65), ensuring transparency and adherence to the established objectives and methodologies for scoping reviews.

Identifying objectives:

The following main objectives were identified as being key areas of interest: What is the prevalence of polypharmacy in COPD? What are the varying definitions of polypharmacy used within COPD populations?

Identifying relevant studies:

Search strategies and databases

A systematic literature search of the electronic databases PubMed, Medline, and EMBASE was conducted using Medical Subject Headings (MeSH) terms and keywords identified from various systematic and scoping reviews relevant to the topic.

The first search was executed in PubMed on January 15, 2024, and the last one on Medline on January 24, 2024. A finalized search strategy was formulated by assessing the number and quality of returns, followed by a literature search executed on January 26, 2024, across three databases: PubMed, Medline, and EMBASE. **[Supplementary Table S1]**

A secondary search conducted in PubMed on February 6, 2024 **[Supplementary table S2]** targeted systematic reviews examining polypharmacy, enhancing the methodological rigor by identifying and incorporating established methods from existing reviews. Acknowledging that eligible studies might be indexed under more general terms not relating to COPD, another secondary search was performed in PubMed on February 10, 2024, focusing on polypharmacy by incorporating terms identified from other systematic and scoping reviews **[Supplementary table S2].**

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Eligibility Criteria

The inclusion criteria for this scoping review were as follows:

1. Publications that clearly defined their COPD population
2. Data on prevalence of polypharmacy that was reported explicitly for COPD cohort

The exclusion criteria for this scoping review were as follows:

1. Publications in languages other than English
2. Publications that were aimed at pulmonary diseases other than COPD
3. Publications that did not mention polypharmacy in patients with COPD
4. Publications that did not detail the rates of polypharmacy in their study population
5. Animal and genetic studies
6. Conference abstracts and non-peer-reviewed articles

Analyzing the literature for relevance

Duplicate studies were removed using EndNote (IBM Systems, Armonk, NY, USA). Two independent reviewers assessed each abstract and formulated a list of "relevant" and "of uncertain relevance" studies. The full manuscripts that met either of these criteria were subsequently independently reviewed by the two reviewers, and eligible studies were identified. When consensus was not met, a third independent reviewer adjudicated.

Data Extraction

A charting form was developed for data extraction. A single reviewer independently extracted the following data from eligible studies: title, author, date of publication, location, study type, methods, study size, total COPD patients in the cohort, care centre, study period, definition of polypharmacy used in the study, and reported prevalence of polypharmacy. The care centre details were extracted from the eligible studies and as each country used different definitions to identify primary/secondary/specialist centres, it was not possible for the authors to standardize these definitions.

We recorded the polypharmacy rates according to the original sources and also wherein possible within the definitions of polypharmacy as the use of ≥5 medications and hyper polypharmacy as use of ≥10 medications as proposed in a systematic review by Masnoon *et al*.[3]

Results:

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The initial database search identified 2573 articles, and 28 studies met the inclusion criteria. The number of studies omitted at each stage and reasons for exclusion are described in Figure 1.[6]

The data was extracted from the 28 eligible articles and has been summarized in **Table 1**. Some papers did not report values for all characteristics, and this is reflected in the table. **[Table 1]**

Study Characteristics

Table 1 presents an overview of the characteristics of the 28 included studies, including author details, year of publication, study design, total patients with COPD, type of care centre, country of publication, study period, definition of polypharmacy used in the study, and prevalence of polypharmacy.

3 studies each were carried out in the United States (10.7%), Japan (10.7%), and Turkey (10.7%) followed by 2 studies each in the United Kingdom (7.1%), Spain (7.1%), Australia (7.1%), Canada (7.1%), Greece (7.1%), and Italy (7.1%). One study was conducted in the Netherlands (3.6%), Brazil (3.6%), Portugal (3.6%), Saudi Arabia (3.6%), Iran (3.6%) and Finland (3.6%). One study (3.6%) was conducted across multiple centres in Europe in Belgium, Finland, Germany, Iceland, Italy, and the Netherlands.

A variety of study designs were reported, including cross-sectional (17, 60.7%); cohort (10, 35.7 %); and observational (1, 3.6%). The settings included secondary care (10, 35.7%), primary care (10, 35.7%), specialist clinic (6, 21.4%), and community-based surveys (2, 7.2%).

