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A Systematic Review on the Association between Schizophrenia and Bipolar Disorder with Chronic Obstructive Pulmonary Disease

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ABSTRACT

A systematic review aimed to investigate the association between schizophrenia and bipolar disorder and chronic obstructive pulmonary disease (COPD), its prevalence and incidence, potential factors associated with its occurrence and its impact on mortality among these patients. We performed the literature search in PubMed, Scopus and PsycInfo from inception to February 2022 and identified 19 studies: ten cross-sectional, 5 that included cross-sectional and longitudinal analyses, and 4 retrospective cohort studies. The reported prevalence of COPD ranged from 2.6% to 52.7% in patients with schizophrenia and between 3.0% and 12.9% in patients with bipolar disorder. Two studies reported an annual incidence of COPD of 2.21 cases/100 person-years in patients with schizophrenia and 2.03 cases/100 person-years in patients with bipolar disorder. Among the risk factors evaluated in three studies, only advanced age was consistently associated with the presence/occurrence of COPD in patients with schizophrenia and bipolar disorder; the role of tobacco consumption was not investigated in those three studies. According to two studies, the likelihood of mortality from COPD showed an over 3-fold increase in patients with schizophrenia and a 2-fold increase in those with bipolar disorder compared to the overall population; COPD was also associated with increased inpatient mortality. Available data indicate that COPD in patients with schizophrenia and bipolar disorder is a major public health problem. National and international health organizations should strive to specifically address this issue by creating awareness about this health problem and developing specific programs for screening and early intervention aimed to reduce the burden of COPD in these populations.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a major public health problem worldwide due to its frequency and impact on individuals and society. The prevalence of COPD among people aged 30–79 years, using the Global Initiative for Chronic Obstructive Lung Disease fixed ratio definition, was estimated globally as 10.3% in 2019, which translates to almost 400 million people affected worldwide [1]. Chronic respiratory diseases were the third-leading cause of death in 2017, after cardiovascular disease and malignancies, and among these diseases, the major contributor to death and disability was COPD [2]. COPD is also associated with a substantial economic burden, especially due to hospitalizations but also because of loss of productivity and early retirement [3]. To further increase this burden, patients with COPD are at higher risk of other medical comorbidities, such as metabolic disorders [4–6], coronary heart disease [7], arrythmias [8], and dementia [9], and it seems to be associated with an increased risk of suicide [10].

Patients with severe mental illness, such as those with schizophrenia or bipolar disorder, have a higher risk of presenting medical comorbidities, including respiratory diseases [11], and exhibit an excess of mortality with a relative risk of all-cause death of 2.89 for schizophrenia and 2.51 for bipolar disorder [12]. When analyzed by cause, after suicide, which is the major contributor to this excess of mortality, respiratory diseases are an important cause of mortality [13,14]. In patients with schizophrenia, the excess mortality due to respiratory diseases was even higher than that due to cardiovascular diseases, with standardized mortality ratios of 3.55 and 1.88, respectively [13]. Similar findings have been described in patients with bipolar disorders, with standardized mortality ratios of 2.92 for respiratory diseases and 1.73 for circulatory diseases [14].

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Despite the importance of respiratory diseases in patients with severe mental illness and that the major risk factor for COPD, that is, tobacco consumption, is much more frequent in patients with severe mental illness than in the general population [15], the association between severe mental illness and respiratory diseases, more specifically COPD, has received much less attention than other comorbidities, such as the association with cardiometabolic disorders. To our knowledge, only two systematic reviews have addressed the association between severe mental illness and respiratory disease. Suetani et al. [16], in a systematic review and meta-analysis, evaluated the prevalence and association of respiratory diseases in persons with schizophrenia. Another systematic review specifically evaluated the association between COPD and schizophrenia and bipolar disorder; however, this otherwise interesting review was published in 2018 and did not include among its objectives to assess the potential determinants of the occurrence or presence of COPD or the impact of COPD on mortality [17].

The aim of this systematic review was to investigate the association between schizophrenia and bipolar disorder and COPD, including its prevalence and incidence and the potential factors associated with its occurrence. We also investigated the impact of COPD on mortality among patients diagnosed with these two clinical entities.

Material and methods

Eligibility criteria

We included studies reporting any measure of frequency and/or association separately for patients with schizophrenia and/or patients with bipolar disorder. Since one of the objectives was to assess the prevalence of COPD, noncomparative studies were also included. In comparative studies, we selected those that analyzed and/or reported the relationship between severe mental illness and COPD and excluded those that studied the reverse relationship. We excluded metanalyses, randomized clinical trials and studies published in languages other than English or Spanish.

Definition of exposure and outcome

The exposure was having a diagnosis of schizophrenia or bipolar disorder regardless of whether it was performed by means of applying diagnostic criteria or was a code registered in an administrative database. Similarly, the outcome was having a diagnosis of COPD regardless of whether it was based on functional tests or was a code registered in the database.

Search methods for study identification

One of the authors (MJJ) performed the literature search in PubMed, Scopus and PsycInfo from inception to February 2022. With adaptations depending on the database, the search strategy was the following: ((((schizophrenia[Title/Abstract]) OR (bipolar disorder[Title/Abstract]) OR (severe mental illness[Title/Abstract]) OR (serious mental illness[Title/Abstract]) OR (severe mental disease[Title/Abstract]) OR (serious mental disease[Title/Abstract])) OR (affective psychosis[Title/Abstract])) AND ((obstructive lung disease[Title/Abstract]) OR (chronic obstructive[Title/Abstract]) OR (chronic bronchitis[Title/Abstract]) OR (chronic airway obstruction[Title/Abstract]) OR (COPD[Title/Abstract]))).

