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CLINICAL REVIEW

Current evidence on prevalence and clinical outcomes of co-morbid obstructive sleep apnea and chronic obstructive pulmonary disease: A systematic review

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SUMMARY

The objective of this systematic review is to synthesize the evidence on prevalence, polysomnographic findings and clinical outcomes of co-morbid obstructive sleep apnea (OSA) and chronic obstructive pulmonary disease (COPD) – known as the "overlap syndrome". We systematically searched PubMed on 1 December 2015 using appropriate medical subject headings (MeSH) and text words to capture prevalence studies and comparative studies of any observational design examining the clinical outcomes in patients with co-existent COPD and OSA. We reviewed 591 articles and included 27 in the final review. In total, 21 observational studies (n = 29,341 participants) provided prevalence estimates. Overlap syndrome is not common in the general and hospital population (range: 1.0–3.6%), but is highly prevalent in patients diagnosed with either obstructive sleep apnea (range: 7.6–55.7%) or COPD (range: 2.9–65.9%). Overlap syndrome patients have been shown to have greater nocturnal oxygen desaturation (NOD) (i.e., reduced mean peripheral capillary oxygen saturation (SpO_2) and increased sleep time spent with SpO_2 < 90% (T90)) and worse sleep quality than patients with only OSA. It is associated with more frequent cardiovascular morbidity, poorer quality of life (QoL), more frequent COPD exacerbation and increased medical costs. This systematic review on overlap syndrome highlights the limitations and knowledge gaps of its prevalence, etiology and underlying pathophysiologic mechanisms related to increased morbidity and mortality.

Introduction

Chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA) are common respiratory diseases. The concurrent presence of these two conditions in one individual is referred to as the "overlap syndrome" [1], a term first introduced by D.C. Flenley [2]. COPD is characterized by airflow obstruction, which is not fully reversible [3]. Obstructive sleep apnea results from obstruction of upper airway during sleep and leads to periodic apneas and hypopneas causing reduction in blood oxygen saturation. This often leads to symptoms like loud snoring, awakening due to gasping and choking and daytime sleepiness [4,5]. There is substantial variation in the reported prevalence estimates for overlap syndrome between epidemiological studies thus far. This is likely to relate to the use of differing definitions for both OSA and COPD, and different study populations. Although narrative reviews exist which have highlighted some of these limitations in the current evidence and outlined gaps in our knowledge [1,6], the evidence has not been systematically reviewed and synthesized.

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Abbreviations

AHI	apnea-hypopnea index
AASM	American academy of sleep medicine
CI	confidence interval
CRP	c-reactive protein
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
ESS	Epworth sleepiness scale
FEV1	forced expiratory volume in 1st second
FVC	forced vital capacity
GERD	gastro esophageal reflux disorder
GOLD	global initiative for chronic obstructive lung disease
HR	hazard ratio
ICD	international classification of diseases
MeSH	medical subject headings
MOOSE	meta-analysis of observational studies in epidemiology
OR	odds ratio
OSA	obstructive sleep apnea
QoL	quality of life
SaO_2	arterial oxygen saturation
SpO_2	peripheral capillary oxygen saturation
T90	total sleep time spent with $SpO_2 < 90\%$

The simultaneous occurrence of COPD and OSA can lead to more pronounced nocturnal oxygen desaturation (NOD) than when either condition occurs in isolation, which subsequently may increase the risk of multiple comorbidities [7,8]. OSA causes repetitive and transient oxygen desaturations that induce oxidative stress, autonomic dysfunction, systemic inflammation and endothelial dysfunction. These have been proposed as possible complex pathophysiological mechanisms for the development of cardiovascular disease among OSA patients [9,10]. Additionally, COPD increases the risk of cardiovascular disease by increased sympathetic nervous activity and persistent low-grade systematic inflammation [11]. However, whether these effects are additive or synergistic in overlap syndrome patients is not yet established and there is no epidemiological evidence studying the possible interaction between these two disorders on the development of cardiovascular diseases.

COPD patients with co-existent OSA have been reported to have poorer health related quality of life (QoL), in part related to sleep disruption and worse nocturnal oxygen desaturation [12]. The presence of sleep apnea has been shown to increase the rate of COPD exacerbation, hospitalization and mortality when compared with COPD-only patients [13,14]. Given that co-existing COPD and OSA patients have increased healthcare utilization, this poses a significant economic burden on the health system [15] Therefore, early identification and timely treatment is imperative for reducing morbidity and mortality in patients with overlap syndrome.

To our knowledge, no systematic review to date has collated evidence on the prevalence and clinical outcomes of overlap syndrome. The objective of this systematic review is to synthesize the evidence from observational epidemiological studies and, subsequently, recommend future research directions in this field.

Methods

We conducted this systematic review by following the meta-analysis of observational studies in epidemiology (MOOSE) guidelines [16].

Data sources and searches

We searched PubMed by developing search strategies specific to the medical subject headings (MeSH) and text words with the help of an expert librarian. Framing of the research question and corresponding keywords for the literature search are described in Box 1.

The literature search was an iterative procedure and we applied different combinations to capture the most comprehensive list of related papers. The final PubMed search detail is described in elsewhere (Appendix A).

Box 1
Framing the research question.

Structured research question.

- **Population**: adult population
- **Exposure**: co-existent COPD and obstructive sleep apnea
- **Outcomes**: cardio-vascular diseases, pulmonary hypertension, resistant hypertension, exacerbation of COPD, mortality, quality of life, hospitalization rate
- **Study design**: prevalence studies and comparative studies of any observational design examining the clinical outcomes in patients with co-existent COPD and OSA

Eligibility criteria

We included studies meeting the following criteria: i) cohort, case-control, cross-sectional studies reporting prevalence and/or clinical outcomes of overlap syndrome ii) adult participants ($\geq$18 y) iii) published in English. We excluded studies if they were: i) narrative reviews, letters, abstracts, case reports, editorials, ecological studies or conference proceedings ii) clinical intervention trials iii) involving non-human subjects iv) did not provide information on prevalence or clinical outcomes of overlap syndrome.

