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Validation of asthma-COPD overlap recording in healthcare records: protocol for a systematic review

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ABSTRACT

Introduction: Asthma-chronic obstructive pulmonary disease (COPD) overlap (ACO) is characterized by patients presenting symptoms of both asthma and COPD. Many efforts have been made to validate different methods of identifying ACO cases based on symptoms, spirometry and medical history in epidemiological studies. Healthcare databases have been increasingly used to assess health related outcomes and to develop disease management strategies. There are various coding algorithm strategies that can be used and selection depends upon targeted validation. The primary objectives of this systematic review are to evaluate and summarize current methods of identifying asthma-COPD overlap.

Methods: MEDLINE, EMBASE databases and the web of science will be systematically searched by using appropriate search strategies that is able to identify studies containing validated codes and algorithms for the diagnosis of ACO in healthcare databases. For each selected study, we require the presence of at least one of the following validation measures: specificity, sensitivity, positive predictive value or negative predictive value. We will also include studies, in which the validated algorithm is compared with an external reference standard such as questionnaires completed by physicians, medical charts review, manual review or an independent second database. For all selected studies, a uniform table will be created to summarize the following vital information: name of author, publication year, country, data source, population, clinical event, algorithms, gold standard method of validation and characteristics of the test measure used to determine validity.

Ethics and dissemination: Ethics approval is not required as this is a synthesis of studies that have previously been published. Results of this systematic review will be submitted to a peer-reviewed journal for publication. Results from this study will be used for asthma-COPD overlap

outcome research and will further serve as a guide to identify case definitions for patients with the ACO disease.

PROSPERO registration number: CRD42018087472

Strengths and limitations of this study

- To the best of our knowledge, this will be the first study to systematically identify and evaluate methods used to validate asthma-COPD overlap disease in healthcare databases.
- Validation of diagnosis codes or algorithms in asthma-COPD overlap using healthcare databases can contribute to health outcome research and inform accurate patient selection for studies involving patients with asthma-COPD overlap.
- It is possible that different databases may validate different algorithms to identify patients with asthma-COPD overlap which can result in important heterogeneity and therefore limit the generalizability of these algorithms to other settings.
- This systematic review will primarily focus on methods used to validate asthma-COPD overlap recordings in databases and not on other outcome results that do not present results on validation. This focus follows the pattern used in methodological studies.

INTRODUCTION

Asthma and chronic obstructive pulmonary disease (COPD) are the 2 most common obstructive airway diseases (OADs). Recently a new phenotype, referred to as asthma-COPD overlap syndrome (ACOS) or asthma-COPD overlap (ACO), has been identified with its first guidelines for treatment and management in effect since 2015.[1] The Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) described asthma-COPD overlap as "persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD", and pointed out that asthma-COPD overlap includes different clinical phenotypes with several underlying mechanisms.[2] In clinical practice, asthma-COPD overlap is therefore characterized by presenting features of both asthma and COPD.[2] Whilst there have been varied definitions of asthma-COPD overlap in the literature, most of the discussions on asthma-COPD overlap have primarily focused on reviewing the evidential features of asthma and COPD coexisting at biological,[3] epidemiological levels,[4, 5] and on its clinical significance.[6, 7]

Just as the basic definitions of asthma and COPD are still debatable,[8, 9] the primary definition of asthma-COPD overlap is not yet clear. The first guideline for identification of asthma-COPD overlap was proposed in the combination of GINA and GOLD guidelines in 2015.[1] The Spanish COPD guideline (GesEPOC) was the first clinical practice guideline to recognize the asthma-COPD overlap phenotype, calling it the mixed asthma-COPD phenotype.[10] The GesEPOC and the Spanish Guideline on the Management of Asthma (GEMA) recently came out with a consensus to unify the criteria for the diagnosis of asthma-COPD overlap.[11] The GesEPOC/GEMA consensus defined the presence of asthma-COPD

overlap in a given patient based on three elements: significant smoking exposure, chronic airflow limitation and asthma. Diagnosis is confirmed when a patient (35 years of age or older), smoker or ex-smoker of more than 10 pack-years, presents with airflow limitation (post-bronchodilator $FEV_1/FVC<0.7$) that persists after treatment with bronchodilators and inhaled corticosteroids (even after systemic corticosteroids in selected cases), and an objective current diagnosis of asthma (based on GEMA criteria).[11] If a diagnosis of asthma cannot be established, the asthma-COPD overlap diagnosis will be confirmed if the bronchodilator response is very positive (≥15% and ≥400 ml), or if eosinophils are observed in blood (≥300 eosinophils/l), or both.[11]

