Systematic review and meta-analysis of prevalence of undiagnosed major cardiac comorbidities in COPD

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Systematic review and meta-analysis of prevalence of undiagnosed major cardiac comorbidities in COPD

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Abstract

It is often stated that heart disease is underdiagnosed in COPD. Evidence for this statement comes from primary studies but these have not been synthesised to provide a robust estimate of the burden of undiagnosed heart disease. A systematic review of studies using active diagnostic techniques to establish the prevalence of undiagnosed major cardiac comorbidities in patients with COPD was carried out. MEDLINE, Embase, Scopus and Web of Science were searched for terms relating to heart failure (specifically, left ventricular systolic dysfunction [LVSD]), coronary artery disease (CAD) and atrial fibrillation (AF), relevant diagnostic techniques and COPD. Studies published since 1980, reporting diagnosis rates using recognised diagnostic criteria in representative COPD populations not known to have heart disease, were included. Studies were classified by condition diagnosed, diagnostic threshold used, and whether participants had stable or exacerbated COPD. Random effects meta-analysis of prevalence was conducted where appropriate. In general, prevalence estimates for undiagnosed cardiac comorbidities in COPD had broad confidence intervals, with significant study heterogeneity. Most notably, a prevalence of undiagnosed LVSD of 15.8% (11.1 – 21.1) was obtained when defined as LVEF <50%. Undiagnosed CAD was found in 2.3 – 18.0% of COPD patients and AF in 1.4% (0.3 – 3.5). Further studies using recent diagnostic advances,
and investigating therapeutic interventions for patients with COPD and heart disease, are needed. (PROSPERO ID CRD42021242972).

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of death worldwide and amongst chronic diseases is associated with the worst quality of life. Heart disease is highly prevalent in COPD, beyond the rate expected due to the common risk factors of tobacco smoking, advanced age and socioeconomic deprivation. When present, it is associated with increased mortality, worse health status and increased hospitalisation.

Accordingly, there is a need to improve the identification of patients in whom heart disease and COPD coexist, and optimise their management. A common assertion of published research in this field is that cardiac comorbidities are substantially underdiagnosed in patients with COPD. However, high-level evidence to support this statement is lacking: meta-analysis-level evidence for rates of cardiac comorbidity in COPD derives from use of clinical coding or medical records. This captures heart disease that has attracted clinical attention through overt signs and symptoms, or conspicuous adverse events such as acute myocardial infarction (MI) or decompensated heart failure (HF), but misses undiagnosed disease. In COPD, underdiagnosis is inevitable because the symptoms of heart disease and COPD overlap: breathlessness caused by HF has no unique characteristics and patients with COPD are more likely to present with atypical chest pain during acute coronary syndromes.

For a more accurate understanding of underdiagnosis, active diagnostic processes must be applied to populations of COPD patients, with results reported for patients without known cardiac diagnoses. The results of such studies estimate undiagnosed disease, rather than simple comorbidity prevalence. A review including studies using echocardiography to diagnose HF in those without CAD exists, however several subsequent primary studies have been published across the spectrum of
heart disease. A systematic literature review was therefore devised to estimate the prevalence of undiagnosed major cardiac comorbidities in COPD patients.

The challenge of measuring underdiagnosis

In considering the problem of underdiagnosis of cardiac comorbidities in COPD it must be recognised that diagnosis of all conditions is subject to errors of both over- and under-estimation, and also that the process of diagnosis is complex and evolves over time, both in the meeting of diagnostic criteria by an individual and the very parameters of these criteria. This latter factor can also vary by location. For the purpose of attempting to measure underdiagnosis in this study, pre-specified diagnostic criteria were not used; rather the authors’ criteria were used provided they aligned with recognised major cardiological society guidelines.

Defining major cardiac comorbidities in COPD

Three major heart diseases were selected for investigation: left ventricular systolic dysfunction (LVSD, more recently termed heart failure with [mildly] reduced ejection fraction, or HF[m]rEF), coronary artery disease (CAD) and atrial fibrillation (AF). This is because they all are associated with worse outcomes in COPD, all have treatments that reduce mortality and adverse events, and represent endpoint manifestations of heart disease. Other cardiovascular comorbidities, such as hypertension, are very common in COPD and likely also underdiagnosed, but can be better considered disease processes than enhance the risk of the major heart diseases listed above. Diastolic heart failure, also known as HFpEF, has been defined with particular variability,(13) and has only very recently been recognised to have outcome-improving treatments(14) and was thus considered outside the scope of this review.
Methods

Search Strategy

A search was made for relevant studies in adults over 18. Studies published prior to 1980 were excluded because echocardiography, the key diagnostic technique for HF, was not fully developed until this point. For consistency, this cut-off was used for the other two conditions.

With these limitations, MEDLINE, Embase, Scopus and Web of Science were searched in to 23rd August 2023 for studies containing terms related to COPD, one of the three major heart diseases, and appropriate diagnostic techniques. Each database was therefore searched three times. For studies relating to LVSD, terms relating to HF were searched for, to avoid overlooking studies that used different terminology. The search terms used are detailed in Appendix 1.

Search results were exported to Endnote 20, duplicates removed and study title and abstracts screened to identify studies that were relevant. These full texts of these studies were reviewed for inclusion by two independent reviewers (JK and CW/GM), with discrepancies settled by a third reviewer (JS).

The review was registered on PROSPERO (ID CRD42021242972) and conducted according to the PRISMA (2009) guidelines (see Appendix 6 for checklist).