Study selection

Titles and abstracts of all identified studies were reviewed by two authors (MSR and CS) to decide whether they were to be included for full text review. Disagreements at this stage and all subsequent stages were resolved by discussion between the two authors (MSR and CS), or, if agreement was not possible, a decision by a third author (SD). After the initial selection, full articles were retrieved and reviewed by two authors (MSR and CS) to ensure they met the eligibility criteria.

Data collection process

From each selected study for review, we extracted necessary information by using a preset data extraction form. Data extraction was done by MSR and CS and further reviewed by SD and GH.

Data items

We extracted data on year of publication, study settings, sample size, study population, polysomnography type, apnea-hypopnea index (AHI) cut-offs, oxygen desaturation levels and flow reduction in hypopnea. We also collected information on polysomnographic findings and clinical outcomes.

Quality assessment

Quality assessment of the included manuscripts was done by two authors (MSR and CS) using the Newcastle Ottawa quality assessment scale [17].

Results

Our final PubMed search yielded 591 articles. We excluded 542 articles after preliminary screening of titles and abstracts against the eligibility criteria. After reviewing full texts of 49 articles, 27 articles were selected for inclusion (Fig. 1). All the studies were conducted on middle aged to elderly populations of participants aged from 40 to 90 y.

Prevalence of overlap syndrome

The included studies reported the prevalence of overlap syndrome in three groups i.e., samples taken from the general and hospital population, OSA patients and COPD patients. The studies that included samples from the general population and hospitals reported much lower prevalence of overlap syndrome than the studies that sampled patients with either OSA or COPD.

Among the general population-based and hospital-based samples

The five studies (total participants = 20,527) with samples drawn from either general populations [18–20] or hospital populations [21,22] showed overall a low prevalence of overlap syndrome (range 1.0%–3.6%) (Table 1). Four out of the five studies used objective measurements to define OSA (i.e., laboratory polysomnography or home-based polysomnography or actigraph) and COPD (i.e., spirometry). Stanchina and colleagues used current procedural terminology (i.e., codes to report different medical, surgical, and diagnostic procedures by physicians, health insurance companies and accreditation organizations) codes to define OSA and COPD [22]. The age of the samples ranged from 40 to 89 y.

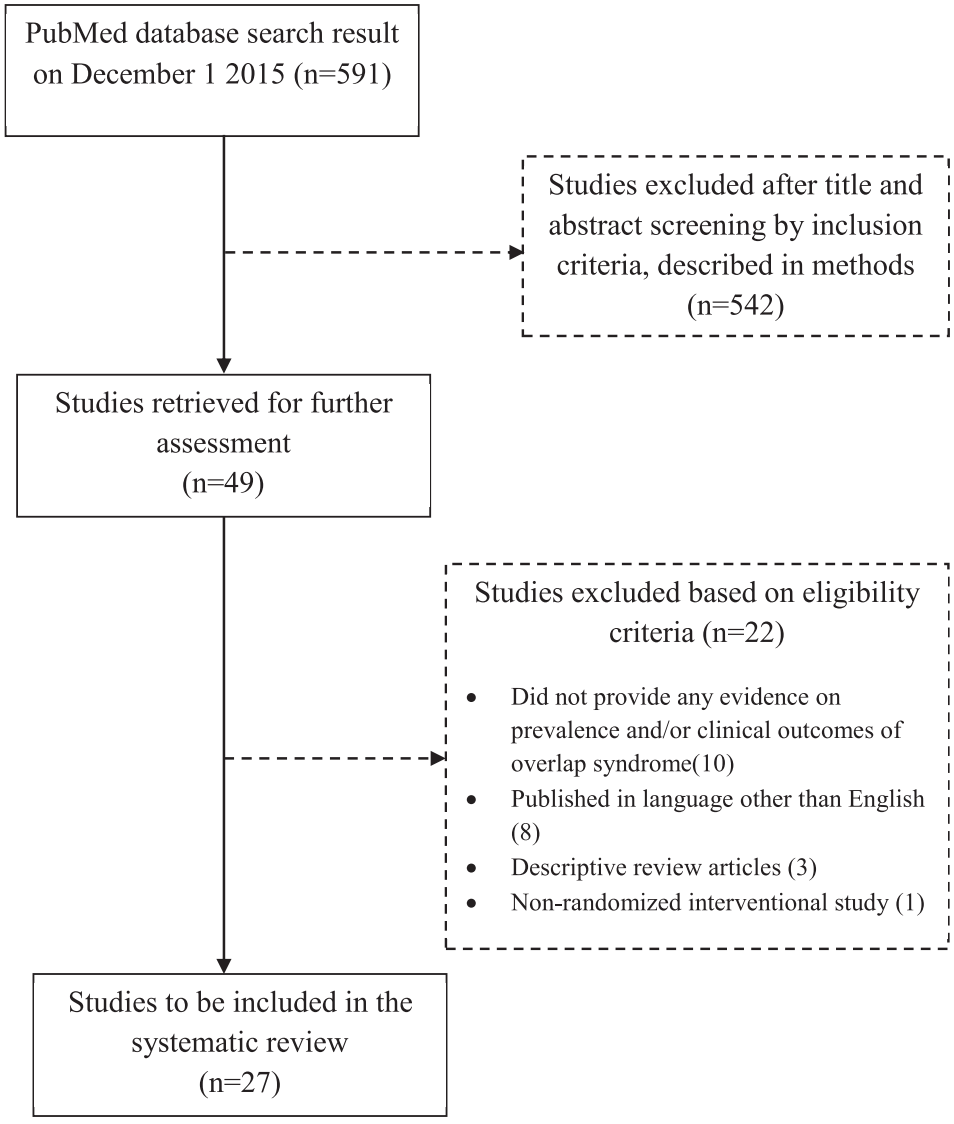

Fig. 1. Identification of studies.

