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CLINICAL REVIEW

Cardiovascular outcomes in patients with COPD-OSA overlap syndrome: A systematic review and meta-analysis

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SUMMARY

Chronic obstructive pulmonary disease (COPD) and obstructive sleep apnoea (OSA) are prevalent respiratory conditions that are independently associated with increased cardiovascular disease (CVD). It is not clear from current evidence whether COPD-OSA overlap syndrome confers an additive risk. This systematic review and meta-analysis investigated whether CVD was more prevalent in patients with overlap syndrome compared to either condition alone. We searched four electronic databases, screened 1826 records against the inclusion criteria. After screening, 18 retrospective, observational studies involving 4613 overlap patients, 16,046 OSA patients and 1679 COPD patients met the inclusion criteria. A random-effects meta-analysis of five studies (I^2 = 61%) showed that overlap was associated with a significantly higher risk of hypertension compared to patients with COPD alone (OR = 1.68, 95%CI 1.21−2.35). Overlap was also associated with an increased risk of peripheral vascular disease compared to OSA alone (OR = 3.30 95%CI 2.66−4.10), with a subset of studies also suggesting an increased risk of ischaemic heart disease, heart failure, and cerebrovascular disease. However, it is worth noting that the findings are limited by the considerable heterogeneity of the studies, all of which were observational and retrospective in nature. This review highlights that patients with overlap syndrome have a high prevalence of CVD with some suggestion of an increased risk compared to patients with either condition alone.

Introduction

Chronic obstructive pulmonary disease (COPD) and obstructive sleep apnoea (OSA) are common respiratory conditions. The combined presence of COPD and OSA in the same individual is referred to as COPD-OSA overlap syndrome, a term first coined in 1985 [1]. There has been substantial variation in prevalence estimates for this condition previously; however, a systematic review in 2017 concluded that while overlap is not common in the general population (1−3.6%) it is highly prevalent when individual populations of either COPD (2.9−65.9%) or OSA (7.6−55.7%) are assessed for overlap [2]. Both COPD and OSA are independently associated with increased cardiovascular disease (CVD), likely secondary to a combination of intermittent hypoxia, systemic inflammation, increased oxidative stress and sympathetic nervous system activation. This complex interplay between COPD, OSA and CVD leads to increased morbidity and mortality [3−5]. It is therefore possible that patients with overlap have an increased CVD which is greater than either condition alone.

There have been two recently published systematic reviews looking at overlap and CVD. The first in 2017 mainly focused on prevalence data. There were some limitations to this review with regards to cardiovascular outcomes. They only used PubMed when developing their search strategy thus limiting their search and reported on outcomes from only four studies [2]. The second, published in 2020 concluded that overlap significantly increased the prevalence of hypertension compared to COPD or OSA [6]. However, their search ended in June 2019 and since then there have been seven publications not included in their review. Furthermore, their inclusion criteria included patients with a physician/self-reported diagnosis of COPD, rather than a diagnosis based on standard spirometric criteria as outlined by the global initiative for

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Glossary of terms

CENTRAL	Cochrane central register of controlled trials
CINAHL	cumulative index of nursing and allied health literature
GOLD	global initiative for chronic obstructive lung disease
MOOSE	meta-analysis of observational studies in epidemiology
PSG	polysomnogrpahy
OR	odds ratio
PRISMA	preferred reporting items for systematic reviews and meta-analysis

Abbreviations list

AHI	apnoea/hyponoea index
CENTRAL	Cochrane central register of controlled trials
CINAHL	cumulative index of nursing and allied health literature
COPD	chronic obstructive pulmonary disease
CVD	cardiovascular disease
FEV1	forced expiratory volume in 1 s
FVC	forced vital capacity
GOLD	global initiative for chronic obstructive lung disease
MOOSE	meta-analysis of observational studies in epidemiology
PSG	polysomnogrpahy
OR	odds ratio
OSA	obstructive sleep apnoea
PRISMA	preferred reporting items for systematic reviews and meta-analysis

chronic obstructive lung disease (GOLD) guidelines [7]. They also excluded studies with no control group and so would have missed studies reporting the CVD prevalence in an overlap population alone.

It is still therefore not known whether overlap increases the occurrence of cardiovascular disease and whether this increase is greater than with either condition alone. Considering new recently published studies we sought to determine in detail, using robust diagnostic criteria for both COPD and OSA, cardiovascular outcomes in overlap. The aim of this review was to determine the incidence and/or prevalence of cardiovascular disease in patients with overlap, and to directly compare these outcomes compared to either condition alone.

Methods

This systematic review and meta-analysis was conducted in accordance with the preferred reporting in systematic reviews and meta-analysis (PRISMA) [8] and meta-analysis of observational studies in epidemiology (MOOSE) guidelines. We prospectively registered the review to PROSPERO (registration number: CRD42020221331).

We searched four databases (medline, embase, the cumulative index to the nursing and allied literature (CINAHL) and Cochrane central register of controlled trials (CENTRAL)), from inception to November 2020. We used an extensive search strategy developed by a specialised librarian (Table S1) and included terms relating to COPD, OSA and cardiovascular outcomes including ischaemic heart disease (acute and chronic); mortality; morbidity; heart failure; atrial fibrillation; systemic hypertension, pulmonary hypertension; cerebrovascular disease and peripheral vascular disease. All studies were uploaded into EndNote to remove duplicates. The remaining studies were uploaded onto Rayyan software (available from: https://www.rayyan.ai/) for titles, abstracts and full text screening by two independent reviewers (AJS and EQ).