Study inclusion/exclusion

Inclusion criteria were: studies in adults over 18 years old, with a clinical diagnosis of COPD and spirometric evidence of airflow obstruction (FEV1/FVC ratio < 0.7); prospective use of a recognised diagnostic technique for diagnosis of one of the cardiac comorbidities of interest; use of stated, recognised diagnostic criteria; reporting of rates of diagnosis in patients not known to have cardiac
disease. Exclusion criteria were: highly selected populations, such as only lung transplant candidates or those that had had all comorbidities rigorously excluded; use of diagnostic tests only in subjects with high prior probability of a positive test – for example angiography in patients with raised serum troponin.

Study critical appraisal

The Joanna Briggs Institute (JBI) critical appraisal checklist for studies reporting prevalence data was used to assess the trustworthiness and relevance of the included papers\(^\text{[16]}\).

Data extraction

Data including number of participants, age (mean/median and measure of spread), COPD severity (as indicated by FEV1% and need for long term oxygen therapy), key inclusion and exclusion criteria, COPD status (exacerbation or stability), study setting, diagnostic technique and criteria, number of patients diagnosed and any control group information were extracted, where available.

Statistical analysis

The primary outcome is the proportion of patients that had a diagnosis of the heart disease in question, i.e. an estimation of its prevalence. Weighted pooled estimations of prevalence were sought. Included studies were classified according to whether patients were stable or hospitalised and diagnostic cut-offs used. Pooled estimations were only created where this would appreciably
increase understanding of the data – the threshold for this was set at where ≥4 studies could be pooled. Sensitivity analysis of the effect of pooling studies across inpatient and outpatient populations on between-study heterogeneity was conducted, due to the possibility of exaggerated diagnostic rates due to reversible cardiac dysfunction that has been described during COPD exacerbation (ECOPD)\(^{(17)}\).

Prevalence data were pooled using the binomial equation, with the variance estimate transformed because otherwise, for small or large prevalences (< 0.1 or > 0.9), the study variance tends towards zero, giving such studies a disproportionately large weight\(^{(18)}\). An appropriate transformation for the data obtained here is the arcsine square root transformation, since while there are, inevitably, differences in sample sizes present, they are not of the several orders of magnitude size that can produce misleading results after back-transformation of the variance\(^{(19)}\). A random-effects model was used due to the inevitability of other sources of variance, besides sampling error, in the prevalence of heart disease between the populations sampled in the studies included. Amongst the sources of variance are age, location and COPD phenotype (see discussion below).

Assessment of study heterogeneity was performed by calculation of the \(I^2\) statistic and its confidence interval (CI) for meta-analyses performed.

Assessment of publication bias is recommended in guidelines for conducting observational study meta-analysis and is commonly performed in meta-analyses of prevalence\(^{(20)}\). However, given the low number of studies anticipated to be pooled in this study, tests of publication bias would be under-powered\(^{(21)}\). Nevertheless, funnel plots were produced for the meta-analyses performed.

Analyses were performed in MedCalc for Windows version 20.027 (MedCalc software, Ostend, Belgium).
Results

Search results and study selection

After removal of duplicates, the searches returned 5947 studies relating to HF, 6167 relating to CAD and 1344 relating to AF.

After title and abstract screening, 125 studies relating to HF, 51 studies relating to CAD and 39 studies relating to AF were selected for independent full text review. After resolution of discrepancies, data were extracted from 15 studies relating to LVSD (after narrowing down from HF), 5 studies relating to CAD and 6 studies relating to AF.

Studies from which data were extracted are summarised in Table 1. Further data about individual study inclusion and exclusion criteria, particularly exclusion criteria relating to known heart disease, and patient COPD severity, are summarised in Supplementary Tables 1-3.

Risk of bias assessment

For included studies, there was lack of clarity or satisfactory information in at most two of the 9 domains assessed by the JBI critical appraisal checklist (See Supplementary Table 4). The inclusion criteria that studies should include representative populations and to diagnose based on recognised criteria meant there was an element of pre-selection for highly scoring studies.
Results synthesis

LVSD

Studies were categorised into i) sampling from populations with stable COPD or ECOPD requiring hospitalisation and ii) using left ventricular ejection fraction (LVEF) threshold used to define LVSD of <50%, <45% and <40%.

Individual study results are presented in the Table and grouped as above. Meta-analysis of prevalence was performed when appropriate as pre-specified above. 95% CIs are in brackets and forest plots are presented in Appendix 4.

From 11 studies using an LVEF threshold of 50%, prevalence of undiagnosed LVSD was 15.8% (11.1 – 21.1). $I^2$ was high at 81% (66 – 89). A sensitivity analysis separating studies of hospitalised and non-hospitalised patients did not significantly change prevalence or $I^2$ (see Appendix 4).

From 3 studies using an LVEF threshold of 45% (all in stable patients), prevalence of undiagnosed LVSD ranged from 2.7% to 16.0%.

Two studies used an LVEF threshold of 40% in hospitalised patients, with prevalence of undiagnosed LVSD reported at 6.8% and 16.0%.

Funnel plots are presented in Appendix 5; in all cases Egger’s test for asymmetry was negative.

CAD
Individual study results are presented in the Table. No meta-analysis of prevalence was performed given differing diagnostic strategies. Reported prevalence of undiagnosed CAD ranged from 2.3% in non-hospitalised patients using Agatston score >400, to 18% in a hospitalised cohort using the same criteria.

AF

Individual study results are presented in the Table. Inclusion of the single study of admitted patients substantially altered the prevalence estimate and I² (see Appendix 4), therefore this study was considered separately. Estimated prevalence of undiagnosed AF in stable patients was low, at 1.4% (0.3 – 3.5). By contrast, in admitted patients receiving serial electrocardiograms, undiagnosed AF was found in 20.2%.