Table 1
Prevalence of overlap syndrome in general and hospital population.

Authors, year, reference	Country	Sampling	Characteristics of study participants	COPD Dx/OSA Dx	AHI cut off per hour	Oxygen desaturation for hypopnea	Prevalence of COPD	Prevalence of OSA	Prevalence of overlap syndrome
General population									
Azuma et al., 2014 [20]	Japan	Sample taken from an urban wholesale company (n = 303)	Mean age 43.9 ± 8.2 and all male	Spirometry/ actigraph	AHI ≥ 5	>3%	6.3%	59.7%	3.6%
Bednarek et al., 2005 [18]	Poland	Random population sample (n = 676)	Age range was 41 −72 y and 52% male	Spirometry/lab PSG	AHI > 5	≥2%	10%	11.7%	1%
Sanders et al., 2003 [19]	USA	Random sample from sleep heart health study (n = 5954)	>40 y were included and mean age of 63 y; 47% male	Spirometry/ unattended home PSG	AHI > 15	≥4%	19.1%	18%	2.7%
Hospital population									
Ganga et al., 2013 [21]	USA	Consecutive elderly (≥65 y) in-patients (n = 2873)	Age range was 65 −89 y	Treatment/ sleep laboratory	AHI > 5	≥3%	15.5%	3%	1%
Stanchina et al., 2013 [22]	USA	Consecutive patients from outpatient department (n = 10,721)	Mean age of OSA = 61.6; COPD = 69 and overlap syndrome = 61.4 y	CPT codes			10.4%	21.3%	2.1%

Abbreviations: AHI = apnea-hypopnea index; COPD = Chronic obstructive CPT = current procedural terminology; Dx = diagnosis; lab = laboratory; n = number of total participants; OSA = obstructive sleep apnea; PSG = polysomnography.

Despite the prevalence of overlap ranging between 1.0% and 3.6% only, substantial variation was observed in the prevalence of OSA (3.0%–59.7%) and COPD (10.0%–19.1%) in these samples.

Among the OSA patients

Seven studies that sampled OSA patients (total no. of participants = 2715) reported the prevalence of overlap syndrome. The prevalence varied between 7.6% and 55.7% (Table 2). Three studies reported a prevalence greater than 40% but these had a relatively small sample sizes [23–25]. All seven studies recruited consecutive sleep laboratory patients, older participants (mean age > 50 y) and were predominantly male (76.5%–100%). COPD was either physician-diagnosed or ascertained by spirometry. Three studies reported that overlap syndrome patients were significantly older than the "OSA only" group (P < 0.01) [7,24,26].

Among the COPD patients

Ten studies that sampled COPD patients (total no. of participants = 6099) reported the prevalence of overlap syndrome. The prevalence varied between 2.9% and 65.9% (Table 3). Most

Table 2
Prevalence of overlap syndrome among OSA patient groups.

Authors, year, reference	Country	Sampling	Characteristics of study participants	COPD Dx/OSA Dx	AHI cut off per hour	Oxygen desaturation for hypopnea	Prevalence of overlap syndrome	Remarks
Chaouat et al., 1995 [7]	France	Consecutively recruited sleep lab patients (n = 265)	Mean age 54 ± 10 y and 92% male	Spirometry/lab PSG	AHI > 20		11%	Older OS group (p = 0.01)
Chokhani et al., 2005 [25]	Nepal	Consecutively recruited sleep patients excluding those with an AHI < 5 (n = 89)	Mean age (OSA) 57 y (range 6 −85); 69.6% male	COPD medication/ home PSG	AHI > 5	≥4%	43.8%	
Greenberg-Dotan et al., 2014 [34]	Israel	Consecutively recruited 1497 adult OSA patients	Mean age 55.5 ± 11.1 y; 76.5% male	ICD9 code/lab PSG	AHI > 5	≥4%	7.6%	
Lopez et al., 2009 [23]	Puerto Rico	Consecutively recruited sleep lab patients (n = 52)		Spirometry/lab PSG	AHI > 5 with symptoms or AHI > 15 without symptoms		55.7%	
O'Brien et al., 2005 [24]	Ireland	Consecutive patients with OSA with CPAP therapy (n = 120)		Physician/ home PSG	AHI > 5 with symptoms or AHI > 10 without symptoms	≥3%	41%	Older OS group (p = 0.008)
Rizzi at el., 1997 [33]	Italy	Consecutively recruited sleep lab patients (n = 168)	Mean age 56 ± 10 y and 86% male	Spirometry/lab PSG	AHI > 15	≥4%	19.5%	
Shiina et al., 2012 [26]	Japan	Consecutively recruited sleep lab patients (n = 524)	Mean age of 50.4 y and all male	Spirometry/lab PSG	AHI ≥ 5	≥3%	12%	Older OS group (p < 0.01)

Abbreviations: AHI = apnea-hypopnea Index; CI = confidence interval; COPD = chronic obstructive pulmonary disease; CPAP = continuous positive airway pressure; Dx = Diagnosis; ICD9 = International Classification of diseases 9; lab = laboratory; n = number of total participants; OS = overlap syndrome; OSA = obstructive sleep apnea; PSG = polysomnography.

Table 3
Prevalence of overlap syndrome among COPD patient groups.