The reference lists from two previous systematic reviews on the topic [16,17] were also reviewed, looking for further references to relevant studies. We also performed a forward citation search and a backward citation search using the articles identified by the literature search.

Study selection

Two authors (CRR and DLM) independently assessed the eligibility of studies by reviewing the title/abstract of each study identified by the search. Studies that clearly did not meet the eligibility criteria were discarded, and the full-text articles of the remaining studies were retrieved. The full-text articles were independently reviewed by the same two authors and finally selected if there was an agreement between the reviewers on whether they met the eligibility criteria. If there was no agreement for a particular study, a third reviewer (MJJ) evaluated the study and finally decided on its eligibility.

The full articles selected were not anonymized before any evaluation or data extraction.

Data extraction and management

Two reviewers (CRR and DLM) independently extracted data from the full-text articles using a standard Microsoft Excel form. Both reviewers checked all data included in the abstraction form, and if a discrepancy in the data extracted arose, it was resolved by consensus between the reviewers. If there was no consensus, a third reviewer (MJJ) was involved in the discussion.

The study characteristics extracted were author and year of publication, country where the study was conducted, study design, setting (i.e. outpatients and/or inpatients), time frame when the study was conducted, source of the data, definition of the exposure and outcome, control group (presence and type of control) and control for confounding (i.e. matching and/or multivariate analysis).

The patients' characteristics included the sample size of each study group, age in years, sex (% female), and smoking status. When the prevalence of COPD was reported, we recorded the point estimate and the 95% confidence interval (CI). For studies reporting the potential association between the exposure and outcome, we recorded the measure of association (i.e. odds ratio [OR], relative risk [RR] or hazard ratio [HR]), the point estimate, the corresponding 95% CI and the p value. Finally, when reported, we extracted data from the risk factors for the occurrence or presence of COPD and data on the association between COPD and mortality.

Data synthesis

Because we expected a large heterogeneity in designs, populations, and definitions of exposures and outcomes, no statistical synthesis was foreseen. Instead, the results are summarized in tables or in the text when very few data were available.

Results

Study selection

Our literature search identified 476 records. After removing duplicates, 285 records remained and were evaluated using the abstract, leading to the discarding of 249 records. Of the remaining 36 records, after reviewing the full paper, 15 met our selection criteria. These latter articles, together with another 4 articles identified through other sources, comprised the 19 articles included in our qualitative synthesis (Figure 1).

Study characteristics

Nine studies were conducted in Europe, mainly in Northern Europe ($n = 5$), 7 in the US, 2 in Taiwan and 1 in Israel (Table 1). The studies were published between 2004 and 2022, but the majority of them were published from 2010 to date.

Ten studies were cross-sectional, 5 included cross-sectional and longitudinal analyses, and 4 were retrospective cohort studies (Table 1). Six studies were categorized by the authors as population-based, and another 6 were conducted using national registers. Two studies did not include a control group. From the comparative studies, 9 included a control group from the general population, 3 included hospital controls, and the remaining 5 included a variety of control groups.

Ten studies focused on schizophrenia, six focused on bipolar disorder, and 2 included information on both clinical entities. Nine studies included both inpatients and outpatients, 6 included only outpatients and 3 included only inpatients; 1 study was unclear in this regard. In 16 studies, the diagnosis of COPD was based on the presence or occurrence of a comorbidity coded as such with some codification system; of the remaining 3 studies, Partti et al. [18], in a study conducted in Finland, defined COPD as being admitted with a diagnosis or having spirometry results indicative of COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, Bendayan et al. [19] used a natural language processing tool, and Sokal et al. [20] based the diagnosis on a health questionnaire used for a national US health survey.

Quality of the studies included in the review

Most studies evaluating the association between schizophrenia and bipolar disorder with COPD were cross-sectional, a design that is not appropriate for evaluating a causal relationship. Information on exposure, cofactors and outcome were mostly based on data from the administrative databases; this implies some concerns regarding the quality and completeness of the data recorded, the latter affecting not only to the comparisons of patients with severe mental illness to those without mental illness or the general population, but also to the analyses of the potential determinants of the occurrence or presence of COPD among these patients (see the discussion below).