Inclusion and exclusion criteria

The inclusion criteria were: 1) studies reporting prevalence and/or incidence of cardiovascular disease in overlap; 2) studies that directly compared cardiovascular outcomes in overlap with COPD or OSA alone; 3) adult patients with a diagnosis of overlap where the COPD diagnosis was made with adequate exposure (>10pack year smoking history) and/or biomass and post-bronchodilator spirometry showing either a forced expiratory volume in 1 s: forced vital capacity ratio (FEV1/FVC) < 0.7 or < lower limit of normal and the OSA diagnosis made from overnight oximetry, limited or full polysomnograpghy (PSG) showing an apnoea/hypopnoea index (AHI) $\geq$ 5events/hr and/or oxygen desaturation index (ODI) $\geq$ 5events/hr. The following studies were excluded: 1) studies not in English, 2) studies using self-reported diagnosis, physician diagnosis or non-validated questionnaires to diagnose OSA or COPD, 3) narrative reviews, non-research letters, abstracts, case reports, conference proceedings, theses and books, 4) systematic reviews and meta-analysis, literature reviews and 5) studies involving non-human subjects.

Study selection

Two authors (AJS and EQ) independently screened titles and abstracts of potential studies. The reviewers were blinded in the screening process and any disagreement was addressed by discussion with a third author (SM). Full text articles were then independently read by two authors (AJS and EQ) to identify studies meeting the inclusion criteria.

Data extraction

From each selected study we extracted relevant information using a pre-set form. Data extraction was completed by two authors (AJS and EQ). We extracted data on the year and country of publication, study settings, sample size and population, study duration, apnoea-hypopnoea (AHI) cut-off, cardiovascular outcome measures and mortality data.

Quality assessment

The methodological quality of included studies was evaluated using the Newcastle–Ottawa Scale (NOS) for assessing case-controlled and cohort studies [9]. Studies can receive a maximum of nine points, with higher numbers equating to lower risk of bias. We used a modified NOS scale for assessing cross-sectional studies [10]. These studies can receive a maximum of 10 points, with higher number equating to a lower risk of bias.

Data synthesis and analysis

We performed a meta-analysis using the Cochrane collaboration's RevMan software (https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman). Odds ratio (OR) [95% CI] was used to compare cardiovascular outcomes between overlap and COPD or OSA. Interstudy heterogeneity was examined by using the I^2 test. If the data had an I^2 >50% it was considered to be of high heterogeneity, in which case a random-effects model was used. Stata® software was used to calculate pooled prevalence data. In the event of substantial clinical or methodological heterogeneity (such as different AHI cut-offs) we did not pool the effect estimates in a meta-analysis.

Results

Our initial search generated 5816 potential studies of which 3990 were immediately excluded due to duplication. After the first screening of titles and abstracts, 36 papers were potentially relevant according to our inclusion criteria and read in full. An additional 18 papers were excluded following full-text review, which resulted in 18 studies satisfying all criteria (Fig. 1, PRISMA flow diagram). The reference lists of relevant papers were also examined.

Characteristics of included studies

A summary of the included studies is presented in Table 1, which included a total of 4613 overlap patients, 16,046 OSA patients and 1679 COPD patients. The sample size of studies varied from 54 patients to 16,466 patients and the majority of patients were male across all studies (range 57–99%). All studies were retrospective and the majority cross-sectional. There was variation amongst diagnostic criteria for overlap with some studies using an AHI cut-off of ≥ 5events/hr, compared to others using a cut-off of ≥30events/hr. Using the Newcastle–Ottawa Scale the methodological quality of the studies was found to vary markedly (Table S2). The majority of studies did not justify their sample size and did not control for confounding factors. Furthermore, the studies used different AHI cut-offs resulting in heterogeneity. Additionally,