Authors, year, reference	Country	Sampling	Characteristics of study participants	COPD Dx/OSA Dx	AHI cut off per hour	Oxygen desaturation for hypopnea	Prevalence of overlap syndrome
Diomidous et al., 2012 [27]	Greece	Elderly COPD patients (≥70 y) purposively selected (n = 500)	55% male	Spirometry/ESS and Berlin questionnaires			21.4%
Kumar et al., 2013 [28]	India	Consecutive patients with confirmed COPD from outpatient clinic (n = 72)		Spirometry/ESS & Berlin questionnaires			18.0%
Larsson et al., 2001 [38]	Sweden	Bronchitic patients were selected from a population study (n = 471)		Treatment/ home PSG	AHI ≥ 10 plus daytime symptoms	≥4%	5.4%
Machado et al., 2010 [29]	Brazil	Consecutively recruited hypoxemic COPD patients receiving LTOT (n = 603)		Spirometry/lab PSG	AHI > 15	≥3%	15.7%
Perimenis et al., 2007 [43]	Greece	Consecutive COPD patients from outpatient Clinic (n = 720)	All male patients	Spirometry/lab PSG	AHI > 5 with symptoms	>2%	10.28%
Shaya et al., 2009 [15]	USA	A COPD cohort from Medicaid insurance beneficiaries (n = 3455)	Mean age 52.4 y	ICD9 codes/ ICD9 codes			2.87%
Soler et al., 2015 [30]	USA	Consecutive patients aged >40 y with confirmed diagnosis of COPD (Moderate to severe cases) and >10 pack-years of smoking exposure (n = 44)	Mean age 67.2 ± 8.1 y; 54% male and 37% received LTOT	Spirometry/ home PSG	AHI ≥ 5	>3%	65.9%
Steveling et al., 2014 [50]	Switzerland	Consecutive patients with confirmed COPD from outpatient clinic (n = 177)	Mean age 64 y & range 42–90 y; 63% male	Spirometry/ home PSG	AHI > 10	>4%	19.0%
Turcani et al., 2014 [31]	Czech Republic	Consecutive patients hospitalized for COPD exacerbations (n = 35)	Median age of 66 y	Physician/lab PSG	AHI ≥ 5	≥3%	51%
Venkateswaran et al., 2014 [51]	Singapore	COPD patients aged ≥ 40 y were recruited from hospital (n = 22)	Mean age 71 ± 9 y; 86% male	Physician/lab PSG	AHI ≥ 5		63.6%

Abbreviations: AHI = apnea-hypopnea index; COPD = chronic obstructive pulmonary disease; Dx = diagnosis; ESS = Epworth sleepiness scale; Lab = laboratory; LTOT = long-term oxygen therapy; ICD9 = international classification of diseases 9; n = number of total participants; OSA = obstructive sleep apnea; PSG: polysomnography.

samples of COPD patients were selected consecutively. OSA was ascertained by polysomnography (either laboratory or home-based) in all studies except two in which the Berlin questionnaire and Epworth sleepiness scale (ESS) were used [27,28]. The prevalence of overlap syndrome was relatively high in studies with elderly COPD patients (21.4%) [27] and patients receiving long-term oxygen therapy (LTOT) (15.7%) [29]. Furthermore, two studies found a prevalence of greater than 50% of overlap syndrome in a small sample of severe COPD cases [30] and patients hospitalized for COPD exacerbations [31].

Polysomnographic findings in overlap syndrome patients

Eight studies reported the findings from polysomnography of overlap syndrome patients and compared them with OSA only patients [7,18,19,26,32–34] (Table 4). There were no significant differences in AHI across the included studies. The oxygen desaturation measured by mean peripheral capillary oxygen saturation (SpO_2) was significantly greater in overlap syndrome patients than OSA patients in most of the studies [7,18,32,33]. In overlap patients, total sleep time spent with $SpO_2 < 90\%$ (T90) was found to be significantly higher [18,32] and sleep efficiency (% of sleep time) was found to be significantly lower [26,33] when compared with the OSA patients. Sanders et al. also reported that the risk of oxygen desaturation in overlap syndrome was greater when compared with patients with either OSA or COPD alone [19].

Clinical outcomes in overlap syndrome patients

The included studies reported various types of clinical outcomes, including cardiovascular diseases, mortality, COPD exacerbation, quality of life, as well as utilization of medical resources and associated costs (Table 5). Overlap syndrome was associated with increased nocturnal oxygen desaturation leading to increased cardiovascular comorbidities, including significantly higher proportions of pulmonary hypertension [7,32]; a higher incidence of new-onset atrial fibrillation [21] and right ventricular remodeling [35]. The QoL among overlap syndrome patients was significantly poorer than that of COPD only patients. There was also increased medical utilization and subsequently increased healthcare costs among overlap syndrome patients. Treatment with continuous positive airway pressure (CPAP) significantly reduced the risk of COPD exacerbation and also mortality among overlap syndrome patients [13,22,29].

Table 4
Polysomnographic findings of overlap syndrome patients in comparison to OSA alone patients.