In advancing a clearer diagnostic criteria for asthma-COPD overlap, Miravitlles[12] proposed "the five commandments of asthma-COPD overlap diagnosis": 1) A patient with asthma may develop non-fully reversible airflow obstruction but this is not COPD, not even ACO; it is obstructive asthma. 2) A patient with asthma who smokes may also develop non-fully reversible airflow obstruction, which differs from obstructive asthma and from "pure" COPD, which he categorized as the most frequent type of patient with ACO. 3) Some patients who smoke and develop COPD may have a genetic type 2 immune responses (Th2) background (even in the absence of a previous history of asthma), which can be identified by high eosinophil counts in peripheral blood. These individuals could be included under the umbrella term of ACO. 4) A patient with COPD and a positive bronchodilator test (>200 mL and >12% FEV_1 change) has reversible COPD but is not an asthmatic. Finally, 5) a patient with COPD and a very positive bronchodilator test (>400 mL FEV_1 change) is more likely to have some features of asthma and could also be classified as ACO.[12]

In asthma-COPD overlap, combination pharmacotherapy treatment consisting of long-acting β_2-agonists/inhaled corticosteroids (ICS) may be the first choice of treatment in patients with a history suggestive of the overlap disease.[2] There is no cure for asthma-COPD overlap. In spite of the uncertainties concerning asthma-COPD overlap definition, there is broad agreement that patients with features of both asthma and COPD experience frequent exacerbations, have poor quality of life, a more rapid decline in lung function and high mortality, and consume a disproportionate amount of healthcare resources than asthma or COPD alone.[1]

There are various kinds of healthcare databases accessible for healthcare research. These databases generally fall into two divisions; administrative (e.g., hospital billing data) and electronic health records (EHRs).[13] The increased use of these two categories of databases has added to the popularity of population-based epidemiology and health outcomes research studies. However, the basic functional use of healthcare databases includes but is not limited to hospital billing, administration, provision of care, laboratory procedures, pharmacy dispensing and physician practice.[13] Recently, there has been an increased use of these healthcare databases for epidemiological studies and population outcome studies as researchers have identified these databases as very useful avenues for clinical research.[14-16]

These databases primarily collect longitudinal information in connection with a patient's demographics, important information regarding healthcare resource utilization such as hospitalizations, referrals to specialists or secondary care, drug prescription, laboratory tests, imaging and lifestyle.[17, 18] Thus, the types of information contained in these databases have become extremely important. The availability of these healthcare databases provide great

opportunity and benefits over several major limitations of randomized controlled trials (RCTs) such as lower cost, increased generalizability and increased statistical power due to larger sample size.[13] The applications of these healthcare datasets in observational studies have become desirable as they are well-suited in hypothesis generation and in advancing previously tested hypotheses.[13]

Algorithms to identify cases in these hierarchically coded healthcare databases can be developed by a single code, combination of multiple codes or sets of codes. As noted by Nissen et al [19] the accuracy of diagnoses recorded in these large databases may be low, which would introduce bias into studies using the data. Unless the algorithms are validated for research, the quality of studies generated from EHRs may be debatable. They developed an algorithm, to increase the ability to identify case definitions for asthma in the Clinical Practice Research Datalink (CPRD) database, using a diagnosis plus spirometry plus specific medication. They found out that extra information on asthma medication prescription (PPV 83.3%), evidence of reversibility testing (PPV 86.0%) or a combination of all three selection criteria (PPV 86.4%) did not result in a higher PPV.[19]

To determine the validity of any health outcome, a clear understanding of the data and the algorithms to be used to identify health outcomes in these databases is required. This can be ascertained using questionnaires completed by a patient or physician, medical charts review, medical notes, manual review or an independent second database.[19, 20] We will conduct a systematic review to evaluate the current body of evidence that have used algorithms or codes based on information in healthcare databases to identify patients with asthma-COPD overlap.

