Prevalence of comorbidities in chronic obstructive pulmonary disease patients

A meta-analysis

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Abstract

Background: This study compares the prevalence rates of comorbidities between chronic obstructive pulmonary disease (COPD) and non-COPD control patients reported in literature.

Method: Literature was searched in several electronic databases. After the selection of studies by following précised eligibility criteria, meta-analyses of odds ratios (ORs) were carried out with subgroup and sensitivity analyses under random effects model.

Results: Eleven studies (47,695,183 COPD and 47,924,876 non-COPD control patients' data) were used for meta-analysis. Average age of COPD patients was 66.66 ± 8.72 years of whom $55.4 \pm 11.9\%$ were males. The prevalence of cardiovascular comorbidities [OR 1.90, 95% confidence interval (95% CI) 1.59-2.28; P < .00001], cerebrovascular comorbidities (OR 1.84, 95% CI 1.47-2.31; P < .00001), hypertension (OR 1.45, 95% CI 1.31-1.61; P < .00001), diabetes mellitus (OR 1.22, 95% CI 1.07-1.38; P = .003), neurological and psychiatric disorders (OR 1.78, 95% CI 1.48-2.14; P < .00001), gut and renal disorders (OR 1.96, 95% CI 1.43-2.68; P < .00001), musculoskeletal disorders (OR 1.51, 95% CI 1.27-1.78; P < .00001), non-COPD respiratory comorbidities (OR 2.81, 95% CI 2.52-3.14; P < .00001), and cancer (OR 1.67, 95% CI 1.25-2.23; P = .0005) were significantly higher in COPD patients than in non-COPD controls.

Conclusion: COPD is associated with significantly higher comorbidities than in other diseases that should be taken into consideration in COPD control strategies.

Abbreviations: COPD = chronic obstructive pulmonary disease, OR = odds ratio, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Keywords: chronic obstructive pulmonary disease, comorbidities, COPD, prevalence

1. Introduction

The chronic obstructive pulmonary disease (COPD) is the fourth most common cause of adult mortality and a leading cause of adult hospitalization in the United States. The global prevalence estimates of COPD suggest that approximately 10% of adults over 40 years of age are suffering from this progressively debilitating disease.^[1] In 2010 alone, global mortality due to COPD was nearly 2.9 million.^[2] It is speculated that that the impact of COPD as a health burden may be underestimated

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because up to 50% mortality in COPD patients is caused by nonrespiratory diseases and COPD may increase death risk from other comorbid conditions.^[3]

This disease is characterized by chronic coughing, expectoration, exertional dyspnea of varying degree, and progressive reduction in expiratory air output.^[4] It is a preventable and treatable disease with its unique physiological and pathophysiological characteristics that are associated with exacerbations and comorbidities.^[5] The COPD is more common in elderly, which is a stage of accruing limitations in health restoration. Tobacco use, low lung function, socioeconomic status, and occupational hazards are the chief risk factors for this disease.^[5] Cigarette smoking is the foremost causative agent of COPD; airflow limitation is observed in nearly 50% of smokers.^[6] Genetic susceptibility leading to a1-antitrypsin deficiency^[7] and childhood severe asthma^[8]</sup> are also reported as risk factors for COPD.</sup>The recurrent episodes of acute exacerbations in COPD often require hospitalization, are associated with significant mortality, and have adverse effects on patients' quality of life, besides accelerating deterioration in lung function.^[9]

COPD is not only a progressive disease but can also affect other organs, including heart, blood vessels, musculature, brain, and the functions of kidney, liver, and guts leading to one or more comorbid conditions of varying degree of severity.^[10] Comorbidities are increasingly recognized as important determinants of COPD management and prognosis. In elderly, especially, the comorbidities are associated with higher mortality, poor adherence to therapeutic interventions, and reduced quality of life.^[11] Although a myriad number of studies have documented

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the prevalence of comorbidities in COPD patients but those which utilized suitable control patients in their designs in order to evaluate difference of prevalence rates in COPD and non-COPD patients are rather less numerous. This necessitates a systematic review of these studies in order to gain updated and refined evidence regarding the differences in prevalence rates of comorbidities in COPD and non-COPD patients. The aim of the present study was to undertake a systematic literature search and perform a meta-analysis of the prevalence rates of various comorbidities in COPD patients in comparison with non-COPD controls observed in relevant studies.