Discussion

This systematic review considered 27 published studies employing active diagnostic techniques to quantify undiagnosed heart disease in populations of COPD patients.

The certainty of the evidence synthesised is reduced by the presence of considerable inconsistency as measured by I² and indicated by wide confidence intervals for prevalence estimates.

Nevertheless, it is noteworthy that the prevalence of undiagnosed LVSD in patients with COPD, when a cut-off LVEF of 50% is applied, is between 10 and 20%. This represents at least 120000 people in the UK alone(22) and tens of millions worldwide(22,23). Due to the study design it may even be an underestimate: patients not tested due to existing CAD have been shown to have the highest undiagnosed rates of HF(24). Two thirds can be expected to have HFrEF and one third mildly reduced LVEF(25), of which at least three quarters would have other structural abnormalities satisfying a
diagnosis of heart failure with mildly reduced ejection fraction (HFmrEF)\(^{(26)}\) – all patients who are not being offered indicated, safe, effective therapy to reduce admissions and mortality.

No further synthesis was possible for studies reporting rates of undiagnosed CAD, although the highest reported rate was seen in a study on patients hospitalised with ECOPD. This is congruent with the association between ECOPD and cardiac events\(^{(27)}\) and also the hypothesis that unrecognised CAD could contribute to the symptoms and signs leading to hospitalisation with a diagnosis of ECOPD. The somewhat lower rate of underdiagnosis of CAD compared with LVSD may reflect the multiple routes to impaired heart function in COPD beyond ischaemic cardiomyopathy; these include myocardial inflammation and fibrosis\(^{(28)}\) as well as direct impairment of cardiac filling due to the increased intrathoracic pressures that accompany lung hyperinflation.\(^{(29)}\)

The discrepancy in rates of undiagnosed AF in stable and hospitalised patients occurs because paroxysms of AF in predisposed patients are much more likely in the conditions of increased sympathetic activity (caused by hypoxia and hypercapnia as well as drug treatment), systemic inflammation and intrathoracic pressure changes associated with ECOPD\(^{(30)}\). These results suggest that screening in stable COPD patients without other known heart disease or risk factors is unlikely to identify much undiagnosed AF.

Limitations and implications for future research

This review has limitations. Firstly, the studies obtained by systematic searching exhibited significant heterogeneity in terms of patient populations and diagnostic strategies employed. This resulted in small sample numbers for meta-analysis, limiting the strength of conclusions. The breadth of the CIs may result from the heterogeneity inherent in the COPD patient population, which may be subdivided into different severity classes and phenotypes. For example, the association of the frequent exacerbator phenotype with higher rates of MI\(^{(27)}\) implies that estimations of rates of CAD in COPD as a whole will be less precise if the prevalence of this phenotype within different study
populations is variable. An individual patient data meta-analysis to explore the relationship of phenotype to the rates of undiagnosed cardiac comorbidities would be worthwhile and may provide further useful prevalence estimates for the other major cardiac diseases.

Regarding LVSD, a reliance on LVEF for diagnosis has disadvantages\(^{(31)}\). As a test for LVSD it may produce false negative results in patients with left ventricular hypertrophy and a small left ventricular cavity\(^{(32)}\). When reduced LVEF is found, it is not regarded as solely sufficient for a diagnosis of the syndromes of HFrEF or HFmrEF\(^{(33)}\), which require the presence of symptoms and/or signs of HF and may be supported by other echocardiographic parameters and biomarker measurements. In most COPD patients, this requirement for symptoms is automatically satisfied due to the presence of breathlessness. However, studies generally do not report a syndromic diagnosis, hence the use of LVSD as defined by ejection fraction in this review. A threshold to define LVSD is also difficult to apply, since historical evidence for effective therapy was established in LVEF < 40%, yet retrospective analysis suggests patients with LVEF < 50% benefit from the same treatments. This higher threshold is included in some international guidelines\(^{(33)}\), but not others\(^{(34)}\); it does however define a population of COPD patients with worse physical and psychological status\(^{(35)}\) and was therefore included here. A final challenge in establishing meaningful LVSD rates was that many studies reported mean LVEF without reporting cases below a threshold, meaning potentially useful data could not be included.

Other studies have explored left-sided cardiac dysfunction in COPD beyond reduced LVEF\(^{(36)}\), and many others have studied the right heart using strain-based indices\(^{(37)}\). Undoubtedly there is value in establishing the true prevalence of non-LVEF-defined cardiac dysfunction in COPD, but it was beyond the scope of this review. Novel, prognosis-informing techniques to evaluate cardiac function, such as global longitudinal strain\(^{(38)}\), plus long-awaited outcome-improving treatment in heart failure with preserved ejection fraction\(^{(14)}\), both have potentially important roles in the care of patients with COPD and should be evaluated further in this population.
Finally, practical and cost-effective approaches to reducing the rates of undiagnosed and untreated heart disease for COPD patients must be identified. The data presented here suggest current approaches are failing; equally, universal application of tests to diagnose heart disease in the large COPD population could overwhelm healthcare resources. A structured approach to guide clinicians would be valuable, perhaps using simple screening tests such as NT-proBNP to identify patients for further testing; further research is needed to establish the ideal thresholds and regularity of testing that would best balance reducing underdiagnosis and cost-effectiveness.

Conclusion

This systematic review and meta-analyses sought to establish if high quality evidence could be found to support the statement that heart disease is substantially underdiagnosed in COPD. Studies were heterogenous and CIs broad. Despite this, a striking estimate of the magnitude of undiagnosed HF was obtained, which should be noteworthy to all clinicians treating COPD patients.