Research question

The primary objectives of this systematic review are to evaluate and summarize current methods of identifying asthma-COPD overlap.

Specifically, the questions of interest are;

1. What type of healthcare databases have been used to obtain information on the diagnosis of asthma-COPD overlap?
2. Which algorithms have been extensively used to define and correctly identify patients with asthma-COPD overlap?
3. What are the estimates (sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV]) of these algorithms to correctly identify patients with asthma COPD overlap in healthcare databases?

METHODS

Literature search

MEDLINE, EMBASE and the Web of Science will be systematically searched for published peer-reviewed articles. We will utilize a search strategy based on a combination of: (1) key-words, Medical Subject Headings (MeSH) and title/abstract (tiab) to identify records in association with "asthma AND COPD"; (2) terms to identify articles probably containing validity or accuracy measures and (3) a search strategy likely to contain studies on the combination of terms and asthma-COPD overlap definitions by Miravitlles,[12] Don Sin *et al*[21] and GesEPOC.[11] In addition, reference lists of primary articles will be reviewed to find relevant articles. An experienced librarian from the Health Science Library (HSL) of Memorial University along with one of the authors will independently conduct a comprehensive search in

MEDLINE, EMBASE and web of science to identify potential articles. The MEDLINE, EMBASE and web of science searches will be independently reviewed by a more senior librarian and another one of the authors.

This systematic review protocol has been prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) and the PRISMA flow diagram from Moher *et al*[22] can be found in figure 1. The PRISMA flow diagram will allow for more transparent flow of information through the different phases of our systematic review. This protocol has been published in the PROSPERO International Prospective Register of Systematic Reviews with registration number CRD42018087472.

Inclusion criteria

Any full-text, peer-reviewed articles published in English before March 2018, that validated the recording of asthma COPD overlap in a healthcare database will be considered for inclusion. We aim to focus on databases, in which the diagnosis of asthma-COPD overlap is primarily based on clinical features, spirometry results, prescription data, radiography and laboratory data. The included studies will be considered if the validated algorithm is compared with an external reference standard such as questionnaires completed by physicians, medical charts review, medical notes, manual review or an independent second database. For each study, we require the presence of at least one study measure such as specificity, sensitivity, positive predictive value and negative predictive value. Also, for our inclusion criteria, we will include algorithms developed from single codes, algorithms formed of multiple case characteristics (e.g.

disease code plus spirometry code plus prescription code) and algorithms generated by natural language processing (NLP) or machine-learning (e.g. Read code, ICD-9 or ICD-10).

Exclusion criteria

Studies without validation of asthma-COPD overlap recording, conference abstracts, surveys and disease registries will be excluded. In addition, studies involving pharmacovigilance databases (spontaneous reporting, signal detection) will be excluded.

Selection Processes

Two independent reviewers will scan titles and abstracts of identified articles and relevant articles will be retrieved based on our research questions and inclusion/exclusion criteria. Discrepancies in determining whether the study met our inclusion criteria during the full-text review will be resolved by consensus between the reviewers. If a consensus could not be reached, arbitration will be decided by a third reviewer.

Data Extraction

The following information will be extracted from each of the included studies by two reviewers independently.

1. Study characteristics (including title, year, country, journal of publication, date of publication and information on the author)
2. Data source, population
3. Sample characteristics
4. Clinical event

5. Algorithms
6. Gold standard of validation
7. Characteristic of the test measure(s) used to determine validity

Risk of bias assessment

Quality assessment will be conducted on all included studies using a component approach. In this regard, we will use Quality Assessment of Diagnostic Accuracy Studies (QUADAS); a risk of bias assessment tool for systematic reviews of diagnostic accuracy studies [23]. This tool comprises 4 domains, which include patient selection, index test, the validation strategy, and reporting of outcomes. Two reviewers will independently assess risk of bias in each domain and report the risk of bias as high, low, or unclear. Disagreements will be resolved by discussion or arbitration with a third reviewer.