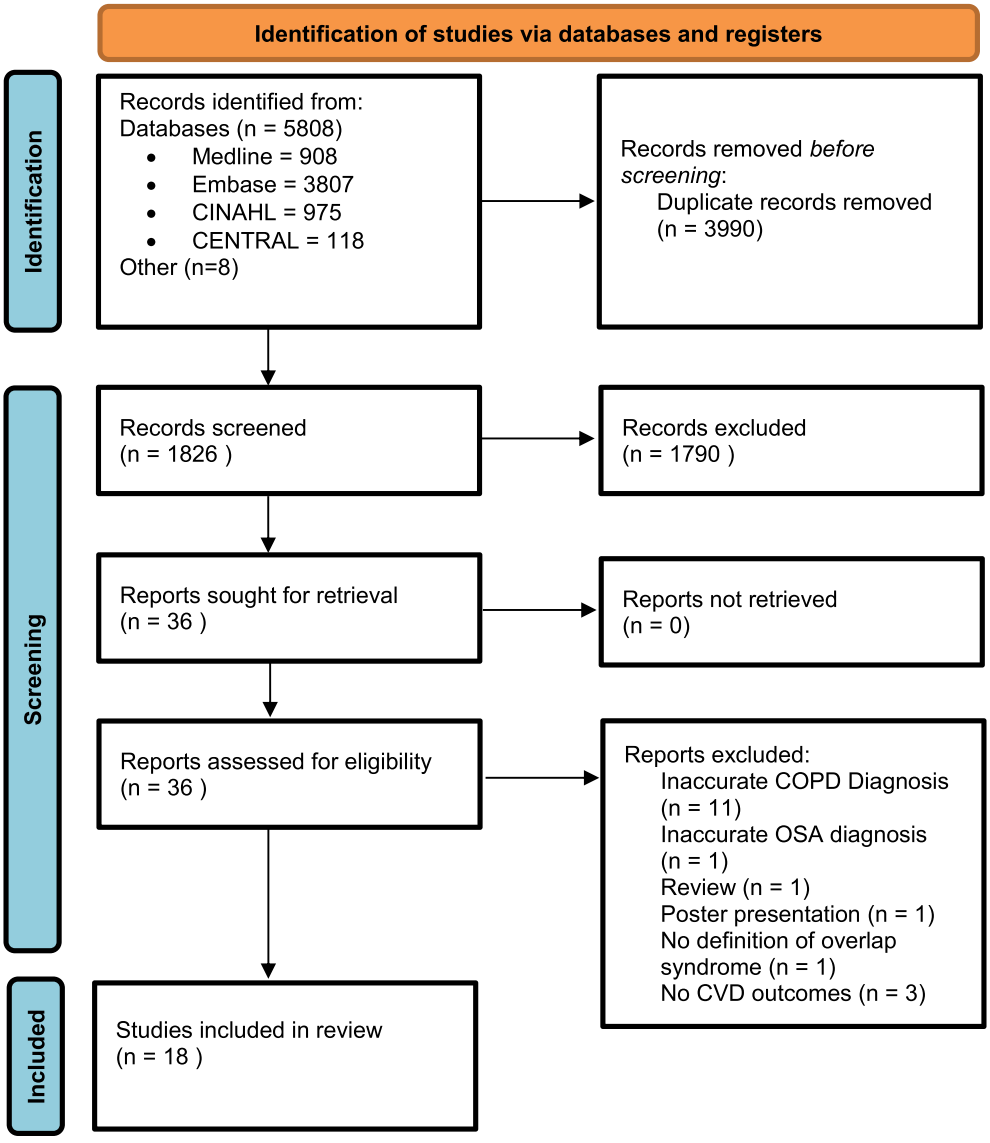

Fig. 1. PRISMA flow chart for included studies.

Table 1
Characteristics of included studies.

Author, Year, Country	Study Design	Sampling (Duration)	Diagnostic Criteria of OS	Population (n =)	Cardiovascular Outcomes	Quality[a]
Adler et al., 2020 [19] France	Cross-sectional	Sample taken from French National Sleep Apnoea Registry between 1997 and 2017 (20 years)	**COPD:** FEV1:FVC <70% (Post − Bronchodilator) **OSA:** AHI ≥15 (Night PSG or Type III cardiopulmonary sleep studies)	**Overlap:** 2098, 81% Male Age: median 64 (56–72) years **OSA:** 14,368, 70% Male Age: median 57 (48–65) years	HTN MI PVD CVA Heart failure	8/10
Akinnusi et al., 2021 [11] USA	Cohort	Patients with confirmed COPD who had a diagnostic sleep study between 2012 and 2019 (7 years)	**COPD:** FEV1:FVC <70% (Post − Bronchodilator) **OSA:** AHI ≥5 (Night PSG)	**Overlap:** 268, 99% Male Age: mean 68 ± 10 years	New-onset AF HTN Chronic heart disease CVA	7/9
Archontogeorgis et al., 2020 [16] Greece	Cross-sectional	Consecutive patients referred to sleep lab diagnosed with OS (Not specified)	**COPD:** FEV1:FVC <70% (Post − Bronchodilator) **OSA:** AHI ≥5 (Night PSG)	**Overlap:** 163, 85% Male Age: overall population mean not presented	HTN Cardiovascular disease CVA	6/10
Hu et al., 2020 [17] China	Cross-sectional	Consecutive patients with confirmed COPD from outpatients, Renmin Hospital, Wuhan between 2016 and 2018 (2 years)	**COPD:** FEV1:FVC <70% (Post − Bronchodilator) **OSA:** AHI ≥5 (Night PSG)	**Overlap:** 660, 85% Male Age: mean 66 ± 10 years **COPD:** 308, 83% Male Age: mean 65 ± 9 years	HTN Cardiovascular disease AF CVA	8/10
Lacedonia et al., 2018 [12] Italy	Cross-sectional	Consecutive patients referred to sleep lab of the University of Foggia (5 years)	**COPD:** FEV1:FVC <70% (Post − Bronchodilator) **OSA:** AHI ≥5 (Home cardio-pulmonary monitoring)	**Overlap**: 123, 80% Male Age: mean 65 ± 11 years **OSA:** 721, 73% Male Age: mean 59 ± 13 years	HTN Heart Disease	4/10
Maestri et al., 2019 [13] Italy	Cross-sectional	Consecutive patients with COPD admitted for inpatient rehab from 2010 to 2017 (7 years)	**COPD:** FEV1:FVC <70% (Post − Bronchodilator) **OSA:** AHI ≥5 + symptoms or AHI ≥15 without symptoms	**Overlap:** 172, 79% Male Age: mean 68 ± 10 years **COPD:** 299, 71% Male Age: mean 70 ± 12 years	HTN Cardiovascular disease	4/10
Marin et al., 2010 [29] Spain	Cross-sectional	Patient referred to a sleep clinic in a Spanish Hospital for suspected sleep disordered breathing (5 years)	**COPD:** FEV1:FVC <70% (Post − Bronchodilator) **OSA:** AHI ≥5 (PSG)	**Overlap:** 213, 93% Male Age: mean 58 ± 7 years **COPD:** 210, 90% Male Age: mean 57 ± 8 years	HTN Cardiovascular mortality	8/10
Papachatzakis et al., 2018 [14] Greece	Case-controlled	Outpatients with new-COPD diagnosis and OSA compared with matched OSA patients over 2014–2016 (2 years)	**COPD:** FEV1:FVC <70% (Post − Bronchodilator) **OSA:** AHI ≥5 + symptoms or AHI ≥15 without symptoms (PSG)	**Overlap:** 38, 71% Male Age: mean 67 ± 9 years **OSA:** 38, 71% Male Age: mean 67 ± 9 years	HTN Cardiovascular disease	5/9
Rizzi et al., 1997 [30] Italy	Cross-sectional	Patient referred to sleep lab diagnosed with OSA (Not specified)	**COPD:** FEV1:FVC <65% (Post − Bronchodilator) **OSA:** AHI >15 (Night PSG)	**Overlap:** 33, 91% Male Age: mean 56 ± 11 years **OSA:** 135, 85% Male Age: mean 56 ± 10 years	Pulmonary HTN	5/10
Silva et al., 2017 [31] Brazil	Cross-sectional	Patients with COPD over 40 admitted to clinical research centre in Brazil between April and Sept 2013 (6 months)	**COPD:** FEV1:FVC <70% (Post − Bronchodilator) **OSA:** AHI ≥15 (PSG)	**Overlap:** 14, 57% Male Age: Mean 70 ± 6 years **COPD:** 25, 68% Male Age: mean 70 ± 10 years	HTN Pulmonary HTN	7/10
Steveling et al., 2014 [15] Switzerland	Cross-sectional	Consecutive COPD patients from outpatient clinics (Not specified)	**COPD:** FEV1:FVC <70% (Post − Bronchodilator) **OSA:** AHI >10 (Home apnoea link device)	**Overlap:** 33, 88% Male Age: mean 66 ± 10 years **COPD:** 144, 58% Male Age: mean 63 ± 9 years	HTN Cardiovascular disease	6/10
Sun et al., 2019 [21] China	Cross-sectional	Consecutive COPD outpatients from 2016 to 2018 (2 years)	**COPD:** FEV1:FVC <70% (Post − Bronchodilator) **OSA:** AHI ≥10 (Home apnoea link device)	**Overlap:** 56, 93% Male Age: mean 70 ± 11 years **COPD:** 50, 90% Male Age: mean 69 ± 9 years	HTN Pulmonary HTN Coronary heart disease Congestive heart failure	7/10
Taranto-Montemurro et al., 2016 [32] Italy	Cross-sectional	Patients suspected of having OSA referred to outpatient department from 2013 to 2014 (1 year)	**COPD:** FEV1:FVC <70% (Post − Bronchodilator) **OSA:** AHI >30 included (Night cardiorespiratory polygraphy)	**Overlap:** 14 Age: mean 61 ± 12 years **COPD:** 16 Age: mean 70 ± 13 years **OSA:** 24 Age: mean 59 ± 9 years	HTN	6/10
Wang 2019 et al. [22] China	Cross-sectional	Patients diagnosed with COPD/OSA/OS in the respiratory department were invited to study over 1 year (1 year)	**COPD:** FEV1:FVC <70% (Post − Bronchodilator) **OSA:** AHI ≥5 (PSG)	**Overlap:** 25, 76% Male Age: 64 ± 4 years **COPD:** 25, 64% Male Age: mean 63 ± 3 years **OSA:** 25, 76% Male Age: mean 62 ± 4 years	HTN Coronary heart disease CVA	3/9
Wang et al., 2020 [18] China	Cross-sectional	Consecutive COPD (GOLD 2–4) enrolled between June 2016 –Dec 2018 (2 years)	**COPD:** FEV1:FVC <70% (Post − Bronchodilator) **OSA:** AHI ≥15 (PSG)	**Overlap:** 106, 85% Male Mean age 68 ± 11 years **COPD:** 171, 85% Male Age: mean 66 ± 11 years	HTN Coronary artery disease MI	7/10