There is great potential benefit in improving the understanding of the diagnostic and treatment gaps relating to heart disease in COPD. Knowing which cardiac conditions are most likely to be present in which patients subgroups, and which treatments give most benefit, would allow mitigation of a major mortality risk for COPD patients.

Funding and Competing Interests

No funding sources or conflicts of interests to declare.

Acknowledgement

The authors thank Andrew Bryant (Newcastle University) for statistical advice.
<table>
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<tr>
<th>Study ID</th>
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<th>Age (mean)</th>
<th>Age (s.d.)</th>
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<th>Setting</th>
<th>Diagnost ic tool</th>
<th>Diagnostic threshold</th>
<th>Number diagnosed</th>
<th>Prevalence</th>
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</table>
Summary of studies reporting prevalence of undiagnosed LVSD in COPD patients. Abbreviations: CMR – cardiac magnetic resonance imaging, TTE – transthoracic echocardiography, CT – computed tomography.

<table>
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<th>Study ID</th>
<th>n</th>
<th>Age (mean)</th>
<th>Age (s.d.)</th>
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<th>Diagnostic threshold</th>
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Summary of studies reporting prevalence of undiagnosed CAD in COPD patients. Prevalence reported to 3 decimal places. 

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<th>Stability</th>
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<th>Diagnostic tool</th>
<th>Number diagnosed</th>
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<td>24h ECG</td>
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<td>0.033</td>
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<td>10.1</td>
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<td>Multicentre outpatient s, US</td>
<td>24h ECG</td>
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Summary of studies reporting prevalence of undiagnosed AF in COPD patients. Prevalence reported to 3 decimal places.
References


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<td>13</td>
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<td>15</td>
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<td>17</td>
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<td>20</td>
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<td>21</td>
</tr>
</tbody>
</table>
Appendix 1: Search terms

Searches performed 7th April 2021

MEDLINE (HF):
1. exp lung diseases, obstructive/ or pulmonary disease, chronic obstructive/ or bronchitis, chronic/ or pulmonary emphysema/
2. copd.mp.
3. "chronic obstructive pulmonary disease".mp.
5. coad.mp.
6. "chronic airflow obstruction".mp.
7. "chronic bronchitis".mp.
8. emphysema.mp.
10. "chronic airway* obstruction".mp.
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. exp heart failure/ or heart failure, diastolic/ or heart failure, systolic/
14. "cardiac failure".mp.
15. ccf.mp.
17. "systolic dysfunction".mp.
18. exp ventricular dysfunction/ or ventricular dysfunction, left/
19. lvsd.mp.
20. lvsf.mp.
21. diastolic failure.mp.
22. diastolic dysfunction.mp.
23. href.mp.
24. hfpef.mp.
25. hfmref.mp.
26. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
27. exp Echocardiography/
28. echocardiogra*.mp.
29. echo.mp.
30. exp Radionuclide Ventriculography/
31. ventriculogra*.mp.
32. exp cardiac imaging techniques/ or exp cardiac-gated imaging techniques/ or cardiac-gated single-photon emission computer-assisted tomography/ or gated blood-pool imaging/ or tomography, x-ray computed/
33. computed tomogra*.mp.
34. CT.mp.
35. magnetic resonance.mp.
36. exp cardiac imaging techniques/ or exp myocardial perfusion imaging/ or exp magnetic resonance imaging/ or exp magnetic resonance angiography/ or exp diagnostic techniques, cardiovascular/ or exp heart function tests/ or magnetic resonance spectroscopy/ or nuclear magnetic resonance, biomolecular/
37. mri.mp.
38. brain natriuretic peptide.mp. or Natriuretic Peptide, Brain/
39. bnp.mp.
40. exp tomography, emission-computed, single-photon/ or cardiac-gated single-photon emission computer-assisted tomography/
41. ("single photon emission computed tomography" or spect).mp.
42. exp Positron-Emission Tomography/
43. ("positron emission tomography" or pet).mp.
44. 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43
45. 11 and 26 and 44
46. limit 45 to (yr="1980 -Current" and english)

MEDLINE (CAD):

1. exp lung diseases, obstructive/ or pulmonary disease, chronic obstructive/ or bronchitis, chronic/ or pulmonary emphysema/
2. copd.mp.
3. "chronic obstructive pulmonary disease".mp.
5. coad.mp.
6. "chronic airflow obstruction".mp.
7. "chronic bronchitis".mp.
8. emphysema.mp.
10. "chronic airway* obstruction".mp.
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. exp coronary disease/ or exp coronary artery disease/ or coronary occlusion/ or coronary stenosis/ or coronary thrombosis/
14. exp myocardial ischemia/ or exp acute coronary syndrome/ or exp angina pectoris/ or exp myocardial infarction/
15. "isch*emic heart disease".mp.
16. "isch*emic cardiac disease".mp.
17. "coronary heart disease".mp.
18. "myocardial infarct*".mp.
19. "cardiac infarct*".mp.
21. Angina, Stable/ or angina.mp. or exp Angina Pectoris/ or Angina, Unstable/
22. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23. angiocardiography/ or exp coronary angiography/
24. "coronary angiogra*".mp.
25. exp Electrocardiography/
26. electrocardiogra*.mp.
27. ecg.mp.
28. ekg.mp.
29. exp echocardiography/ or exp echocardiography, stress/
30. echocardiogra*.mp.
31. echo.mp.
32. exp cardiac imaging techniques/ or exp cardiac-gated imaging techniques/ or cardiac-gated single-photon emission computer-assisted tomography/ or gated blood-pool imaging/ or tomography, x-ray computed/
33. "computed tomography".mp.
34. ct.mp.
35. exp cardiac imaging techniques/ or exp myocardial perfusion imaging/ or exp magnetic resonance imaging/ or exp magnetic resonance angiography/ or exp diagnostic techniques, cardiovascular/ or exp heart function tests/ or magnetic resonance spectroscopy/ or nuclear magnetic resonance, biomolecular/
36. troponin.mp. or exp Troponin/
37. exp tomography, emission-computed, single-photon/ or cardiac-gated single-photon emission computer-assisted tomography/
38. ("single photon emission computed tomography" or spect).mp.
39. exp Positron-Emission Tomography/
40. ("positron emission tomography" or pet).mp.
41. 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40
42. 11 and 22 and 41
43. limit 42 to (yr="1980 -Current" and english)