Study Population

The number of patients with COPD in the 28 articles ranged from 14 to 117,005.

Collectively, the studies had a total population of 909,079 patients, out of which 270,977 (29.8%) patients had COPD. Out of 28 studies, 11 studies (39.3%) [5, 9, 10, 13, 14, 15, 17, 20, 22, 25, 27] consisted of only patients with COPD, while the rest of the 17 studies [4, 7, 8, 11, 14, 16, 18, 19, 21, 23, 24, 26, 28, 29, 30, 31, 32] had a mixed COPD and non-COPD cohort. However, in all 28 studies, the polypharmacy rates for patients with COPD were extractable.

Definition of Polypharmacy

The majority of the studies (17, 60.7%) used a single threshold to define polypharmacy whereas the remaining 11 studies classified polypharmacy into varying subgroups. The most common single threshold was ≥ 5 medications (13, 46.3%), followed by ≥3 medications (2, 7.1%), ≥6 medications (1, 3.6%) and ≥10 medications (1, 3.6%).

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The most common subgroup classification seen was the use of 5-9 and ≥10 medications (4 studies, 14.3%). Three studies (10.8%) classified patients into two groups, those using ≥5 and ≥10 medications. One study (3.6%) classified patients who used ≥10, ≥15 and ≥20 medications; 1 study (3.6%) defined polypharmacy as ≥4 and ≥8 medications followed by use of ≥4 and ≥10 medications (3.6%), and the remaining one study (3.6%) classified polypharmacy as use of ≥6 and ≥10 medications. **[Table 1]**

Polypharmacy and hyper polypharmacy rates were varied across literature. Polypharmacy rates in studies that used a single threshold of ≥5 medications ranged from 9.5% to 91.4%. Studies that classified polypharmacy in subgroups of 5-9 and ≥10 medications had polypharmacy rates ranging from 3.9% to 12.1% and 6.6% to 21.7% respectively. Similarly, polypharmacy rates in subgroup of ≥5 and ≥10 medications ranged from 13% to 78.5% and 11.7% to 23% respectively.

Factors associated with polypharmacy

The most common factors associated with polypharmacy were older age, increasing number of comorbidities, and smoking status.[9]

Age: 12 studies reported that polypharmacy increased with age, typically reporting the significance of the increase was in ages 65 and over. [4, 7, 9, 12, 13, 15, 17, 22, 23, 29, 30, 31]Certain studies showed a statistically significant association[7, 12, 13, 15, 22, 26, 30, 31] however many other studies[4, 9, 17, 23, 29] did not report the statistical association. Most studies showed a strong link with polypharmacy and age, with one study showed a higher rate of polypharmacy in older patients (86.8% among patients aged ≥75 years[13] whilst two studies showed no links between age and polypharmacy.[5, 18] Surprisingly, cross-sectional study across multiple European countries in home care patients showed an inverse association of hyper polypharmacy with age (OR 0.69, 95% CI 0.56–0.83).[16]

Gender: Gender had a significant role to play with polypharmacy status. 4 studies showed a higher prevalence of polypharmacy in females[7, 16, 31, 32] while 2 studies showed a higher prevalence in males.[8, 22] One study showed no statistically significant difference between polypharmacy and gender.[5]

Co-morbidities: Comorbidities and polypharmacy were common phenomena reported in 13 studies.[4, 9, 12, 13, 15, 16, 17, 22, 23, 29, 30, 31, 32] The most common diseases included diabetes mellitus[4, 9, 12, 13, 17, 23, 29, 30], cardiovascular diseases[4, 9, 12, 13, 17, 22, 23, 30], dyslipidemia[12, 23, 30], cerebrovascular diseases[12, 13, 30], dementia[12, 30] and COPD[4, 9, 12, 15, 22, 23, 30], which is relevant to our study. 3 studies[4, 22, 23] also highlighted the increasing risk of polypharmacy in patients with depression-anxiety diagnosis.