Table 1 (*continued*)

Author, Year, Country	Study Design	Sampling (Duration)	Diagnostic Criteria of OS	Population (n =)	Cardiovascular Outcomes	Quality[a]
Xie et al., 2019 [20] China	Cross-sectional	Patients referred to the centre of sleep medicine in Beijing who completed a sleep study from 2011 to 2014 (3 years)	**COPD:** FEV1:FVC <70% (Post − Bronchodilator) **OSA:** AHI ≥15 (PSG)	**Overlap:** 49, 63% Male Age: median 69 (63−76) years **COPD:** 62, 61% Male Age: median 69 (59−77) years **OSA:** 735, 69% M Age: median 64 (54−73)	HTN Coronary artery disease Heart failure CVA	8/10
Zhou et al., 2020 [33] China	Cross-sectional	Consecutive COPD patients enrolled from Jan 2014−Jun 2015 (1.5 years)	**COPD:** FEV1:FVC <70% (Post − Bronchodilator) **OSA:** AHI ≥5 (PSG)	**Overlap:** 28 **COPD:** 123	HTN	6/10
Zhu et al., 2020 [34] China	Cross-sectional	National clinical registry study with COPD patients (>40) from four hospitals. (Not specified)	**COPD:** FEV1:FVC <70% (Post − Bronchodilator) **OSA:** AHI ≥5 (PSG)	**Overlap:** 520, 85% Male Age: 66 ± 10 years **COPD:** 246, 84% Male Age: mean 65 ± 9 years	HTN	9/10

Abbreviations: AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; HTN, hypertension; MI, myocardial infarction; OSA, obstructive sleep apnoea; PSG, polysomnography; PVD, peripheral vascular disease.

[a] The quality rating score is based on the Newcastle Ottawa Scale for assessing case-controlled and cohort studies [9]. Studies can receive a maximum of nine points, with higher numbers equating to lower risk of bias. We used a modified scale for assessing cross-sectional studies [10]. These studies can receive a maximum of 10 points, with a higher number equating to a lower risk of bias.

studies reported ischaemic heart disease with varying terms with little similarity between studies. Finally, the majority of studies did not have cardiovascular outcomes as their primary outcome of interest.

Prevalence of cardiovascular disease on overlap syndrome

Pooled prevalence data for cardiovascular outcomes are reported in Figs. S1−S6.

Ischaemic heart disease

A total of 12 studies (n = 3791) [11−22], looked at the prevalence of ischaemic heart disease in the overlap population (Fig. S1). Studies were heterogenous in terms of their AHI cut-off, with five studies [11,12,16,17,22] using AHI ≥ 5events/hr (n = 1239, pooled prevalence 32%, 95%CI 21%−44%), two [13,14] using AHI ≥ 5events/hr with symptoms (n = 210, pooled prevalence 49%, 95%CI 42%−55%), two [15,21] using AHI >10events/hr (n = 89, pooled prevalence 21%, 95%CI 13%−30%) and three [18−20] using AHI ≥15events/hr (n = 2253, pooled prevalence 44%, 95%CI 0%−89%). There was no difference in prevalence amongst the different severities of overlap (based on AHI cut-off). Studies also differed in their description of ischaemic heart disease. Included terms in the pooled data are chronic heart disease [11,12], cardiovascular disease [13−16], myocardial infarction [17−19], coronary artery disease [18,20−22] and cardiac dysfunction [17].