Authors, year, references	Sleep parameters	Overlap syndrome	OSA only	Remarks
Azuma et al., 2014 [20]	AHI (per hour)	14.2 ± 8.6	16.1 ± 11.9	
	SaO_2 (Mean)	95.9 ± 1.3	95.4 ± 1.7	
	SaO_2 nadir	80.6 ± 11.2	81.2 ± 7.3	
Bednarek et al., 2005 [18]	AHI (per hour)	19.0	25.3	NS
	SaO_2 (Mean)	89.6	92.3	P = 0.00
	T90 (%)	25.4	18.2	P = 0.04
Chaouat et al., 1995 [7]	AHI (per hour)	89 ± 37	76 ± 32	NS
	SaO_2 (Mean)	89 ± 4	91 ± 4	P < 0.05
	SaO_2 nadir	84 ± 7	86 ± 6	NS
	Time spent in apnea/total sleep time ratio (%)	22 ± 15	24 ± 18	NS
Greenberg-Dotan et al., 2014 [34]	AHI (per hour)	41 ± 25	34 ± 25	P = 0.09
	T90 (%)	28 ± 32	14 ± 25	P = 0.02
	Sleep efficiency (%)	77 ± 14	79 ± 19	P = 0.69
Hawrylkiewicz et al., 2004 [32]	AHI (per hour)	64 ± 19	62 ± 22	
	SaO_2 (Mean)	80.2 ± 8.5	87.4 ± 5.4	
	SaO_2 nadir	50.7 ± 19.7	57.4 ± 15.9	
	T90 (%)	76.9 ± 25.7	48.3 ± 25.4	
Rizzi et al., 1997 [33]	AHI (per hour)	31 ± 16	40 ± 11	P = 0.05
	SaO_2 (Mean)	89 ± 5	92 ± 5	P = 0.05
	SaO_2 nadir	75 ± 12	72 ± 16	NS
	Sleep efficiency (% sleep time)	78 ± 14	85 ± 14	P = 0.05
Sanders et al., 2003 [19]	Odds ratio of having > 5% total sleep time spent with SpO_2 < 90% in compared to normal individuals after adjusting for possible confounders	8.06 (95% CI 5.55–11.69)	8.98 (95% CI 6.86–11.74)	
Shiina et al., 2012 [26]	AHI (per hour)	30.9	33.7	P = 0.18
	SaO_2 (mean)	95.0	95.0	P = 0.63
	SaO_2 nadir	81.0	81.0	P = 0.18
	Sleep efficiency (% sleep time)	78.5	83.9	P < 0.01

Abbreviations: AHI = apnea-hypopnea index; CI = confidence interval; OSA = obstructive sleep apnea; SaO_2 = oxygen saturation level; SpO_2 = peripheral capillary oxygen saturation; T90 = percentage of total sleep time with oxygen saturation less than 90%; NS = not significant.

Discussion

From this systematic review, the major findings are: 1) overlap syndrome is not common in the general population (range 1–3.6%), but is highly prevalent when populations of either COPD or OSA are assessed (range: 2.9–65.9%); 2) overlap syndrome patients suffer from a greater degree of NOD (i.e., reduced mean SpO_2 and increased sleep time spent with $SpO_2 < 90\%$) and worse sleep quality than patients with OSA alone; 3) compared to either condition alone, overlap syndrome is associated with more frequent cardiovascular morbidity, poorer quality of life, more frequent COPD exacerbation and increased medical costs. Furthermore, CPAP treatment in overlap patients is associated with reduced mortality compared to untreated patients. This systematic review also highlighted the limited number of studies on the overlap syndrome and many knowledge gaps regarding its prevalence, etiology and the underlying pathophysiologic mechanisms that lead to increased risks of mortality and morbidity compared with either condition alone.

The observed heterogeneity of the prevalence estimates may be largely explained by the methodological diversity between studies. Definitions of COPD and OSA differed widely between studies and substantially affected the prevalence estimates. While many researchers used the global initiative of chronic obstructive lung disease (GOLD) criterion for defining COPD, forced expiratory volume in 1st second(FEV_1)/forced vital capacity (FVC) < 0.7 [36,37], some studies used modifications of this criterion that encompassed $FEV_1/FVC < 0.6$ [7], $FEV_1/FVC < 0.65$ [33] and $FEV_1/FVC < 0.75$ [23]. In other studies, COPD definitions were based on physician diagnosis [24,31], medication list [21,25,38] or international classification of diseases (ICD) codes [15,34]. Obstructive sleep apnea definitions also varied widely as different AHI cut offs (e.g., AHI > 5, 10 or 15 per hour) were used. This reflects the limitation of a categorical definition of overlap syndrome, as it is unclear whether patients with severe COPD and mild OSA should be considered differently to those with mild COPD and severe OSA [8].

Moreover, as the hypopnea scoring rules recommended by the American academy of sleep medicine (AASM) have changed over time [39], we found studies using the ≥3% oxygen desaturation criterion to define a hypopnea reported a higher prevalence of overlap syndrome when compared with studies that used the ≥4% oxygen desaturation criterion. Specifically, studies conducted before 2007 mostly used ≥4% oxygen desaturation for defining hypopnea while studies after 2007 used ≥3% oxygen desaturation with the exception of Greenberg-Dotan et al. This is consistent with findings of Ruehland et al. demonstrating marked differences in AHI index due to change in standard hypopnea definitions and careful insights are needed to interpret results using different hypopnea definitions [40]. Studies using the Berlin questionnaire were limited by outcome misclassification given its wide reported range of sensitivity and specificity [41,42].

Additionally, many of the included studies were not conducted with the primary aim of estimating the prevalence of overlap syndrome and recruited patients in a selective manner. As a result, the samples were not representative of their underlying population. This selection bias included the recruitment of those of an older age distribution [21,27], snorers [19], patients receiving either LTOT [29] or CPAP therapy [24] (indicating more severe cases) and hospitalized patients with COPD exacerbations [31]. These studies reported a much higher prevalence of overlap syndrome than the rest of the studies. Moreover, different studies included COPD and OSA patients with different degrees of disease severity. For example, some authors included mild cases of COPD ($FEV_1 \geq 80\%$ normal) [26] while others included moderate cases (FEV_1 50–79% normal) [22,27,29] or severe cases (FEV_1 30–49% normal) [43]. However, most studies did not report these methodological limitations and did not acknowledge the lack of generalizability to other populations.