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Smoking status: COPD patients with polypharmacy were more frequently ex-smokers as compared to non-smokers (75.4% vs 68.4%; p=0.0005).[9] The average pack years between those with and without polypharmacy was significantly different (58 vs 40 years, p=0.004).[22]

Medication adherence: Polypharmacy was linked to poor medication adherence only in COPD patients aged ≥65 years (OR 1.34, 95% CI 1.13–1.59).[15] Poor adherence with polypharmacy (p<0.001) was also seen in an observational study done by Moradkhani B. *et al.*[25] A regression model was run in this study which showed the odds of patients with polypharmacy having high medication adherence was 81% less than those without polypharmacy, while controlling for other covariates (p = 0.008).[25]

COPD patients were more likely to have polypharmacy (73.3% to 55.6%, p value <0.001) and the combination of COPD and polypharmacy led to poor medication adherence.[31] Vetrano D. *et al*. reiterated in their study how complex regimens lead to poor adherence.[15]

Health status and frailty: In addition to poor functional health status, polypharmacy patients were less likely to be living independently (p=0.017).[26] This may correlate with studies suggesting higher rates of frailty in these group as the Charlson Comorbidity Index, which predicts the 10-year mortality in comorbid patients, was used by Díez-Manglano J. *et al.* to determine that polypharmacy was associated with a worse Charlson score (p=0.004).[9]

Polypharmacy was significantly associated with failure to improve ADL (activities of daily living) in a mixed cohort of COPD-non COPD patients (OR 2.22. 95% CI 0.48-10.16).[11]

Two studies[24, 31] reported that polypharmacy patients were at a higher risk of pain, falls, dyspnea, and flare ups. When asked, polypharmacy patients self-report poor health status as well.[32]

Hospital admissions: Díez-Manglano J. *et al.* reported an increase in medications even after hospital admission for COPD acute exacerbation, with the mean number increasing from 5 to 6.6 at discharge.[9]

The IBenC study by Giovannini S. *et al*. in home care patients (including those with COPD) showed that recent hospitalization in the past 90 days was statistically associated with increased probability of hyper polypharmacy (P-value 0.012).[16]

Severity of COPD: Franssen F. *et al.* reported increasing use of respiratory drugs with advancement in GOLD stages and worsening MRC dyspnea score.[5] An observational study done by Díez-Manglano J. *et al.* showed polypharmacy was associated with severe dyspnea using the mMRC scale (3.7 versus 3.5, p=0.02), however patients with polypharmacy showed no differences in their GOLD staging as compared to non-polypharmacy patients.[9]

Multimorbidity: A cross-sectional study in Greece found majority of the patients with polypharmacy suffering from multimorbidity as compared to those without polypharmacy (98% vs 51%, p<0.001).[22]

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Clinical outcomes of polypharmacy

Most extracted studies provided little information on how polypharmacy was linked to ADRs, hospitalization and mortality in a COPD specific population. A cross-sectional UK biobank study in 8317 patients with self-reported COPD reported higher risk of ADR such as bleeding (OR 4.61, 95% CI 3.35 to 6.19), CNS depression (OR 3.75, 95% CI 3.31 to 4.25), constipation (OR 3.42, 95% CI 3.10 to 3.77), urinary retention (OR 3.38, 95% CI 2.94 to 3.87), falls (OR 2.27, 95% CI 2.13 to 2.42), and renal injury (OR 2.22, 95% CI 1.86 to 2.62).[4]

Similarly, a cross-sectional study from Greece showed that COPD patients with polypharmacy were at a higher cumulative risk of falls, constipations and cardiovascular events. In addition, 15 pairs of major drug-to-drug interactions were recorded in 11.5% cases, however the details of these were not mentioned.[22]

Additionally, Witt LJ *et al.* reported, in a cross-sectional study of 3,005 U.S. community-dwelling older adults, a high risk medications increased ADRs, and this risk furthered with polypharmacy. These high-risk medications included anti-histaminic, anti-cholinergic, benzodiazepines, anti-psychotics, anxiolytics/sedatives, tricyclic anti-depressants, muscle relaxants, anti-arrhythmic, COX-2 inhibitors and narcotics.[26]

Detoni K *et al.* conducted a retrospective review of medication management services delivered to COPD patients and identified the drug therapy problems in these patients. The most common drug therapy problem in COPD patients was ADR (25.8%), followed by unnecessary drug therapy (20.8%), and non-adherence to prescribed medications (18.8%). The most common ADR identified was oral candidiasis associated with the use of inhalers however the frequency of the ADRs were not described.[14]