MEDLINE (AF):

1. exp lung diseases, obstructive/ or pulmonary disease, chronic obstructive/ or bronchitis, chronic/ or pulmonary emphysema/
2. copd.mp.
3. "chronic obstructive pulmonary disease".mp.
5. coad.mp.
6. "chronic airflow obstruction".mp.
7. "chronic bronchitis".mp.
8. emphysema.mp.
10. "chronic airway* obstruction".mp.
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. "atrial fibrillation".mp. or exp Atrial Fibrillation/
13. exp Atrial Flutter/
15. "atrial arrhythmia*".mp.
16. "supraventricular arrhythmia*".mp.
17. 12 or 13 or 14 or 15 or 16
18. exp Electrocardiography/
19. electrocardiogra*.mp.
20. ecg.mp.
21. ekg.mp.
22. exp Pacemaker, Artificial/ or pacemaker.mp. or exp Cardiac Pacing, Artificial/
23. exp Electrocardiography, Ambulatory/
24. holter.mp.
25. exp monitoring, ambulatory/ or exp telemetry/
26. "cardiac monitor*".mp.
27. "heart monitor*".mp.
28. defibrillator.mp.
29. 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30. 11 and 17 and 29
31. limit 30 to (yr="1980 -Current" and english)

Embase (HF):
1. exp chronic obstructive lung disease/
2. "chronic obstructive lung disease".mp.
3. "chronic obstructive pulmonary disease".mp.
4. copd.mp.
5. coad.mp.
6. emphysema.mp.
7. chronic bronchitis.mp.
8. "obstructive airway* disease".mp.
10. "chronic airflow obstruction".mp.
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. exp heart failure/
13. ("heart failure" or "cardiac failure").mp.
14. exp systolic heart failure/ or exp heart failure with reduced ejection fraction/
15. ("systolic heart failure" or "systolic cardiac failure").mp.
16. exp congestive heart failure/
17. ("congestive cardiac failure" or "congestive heart failure" or ccf).mp.
18. exp diastolic dysfunction/ or exp diastolic heart failure/ or exp heart failure with preserved ejection fraction/
19. ("diastolic dysfunction" or "diastolic heart failure" or "diastolic cardiac failure" or "diastolic failure" or "heart failure with preserved ejection fraction" or "hfpef").mp.
20. ("heart failure with medium range ejection fraction" or hfmref).mp.
21. exp left ventricular systolic dysfunction/ or exp heart left ventricle failure/
22. ("left ventricular systolic dysfunction" or "left ventricular systolic failure" or lvsd or lvsf).mp.
23. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24. exp echocardiography/ or exp contrast echocardiography/ or exp doppler echocardiography/
25. (echocardiogra* or echo).mp.
26. exp heart ventriculography/
27. exp radionuclide ventriculography/ or exp heart scintiscanning/
28. ventriculogra*.mp.
29. exp computer assisted tomography/
30. ("computed tomography" or ct).mp.
31. exp single photon emission computed tomography/
32. ("single photo emission compute* tomography" or spect).mp.
33. exp positron emission tomography/
34. ("positron emission tomography" or pet).mp.
35. exp nuclear magnetic resonance imaging/ or exp cardiovascular magnetic resonance/
36. ("magnetic resonance imaging" or mri or "cardiovascular magnetic resonance" or cmr).mp.
37. 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36
38. 11 and 23 and 37
39. limit 38 to (english and yr="1980-Current")

Embase (CAD):
1. exp chronic obstructive lung disease/
2. "chronic obstructive lung disease".mp.
3. "chronic obstructive pulmonary disease".mp.
4. copd.mp.
5. coad.mp.
6. emphysema.mp.
7. chronic bronchitis.mp.
8. "obstructive airway* disease".mp.
10. "chronic airflow obstruction".mp.
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. exp coronary artery disease/ or exp coronary artery atherosclerosis/ or exp coronary artery calcification/ or exp coronary artery obstruction/ or coronary artery occlusion/ or exp coronary artery thrombosis/
13. exp ischemic heart disease/ or exp ischemic cardiomyopathy/ or exp silent myocardial ischemia/
14. ("isch*emic heart disease" or "isch*emic cardiac disease").mp.
15. ("coronary arter*" or "coronary heart disease").mp.
16. exp heart infarction/
17. ("myocardial infarct*" or "cardiac infarct" or mi).mp.
18. exp acute coronary syndrome/
19. ("acute coronary syndrome" or acs).mp.
20. exp angina pectoris/
21. angina.mp.
22. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23. exp echocardiography/ or exp doppler echocardiography/ or exp stress echocardiography/
24. (echocardiogra* or echo).mp.
25. exp computer assisted tomography/
26. ("computed tomography" or ct).mp.
27. exp single photon emission computed tomography/
28. ("single photo emission compute* tomography" or spect or "myocardial perfusion imaging" or mpi).mp.
29. exp positron emission tomography/
30. ("positron emission tomography" or pet).mp.
31. exp nuclear magnetic resonance imaging/ or exp cardiovascular magnetic resonance/
32. ("magnetic resonance imaging" or mri or "cardiovascular magnetic resonance" or cmr).mp.
33. exp coronary angiography/
34. coronary angiogra*.mp.
35. exp computed tomographic angiography/
36. exp electrocardiography/
37. (electrocardiogra* or ecg or ekg).mp.
38. troponin.mp. or exp troponin/
39. 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38
40. 11 and 22 and 39
41. limit 40 to (english and yr="1980 -Current")