Data synthesis

All records will be de-duplicated and screened using Covidence (https://www.covidence.org); a web-based software platform that streamlines the production of systematic reviews and EndNote (Version X7, Thomson Reuters) software will be used to manage the study articles and references. An overview for the validation of asthma-COPD overlap recording will be summarized in narrative composition and in tables describing the methods and results of the included studies. However, no formal meta-analysis is planned. These results may include specificity, sensitivity, PPV and NPV of studies that met our inclusion criteria. Where they are not reported, these test results such as 95% CI, PPV and NPV will be calculated if possible.

Patient and public involvement

No patient will be involved in this review.

ETHICS AND DESSIMINATION

This review protocol will use previously published studies publicly available without directly involving human participants; hence no ethical approval is required. This protocol was published in the PROSPERO International Prospective Register of Systematic Reviews in February 2018 with registration number CRD42018087472. Findings of this review will be presented at epidemiology and pharmacoepidemiology scientific conferences and disseminated through publication in a peer-reviewed journal.

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Authors' contributions

JEA was responsible for drafting the protocol and registering it in PROSPERO. All authors drafted the manuscript and contributed to the development of the research questions, literature search, selection criteria, data extraction criteria, the risk of bias assessment and data synthesis. All authors have critically read, commented on and approved the final version of the manuscript. ZG is responsible for the study management and coordination.

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Competing Interest

None declared.

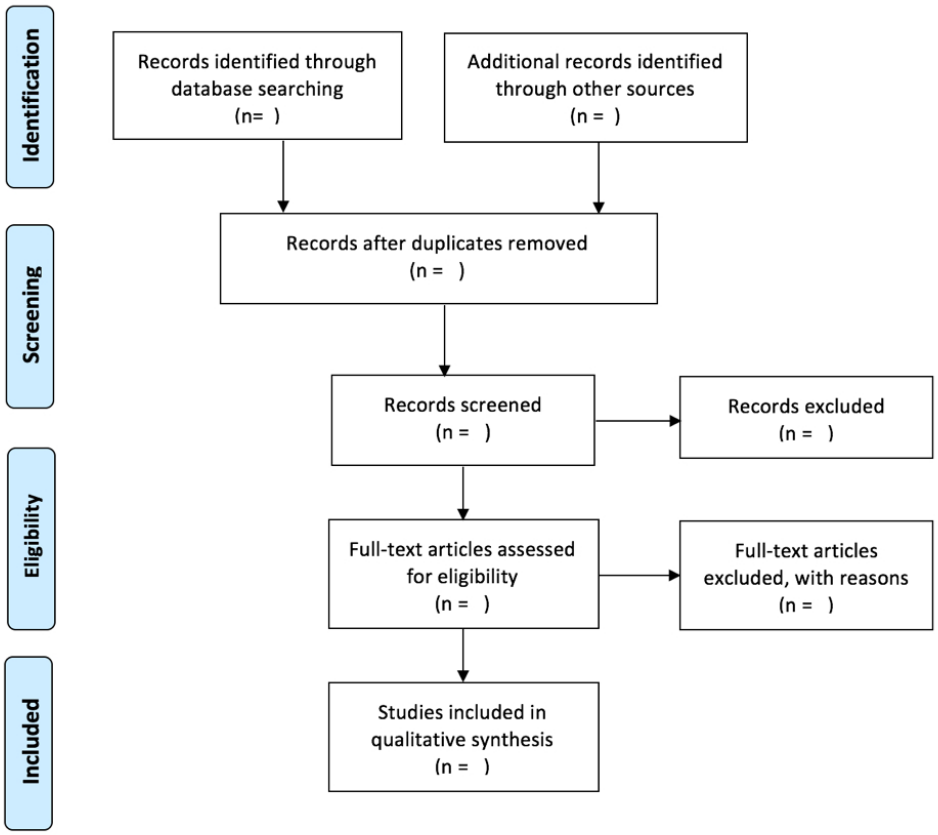

Figure 1 Study screening process: PRISMA flow diagram from Moher et al.