Discussion:

Despite the increasing prevalence of COPD worldwide, polypharmacy in COPD is poorly understood and described in literature. Our literature search identified 28 studies that reported the prevalence of polypharmacy in patients with COPD, however there was no set definition for polypharmacy across these papers. Most studies defined polypharmacy with a threshold of ≥ 5 medications[5, 7, 12, 13, 15, 18, 20, 21, 22, 25, 28, 29, 31] but other studies defined polypharmacy as the use of ≥3 medications[8, 27], ≥6 medications[24], and ≥10 medications.[23] A further subcategory was defined in seven papers wherein hyper polypharmacy was studied along with polypharmacy.[4, 9, 11, 14, 16, 30, 32] These varied definitions create inconsistencies across studies and limit the conclusions that can be drawn from these studies. Allowing for this, the studies suggest varied polypharmacy rates ranging from 9.5% to 91.4% in studies with single definition of polypharmacy (≥ medications). Similarly, studies with polypharmacy subgroups of 5-9 and ≥10 medications had polypharmacy

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rates ranging from 3.9% to 12.1% and 6.6% to 21.7% respectively. This large range likely reflects both the different patient populations and settings as well as the varying definitions.

COPD therapy often involves the use of combination inhalers e.g. triple inhaled long-acting beta agonist, long-acting anticholinergic and inhaled corticosteroid in a single inhaler. Consensus is needed on how best to report these in polypharmacy studies as the use of triple therapy can be classified as either use of three different medications or one single inhaler. Drug-drug interactions are defined by the number of active pharmaceuticals taken but compliance may be different in those with simpler drug regimens as compared to those with "open triple" and "multiple inhalers".

Overall, we found the most common factors associated with polypharmacy were older age, increased comorbidities and smoking status.[4, 5, 8, 9, 13, 16, 22, 26, 31, 32] Some studies showed polypharmacy associated with increased age with several studies reporting a statistically significant association.[7, 12, 13, 15, 22, 26, 30, 31]

However, COPD is commonly associated with MLTC and both MLTC and COPD prevalence increases with age. The various methodologies used in the extracted literature make it difficult to understand what factors independent predictors of polypharmacy are. Notably polypharmacy and comorbidities both contribute to poor adherence to medication in patients with COPD.[12, 31, 15]

Comorbidities are also common in patients with COPD, with the most common ones being cardiovascular diseases. COPD-heart failure and COPD-coronary artery disease clusters are strongly associated with polypharmacy.[9, 7] Apart from cardiovascular diseases and COPD, polypharmacy was also associated with diabetes mellitus and dementia.[12]

These comorbidities are drivers to polypharmacy, increasing the use of potentially inappropriate medications, medication error, poor drug adherence, drug-disease interaction and drug-drug interactions that can lead to severe adverse drug reactions.[8, 9, 20]

Polypharmacy is a concern not only due to the immediate costs of the medication regimens and the increased risk of non-adherence (which in turn increases the risk of COPD exacerbations), but also due to the concern over adverse drug reactions and drug-drug interactions.[14] A major proportion of COPD healthcare costs relate to hospitalizations. Notably, hospitalized patients with COPD are twice as likely to have polypharmacy regimens than non-COPD hospitalized patients.[23] The available literature, however, is limited in looking at the independent contributions of polypharmacy, frailty and multimorbidity in driving hospitalizations. Relatively few studies do comment on potential adverse drug reactions in COPD as possible factors associated with admission.[22] Ierodiakonou D. *et al*., found specific DDIs (drug-drug interactions), such as liver damage, rhabdomyolysis and arrhythmia increased with polypharmacy, suggesting side effects of multiple medications being a cause for increased hospital admission.[22]

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Detoni K. *et al*., investigated the most common types of medication related problems in a cohort of 83 patients with COPD and non-COPD patients in Brazil and found that ADRs were the most common (25.8%), with unnecessary medication use (defined as duplicate therapy, no medical indication, or where non-medication therapy was more appropriate) and non-adherence the second and third most common problems respectively (20.8% and 18.8% respectively).[14] High levels of inappropriate medication use in patients with COPD suggests the need to emphasize and screen for potentially inappropriate medications in these patients to help reduce medication burden, improve adherence and risk of hospitalization. One of our stated aims was to report the medication related harms in COPD but we found the literature lacking in this detail. Therefore, future prospective studies should consider this in their study design.