Embase (AF):

1. exp chronic obstructive lung disease/
2. "chronic obstructive lung disease".mp.
3. "chronic obstructive pulmonary disease".mp.
4. copd.mp.
5. coad.mp.
6. emphysema.mp.
7. "chronic bronchitis".mp.
8. "obstructive airway* disease".mp.
10. "chronic airflow obstruction".mp.
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. exp atrial fibrillation/ or exp heart atrium arrhythmia/ or exp paroxysmal atrial fibrillation/
13. ("atrial fibrillation" or af).mp.
14. "atrial flutter".mp. or exp heart atrium flutter/
15. "atrial arrhythmia*".mp. or exp heart atrium arrhythmia/
16. exp heart supraventricular arrhythmia/ or "supraventricular arrhythmia*".mp.
17. 12 or 13 or 14 or 15 or 16
18. exp electrocardiography/
19. (electrocardiogra* or ecg or ekg).mp.
20. exp ambulatory electrocardiography/ or exp electrocardiography monitoring/ or exp holter monitoring/
21. ("cardiac monitor*" or "heart monitor*" or holter or "ambulatory electrocardiography" or "ambulatory ecg").mp.
22. pacemaker.mp. or exp cardiac rhythm management device/
23. exp defibrillator/ or defibrillator.mp.
24. 18 or 19 or 20 or 21 or 22 or 23
25. 11 and 17 and 24
26. limit 25 to (english and yr="1980 -Current")

Scopus (HF): (TITLE-ABS-KEY((chronic obstructive pulmonary disease)) OR TITLE-ABS-KEY COPD) OR TITLE-ABS-KEY((obstructive lung disease)) OR TITLE-ABS-KEY(COAD) OR TITLE-ABS-KEY((chronic airflow obstruction)) OR TITLE-ABS-KEY((chronic bronchitis)) OR TITLE-ABS-KEY(EMPHYSEMA) OR TITLE-ABS-KEY((obstructive airway* disease)) OR TITLE-ABS-KEY((chronic airway* obstruction)) AND (TITLE-ABS-KEY((heart failure)) OR TITLE-ABS-KEY((cardiac failure)) OR TITLE-ABS-KEY(CCF) OR TITLE-ABS-KEY(Systolic failure) OR TITLE-ABS-KEY(Systolic dysfunction) OR TITLE-ABS-KEY(LVSD) OR TITLE-ABS-KEY(LVsf) OR TITLE-ABS-KEY((diastolic failure)) OR TITLE-ABS-KEY((diastolic dysfunction)) OR TITLE-ABS-KEY(HFpEF) OR TITLE-ABS-KEY(HFmrEF) OR TITLE-ABS-KEY(HFmrEF)) AND (TITLE-ABS-
tomography”) AND LANGUAGE: (English) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2021

Web of Science (CAD): (ALL=(“chronic obstructive pulmonary disease” OR copd OR “chronic obstructive lung disease*” OR coad OR “chronic airflow obstruction” OR “chronic bronchitis” OR emphysema OR “obstructive lung disease*” OR “obstructive airway* disease*” OR “chronic obstructive airway* disease*” OR “chronic airway* obstruction”) AND ALL=(“coronary artery disease” OR isch*emic heart disease OR “isch*emic cardiac disease” OR “coronary heart disease” OR “myocardial infarct*” OR “cardiac infarct*” OR “acute coronary syndrome” OR angina) AND ALL=(“coronary angiogram*” OR ecg OR electrocardiagra* OR echo cardiagra* OR echo OR “computed tomography” OR ct OR “magnetic resonance” OR CMR OR MRI OR troponin OR SPECT OR “single photon emission computed tomography” OR PET OR “positron emission tomography” OR “myocardial perfusion imaging” OR MPI)) AND LANGUAGE: (English) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2021

Web of Science (AF):
ALL=(“chronic obstructive pulmonary disease” OR copd OR “chronic obstructive lung disease*” OR coad OR “chronic airflow obstruction” OR “chronic bronchitis” OR emphysema OR “obstructive lung disease*” OR “obstructive airway* disease*” OR “chronic obstructive airway* disease*” OR “chronic airway* obstruction”) AND ALL=(“atrial fibrillation” OR af OR atrial flutter OR “atrial arrhythmia*” OR “supraventricular arrhythmia*”) AND ALL=(electrocardiogra* OR ecg OR ekg OR Holter OR pacemaker OR defibrillator OR “cardiac monitor*” OR “heart monitor*”)
AND LANGUAGE: (English) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2021
Appendix 2: Included study references


<table>
<thead>
<tr>
<th>Citation</th>
<th>Reference</th>
</tr>
</thead>
</table>
## Appendix 3: Included studies: additional extracted data