2. Methods

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines^[12] are followed while performing this meta-analysis and associated systematic review. As this study is a meta-analysis of data in the literatures, the ethical approval was waived.

2.1. Literature search

Several electronic databases including Embase, Google Scholar, Ovid SP, Pubmed/Medline, and Web of Science were searched for the relevant articles. The major MeSH terms and keywords used for the search of relevant articles included COPD, comorbidity/comorbidities, cardiovascular, heart disease, stroke, myocardial infarction, thrombosis, atherosclerosis, hypertension, diabetes, obesity, thyroid disease, skin disease, cancer, malignancy, psychiatric disorders, depression, neurological disorders, psychosis, respiratory conditions, gastrointestinal diseases, etc. These terms were used in different logical combinations and phrases. The search encompassed original research papers published before April 2016. Quality of the included studies was assessed by using Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.^[13]

2.2. Inclusion and exclusion criteria

The inclusion criterion was studies reporting the prevalence of the comorbidities in COPD patients along with comparing the prevalence rates with suitable non-COPD controls. The exclusion criteria were studies providing comorbidity prevalence data in COPD patients without control data or studies utilizing COPD controls; studies involving non-COPD conditions as primarily; studies utilizing medical claim data and providing claim rates rather than actual prevalence of comorbidities; and studies providing data in forms that were unable to be utilized in the meta-analyses of odds ratios (ORs).

2.3. Data extraction, synthesis, and statistical analysis

Required data and corresponding demographics were obtained from the selected research articles and synthesized on spreadsheets for use in the meta-analyses. Meta-analyses were carried out with the Cochrane Collaboration's RevMan (Version 5.3) software under random effects model. For the meta-analyses, the prevalence data was used to calculate ORs of each study data and then overall effect sizes were generated. The overall effect of each meta-analysis was a weighted average of the inverse variance adjusted effect sizes of individual studies [ORs (ORs) along with 95% confidence interval, 95% CI]. The statistical heterogeneity between studies was tested by I^2 index. Sensitivity analyses were also performed in order to explore the sources of higher heterogeneity.

3. Results

Data were taken from 11 studies, $^{[14-24]}$ which fulfilled the eligibility criteria after literature search and screening (Fig. 1). The quality of these observational studies was considerably good keeping in view the manifesto of research (Table 1). These studies utilized data of 47,695,183 COPD and 47,924,876 non-COPD control patients. The average age (mean±standard deviation and range) of COPD patients was 66.66 ± 8.72 ($51\pm 17.3-77\pm 10.5$) years of whom $55.4\pm 11.9\%$ were males (range 40–71.4%).

The prevalence of cardiovascular comorbidities was significantly higher in the COPD patients (OR 1.90, 95% CI 1.59–2.28; P < .00001; Fig. 2). The prevalence of cerebrovascular comorbidities was also significantly higher in COPD patients than in non-COPD controls (OR 1.84, 95% CI 1.47–2.31; P < .00001; Fig. 2).

The prevalence of hypertension (OR 1.45, 95% CI 1.31–1.61; P < .00001) and diabetes mellitus (OR 1.22 [1.07, 1.38]; P= 0.003) was also significantly higher in COPD than in the non-COPD patients (Fig. 3). However, data from 2 studies revealed that lipid disorders were significantly higher in non-COPD than in the COPD patients (OR 0.82, 95% CI 0.68–0.99; P = .04; Fig. 3).