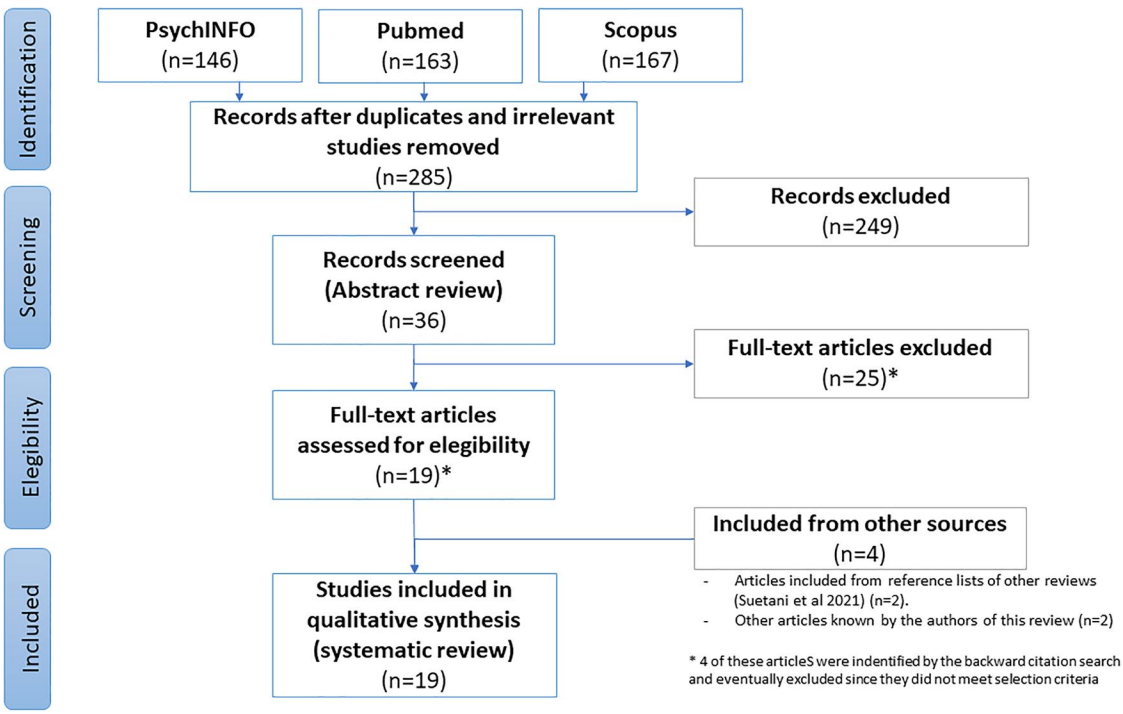

Figure 1. Flow diagram study selection.

Table 1. Main characteristics of the studies evaluating chronic obstructive pulmonary disease in patients with schizophrenia or bipolar disorder.

Author/Year	Study design	Country[a]	Data source	Time frame LOFU	Setting	Exposure definition[b]			Outcome definition[b]
						Schizophrenia	Bipolar disorder	Control	
Bendayan 2022 [19]	CS	UK	A case register platform from the South London and Maudsley National Health Service Foundation Trust (UK)	2007-2018 NA	Out	ICD-10	ICD-10	No	Mapping with MedCaT, a natural language processing tool
Brink 2019 [21]	RC[c] NRB	Denmark	National Danish Registries	1970-1979 10 years	In & Out	Patients admitted to a psychiatry hospital with ICD-8 Dx	–	General population (without schizophrenia)	ICD-8 and ICD-10 codes
Carney 2006 [27]	CS PB[d]	US	Wellmark Blue Cross/Blue Shield of Iowa (USA) administrative claims database	1996-2001 NA	In & Out	Schizophrenia or schizoaffective disorder (ICD-9)	–	General population (without mental disorder)	Elixhauser Comorbidity Index
Carney 2006 [32]	CS PB[b]	US	Wellmark Blue Cross/Blue Shield of Iowa (USA) administrative claims database	1996-2001 NA	In & Out	–	ICD-9	General population (without mental disorder)	Elixhauser Comorbidity Index
Copeland 2007 [28]	CS NRB	US	Patients discharged at death from Veterans Administration hospitals (USA)	October 1, 2001-September 30, 2002 NA	Unclear	Diagnosis of schizophrenia (ICD-9) in the past year	–	Without schizophrenia	Diagnosis of COPD (ICD-9) during the last year of life (or during the last hospitalization)
Crump 2013 [22]	RC NRB	Sweden	Swedish national linked registries	2003-2009 7 years	In & Out	ICD-10	–	General population (without schizophrenia)	ICD-10
Crump 2013 [26]	RC	Sweden	Swedish national linked registries	2003-2009 7 years	In & Out	-	ICD-10	General population (without bipolar disorder)	ICD-10
Hendrie 2014 [35]	CS & RC	US	Wishard Health Services. Health provider to the uninsured or underinsured (Indianapolis, US). Patients who reached 65 years within the study time frame period	1999-2008 Mean: 5.7 years (cases) and 6.7 years (controls)	Out	ICD-9	–	Patients without schizophrenia	ICD-9
Hetlevik 2015 [29]	CS NRB	Norway	The Regular GP database, a national Norwegian database of general practitioners claims data	2009 NA	Out	International Classificaction of Primary Care (ICPC) code	No	General population	Diagnosis of obstructive lung disease (ICPC)
Hsu 2013 [23]	CS & RC PB[b]	Taiwan	National Health Research Institute (NHRI) medical claims database (Taiwan)	2005-2008 4 years	In & Out	ICD-9	No	General population	ICD-9
Hsu 2017 [25]	CS & RC PB[b]	Taiwan	National Health Research Institute (NHRI) medical claims database (Taiwan)	2005-2010 6 years	In & Out	No	ICD-9	General population	ICD-9
Khaykin 2010 [30]	CS NRB	US	Nationwide Inpatient Sample (NIS) study of United States hospital discharges for adults 18 years and older	2002-2007 NA	Inpatient (nonpsychiatric hospitalizations)	ICD-9	–	Hospital controls (hospitalizations without schizophrenia)	AHRQ's clinical classification software