Since polypharmacy is associated with high risk of ADRs, DDI and reduced medication adherence, specialist pharmacy services can be utilized in respiratory clinics to reduce the impact of polypharmacy and provide regular medication review to patients. In addition, COPD is associated with multimorbidity (especially cardiovascular diseases) which is often managed by specialists or primary care physicians, hence a high degree of care coordination and effective communication between multidisciplinary teams will improve patient outcomes.

A few studies we identified have analyzed polypharmacy in hospitalized elderly patients wherein polypharmacy was more common in those 75 years or older and with multiple comorbidities.[7, 16] These patients with polypharmacy are at increased risk of frailty and worse long-term outcomes.[8, 11] In terms of smoking status and medication adherence, non-smokers were more compliant with long term treatment than smokers and ex-smokers.[15]

Future studies require attempts to avoid unhelpful variation in definitions. It is commonly held that polypharmacy is defined as the use of ≥ 5 medications and hyper polypharmacy is ≥ 10 medications. These will usefully be applied in future studies as they are aligned with current thinking. However, future studies should also consider analyses where drug count is also analyzed using continuous statistical approaches beyond the current categorical approach. Future studies would be advised to be methodical in reporting drug regimens as the complexities of COPD pharmacotherapy with open and closed triple inhalers needs critical thought. Closed triple inhaled therapy represents a reduced treatment burden for example and the potential for drug-drug interactions may be different to that where patients are variably complying with open triple therapy. Future studies should state where COPD was diagnosed by spirometry and ideally broader studies looking at patients who are solely managed in primary care are compared to those who have been hospitalized or receive outpatient hospital-based COPD care.

Future work with a clear definition for polypharmacy is needed with more cross sectional and longitudinal studies of polypharmacy in people living COPD. Better clarity on the independent predictors of hospitalizations is also needed, and these studies should consider the complex interactions between adherence, MLTC and frailty, polypharmacy and age. Studies that highlight the patient factors and medication combinations that enhance the risk of adverse medication

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reactions are needed. Additionally, prospective studies should consider analyses by sex and smoking status. Interventional studies to rationalize medication regimens are also welcomed.

One of the limitations of the study was that the available literature notes a diagnosis of COPD but the studies herein rarely if ever documented if this was a spirometry supported COPD diagnosis. In addition, the available literature does not allow us to make recommendations of suitable interventions to minimize treatment burdens or risk of drug-drug interactions".

Conclusion:

Polypharmacy in COPD patients is common yet poorly understood due to difficulty in comparing previous literature with differences in methodologies, patient population and definitions of polypharmacy. The most common factors associated with polypharmacy were old age, number of comorbidities and smoking status. There is likely a complex interaction between the multimorbidity present within a COPD population that amplifies risks of polypharmacy. Polypharmacy is a growing concern due to increasing costs, non-adherence to medications, adverse drug reactions and drug-drug interactions. Clinicians should be mindful of the patient's age, comorbidities and risks of drug-drug interactions while prescribing medications in the COPD clinic.

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Table 1. Characteristics of eligible studies.