The prevalence of neurological and psychiatric disorders (OR 1.78, 95% CI 1.48–2.14; P < .00001; Figure S1, http://links.lww.com/MD/B685), gut and renal disorders (OR 1.96, 95% CI 1.43–2.68; P < .00001; Figure S2, http://links.lww.com/MD/B685), musculoskeletal disorders (OR 1.51, 95% CI 1.27–1.78; P < .00001; Figure S3, http://links.lww.com/MD/B685), non-COPD respiratory comorbidities (OR 2.81, 95% CI 2.52–3.14; P < .00001; Figure S4, http://links.lww.com/MD/B685), and cancer (OR 1.67, 95% CI 1.25–2.23; P = .0005; Figure S5, http://links.lww.com/MD/B685) was also significantly higher in COPD patients in comparison with controls.

The prevalence of other diseases, including anemia, atopic dermatitis and other skin diseases, sinusitis, alcohol abuse and head injury, was also found to be significantly higher in COPD patients than in non-COPD controls (OR 2.31, 95% CI 1.24–4.32; P=.008).

4. Discussion

The present study has found that the comorbid conditions, including cardiovascular and cerebrovascular diseases, endocrine and metabolic disorders, psychiatric and neurological disorders, gastrointestinal diseases, musculoskeletal disorders, non-COPD respiratory conditions, and cancer, were significantly higher in COPD patients than in the non-COPD control patients.

In the present meta-analysis, studied population of 47,695,183 COPD patients consisted of predominantly older aged individuals. With aging, the number of comorbid conditions in COPD patients increase. Approximately three times higher inpatient and 90-day mortality is reported in very elderly patients with a COPD exacerbation than in younger patients.^[25] In asthma patients too (1,195,109 patients), the overall prevalence of 10 selected comorbidities was found to be less than 1% in patients under

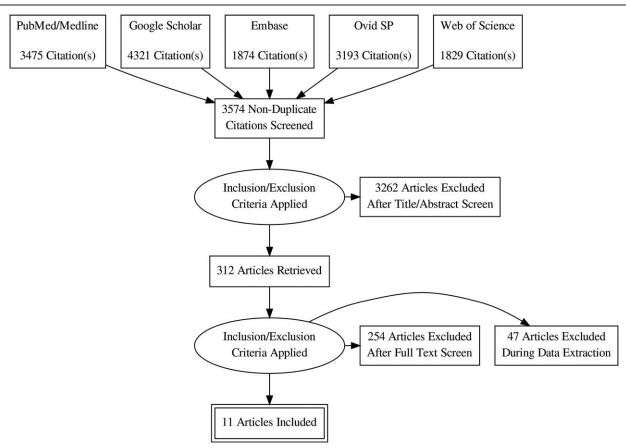


Figure 1. A flowchart of the literature search, study screening, and selection process.

Table 1

Assessment of quality of the included studies with Quality Assessment Tool for observational cohort and cross-sectional studies.

		Criteria [*]														
Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14		
Chen et al ^[14]	Y	Y	NA	Ν	Ν	NA	Y	NA	Y	Y	Y	Ν	NA	Ν		
Craig et al [15]	Y	Y	NA	Ν	Ν	NA	Y	NA	Y	Y	Y	Ν	NA	Ν		
Holguin et al ^[16]	Y	Y	NA	Y	Ν	NA	Y	NA	Y	Y	Y	Ν	NA	Ν		
Hung et al [17]	Y	Y	NA	Ν	Ν	NA	Y	NA	Y	Y	Y	Ν	NA	Ν		
Jo et al ^[18]	Y	Y	NA	Y	Ν	NA	Y	NA	Y	Y	Y	Ν	NA	Ν		
Lahousse et al ^[19]	Y	Y	NA	Ν	Ν	NA	Y	NA	Y	Y	Y	Ν	NA	Ν		
Liao et al ^[20]	Y	Y	NA	Ν	Ν	NA	Y	NA	Y	Y	Y	Ν	NA	Ν		
Liao et al ^[21]	Y	Y	NA	Ν	Ν	NA	Y	NA	Y	Y	Y	Ν	NA	Ν		
Lopez Varela et al [22]	Y	Y	NA	Y	Ν	NA	Y	NA	Y	Y	Y	Ν	NA	Ν		
Soderholm et al [23]	Y	Y	NA	Ν	Ν	NA	Y	NA	Y	Y	Y	Ν	NA	Ν		
Van Manen et al ^[24]	Y	Y	NA	Y	Ν	NA	Y	NA	Y	Y	Y	Ν	NA	Ν		

* Criteria included the following:

¹Was the research question or objective in this paper clearly stated?