Table 5
Clinical outcomes of overlap syndrome.

Outcomes	Authors, year, references	Country	Study design	Study population	Confounders adjusted for	Main findings
Cardiovascular disease	Chaouat et al., 1995 [7]	France	Cross-sectional	Consecutively recruited sleep lab patients (n = 265)	PaO_2, $PaCO_2$, FEV1	OS patients had significantly higher pulmonary hypertension than OSA patients (42% vs. 13%; p < 0.001)
	Ganga et al., 2013 [21]	USA	Retrospective cohort with 2 y follow-up	Consecutive recruited elderly (≥65 y) from inpatients (n = 2873)	Age, male, COPD, heart failure, valvular disorders, hypertension, chronic kidney disease	Incidence of new-onset atrial fibrillation was significantly higher in OS patients than OSA patients (21.4% vs. 6.7%; P < 0.05). Odds ratio: 3.66, 95% CI: 1.056 −6.860, (P = 0.007)
	Hawrylkiewicz et al., 2004 [32]	Poland	Cross-sectional	67 OSA patients and 17 overlap syndrome patients		The occurrence of pulmonary hypertension was higher in OS patients than OSA patients (82% vs. 16%). Pulmonary hypertension did not correlate with severity of nocturnal desaturation
	Sharma et al., 2013 [35]	USA	Cross-sectional	18 COPD patients included and seven of them had overlap syndrome		RVMI was significantly higher in overlap patients than COPD only patients (19 ± 6 versus 11 ± 6; p = 0.02)
On quality of life	Mermigkiset al., 2007 [12]	Greece	Case-control	30 OS patients and 15 age-matched COPD controls		Overlap syndrome patients had significantly lower quality of life (as measured by St. George's respiratory questionnaire) than the controls
	Zohal et al., 2014 [49]	Iran	Cross-sectional	139 COPD patients were included and assessed for OS		OS patients had worse quality of life (score 60.6 ± 10.4) than COPD patients (Score 40.2 ± 11.8) P value < 0.001
On mortality	Machado et al., 2010 [29]	Brazil	Prospective cohort with 10 y follow-up	95 COPD patients receiving LTOT and concurrently diagnosed with OSA. 61 received CPAP and 34 did not	Age, smoking history, obesity, CPAP, PaO_2, $PaCO_2$, bronchodilator, FEV1, AHI, T90	5 y survival was significantly higher in CPAP-treated patients (71%) compared to the non-treated group (26%) (p < 0.0001). The hazard ratio for death in CPAP-treated versus non-treated patients was 0.19 (95% CI 0.08 −0.48).
	Marin et al., 2010 [13]	Spain	Prospective cohort with median follow-up of 9.4 y	228 patients with OS treated with CPAP, 213 patients with OS not treated with CPAP, and 210 COPD-only patients	Age, BMI, current smoker, alcohol use, Charlson index, severity of COPD, COPD exacerbation, COPD group, ESS	Patients with overlap syndrome not treated with CPAP had a higher mortality (relative risk, 1.79; 95% CI: 1.16 −2.77) versus the COPD-only group.
	Stanchina et al., 2013 [22]	USA	Prospective cohort	227 patients with overlap syndrome treated with CPAP.	CPAP, gender, FEV1, AHI, BMI, age, tobacco active use, Charlson index	Hours of CPAP use and age were independent predictors of mortality (HR 0.71 and 1.14, p < 0.001, 0.002).
COPD exacerbation	Marin et al., 2010 [13]	Spain	Prospective cohort with median follow-up of 9.4 y	228 patients with OS treated with CPAP, 213 patients with OS not treated with CPAP, and 210 COPD-only patients	Age, BMI, current smoker, alcohol use, Charlson index, severity of COPD, COPD exacerbation, COPD group, ESS	Patients with overlap syndrome not treated with CPAP were more likely to suffer a severe COPD exacerbation leading to

Table 5 (*continued*)

Outcomes	Authors, year, references	Country	Study design	Study population	Confounders adjusted for	Main findings
						hospitalization (relative risk, 1.70; 95% CI: 1.21 −2.38) versus the COPD-only group.
Medical utilization and costs	Shaya et al., 2009 [15]	USA	Prospective cohort	3455 COPD patients from which 2.87% had concomitant diagnosis of OSA	Age, gender, race, obesity, Charlson index, and number of days in cohort	OS patients had greater medical utilizations (13.4 vs. 8.2) compared to COPD ($p < 0.001$). Mean overall annual costs for OS patients were significantly higher ($8903 vs. $4748) than COPD only group. ($p = 0.035$)

Abbreviations: $ = US dollar; AHI = apnea-hypopnoea index; BMI = body mass index; CI = confidence interval; COPD = chronic obstructive pulmonary disease; CPAP = continuous positive airway pressure; ESS = Epworth sleepiness scale; FEV1 = forced expiratory volume in 1s; HR = hazard ratio; LTOT = long term oxygen therapy; OS = overlap syndrome; OSA = obstructive sleep apnea; PaO_2 = arterial oxygen tension; $PaCO_2$ = arterial carbon dioxide tension; RVMI = right ventricular mass index; T90 = percentage of total sleep time with oxygen saturation less than 90%.

Regarding the association between COPD and OSA, two studies reported that there were no statistically significant associations between COPD and OSA [18,19]. On the other hand, Greenberg-Dotan et al. conducted a case-control study where they found that the occurrence of COPD was almost double [odds ratio (OR) 2.2; 95% confidence interval (CI) 1.5−3.1] in OSA patients than in OSA-free patients recruited from the general population ($P < 0.0001$), after adjusting for possible confounding factors [34]. Another study showed that occurrence of OSA in bronchitic patients was 2.3 times higher than those without respiratory symptoms [38].