Kilbourne 2004 [34]	CS PB[b]	US	National Patient Care Database of the Veterans Health Administration (US)	2001 NA	In & Out	–	ICD-9	General Veterans Administration patient population	ICD-9
Krieger 2019 [24]	RC NRB	Israel	Nationwide data, derived from the Clalit Health Services (CHS) databases, the largest public managed health care organization in Israel	2017 NR	Out	ICD 9-10 (smoking)	–	Healthy smoking controls	ICD-9
Partti 2015 [18]	CS PB[b]	Finland	The Health 2000 Survey, a nationwide health examination study conducted in Finland	September 2000, June 2001	Out	DSM-IV-TR based on health survey questionnaire and medical records	Affective psychosis, including BD (DSM-IV-TR)	General population (without psychosis)	Hospital admission because of COPD or diagnosis by spirometry
Perugi 2015 [36]	CS	Italy	Units of the Department of Psychiatry at the University of Pisa	NR	In & Out	–	DSM-IV (SCID-I)	No	Diagnosis by a physician
Schoepf 2014 [31]	CS & RC	UK	General Manchester NHS Hospitals	January 1, 2000-June 30, 2012 12.5 years	Inpatient	ICD-10 admitted to a general hospiatal	No	Hospital controls	Diagnosis at discharge
Schoepf 2014 [37]	CS & RC	UK	General Manchester NHS Hospitals (UK)	January 1, 2000-June 30, 2012 12 years	Inpatient	No	ICD-10 admitted to a general hospital	Hospital controls	Diagnosis at discharge
Sokal 2004 [20]	CS	USA	Psychiatric care facilities at two centers in Maryland (US)	2000	Out	Unclear shizophrenia and schizaffective disorder	Unclear affective disorder	Historical controls from the US National Health Interview Survey and the National Health and Nutrition Examination Survey	Diagnosis of comorbidities using the NHIS and NHANES questionnaire, including chronic bronchitis and emphysema

[a]Country where the study was conducted; [b]When only appears, the coding system means that diagnosis was based on the existence of the corresponding code; [c]Although described by the authors as a nested case–control study, we think it could be considered a retrospective cohort study evaluating the relationship between an exposure (i.e. having or not having a diagnosis of schizophrenia) and several outcomes including incident cases of COPD; [d]As categorized by the authors.

CS, cross-sectional study; ICD, International Classification of Diseases; In, inpatients; IPCP, International Classification of Primary Care coding system; LOFU, length of follow-up; NA, not applicable; NR, not reported; NRB, national register-based; Out, outpatients; PB, population-based; RC, retrospective cohort study.

The association between schizophrenia and bipolar disorder with chronic obstructive pulmonary disease

The association between schizophrenia and the occurrence of COPD has been investigated in 4 longitudinal studies [21–24] and is summarized in Table 2. Using a retrospective cohort design, Brink et al. [21], adjusting for sex and calendar year, reported that the risk of COPD increased with age, with a risk ratio (RR) significantly increased for the strata of 40–49 years (1.78, 95% CI 1.39 to 2.27), 50–59 years (1.86, 95% CI 1.59 to 2.17), 60–69 years (1.94, 95% CI 1.66 to 2.27) and 70–79 years (1.75, 95% CI 1.30 to 2.36). Hsu et al. [23] and Krieger et al. [24] reported similar results, with an RR of 1.83 (95% CI 1.62 to 2.07) and an OR of 2.53 (95% CI 2.23 to 2.87). Crump et al. [22] reported that the likelihood of occurrence of COPD in patients with schizophrenia is higher in women (hazard ratio [HR] 2.06, 95% CI 1.80 to 2.34) than in men (HR 1.53, 95% CI 1.32 to 1.76).

Two studies reported a significantly increased likelihood of occurrence of COPD in patients with bipolar disorder (Table 3) [25,26]. Hsu et al. [25] reported an HR of 1.94 (95% CI 1.65 to 2.29), while Crump et al. [26] reported a similar increased likelihood of occurrence in women (HR 2.09, 95% CI 1.45 to 3.02) compared to men (HR 2.03, 95% CI 1.26 to 3.27).

The association between these two clinical entities was also investigated in 11 cross-sectional studies (Supplementary Table 1). Most studies reported an over 50% increase in the likelihood of the presence of COPD in patients with schizophrenia compared to controls [18,23,27–31]. Similarly, in patients with bipolar disorder, the increased likelihood of COPD was over twofold in all studies [18,25,32,33] but one [34].

Prevalence and incidence of chronic obstructive pulmonary disease

Ten cross-sectional studies provided data on the prevalence of COPD in patients with schizophrenia [18–20,23,27–31,35] (Table 4). The key characteristics of the patients varied largely across the studies; thus, the proportion of women ranged from 3.3% to 69.2%, the mean age ranged from 40.2 to 70.0 years and, in the 5 studies reporting the proportions of smokers, the range varied from 8.8% to 79.0%. The reported prevalence of COPD ranged from 2.6% to 52.7%. Three studies reported a prevalence over 25% [28,30,35], and these studies were conducted in the oldest patients.

Only two studies originally aimed to evaluate the prevalence of COPD in patients with schizophrenia [18,23]. Using a population-based design with a national medical claim database in Taiwan, Hsu et al. [23] reported a prevalence of primary or secondary diagnosis COPD in patients with schizophrenia of 3.8%. Another study, using a national representative sample from Finland, defining COPD as being admitted with a diagnosis of COPD or having spirometry results indicative of COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, found a prevalence of COPD of 12.2% among 67 patients with schizophrenia [18].

Seven cross-sectional studies reported data on the prevalence of COPD in patients with bipolar disorder [18,19,25,32–34,36] (Table 5). The included patients were middle-aged, with a proportion of females that ranged from 10% to 68.0%. Only two studies reported the proportion of smokers, at 9.1% and 18.0%. In these studies, the prevalence of COPD varied between 3.0% and 12.9%. Three studies were specifically devoted to evaluating the prevalence of COPD in patients with bipolar disorder and found a prevalence of 5.68% in a population-based study in Taiwan [25], 10.6% among patients from the Veterans Administration database (US) [34], and 12.4% among a sample of 49 patients with affective psychosis in the Finnish database with the diagnosis based on being admitted with a diagnosis of COPD or having spirometry results indicative of COPD GOLD criteria [18].