Hypertension

A total of 17 studies [11−22,29,31−34] (n = 4580) looked at the prevalence of hypertension in the overlap population (Fig. S2). Studies were heterogenous in terms of their AHI cut-off, with eight studies [11,12,16,17,22,29,33,34] using AHI ≥ 5events/hr (n = 2000, pooled prevalence 57%, 95%CI 44%−71%); two [13,14] using AHI ≥ 5events/hr with symptoms (n = 210, pooled prevalence 74%, 95%CI 68%−79%); two [15,21] using AHI >10events/hr (n = 89, pooled prevalence 50%, 95%CI, 39%−60%); four [18−20,31] using AHI ≥15events/hr (n = 2267, pooled prevalence 60%, 95%CI 49%−71%) and one [32] using AHI ≥30events/hr (n = 14, pooled prevalence 64%, 95%CI 51%−66%).

Atrial fibrillation (AF)

A total of two [11,17] studies (n = 928) looked at the prevalence of AF in the overlap population (Fig. S3) with a pooled prevalence of 4% (95%CI, 3%−5%). Both studies used an AHI cut-off ≥ 5events/hr.

Heart failure (HF)

A total of three studies [19−21]] (n = 2203) looked at the prevalence of HF in the overlap population (Fig. S4). One study [21] used an AHI cut-off >10events/hr (n = 56, pooled prevalence 16%, 95%CI 9%−28%), while two studies [19,20] used an AHI cut-off ≥15events/hr (n = 2147, pooled prevalence 4%, 95%CI 4%−5%).

Pulmonary hypertension

Two studies [21,31] (n = 70) looked at the prevalence of pulmonary hypertension in the overlap population (Fig. S5). The first study [21] had an AHI cut-off >10events/hr (n = 56, prevalence 25%, 95%CI 16%−38%) and the second study [31] used an AHI cut-off ≥15events/hr (n = 14, prevalence 18%, 95%CI 9%-265).

Stroke

A total of six studies [11,16,17,19,20,22] (n = 3263) looked at the prevalence of cerebrovascular disease (stroke) in the overlap population (Fig. S6). Studies were heterogenous in terms of their AHI cut-off with four [11,16,17,22] using ≥ 5events/hr (n = 1116, pooled prevalence 6%, 95%CI 1%−11%) and two [19,20] using ≥15events/hr (n = 2147, pooled prevalence 4%, 95%CI 3%−5%).

Peripheral vascular disease (PVD)

Only one study [19] (n = 2098) looked at the prevalence of PVD in the overlap population and used an AHI cut-off of ≥15events/hr. This study showed that the prevalence of PVD was 6%, 95%CI 5%−7%.

Comparison of cardiovascular outcomes between patients with overlap and patients with COPD

There was a large degree of heterogeneity amongst studies given the use of different AHI cut-offs. A meta-analysis was therefore only possible when comparing hypertension prevalence between patients with overlap and COPD in studies using an AHI cut-off ≥ 5events/hr. A total of 1446 patients with overlap and 912 patients with COPD were included from five studies (I^2 = 61%). Fig. 2 shows

the results from a random effects meta-analysis. Overlap syndrome was associated with a significantly higher risk of hypertension compared to patients with COPD alone (OR = 1.68, 95%CI 1.21−2.35). Sensitivity analysis is shown in Table S3. Regardless of whether we restricted the studies by population size or by quality the OR did not change significantly.

The calculated OR comparing other cardiovascular outcomes between patients with overlap and patients with COPD are shown in Table 2. Studies have been broken down by AHI cut-off. With regards to cardiovascular risk, only Wang 2020 [18] using an AHI cut-off of ≥15events/hr, found a significantly higher cardiovascular risk in patients with overlap compared to COPD (OR 1.90, 95%CI 1.16−3.12). Six other studies [13,15,17,20−22] found no significant difference. Two studies, one using an AHI cut-off ≥ 5events/hr with symptoms [13] and one >10events/hr [15] found a significantly increased risk of hypertension in the overlap population compared to the COPD population [OR = 2.42, 95%CI 1.58−3.69) and OR 2.56, 95%CI 1.18−5.57 respectively]. While a remaining five studies [18,20,21,31,32] found no significant difference. Only one study investigated cardiovascular mortality [15] and found a significantly increased risk in patients with overlap compared to COPD patients (OR = 2.81, 95%CI 1.40−5.64). With regards to other cardiovascular outcomes, one study [17] investigated atrial fibrillation, two [20,21] heart failure, one [31] pulmonary hypertension and two [17,22] cerebrovascular disease. None of these studies found any significant differences between overlap and COPD patients.

Comparison of cardiovascular outcomes between patients with overlap and patients with OSA alone

There was a large degree of heterogeneity amongst studies given the use of different AHI cut-offs and a meta-analysis could not be performed on any outcome measure. Furthermore, Adler et al., 2020 [19] had a significantly larger sample size compared to all other studies and so a meta-analysis would not have been dominated by the one study and so not of any additional value. The calculated OR comparing cardiovascular outcomes between patients with overlap and patients with OSA are shown in Table 3. The studies have been split by AHI cut-off.

With regards to cardiovascular risk, two studies [19,20] using an AHI cut-off of ≥15events/hr, found a significantly higher cardiovascular risk in patients with overlap compared to OSA [OR = 1.94, 95%CI 1.68−2.23) and OR 2.63, 95%CI 1.46−4.73 respectively]. The remaining three studies [12,14,22] did not find a significantly increased risk.

Two studies [19,20] using an AHI cut-off of ≥15events/hr, found a significantly higher risk of heart failure in patients with overlap compared to OSA [OR = 2.04, 95%CI 1.61−2.58) and OR 3.92, 95%CI 1.98−7.78 respectively].

With regards to hypertension, four studies found a significantly higher risk in patients with overlap compared to OSA patients. Two studies [12,22] used an AHI cut-off of ≥ 5events/hr [OR = 3.12, 95%CI 1.92−5.07) and OR 6.00, 95%CI 1.69−21.26 respectively] and two studies [19,20] used an AHI cut-off of ≥15events/hr [OR = 1.47, 95%CI 1.34−1.61) and OR 2.37, 95%CI 1.26−4.49 respectively]. The remaining two studies [14,32] found no significant difference.