Sr. No.	Author	Year	Study Type	Total study	Total COPD patients in the cohort	Care Centre	Country	Study Period	Polypharmacy definition (medications per day)	Prevalence of polypharmacy
1.	Franssen F. *et al.*[5]	2011	Cross sectional	1859	1859	Specialist Clinic	Netherlands	2005-2009	≥ 5	22%
2.	Mizokami F. *et al.* [7]	2012	Cross Sectional	1768	150	Secondary Care	Japan	2009	≥5	53%
3.	Calderón-Larrañaga A. *et al.* [8]	2013	Cross Sectional	79089	1351	Primary Care	Spain	2008	≥3	37.93%
4.	Diez-Manglano J. *et al.* [9]	2014	Cross sectional	398	398	Specialist Centre	Spain	2007-2008	≥ 5 ≥ 10	78.5% 11.7%
5.	Notebloom B. *et al.* [10]	2014	Cross Sectional	70	70	Specialist Centre	Australia	2010	≥4 ≥8	57% 29%
6.	Runganga M. *et al.* [11]	2014	Cohort	347	44	Secondary Care	Australia	2009-2010	5-9 ≥10	9.7% 20.1%
7.	Vrettos I. *et al.* [12]	2017	Cohort	310	30	Secondary Care	Greece	2015-2016	≥5	13.9%
8.	Savaria F. *et al.* [13]	2017	Cohort	113,435	113,435	Primary Care	Canada	2003-2014	≥ 5	81.4%
9.	Detoni K. *et al.* [14]	2017	Cross sectional	83	83	Primary Care	Brazil	2014-2016	5-9 ≥ 10	48.2% 21.7%
10.	Vetrano D. *et al.* [15]	2017	Cohort	22505	22505	Primary Care	Italy	2002-2012	≥ 5	59.5%
11.	Hanlon P. *et al.* [4]	2018	Cross sectional	502,640	8317	Primary Care	United Kingdom	2006-2010	≥ 5 ≥10	51.8% 15.3%
12.	Giovannini S. *et al.* [16]	2018	Cross Sectional	1873	220	Community based survey	Belgium, Finland, Germany, Iceland, Italy, and the Netherlands	2014-2016	5-9 ≥10	12.1% 15.5%
13.	Sirois C. *et al.* [17]	2019	Cohort	117,005	117,005	Primary Care	Canada	2000-2015	≥ 10 ≥ 15 ≥ 20	74.6% 45.4% 22.4%
14.	Urzal J. *et al.* [18]	2019	Cohort	483	67	Secondary Care	Portugal	2017	≥5	16.3%
15.	Kaplan C. *et al.* [19]	2019	Cohort	835	177	Secondary Care	Turkey	2016	≥6 ≥10	11% 7%
16.	Proietti M. *et al.* [20]	2019	Observational	6046	1302	Specialist Clinic	Italy	2008-2016	≥5	73.3%
17.	Balkhi B. *et al.* [21]	2021	Cross Sectional	17237	14	Secondary Care	Saudi Arabia	2016	≥5	78.6%

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18.	Ierodiakonou D. *et al.* [22]	2021	Cross sectional	245	245	Primary Care	Greece	2019	≥ 5	55.23%
19.	Brinker L. M. *et al.* [23]	2021	Cohort	231	62	Specialist Clinic	United States	2016-2019	≥10	33%
20.	Yamaoka M. *et al.* [24]	2021	Cohort	2603	58	Secondary Care	Japan	2014-2017	≥6	4.6%
21.	Moradkhani B. *et al.* [25]	2021	Cross sectional	100	100	Specialist Clinic	Iran	2019-2020	≥ 5	58%
22.	Witt J. *et al.* [26]	2022	Cross Sectional	3005	322	Community based survey	United States	2005-2006	≥4 ≥10	80.6% 37.5%
23.	Prosser T. R. *et al.* [27]	2023	Cross-sectional	709	709	Primary Care	United States	2016-2017	≥ 3	27.9%
24.	Veizi BGY. *et al.* [28]	2023	Cross sectional	235	32	Secondary Care	Turkey	2016-2019	≥ 5	81.3%
25.	Faquetti M. L. *et al.* [29]	2023	Cohort	34169	2291	Primary Care	United Kingdom	2016-2019	≥ 5	10.3%
26.	Kanai M. *et al.* [30]	2024	Cross sectional	884	43	Secondary Care	Japan	2014-2019	5-9 ≥ 10	3.9% 6.6%
27.	Ozkok S. *et al.* [31]	2021	Cross-sectional	392	24	Secondary Care	Turkey	2016-2020	≥ 5	9.5%
28.	Jyrkka J *et al.* [32]	2009	Cross-sectional	523	64	Primary Care	Finland	1998	≥ 5 ≥ 10	13% 23%