The incidence of COPD has been reported in only two studies performed by the same research group in Taiwan [23,25]. The annual incidence of COPD was 2.21 cases/100 person-years in patients with schizophrenia and 1.43 cases/100 person-years in the general population (rate ratio 1.83, 95% CI, 1.62 to 2.07, $p < 0.01$) [23]; the corresponding figures in patients with bipolar disorder were 2.03 cases/100 person-years and 1.03 cases/100 person-years, respectively (rate ratio 1.94, 95% CI, 1.65 to 2.29, $p < 0.001$). [25].

Factors associated with the presence or occurrence of chronic obstructive pulmonary disease

Using multivariate models, three studies evaluated factors associated with the presence (cross-sectional analysis) or occurrence (longitudinal analysis) of COPD in patients with schizophrenia [23] or bipolar disorder [25,34]; the results of these studies are summarized in Table 6.

In patients with schizophrenia, a population-based study conducted in Taiwan showed in the longitudinal analysis that increasing age and being male were associated with the occurrence of COPD; there was no association with COPD for the remaining factors included in the model, namely, insurance amount, region, urbanicity and antipsychotic use (first or second generation vs. no use) [23]. Regarding bipolar disorder, the same authors with the same design found in a cross-sectional analysis that increasing age, being male, use of second-generation antidepressants and the presence of hypertension were associated with the presence of COPD [25]. However, in the longitudinal analysis of that study, only increasing age was associated with the occurrence of COPD; the remaining factors (i.e. sex, insurance amount, region and urbanicity, antipsychotic use, antidepressant use, mood stabilizer use, diabetes, hypertension, and hyperlipidemia) were not [25]. Another cross-sectional study conducted in the US using the Veterans Administration database showed that increasing age, no copayment and being

Table 2. Longitudinal studies evaluating the association between schizophrenia and the occurrence of COPD.

					Smoking status		Association		
Author/Year	Study group	Sample size	Age (year)	Sex (% female)	Measure	%	Effect measure Covariates	Point estimate (95% CI)	p value
Brink 2018 [21]	Schizophrenia	4.544	34,3	33,6	NR	NR	RR Age, sex, calendar year	30-39 years: 1.43 40-49 years: 1.06 50-59 years: 1.53* 60-69 years: 1.70* 70-79 years: 1.98*	*Statistically significant
	Control	22.597	33,9	32,1	NR	NR			
Crump 2013 [22]	Schizophrenia	8277	NR	42.2	Reported smoking prevalences	70	HR A. Age and other sociodemographics B. Plus substance use disorder	Women/Men A. 2.58 (2.26-2.94)/ 2.12 (1.84-2,45) B. 2.06 (1.80-2.34)/ 1.53 (1.32-1.76)	NR
	Control	6097834	NR	51.3	Reported smoking prevalences	25			
Hsu 2013 [23]	Schizophrenia	4417	NR	NR	NR	NR	RR Age, sex, insurance amount	1.83 (1.62-2.07)	<0.001
	Control	762010	NR	NR	NR	NR			
Krieger 2019 [24]	Schizophrenia	10502	49.66	NR	Unclear (# cigarettes)	14.0	OR (for having a diagnosis of COPD after first documented smoking) Age, sex, socioeconomic status, marital status, obesity, diabetes, hypertension, CHF, cardiomyopathy, hyperlipidemia, alcohol abuse, drug abuse	2.53 (2.23-2.87)	<0.001
	Control (smokers)	10502	49.66	NR	Unclear (# cigarettes)	14.3			

CI, confidence interval; HR, hazard ratio; NR, not reported; OR, odds ratio; RR, relative risk/rate ratio.
[a]Crude estimation from the proportion of patients with COPD provided in the article.

Table 3. Longitudinal studies evaluating the association between bipolar disorder and the occurrence of COPD.

					Smoking status		Association		
Author/Year	Study group	Sample size	Age (year)	Sex (% female)	Measure	%	Effect measure Covariates	Point estimate (95% CI)	p value
Crump 2013 [26]	Bipolar	6618	No	59.2	Reported smoking prevalences	70	HR A. Age and other sociodemographics B. Plus substance use disorders	Women/Men A. 2,86 (1.99-4.12)/ 2.57 (1.60-4.14) B. 2.09 (1.45-3.02)/ 2.03 (1.26-3.27)	No
	Control	6587036	No	51.1	Reported smoking prevalences	25			
Hsu 2017 [25]	Bipolar	1848	No	No	No	No	RR Age, sex, insurance status, region, urbanicity	1.94 (1.65-2.29)	<0.001
	Control	764579	No	No	No	No	No	No	No

CI, confidence interval; HR, hazard ratio; RR, relative risk/rate ratio.

Table 4. Prevalence of chronic obstructive pulmonary disease in patients with schizophrenia in cross-sectional studies.