²Was the study population clearly specified and defined?

³Was the participation rate of eligible persons at least 50%?

⁴Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study pre-specified and applied uniformly to all participants?

⁵Was a sample size justification, power description, or variance and effect estimates provided?

⁶For the analyses in this paper, were the exposure(s) of interest measured before the outcome(s) being measured?

⁷Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?

⁸For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)? ⁹Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?

¹⁰Was the exposure(s) assessed more than once over time?

¹¹Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?

¹²Were the outcome assessors blinded to the exposure status of participants?

13Was loss to follow-up after baseline 20% or less?

¹⁴Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

CD = cannot determine, NA = not applicable, NR = not reported.

	COPD Con			trols		Odds Ratio	Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI		
1.1.1 Cardiovascular comorb	oidities						An a state of the second second second second second		
Chen 2015 CAD	8923	58706	4573	58448	6.2%	2.11 [2.03, 2.19]			
Craig 2008 Any HD	861	21525	1037	51861	6.1%	2.04 [1.86, 2.24]	-		
Holguin 2009 CHF	4740470	47404700	1896188	47404700	6.2%	2.67 [2.66, 2.67]			
Holguin 2009 IHD	7110705	47404700	4740470	47404700	6.2%	1.59 [1.59, 1.59]			
Hung 2009 Any HD	175	492	534	3658	5.7%	3.23 [2.63, 3.97]			
Jo 2015 CAD	22	744	73	3313	4.2%	1.35 [0.83, 2.19]			
Lahousse 2015 CAD	60	1615	367	11856	5.4%	1.21 [0.91, 1.60]			
Lahousse 2015 Heart failure	52	1615	235	11856	5.2%	1.65 [1.21, 2.23]			
Lahousse 2015 MI	118	1615	581	11856	5.7%	1.53 [1.25, 1.88]	-		
Liao 2015 CAD	1627	8640	1703	17280	6.1%	2.12 [1.97, 2.28]	-		
Liao WC 2015 CAD	8278	20492	9130	40765	6.2%	2.35 [2.26, 2.44]			
Lopez Varela 2013 Any CVD	315	759	1767	4555	5.9%	1.12 [0.96, 1.31]	+-		
Lopez Varela 2013 Any HD	104	759	579	4555	5.6%	1.09 [0.87, 1.36]	+		
Soderholm 2016 Atrial fibril.	6618	103419	3205	103419	6.2%	2.14 [2.05, 2.23]	+		
Soderholm 2016 Heart failure	11272	103419	2999	103419	6.2%	4.10 [3.93, 4.27]			
Soderholm 2016 IHD	14479	103419	7963	103419	6.2%	1.95 [1.90, 2.01]			
van Manen 2001 Any HD	38	290	45	421	4.4%	1.26 [0.80, 2.00]			
van Manen 2001 Atherosci.	16	290	7	421	2.4%	3.45 [1.40, 8.50]			
Subtotal (95% CI)	10	95237199		95340502	100.0%	1.90 [1.59, 2.28]	•		
Total events	11904133		6671456				10.255.55		
Total events Heterogeneity: Tau ² = 0.13: Ch	11904133 $ni^2 = 228864$.93. df = 17	6671456 (P < 0.000	01): l ² = 100	0%				
Total events Heterogeneity: Tau² = 0.13; Ch Test for overall effect: Z = 7.09	ni² = 228864			01); I² = 100)%		10.500		
Heterogeneity: Tau ² = 0.13; Ch	hi² = 228864 (P < 0.0000			01); I² = 100	0%				