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ABSTRACT

Introduction: Asthma-chronic obstructive pulmonary disease (COPD) overlap (ACO) is characterized by patients presenting symptoms of both asthma and COPD. Many efforts have been made to validate different methods of identifying asthma-COPD overlap cases based on symptoms, spirometry and medical history in epidemiological studies using healthcare databases. There are various coding algorithm strategies that can be used and selection depends upon targeted validation. The primary objectives of this systematic review are to identify validated methods (or algorithms) that identify patients with asthma-COPD overlap from healthcare databases and summarize the reported validity measures of these methods.

Methods: MEDLINE, EMBASE databases and the Web of Science will be systematically searched by using appropriate search strategies that is able to identify studies containing validated codes and algorithms for the diagnosis of asthma-COPD overlap in healthcare databases published, in English, before October 2018. For each selected study, we require the presence of at least one test measure (e.g., sensitivity, specificity etc.). We will also include studies, in which the validated algorithm is compared with an external reference standard such as questionnaires completed by patients or physicians, medical charts review, manual review or an independent second database. For all selected studies, a uniform table will be created to summarize the following vital information: name of author, publication year, country, data source, population, clinical outcome, algorithms, reference standard method of validation and characteristics of the test measure used to determine validity.

Ethics and dissemination: Ethics approval is not required as this is a protocol for a systematic review. We will submit the results of this study to a peer-reviewed journal for publication. Results from this review will be used for asthma-COPD overlap outcome research and will

further serve as a guide to identify case definitions for patients with the asthma-COPD overlap disease.

PROSPERO registration number: CRD42018087472

Strengths and limitations of this study

- To the best of our knowledge, this will be the first study to systematically identify and evaluate methods used to validate asthma-COPD overlap disease in healthcare databases.
- Identification of properly-validated algorithms to identify patients with asthma-COPD overlap from healthcare databases will inform more accurate patient selection in future studies.
- Different healthcare databases may validate different codes or algorithms to identify patients with asthma-COPD overlap. This can result in important heterogeneity and therefore limit the generalizability of these algorithms to other settings as they are context-specific depending on the type of database.
- This systematic review will primarily focus on validated methods or algorithms of asthma-COPD overlap recordings in healthcare databases and not on outcome results of studies. This situation may result in publication bias as algorithms without accompanied validity assessment or methods that do not find positive results may be less likely to have been published

INTRODUCTION

Asthma and chronic obstructive pulmonary disease (COPD) are the 2 most common obstructive airway diseases (OADs). Recently a new phenotype, referred to as asthma-COPD overlap syndrome (ACOS) or asthma-COPD overlap (ACO), has been identified with its first guidelines for treatment and management in effect since 2015.[1] The Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) described asthma-COPD overlap as "persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD", and pointed out that asthma-COPD overlap includes different clinical phenotypes with several underlying mechanisms.[2] Whilst there have been varied definitions of asthma-COPD overlap in the literature, most of the discussions on asthma-COPD overlap have primarily focused on reviewing the evidential features of asthma and COPD coexisting at biological,[3] epidemiological levels,[4, 5] and on its clinical significance.[6, 7]

Just as the basic definitions of asthma and COPD are still debatable,[8, 9] the primary definition of asthma-COPD overlap is not yet clear. The first guideline for identification of asthma-COPD overlap was proposed in the combination of GINA and GOLD guidelines in 2015.[1] The Spanish COPD guideline (GesEPOC) was the first clinical practice guideline to recognize the asthma-COPD overlap phenotype, calling it the mixed asthma-COPD phenotype.[10] The GesEPOC and the Spanish Guideline on the Management of Asthma (GEMA) recently came out with a consensus to unify the criteria for the diagnosis of asthma-COPD overlap.[11] The GesEPOC/GEMA consensus defined the presence of asthma-COPD

overlap in a given patient based on three elements: significant smoking exposure, chronic airflow limitation and asthma.