Only one study [19] using an AHI cut-off of ≥15events/hr found a significantly higher risk of cerebrovascular disease in patients with overlap compared to OSA [OR = 1.56, 95%CI 1.23−1.97]. The other two [20,22] found no significant difference.

Finally, only one study [19] using an AHI cut-off of ≥15events/hr looked at peripheral vascular disease, finding a significantly higher risk in patients with overlap compared to OSA [OR = 3.30, 95%CI 2.66−4.10].

Adler et al., 2020 [19] is the largest study to date comparing cardiovascular outcomes in patients with overlap and OSA. They used an AHI cut-off ≥ 15events/hr and is the only study that adjusted their OR for age, gender, BMI, smoking, AHI and type of sleep study. The only adjusted OR that remained significant was that of peripheral vascular disease (OR 1.91 [1.52−2.4]).

Cardiovascular outcomes in relation to overlap severity

Only two studies have looked at whether overlap disease severity affects cardiovascular outcomes. Adler et al., 2020 [19] looked at whether COPD severity (defined by the GOLD criteria [7]) and/or OSA severity (AHI ≥30 vs. 15 ≥ AHI <30) effected cardiovascular outcomes. They concluded that in the overlap population, the probability of having hypertension was higher in those with severe OSA (AHI >30 events/hr) compared to the non-severe group (15 > AHI <30) but was not impacted by COPD severity. COPD was associated with an increased probability of coronary artery disease, heart failure and peripheral vascular disease in a dose-dependent manner in both moderate and severe OSA patients. Patients with moderate OSA and no COPD served as the reference group. Hu et al., 2020 [17] found that OSA severity (in overlap patients) was associated with an increased risk of hypertension compared to patients with COPD alone post adjustment for sex, age, body-mass index (BMI) and neck circumference [mild overlap OR 1.11, 95%CI 0.79−1.56; moderate overlap OR 1.53, 95%CI 1.03−2.29; severe overlap OR 1.62, 95%CI 1.02−2.58). OSA severity (in overlap patients) was not associated with an increased risk of cardiovascular disease.

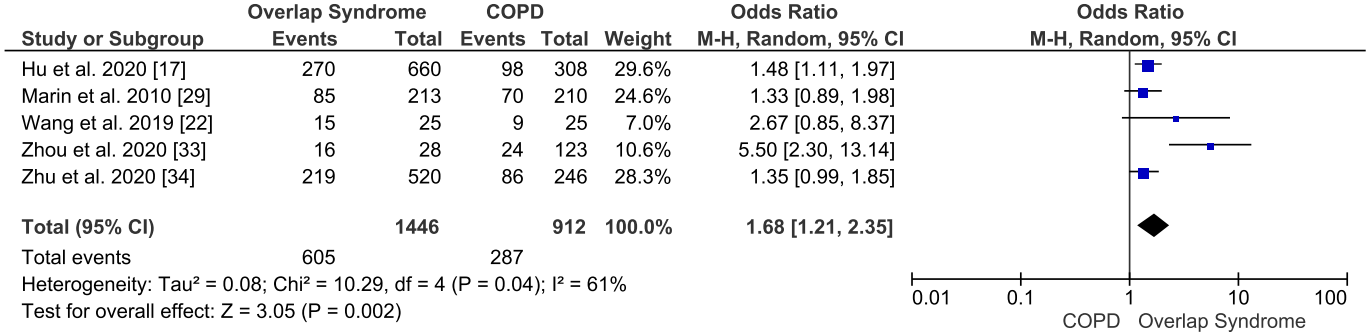

Fig. 2. Forest plot showing the comparison of hypertension prevalence between patients with overlap and patients with COPD. The size of the squares is proportional to the weight of each study. Horizontal lines indicate the 95% confidence interval; diamond shows the pooled prevalence estimate with 95% confidence interval.

Table 2
Cardiovascular prevalence in patients with overlap syndrome compared to COPD.

Cardiovascular Outcome	AHI cut off per hour	Author, year	Prevalence in Overlap (%)	Prevalence in COPD (%)	Calculated OR
CVD (MI, CAD, Angina, Cardiac dysfunction)	≥5	Hu et al., 2020 [17]	161/660 (24)	66/308 (21)	1.18 [0.85–1.64]
		Wang et al., 2019 [22]	9/25 (36)	4/25 (16)	2.95 [0.77–11.34]
	≥5 + symptoms or ≥15 without	Maestri et al., 2019 [13]	85/172 (49)	130/299 (43)	1.27 [0.87–1.85]
	>10	Steveling et al., 2014 [15]	6/33 (18)	18/144 (13)	1.56 [0.56–4.28]
		Su et al., 2019 [21]	13/56 (23)	7/50 (14)	1.86 [0.68–5.11]
	≥15	Xie et al., 2019 [20]	22/49 (45)	32/62 (52)	0.76 [0.36–1.62]
		Wang et al., 2020 [18]	64/106 (60)	76/171 (44)	1.90 [1.16–3.12]
Atrial Fibrillation	≥5	Hu et al., 2020 [17]	17/660 (3)	7/308 (2)	1.14 [0.47–2.77]
Heart Failure	>10	Sun et al., 2019 [21]	9/56 (16)	6/50 (12)	1.40 [0.46–4.27]
	≥15	Xie et al., 2019 [20]	13/49 (27)	8/62 (13)	2.44 [0.92–6.47]
Pulmonary HTN	≥15	Silva et al., 2017 [31]	1/14 (7)	0/25 (0)	5.67 [0.22–148]
HTN	≥5 + symptoms or ≥15 without	Maestri et al., 2019 [13]	133/172 (77)	175/299 (59)	2.42 [1.58–3.69]
	>10	Steveling et al., 2014 [15]	20/33 (61)	54/144 (38)	2.56 [1.18–5.57]
		Sun et al., 2019 [21]	24/56 (43)	23/50 (46)	0.88 [0.41–1.90]
	≥15	Silva et al., 2017 [31]	6/14 (43)	14/25 (56)	0.59 [0.16–2.21]
		Wang et al., 2020 [18]	71/106 (67)	111/171 (65)	1.10 [0.66–1.83]
		Xie et al., 2019 [20]	35/49 (71)	37/62 (60)	1.69 [0.76–3.76]
	>30	Taranto-Montemurro et al., 2016 [32]	9/14 (64)	9/16 (56)	1.40 [0.32–6.11]
Cerebrovascular Disease	≥5	Hu et al., 2020 [17]	63/660 (10)	28/308 (9)	1.06 [0.66–1.68]
		Wang et al., 2019 [22]	5/25 (20)	1/25 (4)	6.00 [0.65–55.66]
	≥15	Xie et al., 2019 [20]	2/49 (4)	1/62 (2)	2.60 [0.23–29.50]
Cardiovascular Mortality	≥5	Marin et al., 2010 [29]	31/213 (15)	12/210 (6)	2.81 [1.40–5.64]