Heterogeneity: Tau ² = 0.13; Ch Test for overall effect: Z = 7.09	hi² = 228864 (P < 0.0000			01); l² = 100 58448	16.3%	2.37 [2.23, 2.53]			
Heterogeneity: Tau ² = 0.13; Ch Test for overall effect: Z = 7.09 1.1.2 Cerebrovascular como	hi² = 228864 (P < 0.0000 rbidities	01)	(P < 0.000			2.37 [2.23, 2.53] 1.32 [1.26, 1.38]			
Heterogeneity: Tau ² = 0.13; Ch Test for overall effect: Z = 7.09 1.1.2 Cerebrovascular como Chen 2015 Stroke	ni ² = 228864 (P < 0.0000 rbidities 3285	58706	(P < 0.000 1424	58448	16.3%				
Heterogeneity: Tau ² = 0.13; Ch Test for overall effect: Z = 7.09 1.1.2 Cerebrovascular como Chen 2015 Stroke Craig 2008 Stroke	ni ² = 228864 (P < 0.0000 rbidities 3285 3014	58706 21525	(P < 0.000 1424 5705	58448 51861	16.3% 16.4%	1.32 [1.26, 1.38]	•		
Heterogeneity: Tau ² = 0.13; Ch Test for overall effect: Z = 7.09 1.1.2 Cerebrovascular como Chen 2015 Stroke Craig 2008 Stroke Hung 2009 Stroke	ni ² = 228864 (P < 0.0000 rbidities 3285 3014 41	58706 21525 492	(P < 0.000 1424 5705 102	58448 51861 3658	16.3% 16.4% 11.2%	1.32 [1.26, 1.38] 3.17 [2.18, 4.61]	•		
Heterogeneity: Tau ² = 0.13; Ch Test for overall effect: Z = 7.09 1.1.2 Cerebrovascular como Chen 2015 Stroke Craig 2008 Stroke Hung 2009 Stroke Jo 2015 Stroke	hi ² = 228864 (P < 0.0000 rbidities 3285 3014 41 20	58706 21525 492 744	(P < 0.000 1424 5705 102 63	58448 51861 3658 3313	16.3% 16.4% 11.2% 8.9%	1.32 [1.26, 1.38] 3.17 [2.18, 4.61] 1.43 [0.86, 2.37] 2.49 [2.29, 2.70]	·		
Heterogeneity: Tau ² = 0.13; Ch Test for overall effect: Z = 7.09 1.1.2 Cerebrovascular como Chen 2015 Stroke Craig 2008 Stroke Hung 2009 Stroke Jo 2015 Stroke Liao 2015 Stroke Liao WC 2015 Stroke	hi ² = 228864 (P < 0.0000 rbidities 3285 3014 41 20 1414 5059	58706 21525 492 744 8640	(P < 0.000 1424 5705 102 63 1261 6677	58448 51861 3658 3313 17280 40765	16.3% 16.4% 11.2% 8.9% 16.1%	1.32 [1.26, 1.38] 3.17 [2.18, 4.61] 1.43 [0.86, 2.37] 2.49 [2.29, 2.70] 1.67 [1.61, 1.74]	. <u>.</u>		
Heterogeneity: Tau ² = 0.13; Ch Test for overall effect: Z = 7.09 1.1.2 Cerebrovascular como Chen 2015 Stroke Craig 2008 Stroke Hung 2009 Stroke Jo 2015 Stroke Liao 2015 Stroke	hi ² = 228864 (P < 0.0000 rbidities 3285 3014 41 20 1414	58706 21525 492 744 8640 20492	(P < 0.000 1424 5705 102 63 1261	58448 51861 3658 3313 17280	16.3% 16.4% 11.2% 8.9% 16.1% 16.4%	1.32 [1.26, 1.38] 3.17 [2.18, 4.61] 1.43 [0.86, 2.37] 2.49 [2.29, 2.70] 1.67 [1.61, 1.74] 1.52 [0.96, 2.39]	·		
Heterogeneity: Tau ² = 0.13; Cf Test for overall effect: Z = 7.09 1.1.2 Cerebrovascular como Chen 2015 Stroke Craig 2008 Stroke Hung 2009 Stroke Jo 2015 Stroke Liao 2015 Stroke Liao WC 2015 Stroke Lopez Varela 2013 CVA van Manen 2001 Stroke	hi ² = 228864 (P < 0.0000 rbidities 3285 3014 41 20 1414 5059 24	58706 21525 492 744 8640 20492 759	(P < 0.000 1424 5705 102 63 1261 6677 96	58448 51861 3658 3313 17280 40765 4555	16.3% 16.4% 11.2% 8.9% 16.1% 16.4% 9.8%	1.32 [1.26, 1.38] 3.17 [2.18, 4.61] 1.43 [0.86, 2.37] 2.49 [2.29, 2.70] 1.67 [1.61, 1.74]	· · · · · · · · · · · · · · · · · · ·		