Author/Year	Study group	Sample size	Age, years (mean)	Sex (% female)	Smoking status		Prevalence (%)
					Measure	%	
Bendayan 2022 [19]	Schizophrenia spectrum disorders	13019	NR	41.6	NR	NR	2.6
Carney 2006 [27]	Schizophrenia	1.074	40,2	53	Nicotine abuse/ dependence conditions	8,8	10.8
Copeland 2007 [28]	Schizophrenia	943	69.7	3.3	Nicotine dependence (including prescription)	9.7	45.7
Hendrie 2014[a] [35]	Schizophrenia	757	69.96	69.22	Ever smoked	56.7	52.71
Hetlevik 2015 [29]	Schizophrenia	10112	43	38.1	NR	NR	6.7
Hsu 2013 [23]	Schizophrenia	4417	NR	NR	NR	NR	3.83
Khaykin 2010 [30]	Schizophrenia	269387	56.2	51.9	NR	NR	26.6
Partti 2015 [18]	Schizophrenia	67	53.4	56.7	Smoking >1 pack per day	30.8	12.2
Schoepf 2014 [31]	Schizophrenia	1418	49.8	39.4	NR	NR	8.1
Sokal 2004 [20]	Schizophrenia	92	42.4	37	Ever smoked	79.0	Chronic bronchitis: 15.2 Emphysema: 9.8

NR, not reported.
[a]The design of this study is unclear. However, it seems that it provided cross-sectional data for comorbidities and longitudinal results for mortality; thus, when describing characteristics of patients and presenting the frequency of comorbidities, the authors used the term "prevalence".

Table 5. Prevalence of chronic obstructive pulmonary disease in patients with bipolar/affective psychosis in cross-sectional studies.

Author/Year	Study group	Sample size	Age (year)	Sex (% female)	Smoking status		Prevalence (%)
					Measure	%	
Bendayan 2022 [19]	Bipolar disorder	4481	NR	60.3	NR	NR	3.0
Carney 2006 [32]	Bipolar disorder	3557	39.3	60.8	Nicotine abuse/ dependence conditions	9.1	12.9
Hsu 2017 [25]	Bipolar disorder	1848	NR	NR	NR	NR	5.68
Kilbourne 2004 [34]	Bipolar disorder	4310	53	10	NR	NR	10.6
Partti 2015 [18]	Affective psychosis[a]	49	53.9	46.9	Smoking >1 pack per day	18.0	12.4
Perugi 2015 [36]	Bipolar disorder	347	47.7	62.8	NR	NR	5.5
Schoepf 2014 [37]	Bipolar disorder	621	47.3	58.9	NR	NR	7.6

NR, not reported.
[a]It included major depressive disorder with psychotic features and bipolar I disorder.

unmarried were associated with the presence of COPD; sex was not [34].

None of the reviewed studies provided specific data on the role of smoking in the risk of having or developing COPD, and none provided data on cumulative tobacco consumption.

Chronic obstructive pulmonary disease and mortality

Four studies evaluated to some extent the association between COPD and mortality, two studies each in patients with schizophrenia [22,31] and in patients with bipolar disorders [26,37].

Using a population-based design with a Swedish national cohort, Crump et al. [22] found that after controlling for age, marital status and educational level, patients with schizophrenia compared to the overall population showed a significantly increased likelihood of dying from COPD both in women (HR 3.31, 95% CI 2.23 to 4.91) and in men (HR 6.28, 95% CI 4.66 to 8.46); this association was somewhat attenuated after controlling for the presence of a diagnosis of substance use disorder but remained strong [22]. Schoepf et al. [31], among 1418 patients with schizophrenia admitted to three general hospitals in the UK, reported that COPD was among the risk factors associated with hospital mortality (OR 2.8, 95% CI 1.9 to 4.2), although the association was not stronger than in a matched cohort of hospital controls (OR 5.7, 95% CI 4.7 to 7.0).

Using the same population-based design and analyses with the Swedish national cohort mentioned above, Crump et al. [26] showed that compared to the overall population, patients with bipolar disorder had a higher likelihood of dying from COPD both in women (HR 2.86, 95% CI 1.99

Table 6. Factors associated with the presence or occurrence of COPD in patients with schizophrenia or bipolar disorder.

Author/Year	Study design	Exposure	Matching	Multivariate analysis and covariates	Results
Hsu 2013 [23]	Population-based CS & RC	Schizophrenia vs. General population	Age, sex, insurance amount	Cox regression: age, sex, insurance amount, region, urbanicity, antipsychotic use	*Longitudinal analysis*: HR Age (18–29): 30–39: 1.21 (0.78–1.89); 40–49: 1.54 (1.01–2.36); 50–59: 2.65 (1.72–4.07); 60–69: 2.85 (1.67–4.86); 70 or over: 3.61 (1.97–6.62) Sex (Female): Male: 1.37 (1.07–1.76) The remaining factors were not significantly associated
Hsu 2017 [25]	Population-based CS & RC	Bipolar disorder vs. General population	Age, sex, insurance amount, region and urbanicity	Logistic regression & Cox regression analyses: age, sex, insurance amount, region and urbanicity, antipsychotic use, antidepressant use, mood stabilizer use, diabetes, hypertension, and hyperlipidemia	*Cross-sectional analysis*: OR Age (18–29): 30–39: 1.73 (0.69–4.35); 40–49: 2.55 (1.09–5.98); 50–59: 2.78 (1.14–6.75); 60–69: 2.89 (1.13–7.39); 70 or over: 7.16 (2.90–17.67) Sex (female): Male: 1.68 (1.10–2.58). Antidepressant use (none): first generation: 0.28 (0.04–2.18); second generation 1.92 (1.23–2.99) Hypertension (No): 2.11 (1.30–3.43) The remaining factors were not significantly associated with the presence of COPD *Longitudinal analysis*: HR Age (18–29): 30–39: 2.12 (1.10–4.11); 40–49: 3.12 (1.66–5.84); 50–59: 3.51 (1.81–6.82); 60–69: 3.00 (1.39–6.51); 70 or over: 9.39 (4.32–20.40). The remaining factors were not significantly associated with the occurrence of COPD
Kilbourne 2004 [34]	CS	Bipolar disorder vs. General population	No	Logistic regression (race, age, sex, copayment status and marital status)	African–American: 0.58 (0.39–0.84) Age 60 or over: OR 3.04 (2.47–3.74) Female: 1.03 (0.73–1.46) No copayment: 1.75 (1.14–2.67) Not married: 1.24 (1.00–1.54)[a]

CS, cross-sectional study; RC, retrospective cohort study.