AbbreviationsAHI, apnoea-hypopnea index; CAD, coronary artery disease; CVD, cardiovascular disease; HTN, hypertension; MI, myocardial infarction.
All Odds Ratios (OR) are unadjusted.

Table 3
Cardiovascular prevalence in patients with overlap syndrome compared to OSA.

Cardiovascular Outcome	AHI cut off per hour	Author, year	Prevalence in Overlap (%)	Prevalence in OSA (%)	Calculated OR
CVD (MI, CAD, heart disease)	≥5	Lacedonia et al., 2018 [12]	34/123 (28)	209/721 (29)	0.94 [0.61–1.43]
		Wang et al., 2019 [22]	9/25 (36)	3/25 (12)	4.13 [0.96–17.70]
	≥5 + symptoms or ≥15 without	Papachatzakis et al., 2018 [14]	17/38 (45)	10/38 (26)	2.27 [0.86–5.95]
	≥15	Adler et al. 2020[a] [19]	281/2098 (13)	1063/14,368 (7)	1.94 [1.68–2.23]
		Xie et al., 2019 [20]	22/49 (45)	174/735 (24)	2.63 [1.46–4.73]
Heart Failure	≥15	Adler et al. 2020[a] [19]	92/2098 (4)	316/14,368 (2)	2.04 [1.61–2.58]
		Xie et al., 2019 [20]	13/49 (27)	62/735 (8)	3.92 [1.98–7.78]
HTN	≥5	Lacedonia et al., 2018 [12]	101/123 (82)	429/721 (60)	3.12 [1.92–5.07]
		Wang et al., 2019 [22]	15/25 (60)	5/25 (20)	6.00 [1.69–21.26]
	≥5 + symptoms or ≥15 without	Papachatzakis et al., 2018 [14]	19/38 (50)	16/38 (42)	1.38 [0.56–3.40]
	≥15	Adler et al. 2020[a] [19]	1120/2098 (53)	6293/14,368 (44)	1.47 [1.34–1.61]
		Xie et al., 2019 [20]	35/49 (71)	377/735 (51)	2.37 [1.26–4.49]
	>30	Taranto-Montemurr et al., 2016 [32]	9/14 (64)	15/24 (63)	1.08 [0.27–4.25]
Cerebrovascular Disease	≥5	Wang et al., 2019 [22]	5/25 (20)	4/25 (16)	1.31 [0.31–5.60]
	≥15	Adler et al. 2020[a] [19]	90/2098 (4)	402/14,368 (3)	1.56 [1.23–1.97]
		Xie et al., 2019 [20]	2/49 (4)	40/735 (5)	0.74 [0.17–3.15]
Peripheral Vascular Disease	≥15	Adler et al. 2020[a] [19]	126/2098 (6)	273/14,368 (2)	3.30 [2.66–4.10]

Abbreviations: AHI, apnea-hypopnea index; CAD, coronary artery disease; HTN, hypertension; MI, myocardial infarction.
[a] Un-adjusted odds ratio presented. The paper has performed logistic regression and adjusted for age, gender, BMI, smoking, AHI and type of sleep study and the only OR that remained significant was that of peripheral vascular disease (OR 1.91 [1.52–2.4]). No other papers have adjusted their prevalence data for confounding factors.

Discussion

This systematic review and meta-analysis, has shown that: 1) there is a high prevalence of cardiovascular disease, especially ischaemic heart disease (36%) and hypertension (58%) in patients with overlap syndrome; 2) overlap syndrome is associated with a higher risk of hypertension compared to patients with COPD alone (OR 1.68 (95%CI 1.21–2.35)) and patients with OSA alone; 3) overlap patients have an increased risk of peripheral vascular disease compared to patients with OSA alone (although this is based on one study alone [19]); with a subset of studies also suggesting an increased risk of ischaemic heart disease, heart failure, and cerebrovascular disease; 4) increasing severity of OSA in the overlap population results in a greater prevalence of hypertension (demonstrated in two studies [17,19]); 5) increasing severity of COPD in the overlap population results in a greater prevalence of coronary artery disease, heart failure and peripheral vascular disease (single study only [19]); 6) patients with overlap have increased cardiovascular mortality compared to COPD patients (based on one study [29]). This review has also highlighted the large degree of heterogeneity amongst currently published studies with varying criteria used in diagnosing overlap syndrome. The retrospective and observational nature of the studies with little or no adjustment for confounding factors means that firm conclusions

regarding cardiovascular risk between overlap and COPD and/or OSA are difficult. There is clearly need for further well-designed prospective studies with a long follow-up duration to fully answer this question.

There have been two previous systematic reviews investigating the prevalence of CVD and clinical outcomes in patients with comorbid COPD and OSA (overlap). The first in 2017 only included a PubMed search and their main outcome of interest was prevalence of overlap syndrome. They included four papers which reported on cardiovascular outcomes [2]. Additionally, these did not use post-bronchodilator spirometry for a COPD diagnosis (gold-standard) and therefore were not included in our review. The second review published in 2020, included studies published prior to June 2019 [6]. There were 12 English and five Chinese studies included, however there were some limitations to this review. The authors included studies with less robust COPD and OSA diagnostic criteria, (physician reported, self-reported and international classification of diseases (ICD)) and also combined studies with varying AHI cut-off's in their meta-analysis. They concluded that patients with overlap have increased risk of hypertension compared to COPD and/or OSA patients, pulmonary hypertension when compared with OSA patients, with no difference was seen in coronary heart disease prevalence.