Heterogeneity: Tau ² = 0.13; Cf Test for overall effect: Z = 7.09 1.1.2 Cerebrovascular como Chen 2015 Stroke Craig 2008 Stroke Hung 2009 Stroke Jo 2015 Stroke Liao 2015 Stroke Liao WC 2015 Stroke Lopez Varela 2013 CVA	hi ² = 228864 (P < 0.0000 rbidities 3285 3014 41 20 1414 5059 24	58706 21525 492 744 8640 20492 759 290	(P < 0.000 1424 5705 102 63 1261 6677 96	58448 51861 3658 3313 17280 40765 4555 421	16.3% 16.4% 11.2% 8.9% 16.1% 16.4% 9.8% 4.9%	1.32 [1.26, 1.38] 3.17 [2.18, 4.61] 1.43 [0.86, 2.37] 2.49 [2.29, 2.70] 1.67 [1.61, 1.74] 1.52 [0.96, 2.39] 0.87 [0.37, 2.01]			
Heterogeneity: Tau ² = 0.13; Cf Test for overall effect: Z = 7.09 1.1.2 Cerebrovascular como Chen 2015 Stroke Craig 2008 Stroke Hung 2009 Stroke Jo 2015 Stroke Liao 2015 Stroke Liao 2015 Stroke Lopez Varela 2013 CVA van Manen 2001 Stroke Subtotal (95% Cl) Total events	hi ² = 228864 (P < 0.0000 rbidities 3285 3014 41 20 1414 5059 24 9 12866	58706 21525 492 744 8640 20492 759 290 111648	(P < 0.000 1424 5705 102 63 1261 667 96 15 15343	58448 51861 3658 3313 17280 40765 4555 421 180301	16.3% 16.4% 11.2% 8.9% 16.1% 16.4% 9.8% 4.9%	1.32 [1.26, 1.38] 3.17 [2.18, 4.61] 1.43 [0.86, 2.37] 2.49 [2.29, 2.70] 1.67 [1.61, 1.74] 1.52 [0.96, 2.39] 0.87 [0.37, 2.01]	· · · · · · · · · · · · · · · · · · ·		
Heterogeneity: Tau ² = 0.13; Cf Test for overall effect: Z = 7.09 1.1.2 Cerebrovascular como Chen 2015 Stroke Craig 2008 Stroke Hung 2009 Stroke Jo 2015 Stroke Liao 2015 Stroke Liao WC 2015 Stroke Lopez Varela 2013 CVA van Manen 2001 Stroke Subtotal (95% Cl)	hi ² = 228864 (P < 0.0000 rbidities 3285 3014 41 200 1414 5059 24 9 12866 hi ² = 316.74,	58706 21525 492 744 8640 20492 759 290 111648 df = 7 (P <	(P < 0.000 1424 5705 102 63 1261 667 96 15 15343	58448 51861 3658 3313 17280 40765 4555 421 180301	16.3% 16.4% 11.2% 8.9% 16.1% 16.4% 9.8% 4.9%	1.32 [1.26, 1.38] 3.17 [2.18, 4.61] 1.43 [0.86, 2.37] 2.49 [2.29, 2.70] 1.67 [1.61, 1.74] 1.52 [0.96, 2.39] 0.87 [0.37, 2.01]	· · · · · · · · · · · · · · · · · · ·		
Heterogeneity: Tau ² = 0.13; Cf Test for overall effect: Z = 7.09 1.1.2 Cerebrovascular como Chen 2015 Stroke Craig 2008 Stroke Hung 2009 Stroke Jo 2015 Stroke Liao 2015 Stroke Lopez Varela 2013 CVA van Manen 2001 Stroke Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.08; Cf	hi ² = 228864 (P < 0.0000 rbidities 3285 3014 41 200 1414 5059 24 9 12866 hi ² = 316.74,	58706 21525 492 744 8640 20492 759 290 111648 df = 7 (P <	(P < 0.000 1424 5705 102 63 1261 667 96 15 15343	58448 51861 3658 3313 17280 40765 4555 421 180301	16.3% 16.4% 11.2% 8.9% 16.1% 16.4% 9.8% 4.9%	1.32 [1.26, 1.38] 3.17 [2.18, 4.61] 1.43 [0.86, 2.37] 2.49 [2.29, 2.70] 1.67 [1.61, 1.74] 1.52 [0.96, 2.39] 0.87 [0.37, 2.01]			