*Superscript numbers refer to reference list in Appendix 2*

<table>
<thead>
<tr>
<th>Study ID</th>
<th>GOLD1 (%)</th>
<th>GOLD2 (%)</th>
<th>GOLD3 (%)</th>
<th>GOLD4 (%)</th>
<th>LTOT (%)</th>
<th>FEV1% (x̄)</th>
<th>FEV1% (s.d.)</th>
<th>Other Measure</th>
<th>Other inclusion</th>
<th>CVD and other exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akpinar 2020</td>
<td>2.3</td>
<td>32.6</td>
<td>33.7</td>
<td>31.4</td>
<td></td>
<td></td>
<td></td>
<td>Nil relevant</td>
<td>HF symptoms, Renal/lung disease, ACS, high Well's over 65</td>
<td>Known HF</td>
</tr>
<tr>
<td>Boudestein 2009</td>
<td>32.4</td>
<td>49.2</td>
<td>18</td>
<td>0.4</td>
<td></td>
<td></td>
<td></td>
<td>Nil relevant</td>
<td>Patients without heart disease presented separately</td>
<td></td>
</tr>
<tr>
<td>Freixa 2013</td>
<td>6</td>
<td>48</td>
<td>39</td>
<td>8</td>
<td>52.4</td>
<td>16.2</td>
<td></td>
<td>Nil relevant</td>
<td>Acute cardiorespiratory condition, LVF</td>
<td></td>
</tr>
<tr>
<td>Guo 2018</td>
<td>60.8</td>
<td>20.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nil relevant</td>
<td>Free of clinical cardiovascular disease</td>
<td></td>
</tr>
<tr>
<td>Hilde 2020</td>
<td>43.1</td>
<td>16.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nil relevant</td>
<td>Fit for TTE &lt;48h Renal failure, ACS, clinical HF, other respiratory</td>
<td></td>
</tr>
<tr>
<td>Lee 2013</td>
<td>35.4</td>
<td>12.43</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nil relevant</td>
<td>117 patients without HF</td>
<td></td>
</tr>
<tr>
<td>Leong 2021</td>
<td>20</td>
<td>42.8</td>
<td>18.5</td>
<td></td>
<td>FEV1 30-50%</td>
<td></td>
<td></td>
<td>Nil relevant</td>
<td>Known LVSD, IHD, AF, PVD, Charlson score&gt; 5</td>
<td></td>
</tr>
<tr>
<td>Lopez-Sanchez 2013</td>
<td>18</td>
<td>36.1</td>
<td>32.8</td>
<td>13.1</td>
<td>56</td>
<td>23.8</td>
<td></td>
<td>Nil relevant</td>
<td>Intubation, pneumothorax, HF</td>
<td></td>
</tr>
<tr>
<td>Nishimura 2014</td>
<td>41</td>
<td>15</td>
<td></td>
<td></td>
<td>FEV1 0.34 - 1.47L</td>
<td></td>
<td></td>
<td>Nil relevant</td>
<td>History of cardiac failure</td>
<td>Emphysematous</td>
</tr>
<tr>
<td>Noordegraaf 1997</td>
<td>2.5</td>
<td>42.5</td>
<td>35</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
<td>Nil relevant</td>
<td>Other lung disease, HTN, acquired CVD</td>
<td></td>
</tr>
<tr>
<td>Pothal 2018</td>
<td>92.8</td>
<td>5.2</td>
<td>2.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nil relevant</td>
<td>Other lung disease, HF, IHD, poor TTE images</td>
<td></td>
</tr>
<tr>
<td>Rachakonda 2016</td>
<td>12</td>
<td>34</td>
<td>44</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td>Nil relevant</td>
<td>Known CV disease</td>
<td></td>
</tr>
<tr>
<td>Rahman 2022</td>
<td>12</td>
<td>34</td>
<td>44</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td>Nil relevant</td>
<td>HTN, IHD, known HF</td>
<td></td>
</tr>
<tr>
<td>Vonk-Noordegraaf 2005</td>
<td>20</td>
<td>34</td>
<td>25</td>
<td>21</td>
<td>56.3</td>
<td>22.2</td>
<td></td>
<td>Nil relevant</td>
<td>Clinical HF</td>
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</tr>
</tbody>
</table>

Supplementary Table 1: Data extracted from studies of LVSD. Abbreviations: GOLD: Global initiative for chronic Obstructive Lung Disease, LTOT – long term oxygen therapy, FEV1% - % predicted forced expiratory volume in 1 second, , HF – heart failure, LVF - left ventricular failure, ACS - acute coronary syndrome IHD - ischaemic heart disease, AF – atrial fibrillation, BBB – bundle branch block, PVD - peripheral vascular disease, HTN – hypertension, TTE – transthoracic echocardiography.
### COPD severity

<table>
<thead>
<tr>
<th>Study ID</th>
<th>GOLD1 (%)</th>
<th>GOLD2 (%)</th>
<th>GOLD3 (%)</th>
<th>GOLD4 (%)</th>
<th>LTOT (%)</th>
<th>FEV1% (x̄)</th>
<th>FEV1% (s.d.)</th>
<th>Other inclusion</th>
<th>CVD and other exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhatt 2018[16]</td>
<td>Unclear: classes not presented for COPD cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nil relevant</td>
<td>Other respiratory disease; 928 patients without CAD</td>
</tr>
<tr>
<td>Gaisl 2015[17]</td>
<td>5</td>
<td>23</td>
<td>16</td>
<td>56</td>
<td>28*</td>
<td>22-66*</td>
<td></td>
<td>Previous CACS available</td>
<td>Coronary symptoms, congenital heart disease</td>
</tr>
<tr>
<td>Kahnert 2022[18]</td>
<td>11.8</td>
<td>47.4</td>
<td>32.3</td>
<td>22.6</td>
<td>20</td>
<td>42.8</td>
<td>18.5</td>
<td>Nil relevant</td>
<td>45 of +ve cases had known CAD</td>
</tr>
<tr>
<td>Leong 2021[7]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nil relevant</td>
<td>100 patients without ASCVD (personal communication from author)</td>
</tr>
<tr>
<td>Ozylimaz 2016[19]</td>
<td>100</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>GOLD 2</td>
<td>Known CAD, LVSD</td>
</tr>
</tbody>
</table>