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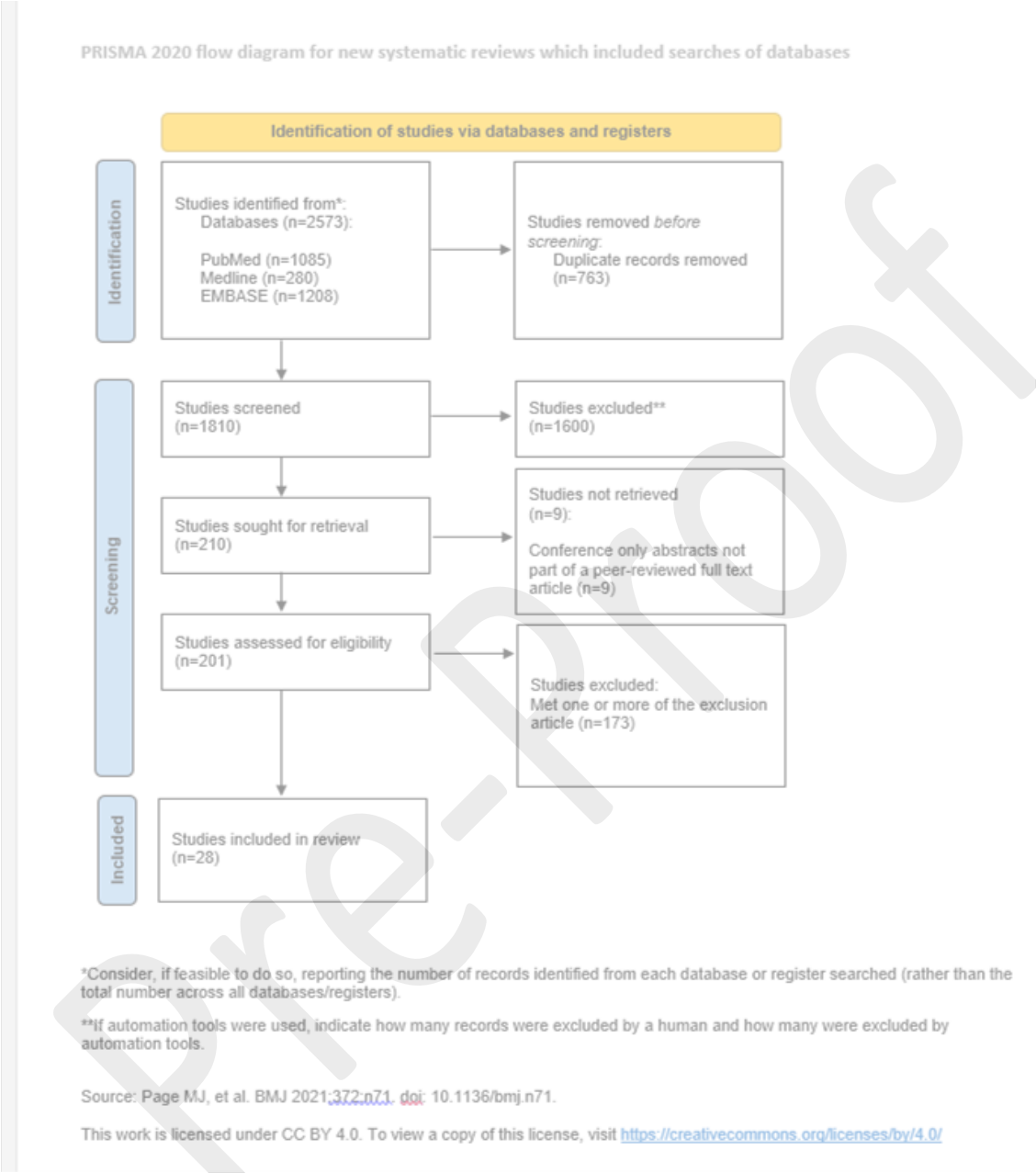
Figure 1: PRISMA flow diagram for study inclusion



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Online Supplement

Supplementary Table S1. *Primary search strategy used to identify eligible studies.*