Figure 2. Forest plot showing the significantly higher prevalence of cardiovascular and cerebrovascular comorbidities in COPD patients in comparison with non-COPD patients. CAD=coronary artery disease, CHF=congestive heart failure, CVA=cerebrovascular accident, CVD=cardiovascular disease, HD=heart disease, IHD=ischemic heart disease.

18 years of age, 3.4% in 18 to 54 years age group, and 12% in patients over 55 years of age. $^{[26]}$

A similar pattern of the prevalence of comorbidities has been found in COPD and asthma patients.^[27,28] In an analysis of 262,014 elderly COPD patients from 3 different studies, it was found that the percentage of patients with one kind of comorbidity was 36%, whereas 30% of the patients had more than one kinds of comorbidity.^[27–29] Other studies have also reported significantly higher prevalence of comorbidities in elderly in comparison with nonelderly COPD patients.^[30,31] Indeed, up to 90% COPD patients can have at least one comorbidity.^[32,33]

Potential impacts of comorbidities and their management issues such as those related to drug interactions and adverse events resulting from polypharmacy and adherence to therapy are important considerations.^[32] This may also be reflected from some studies, for example Sundh et al^[34] found that in COPD patients, comorbidities such as cardiac diseases, depression, and low body weight were independently associated with a poor quality of life. Thus, comorbidity should be considered with more emphasis in COPD control strategies and should be an important component of covariate analyses in studies with subjective health outcomes.^[27]

Because the COPD is a progressive disease with only partially reversible airflow obstruction associated with a pathological inflammatory response by the lungs to noxious environmental particles, these are associated with chronic systemic inflammation, which may contribute to significant extrapulmonary complications such as skeletal muscle dysfunction, osteoporosis, neoplasmatic disease, infections, and cardiovascular complications.^[35] Interactions between COPD and some chronic conditions are recently delineated. Some diseases may influence COPD progression and exacerbation frequency and cause higher costs of management^[36] besides higher mortality.^[37] Some diseases affect certain subgroups of COPD. Moreover, some chronic conditions can influence COPD management decisionmaking.^[5]

This study has some limitations due to high statistical heterogeneity between studies in some comparisons. However, as this study has the epidemiological nature, the impact of higher statistical heterogeneity may be dwarfed by the difference margins in incidence rates observed herein. Future studies with higher sample size could further enhance these findings. The other limitation is that the included studies only reported selected comorbidities; therefore, not all comorbid conditions are studies in this study.