[a] The authors stated that "Patients not requiring a copayment ("no copayment") are considered lower income, and hence, this variable is a proxy for socioeconomic status".

to 4.12) and in men (HR 2.57, 95% CI 1.60 to 4.14); similar to the study in patients with schizophrenia, this association was attenuated but remained strong after controlling for the presence of a diagnosis of substance use disorder [26]. Although the authors did not provide disaggregated data, the association between bipolar disorder and mortality from chronic diseases (ischemic heart disease, diabetes, COPD and cancer) was weaker among the patients with a prior diagnosis of those conditions (HR 1.40, 95% CI 1.26 to 1.56) than in those without a prior diagnosis (HR 2.38, 95% CI 1.95 to 2.90) [26]. Schoepf et al. [37], with the same design mentioned above, reported that in patients with bipolar disorder, after adjusting for other comorbidities identified as risk factors for hospital mortality, COPD was among the risk factors associated with hospital-based mortality (OR 4.3, 95% CI 2.1 to 8.7), but again, the strength of the association was not higher than in controls (OR 6.7, 95% CI 4.8 to 9.4).

Another study included in this review evaluated specific causes of death in older patients with schizophrenia and patients without schizophrenia and found a significantly higher proportion of patients dying from pulmonary diseases (the authors did not specify the specific diseases) among patients with schizophrenia (16.26% vs. 9.68%, $p = 0.004$) [35].

Discussion

Our results show that there is consistent evidence that schizophrenia and bipolar disorder are associated with a greater likelihood of presenting or developing COPD compared to that in the general population. However, the prevalence or incidence of the disease in these populations has been scarcely investigated in studies designed specifically for those purposes. Similarly, we have very little information on the potential determinants of COPD in these patients, including a somewhat surprising lack of information on the role of smoking in its occurrence. The limited evidence also shows that patients with schizophrenia and bipolar disorder show a higher likelihood of dying from COPD compared to the overall population.

Our review has several limitations. We restricted our literature search to the terms strictly related with COPD, namely, 'obstructive lung disease', 'chronic obstructive', 'chronic bronchitis' and 'chronic airway obstruction'; it is possible that we have missed some studies because of being too specific in our literature search. In addition, our systematic review was not registered at PROSPERO. In our view, the major strengths of our study are that we provide an updated review on topic and, compared to previous systematic reviews on this issue, we have broadened the objectives of the review to include information on potential determinants of COPD and the role of COPD on mortality in this population.

The prevalence of COPD varies largely across studies. However, it should be noted that most of the studies were focused on evaluating the frequency of comorbidities and were based on administrative databases where the diagnosis was based on a recorded code for COPD. Importantly, although most of the studies were labeled population-based studies or were conducted using national registers, the study samples show important variations in age, sex distribution

and, when reported, proportion of smokers; this variability, especially in mean age, could explain the variations in the prevalence rates. Consistent with this variability, Suetani et al. [16], in a systematic review of the literature, reported a pooled prevalence of COPD in patients with schizophrenia of 7.7% (95% CI 4.0 to 14.4), with a large heterogeneity (i.e. I^2 99.9%), which in our view makes that figure of limited value; moreover, when adjusted for publication bias, the prevalence of COPD increased up to 19.9% (95% CI: 9.6 to 36.7) [16]. Only four studies conducted in Taiwan, Finland and the US specifically aimed to study the prevalence of COPD in patients with schizophrenia [18,23] and/or bipolar disorder/affective psychosis [18,25,34]. The results of these studies largely differ. In the studies conducted in Taiwan, the diagnosis of COPD was based on the code registered in the national administrative database and reported prevalence of 3.8% in patients with schizophrenia compared to 2.88 in the general population [23] and 5.8% in patients with bipolar disorder compared to 2.68 in the general population [25]. In the Finnish studies, diagnosis was based on being admitted to the hospital with a diagnosis of COPD or having spirometry results compatible with the GOLD criteria for COPD [18]. The authors of this latter study, the only one that used spirometry for evaluating lung function among those included in our review, reported a prevalence of approximately 12% both in patients with schizophrenia and patients with affective psychosis; however, compared to the general population, the likelihood of presenting COPD in patients with affective psychosis was not significantly increased (12.4% vs. 4.3%, OR 2.70 [95% CI 0.83 to 8.80], $p = 0.099$) [18], probably because of the small sample size of the affective psychosis group. Kilbourne et al. [34], using the Veterans Administration database (US) and having the general Veterans Administration patient population as a control, found a prevalence of COPD based on the diagnosis code of 10.6% among patients with bipolar disorder and 9.4% among the control group ($p = 0.005$). The differences between the study conducted in Taiwan and the one conducted in the US could rely on the differences in the characteristics of the population; although the study in Taiwan did not report the characteristics of the patients, based on the data of the exposure provided, they were more frequently women and younger than those of the study in the US. It should be noted that the generalizability of data from the Veteran Administration database has been questioned since the population is predominantly male, older and with a higher prevalence of chronic health conditions and risk behaviors than the US general population [38,39]. The incidence of COPD in these populations has been scarcely investigated, and it has been reported to be significantly increased by 80–90% compared to the general population.