Database	Date	Search Query
PubMed	26/01/24	1. "chronic obstructive lung disease*"[Title/Abstract] OR "chronic obstructive lung disorder*"[Title/Abstract] OR "chronic obstructive airway disease*"[Title/Abstract] OR "chronic obstructive airway disorder*"[Title/Abstract] OR "chronic obstructive pulmonary disease*"[Title/Abstract] OR "chronic obstructive pulmonary disorder*"[Title/Abstract] OR "copd"[Title/Abstract] OR "coad"[Title/Abstract] OR "chronic obstructive respiratory disease*"[Title/Abstract] OR "chronic obstructive respiratory disorder*"[Title/Abstract] OR "Pulmonary Disease, Chronic Obstructive"[MeSH Terms] 2. "multiple medication*"[Title/Abstract] OR "multiple medicine*"[Title/Abstract] OR "multiple drug*"[Title/Abstract] OR "many medication*"[Title/Abstract] OR "many medicine*"[Title/Abstract] OR "many drug*"[Title/Abstract] OR "multi-drug therap*"[Title/Abstract] OR "multidrug therap*"[Title/Abstract] OR "drug-drug interaction*"[Title/Abstract] OR polypharmacy[Title/Abstract] OR polypharmacy[MeSH Terms] 3. #1 AND #2
Medline	26/01/24	1. "chronic obstructive lung disease*".ab,kw,ti. OR "chronic obstructive lung disorder*".ab,kw,ti. OR "chronic obstructive airway disease*".ab,kw,ti. OR "chronic obstructive airway disorder*".ab,kw,ti. OR "chronic obstructive pulmonary disease*".ab,kw,ti. OR "chronic obstructive pulmonary disorder*".ab,kw,ti. OR copd.ab,kw,ti. OR coad.ab,kw,ti. OR "chronic obstructive respiratory disease*".ab,kw,ti. OR "chronic obstructive respiratory disorder*".ab,kw,ti. OR exp Pulmonary Disease, Chronic Obstructive/ 2. "multiple medication*".ab,kw,ti. OR "multiple medicine*".ab,kw,ti. OR "multiple drug*".ab,kw,ti. OR "many medication*".ab,kw,ti. OR "many medicine*".ab,kw,ti. OR "many drug*".ab,kw,ti. OR "multi-drug therap*".ab,kw,ti. OR "multidrug therap*".ab,kw,ti. OR "drug-drug interaction*".ab,kw,ti. OR polypharmacy.ab,kw,ti. OR exp Polypharmacy/ 3. #1 AND #2

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Embase	26/01/24	1. "chronic obstructive lung disease*".ab,kw,ti. OR "chronic obstructive lung disorder*".ab,kw,ti. OR "chronic obstructive airway disease*".ab,kw,ti. OR "chronic obstructive airway disorder*".ab,kw,ti. OR "chronic obstructive pulmonary disease*".ab,kw,ti. OR "chronic obstructive pulmonary disorder*".ab,kw,ti. OR copd.ab,kw,ti. OR coad.ab,kw,ti. OR "chronic obstructive respiratory disease*".ab,kw,ti. OR "chronic obstructive respiratory disorder*".ab,kw,ti. OR exp Pulmonary Disease, Chronic Obstructive/ 2. "multiple medication*".ab,kw,ti. OR "multiple medicine*".ab,kw,ti. OR "multiple drug*".ab,kw,ti. OR "many medication*".ab,kw,ti. OR "many medicine*".ab,kw,ti. OR "many drug*".ab,kw,ti. OR "multi-drug therap*".ab,kw,ti. OR "multidrug therap*".ab,kw,ti. OR "drug-drug interaction*".ab,kw,ti. OR polypharmacy.ab,kw,ti. OR exp Polypharmacy/ 3. #1 AND #2

Supplementary Table S2. *Secondary search strategy used to identify systematic reviews on polypharmacy and eligible articles on multimorbidity and polypharmacy.*

Database	Date	Search Query
PubMed	06/02/24	1. systematic review[Publication Type] 2. "multiple medication*"[Title/Abstract] OR "multiple medicine*"[Title/Abstract] OR "multiple drug*"[Title/Abstract] OR "many medication*"[Title/Abstract] OR "many medicine*"[Title/Abstract] OR "many drug*"[Title/Abstract] OR "multi-drug therap*"[Title/Abstract] OR "multidrug therap*"[Title/Abstract] OR polypharmacy[Title/Abstract] OR polypharmacy[MeSH Terms] 3. #1 AND #2
PubMed	10/02/24	1. ("multimorbidity" OR "comorbidity" OR "co-morbidity")[All Fields] 2. ("multiple medication*" OR "multiple medicine*" OR "multiple drug*" OR "many medication*" OR "many medicine*" OR "many drug*" OR "multi-drug therap*" OR "multidrug therap*" OR polypharmacy)[All Fields] 3. #1 AND #2

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