Our study incorporated seven newly published studies in 2020 and used more robust diagnostic criteria for both COPD and OSA, thus excluding several studies previously presented in prior reviews. To our knowledge it is therefore the largest and most rigorous systematic review of CVD risk in overlap patients to date.

Meta-analysis was challenging due to the significant heterogeneity amongst studies, many of which used differing AHI cut-offs. However, it seems likely that overlap syndrome is associated with a significantly greater risk of hypertension compared to patients with COPD alone, a finding previously suggested in prior reviews. The data also point to an increased risk of hypertension in the overlap population when compared to OSA patients, also suggested in prior reviews. However, the majority of studies have not adjusted for confounding factors. Adler et al. [19], who had a larger population (n = 16,466) than all other studies combined, found an increased prevalence of hypertension in the overlap population compared to patients with moderate OSA. However, when this was adjusted for age, gender, BMI, smoking, AHI and type of sleep study, this difference disappeared. However, this study did find that when a subset of severe overlap (defined with an AHI $\geq$30) was investigated, there was a higher prevalence of hypertension compared to moderate overlap, with the moderate OSA population serving as a reference population. These findings were also reported by Hu et al. [17]. COPD severity had no impact on hypertension prevalence. This data suggests OSA is an independent predictor of hypertension, rather than the combined presence of COPD and OSA (overlap) contributing to an increased risk. This would also explain our findings that patients with overlap have a higher prevalence of hypertension compared to patients with COPD alone. This is not unsurprising as findings from a recent systematic review (26 studies, n = 51,623) concluded that mild, moderate and severe OSA in the absence of overlap is associated with hypertension in a dose–response manner [23]. There have been several potential mechanisms theorised to help explain the association between OSA and hypertension. OSA results in intermittent hypoxia, increased oxidative stress, vascular endothelium dysfunction as well as increased sympathetic nervous system activation, all of which can contribute to a higher prevalence of hypertension.

With regards to other cardiovascular outcomes, there were limited data to support an increased risk when comparing the overlap population to those with COPD alone. This suggests that OSA does not seem to have an additive impact when combined with COPD. However, the converse seems true when the overlap population is compared with patients with OSA alone. Several studies suggested an increased prevalence of ischaemic heart disease, heart failure and peripheral vascular disease in overlap compared to OSA patients. However, most studies were unadjusted. Adler et al. [19] found that an increased prevalence of peripheral vascular disease remained following adjustment for common confounders but not for ischaemic heart disease or heart failure. Furthermore, they also concluded that in patients with overlap, different spirometric severities of COPD (based on GOLD criteria) led to a higher probability of having coronary artery disease, heart failure and peripheral vascular disease in a dose-dependent manner compared to patients with moderate OSA alone. This was post adjustment of common confounding factors. This may suggest that COPD contributes an additive risk in the overlap population compared to those with OSA alone. This is perhaps expected as a systematic review on cardiovascular comorbidity in COPD concluded that COPD is associated with an increased CVD risk and this risk increases with the degree of airflow limitation (COPD severity) [24]. COPD represents a chronic inflammatory state coupled with lung hyperinflation, hypoxaemia and increased oxidative stress. All of these can contribute to an increased cardiovascular risk profile [3].

While prior reviews have commented on an increased risk of pulmonary hypertension and AF, these studies have used varying defining criteria of COPD and thus were excluded from this review [25–28]. It therefore remains to be seen whether overlap contributes to an increased risk of pulmonary hypertension and AF.

The most important limitation to this systematic review is that its findings are limited by the considerable heterogeneity of the studies. All studies are observational and retrospective in nature with a varied AHI cut-off which makes combining studies difficult and inaccurate. Furthermore, there was also a difference in outcome measures with regards to ischaemic heart disease which was defined variably in the studies. Few studies measured CVD as a predefined study design and the majority of studies had a different primary outcome of interest.

In conclusion, this review suggests that patients with overlap have a high prevalence of CVD. The main additive risk compared to patients with COPD alone appears to be hypertension, while the main additive risks compared to patients with OSA alone appear to be ischaemic heart disease, heart failure and peripheral vascular disease. While there is some suggestion of increased cardiovascular mortality, more work is needed in this field. Further work might also explore risk in relation to different phenotypes of COPD reflecting heterogeneity in this condition that extends beyond the severity of airflow obstruction. There is a need for future high quality prospective studies comparing overlap, COPD and OSA to fully ascertain whether overlap confers an increased CVD risk compared to COPD and/or OSA alone.

Contributors

AJS, JRH and SM conceived the study. All authors were involved in creating the search strategy. AJS, EQ conducted the initial searches and screened potential studies in a blinded fashion. Any disputes were settled by SM. AJS and JSA did the statistical analysis. AJS and EQ wrote the initial draft of the manuscript and all authors reviewed, edited and approved the final manuscript.

Practice points:

1) There is a high prevalence of cardiovascular disease, especially ischaemic heart disease and hypertension in patients with overlap syndrome
2) Overlap syndrome is associated with a higher risk of hypertension compared to patients with COPD or OSA alone
3) Patients with overlap syndrome are likely to have an increased risk of peripheral vascular disease, ischaemic heart disease, heart failure and cerebrovascular disease compared to patients with OSA alone

Research agenda

This review showed that current evidence with regards to overlap syndrome and cardiovascular disease is retrospective, observational and heterogeneous. There is a need for well designed, prospective studies to definitively answer the following questions.

1) Do patients with overlap syndrome have an increased cardiovascular risk compared to patients with COPD and/or OSA alone?
2) Will patients with overlap syndrome benefit from earlier and targeted cardiovascular risk factor modification?
3) Does positive airway pressure therapy improve cardiovascular outcomes in patients with overlap syndrome?

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Conflicts of interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.smrv.2022.101627.

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