Several authors have postulated different putative pathways to explain how COPD and OSA might influence each other in a potentially bidirectional relationship. COPD is thought to contribute to obstructive sleep apnoea by several mechanisms, such as inflammatory airway swelling with increased sputum production increasing upper airways resistance and predisposing to snoring and OSA [38]. Chaouat et al. hypothesized there may be an increased risk of sleep apnoea in COPD patients due to a reduction in ventilatory drive, which is frequently observed in hypoxemic and hypercapnic COPD patients [7]. For those who have co-existent right heart failure, rostral shifts of peripheral edema when sleeping supine might potentially contribute to OSA severity [44]. On the other hand, OSA may augment the expiratory airflow resistance of COPD by vagally-mediated bronchoconstriction, and by subjecting the lower respiratory airways to a greater resistive load [1,45]. A pro-inflammatory cytokine profile and gastro-esophageal reflux disease (GERD) might also be thought of as a link between COPD and OSA. Several studies have suggested that OSA is involved in the pathogenesis of GERD [46,47], where GERD is common in COPD patients and its presence is associated with increased symptoms [48].

The simultaneous presence of OSA and COPD may have a synergistic adverse effect on pulmonary hemodynamics leading to right ventricular dysfunction. Overlap syndrome patients are reported to have greater degree of pulmonary hypertension than patients with OSA alone in several studies [7,32]. The incidence of new-onset atrial fibrillation in elderly patients is also significantly higher among the overlap syndrome group than in COPD only or OSA only group [21]. A recent small pilot study showed that overlap syndrome is associated with increased right ventricular mass and remodeling when compared with COPD alone [35]. It is hypothesized that a greater amount of NOD or total hypoxemic load leads to adverse cardiovascular physiology and outcome. For example, Chaouat et al. found pulmonary hypertension in 42% of overlap patients vs. 13% in OSA only patients ($p < 0.001$). They did not observe any significant difference between the two groups in polysomnographic findings except for a lower mean overnight SpO_2 in the overlap syndrome group [7].

Several pathophysiological pathways have been speculated by Ganga et al. to link overlap syndrome and cardiovascular outcomes. These include - i) overlap syndrome patients have a higher degree of hypoxemia and hypercapnia induced sympathetic drive; ii) increased systemic inflammation, reflected by c-reactive protein (CRP) and other systemic inflammatory cytokines; iii) increased arterial stiffness caused by both OSA and COPD; iv) high negative intra-thoracic pressure against an occluded upper airway in OSA patients [21].

Recent studies suggested that mortality was significantly reduced in those with overlap syndrome when treated with continuous positive airway pressure (CPAP) [13,22,29]. Stanchina et al. found hours of CPAP use and age as independent predictors of mortality (hazard ratio (HR) 0.71 and 1.14, $p < 0.001$, 0.002) in overlap syndrome patients. The beneficial effect of CPAP treatment was mostly related to a significant reduction in cardiovascular mortality and greater time on CPAP was associated with reduced mortality [22]. Marin et al. also found a beneficial effect of CPAP in reducing COPD exacerbations in overlap syndrome patients [13]. While the true effect of CPAP on overlap syndrome patients has not been yet established through randomized controlled trials, some researchers support the use of CPAP with supplemental oxygen (when needed) as the standard treatment for overlap syndrome [8].

Studies by Mermigkis et al. and Zohal et al. showed that, in addition to increased mortality & morbidity, overlap patients had QoL, as measured by the St. George's respiratory questionnaire [12,49]. This may relate in part to the dual pathologies that include progressive respiratory impairment and functional limitation from COPD and the sleep disturbance from OSA. In Mermigkis' study, even though two-thirds of the COPD patients with habitual snoring had AHI >5/h, most of them did not report excessive daytime sleepiness [12]. These comorbidities may lead to increased healthcare utilization and, subsequently, healthcare costs as highlighted by Shaya et al. [15].

There are two main limitations of this systematic review. Firstly, we only included studies published in English during full-text review which introduced language bias in the paper selection

process. In addition, PubMed was the only database used for literature search.

Conclusion

This systematic review documents that even though COPD and OSA are individually quite common in the general population, their co-existence is not highly prevalent at a population level. However, overlap syndrome is much more common when considering populations diagnosed with either OSA or COPD. Unfortunately, current evidence is not sufficient to delineate the true association between these two diseases due to variations in study population, definition, and methodology. The overlap syndrome is also found to be associated with a variety of adverse clinical outcomes, especially cardiovascular diseases, poorer quality of life and COPD exacerbations, but it is not clear whether there is a modifiable interaction between COPD and OSA in relation to these long-term outcomes. This review highlights the necessity for future large-scale prevalence studies with representative sample selections and standard case definitions.

Practice points

1) There is accumulating evidence that overlap syndrome is highly prevalent in patients diagnosed with either OSA or COPD; however overlap syndrome is much less common in the general population.
2) Overlap syndrome patients suffer from a greater amount of nocturnal hypoxemia than patients with OSA alone, indicating more severe sleep disordered breathing.
3) The simultaneous presence of OSA and COPD may have a synergistic adverse effect on pulmonary hemodynamics leading to right ventricular dysfunction and more frequent cardiovascular morbidity i.e., pulmonary hypertension, atrial fibrillation, right ventricular remodeling.
4) Compared to either condition alone, overlap syndrome is associated with more severe disease and adverse outcomes i.e., decreased survival, poorer quality of life, more frequent COPD exacerbation and increased medical costs.
5) CPAP treatment in overlap syndrome patients is associated with reduced mortality compared to untreated patients in observational studies.