Supplementary Table 2: Data extracted from studies of Coronary Artery Disease (CAD). *Median and interquartile range. Abbreviations. ASCVD – atherosclerotic cardiovascular disease, LVSD – left ventricular systolic dysfunction

<table>
<thead>
<tr>
<th>Study ID</th>
<th>GOLD1 (%)</th>
<th>GOLD2 (%)</th>
<th>GOLD3 (%)</th>
<th>GOLD4 (%)</th>
<th>LTOT (%)</th>
<th>FEV1% (x̄)</th>
<th>FEV1% (s.d.)</th>
<th>Other inclusion</th>
<th>CVD and other exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carta 2021[20]</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>Nil relevant</td>
<td>History or symptoms of CV disease</td>
</tr>
<tr>
<td>Einvik 2017[21]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.4</td>
<td>43.4</td>
<td>11.4</td>
<td>Nil relevant</td>
<td>Known AF, psychiatric disease</td>
</tr>
<tr>
<td>Hanrahan 2008[22]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>42.8</td>
<td>15.3</td>
<td></td>
<td>On no LABA</td>
<td>Abnormal ECG, CVD, beta blocker use</td>
</tr>
<tr>
<td>Morganroth 2014[23]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>39</td>
<td></td>
<td></td>
<td>Nil relevant</td>
<td>Arrhythmia, MI, HF hospitalisation</td>
</tr>
<tr>
<td>Shivnitwar 2023[24]</td>
<td>5.3</td>
<td>38.0</td>
<td>35.3</td>
<td>21.3</td>
<td>72.5</td>
<td>8.2</td>
<td></td>
<td>Hypercapnoeic</td>
<td>History of cardiac disease</td>
</tr>
<tr>
<td>Terzano 2014[25]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IHD, valvular heart disease</td>
</tr>
</tbody>
</table>

Supplementary Table 3: Data extracted from studies of Atrial Fibrillation (AF). Abbreviations: LABA – long acting beta agonist, ECG - electrocardiogram
Appendix 4: Forest plots and $I^2$ results

This section contains Forest plots that summarise estimates of prevalence of underdiagnosis from individual studies, and the overall pooled estimates obtained by meta-analysis of prevalence.

Figure A: Forest plot of 11 studies reporting prevalence of undiagnosed LVSD (defined as LVEF <50%) in COPD. Pooled prevalence estimate 15.8% (11.1 – 21.1).

Heterogeneity: $I^2$ 81% (95% Confidence interval [CI] 66 – 89)

Figure B: Forest plot of 5 studies reporting prevalence of undiagnosed LVSD (defined as LVEF <50%) in hospitalised patients with COPD. Pooled prevalence estimate 16.4% (11.7 – 21.6)

Heterogeneity: $I^2$ 55% (95% CI 0 – 84)
Figure C: Forest plot of 6 studies reporting prevalence of undiagnosed LVSD (defined as LVEF < 50%) in stable patients with COPD. Pooled prevalence estimate 15.8% (7.5 – 26.3).
Heterogeneity: $I^2$ 88% (95% CI 76 – 94)

Figure D: Forest plot of 6 studies reporting prevalence of AF in patients with COPD. Pooled prevalence estimate 3.2% (0.4 – 8.8).
Heterogeneity: $I^2$ 96% (95% CI 93 – 97)
Figure E: Forest plot of 5 studies reporting prevalence of AF in patients with stable COPD. Pooled prevalence estimate 1.4% (0.3 – 3.5).

Heterogeneity: I² 82% (95% CI 57 – 92)

Appendix 5: Funnel plots and Egger’s test results
Funnel plot A: 11 studies reporting prevalence of undiagnosed LVSD (defined as LVEF <50%) in COPD
Egger’s test: P = 0.913

Funnel plot C: 6 studies reporting prevalence of AF in patients with COPD
Egger’s test: P = 0.338
## Appendix 6: JBI critical appraisal checklist results

### Supplementary Table 4:
**JBI Critical Appraisal Checklist for Analytic Cross Sectional Studies results**

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## Appendix 7: PRISMA (2009) checklist

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<td>Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.</td>
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<td>Objectives</td>
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<td>Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).</td>
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<td>Protocol and registration</td>
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<td>Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.</td>
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<td>Data collection process</td>
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<td>Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.</td>
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<td>List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.</td>
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<td>Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.</td>
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<td>Summary measures</td>
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<td>State the principal summary measures (e.g., risk ratio, difference in means).</td>
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<tr>
<td>Synthesis of results</td>
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<td>Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis.</td>
<td>7-8</td>
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| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 6 |
| Additional analyses        | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 7 |

**RESULTS**

| Study selection           | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 9 |
| Study characteristics     | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | Table, Appendices 2&3 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 9 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 10-11; Figure, appendix 4 |
| Synthesis of results      | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 10-11; Appendix 4 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 9 |
| Additional analysis       | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression) | 10-11; Appendix 4 |

**DISCUSSION**
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<td>Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).</td>
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<td>Limitations</td>
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<td>Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).</td>
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<td>Conclusions</td>
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<td>Provide a general interpretation of the results in the context of other evidence, and implications for future research.</td>
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**FUNDING**

| Funding               | 27   | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.                                                                                                                                                                                                                       |

For more information, visit: [www.prisma-statement.org](http://www.prisma-statement.org).*