	CO	PD	Controls			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
1.2.1 Hypertension							
Chen 2015	18946	58706	12735	58448	10.4%	1.71 [1.67, 1.76]	
Craig 2008	13130	21525	29042	51861	10.3%	1.23 [1.19, 1.27]	
Holguin 2009	8058799	47404700	6162611	47404700	10.5%	1.37 [1.37, 1.37]	
Hung 2009	268	492	1597	3658	7.6%	1.54 [1.28, 1.87]	-
Jo 2015	418	744	1426	3313	8.3%	1.70 [1.45, 1.99]	-
Lahousse 2015	741	1615	5344	11856	9.4%	1.03 [0.93, 1.15]	+
Liao 2015	4095	8640	6423	17280	10.2%	1.52 [1.45, 1.60]	-
Liao WC 2015	12813	20492	19105	40765	10.3%	1.89 [1.83, 1.96]	
Lopez Varela 2013	282	759	1549	4555	8.3%	1.15 [0.98, 1.35]	-
Soderholm 2016	6618	103419	3826	103419	10.3%	1.78 [1.71, 1.85]	
van Manen 2001	65	290	87	421	4.4%	1.11 [0.77, 1.59]	
Subtotal (95% CI)		47621382	5.	47700276		1.45 [1.31, 1.61]	•
Total events	8116175		6243745				
Heterogeneity: Tau ² =		= 870.35. df		0.00001): l ²	= 99%		
Test for overall effect:	and the second second second		10 (1 1		3070		
		0.00001)					
1.2.2 Diabetes							
Chen 2015	6012	58706	4241	58448	10.7%	1.46 [1.40, 1.52]	
Craig 2008	3875	21525	8298	51861	10.7%	1.15 [1.11, 1.20]	
Holguin 2009	4740470	47404700		47404700	10.8%	1.12 [1.12, 1.13]	
Hung 2009	82	492	457	3658	7.6%	1.40 [1.08, 1.81]	
Jo 2015	324	744	1489	3313	9.3%	0.94 [0.81, 1.11]	-
Lahousse 2015	154	1615	1196	11856	9.0%	0.94 [0.79, 1.12]	-
Liao 2015	2043	8640	2962	17280	10.5%	1.50 [1.40, 1.60]	-
Liao WC 2015	4585	20492	7527	40765	10.7%	1.27 [1.22, 1.33]	
Lopez Varela 2013	4303	759	450	4555	7.3%	0.84 [0.64, 1.10]	
Soderholm 2016	5584	103419	2999	103419	10.7%	1.91 [1.83, 2.00]	
van Manen 2001	13	290	2955	421	2.8%	0.63 [0.32, 1.24]	
Subtotal (95% CI)	13	47621382	29	47700276		1.22 [1.07, 1.38]	•
Total events	4763206	II OL TOUL	4296071				
Heterogeneity: Tau ² =		- 915 02 46		00001)- 12	- 00%		
Test for overall effect:		and the second second	- 10 (P < 1	0.00001); I*	- 39%		
resciol overall effect.	2 - 2.34 (P	- 0.003)					
1.2.4 Other metaboli	c/endocrine	e comorbid	ities				
Jo 2015 Hyperchol.	581	744	2654	3313	29.2%	0.89 [0.73, 1.07]	
Jo 2015 Obesity	232	744	1335	3313	31.5%	0.67 [0.57, 0.80]	
Liao 2015 Hyperlip.	950	8640	2071	17280	31.5%	0.91 [0.84, 0.98]	
Subtotal (95% CI)	900	10128	20/1	23906	39.3% 100.0%	0.82 [0.68, 0.99]	
	1760	10120	6060	20000	.00.070	0.02 [0.00, 0.03]	
Total events	1763	- 0.00 df -	6060 CD = 0.00	7). 12 - 0.00/			
Heterogeneity: Tau ² =			2(P = 0.00)	1), 1- = 80%			
Test for overall effect:	Z = 2.09 (P	= 0.04)					
							0.2 0.5 1 2 5
							Non-COPD COPD

Figure 3. Forest plot showing the significantly higher prevalence of hypertension and diabetes mellitus.

5. Conclusion

The comorbid conditions comorbid conditions including cardiovascular and cerebrovascular diseases, endocrine and metabolic disorders, psychiatric and neurological disorders, gastrointestinal diseases, musculoskeletal disorders, non-COPD respiratory conditions, and cancer were significantly higher in patients suffering from COPD than in comparison the non-COPD control patients. Management of comorbidities should be an important part of COPD control strategies that can improve overall outcomes.

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