Among the risk factors evaluated in three studies [23,25,34], only advanced age, a well-known risk factor for COPD, was consistently associated with the presence or occurrence of COPD in patients with schizophrenia or bipolar disorder. Being male, another risk factor for COPD, using the same data source, was associated with the occurrence of COPD in patients with schizophrenia but not in patients with bipolar disorder. It is important to stress that the studies evaluating risk factors associated with the occurrence of COPD did not include factors that are associated with the risk of developing COPD, such as level of education, body mass index, family or personal history of respiratory disease, occupational exposure to dust or smoke and, especially, cigarette smoking [1,40]. Partti et al. [18] found a significantly greater likelihood of presenting an obstructive ventilatory pattern among patients with schizophrenia than in the general population adjusting for age and sex, but this association was lost in their multivariate model when adjusted for age, gender, physical activity and smoking status; in this latter analysis, only age, being male, and smoking status were significantly associated with presenting an obstruction pattern, thus suggesting that, as expected, smoking status was the major contributor to the presence of COPD in patients with schizophrenia [18]. However, these authors, in the multivariate model of lung function, found that even after controlling for all those factors and some metabolic factors, the presence of schizophrenia was associated with a significant impairment of lung function [18]. Krieger et al. [24] compared patients with schizophrenia who were smokers with "healthy" smoking controls and, after controlling for sociodemographic variables and clinical variables that included obesity and metabolic disorders, found an over 2-fold increased likelihood of receiving a diagnosis of COPD after the first documented smoking; in the survival analysis, the time to the occurrence of COPD diagnosis was significantly shorter among smokers with schizophrenia. Copeland et al. [28], in a cross-sectional study among decedents from the Veterans Administration hospital (US), showed that, even after controlling for smoking history, schizophrenia was significantly associated with an increased likelihood of presenting COPD. These results suggest that factors other than smoking status and obesity or metabolic disorders contribute to a relevant extent to the presence of COPD in these patients.

Two longitudinal studies conducted by the same research group using a Swedish national cohort showed an increased likelihood of mortality from COPD both in patients with schizophrenia [22] and those with bipolar disorder [26]. In patients with schizophrenia, among the causes of death analyzed, the largest effect size was observed for influenza and pneumonia in both sexes and for COPD in men [22]. In patients with bipolar disorder, although the largest effect sizes for mortality in both sexes were observed for suicide and unnatural causes, COPD also showed a large hazard ratio for mortality [26]. In these studies, compared to the general population, in patients with schizophrenia, life expectancy was reduced by 15 years in men and 12 years in women and in patients with bipolar disorder by 8.5 years and 9.0 years in men and women, respectively. The fact that COPD was a major contributor to this premature mortality stresses the importance of this comorbidity in patients with schizophrenia and bipolar disorder. In the Swedish study, the association between bipolar disorder and mortality from COPD (also from ischemic heart disease, diabetes or cancer) was weaker among those with a prior diagnosis of the condition. Similarly, Brink et al. [21], using a national Danish registry, found a significantly reduced likelihood of being

diagnosed with these clinical entities (instead of COPD, the authors evaluated pulmonary diseases, which included COPD and lung infections) prior to death among patients with schizophrenia. These findings suggest that early diagnosis of COPD among patients with schizophrenia and bipolar disorder could be associated with reduced mortality, highlighting the importance of early diagnosis. Interestingly, results from randomized controlled trials of integrated care programs for COPD suggest that it is possible to increase survival among these patients [41,42]. The implementation of similar programs adapted for patients with severe mental illness could reduce the burden of COPD in these patients. However, there are several barriers to their implementation. First, as has been reported in the general population [43–46], some data suggest that COPD is underdiagnosed and undertreated in patients with severe mental illness. In a sample of 113 patients with schizophrenia or bipolar disorder, using spirometry, we found that 24% of the patients had undiagnosed COPD [47]. Partti et al. [18] reported that although the prevalence of COPD and other respiratory diseases was higher among patients with schizophrenia than in the general population, the use of medications for respiratory disease did not differ between the two study groups. Second, very little attention has been given to the management of COPD in patients with severe mental illness. A recent review found 15 guidelines dealing with physical health in patients with severe mental illness, 6 of which were specifically devoted to cardiometabolic illness, and although most of them included recommendations on smoking cessation, none included specific recommendations on the management of COPD [48]. Finally, the quality of medical care in patients with severe mental illness appears to be poorer than that of the overall population [49]. In any case, an objective of the programs for the management of COPD in patients with severe mental illness should be early diagnosis and intervention, the former implying adequate screening. Brink et al. [21], in a population-based study conducted in Denmark, reported that the risk of mortality from pulmonary diseases in patients with schizophrenia was numerically increased in all age strata, including those aged 30–39 years. The increased risk was statistically significant from the stratum of 40–49 years onward, and the largest effect size was found among those who were 40–49 years of age (RR 8.13) [21].

In conclusion, available data indicate that COPD in patients with schizophrenia and bipolar disorder is per se a major public health problem that affects a high proportion of these patients and is a major contributor to their shorter life expectancy. This issue is further aggravated by the well-known disparity in health care provision for patients with severe mental illness [50]. National and international health organizations should strive to specifically address this issue by creating awareness about this health problem and developing specific programs for screening and early intervention with the aim of reducing the burden of COPD in these populations.

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Declaration of interest

The authors report no conflict of interest

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Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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