Research agenda

1. This review highlights the necessity for future large-scale prevalence studies with representative sample selections and standard case definitions.
2. Careful consideration of the severity of both OSA and COPD is required when determining the significance of overlap syndrome as a clinically relevant entity.
3. There is a need to determine whether there is a modifiable interaction between COPD and OSA in relation to long-term adverse outcomes.
4. This systematic review warrants large scale prospective and randomized controlled intervention studies to determine the natural history, clinical consequences and prognosis of overlap syndrome.

Conflicts of interest

The authors do not have any conflicts of interest to disclose.

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Appendix A

The final PubMed search detail is shown below:

((“pulmonary disease, chronic obstructive”[MeSH Terms] OR (“pulmonary”[All Fields] AND “disease”[All Fields] AND “chronic”[All Fields] AND “obstructive”[All Fields]) OR “chronic obstructive pulmonary disease”[All Fields] OR “COPD”[All Fields])

AND.

(((((((((“heart failure”[MeSH Terms] OR (“heart”[All Fields] AND “failure”[All Fields]) OR “heart failure”[All Fields]) OR (exacerbation [All Fields] AND (“pulmonary disease, chronic obstructive”[MeSH Terms] OR (“pulmonary”[All Fields] AND “disease”[All Fields] AND “chronic”[All Fields] AND “obstructive”[All Fields]) OR “chronic obstructive pulmonary disease”[All Fields] OR “COPD”[All Fields]))) OR (“quality of life”[MeSH Terms] OR (“quality”[All Fields] AND “life”[All Fields]) OR “quality of life”[All Fields])) OR ((“hospitalisation”[All Fields] OR “hospitalization”[MeSH Terms] OR “hospitalization”[All Fields]) AND rate[All Fields])) OR (resistant[All Fields] AND (“hypertension”[MeSH Terms] OR “hypertension”[All Fields]))) OR (“hypertension, pulmonary”[MeSH Terms] OR (“hypertension”[All Fields] AND “pulmonary”[All Fields]) OR “pulmonary hypertension”[All Fields] OR (“pulmonary”[All Fields] AND “hypertension”[All Fields]))) OR (“cardiovascular diseases”[MeSH Terms] OR (“cardiovascular”[All Fields] AND “diseases”[All Fields]) OR “cardiovascular diseases”[All Fields] OR (“cardiovascular”[All Fields] AND “disease”[All Fields]) OR “cardiovascular disease”[All Fields])) OR (clinical consequence[All Fields] OR clinical consequences[All Fields])) OR (“epidemiology”[Subheading] OR “epidemiology”[All Fields] OR “prevalence”[All Fields] OR “prevalence”[MeSH Terms])))

AND.

((((((apnea[All Fields] OR apnea'[All Fields] OR apnea's[All Fields] OR apnea6[All Fields] OR apneae[All Fields] OR apneaex[All Fields] OR apneagragh[All Fields] OR apneagraph[All Fields] OR apneagraphy[All Fields] OR apneahypopnea[All Fields] OR apneaic[All Fields] OR apneal[All Fields] OR apnealhypopnea[All Fields] OR apnealike[All Fields] OR apnealink[All Fields] OR apnealink's[All Fields] OR apneama[All Fields] OR apneas[All Fields] OR apneas'[All Fields] OR apneash[All Fields]) AND together[All Fields] AND (“pulmonary disease, chronic obstructive”[MeSH Terms] OR (“pulmonary”[All Fields] AND “disease”[All Fields] AND “chronic”[All Fields] AND “obstructive”[All Fields]) OR “chronic obstructive pulmonary disease”[All Fields] OR “COPD”[All Fields])) OR ((apnea[All Fields] OR apnea'[All Fields] OR apnea's[All Fields] OR apnea6[All Fields] OR apneae[All Fields] OR apneaex[All Fields] OR apneagragh [All Fields] OR apneagraph[All Fields] OR apneagraphy[All Fields] OR apneahypopnea[All Fields] OR apneaic[All Fields] OR apneal[All Fields] OR apnealhypopnea[All Fields] OR apnealike[All Fields] OR apnealink[All Fields] OR apnealink's[All Fields] OR apneama[All Fields] OR apneas[All Fields] OR apneas'[All Fields] OR apneash[All Fields]) AND (coexisten[All Fields] OR coexistence[All Fields] OR coexistence'[All Fields] OR coexistenceand[All Fields] OR coexistences[All Fields] OR coexistencia[All Fields] OR coexistencial [All Fields] OR coexistencies[All Fields] OR coexistency[All Fields] OR coexistend[All Fields] OR coexistene[All Fields] OR coexistense[All

Fields] OR coexistensive[All Fields] OR coexistent[All Fields] OR coexistenta[All Fields] OR coexistente[All Fields] OR coexistentei[All Fields] OR coexistentence[All Fields] OR coexistentes[All Fields] OR coexistential[All Fields] OR coexistently[All Fields] OR coexistents [All Fields]) AND ("pulmonary disease, chronic obstructive"[MeSH Terms] OR ("pulmonary"[All Fields] AND "disease"[All Fields] AND "chronic"[All Fields] AND "obstructive"[All Fields]) OR "chronic obstructive pulmonary disease"[All Fields] OR "COPD"[All Fields])) OR (overlap[All Fields] AND ("syndrome"[MeSH Terms] OR "syndrome"[All Fields])) OR osa[All Fields]) OR ("obstructive sleep apnea"[All Fields] OR "sleep apnea, obstructive"[MeSH Terms] OR ("sleep"[All Fields] AND "apnea"[All Fields] AND "obstructive"[All Fields]) OR "obstructive sleep apnea"[All Fields] OR ("obstructive"[All Fields] AND "sleep"[All Fields] AND "apnea"[All Fields])))

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