In advancing a clearer diagnostic criteria for asthma-COPD overlap, Miravitlles[12] proposed "the five commandments of asthma-COPD overlap diagnosis": 1) A patient with asthma may develop non-fully reversible airflow obstruction but this is not COPD, not even ACO; it is obstructive asthma. 2) A patient with asthma who smokes may also develop non-fully reversible airflow obstruction, which differs from obstructive asthma and from "pure" COPD, which he categorized as the most frequent type of patient with ACO. 3) Some patients who smoke and develop COPD may have a genetic type 2 immune responses (Th2) background (even in the absence of a previous history of asthma), which can be identified by high eosinophil counts in peripheral blood. These individuals could be included under the umbrella term of ACO. 4) A patient with COPD and a positive bronchodilator test (>200 mL and >12% FEV_1 change) has reversible COPD but is not an asthmatic. Finally, on the 5th commandment, a patient with COPD and a very positive bronchodilator test (>400 mL FEV_1 change) is more likely to have some features of asthma and could also be classified as ACO.

In asthma-COPD overlap, combination pharmacotherapy treatment consisting of long-acting β_2-agonists/inhaled corticosteroids (ICS) may be the first choice of treatment in patients with a history suggestive of the overlap disease.[2] In spite of the uncertainties concerning asthma-COPD overlap definition, there is broad agreement that patients with features of both asthma and COPD experience more frequent exacerbations, have poorer quality of life, a more

rapid decline in lung function and high mortality, and utilize a disproportionately larger amount of healthcare resources than people with asthma or COPD alone.[1]

There are various kinds of healthcare databases accessible for healthcare research. These databases generally fall into two divisions; administrative (e.g., hospital billing data) and electronic health records (EHRs).[13] The increased use of these two categories of databases has added to the popularity of population-based epidemiology and health outcomes research studies. However, the basic functional use of healthcare databases includes but is not limited to hospital billing, administration, provision of care, laboratory procedures, pharmacy dispensing and physician practice.[13] Recently, there has been an increased use of these healthcare databases for epidemiological studies and population outcome studies as researchers have identified these databases as very useful avenues for clinical research.[14-16]

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The development of an algorithm to measure a health outcome from a particular database requires a clear understanding of data provenance and structure. The validity of an algorithm can be assessed against measures based on questionnaires completed by a patient or physician, medical charts review, medical notes, manual review or an independent second database.[19, 20] We will conduct a systematic review to evaluate the current body of evidence that have used algorithms or codes based on information in healthcare databases to identify patients with asthma-COPD overlap.

Research question

The primary objectives of this systematic review are to identify validated methods (or algorithms) that identify patients with asthma-COPD overlap from healthcare databases and summarize the reported validity measures of these methods.

Specifically, the questions of interest are;

1. What type of healthcare databases have been used to obtain information on the diagnosis of asthma-COPD overlap?
2. Which algorithms have been extensively used to define and correctly identify patients with asthma-COPD overlap?
3. Against which reference standards were the validity of these algorithms assessed? And what were the diagnostic accuracy estimates?

METHODS

Literature search

MEDLINE, EMBASE and the Web of Science will be systematically searched for published peer-reviewed articles. We will utilize a search strategy based on a combination of: (1) key-words, Medical Subject Headings (MeSH) and title/abstract (tiab) to identify records in association with "asthma AND COPD"; (2) terms to identify articles probably containing validity or accuracy measures and (3) a search strategy likely to contain studies on the combination of terms and asthma-COPD overlap definitions by Miravitlles,[12] Don Sin *et al*[21] and GesEPOC.[11] In addition, reference lists of primary articles will be reviewed to find relevant articles that adopt different standards for asthma-COPD description. An experienced

librarian from the Health Science Library (HSL) of Memorial University along with one of the authors will independently conduct a comprehensive search in MEDLINE, EMBASE and Web of Science to identify potential articles. The MEDLINE, EMBASE and Web of Science searches will be independently reviewed by a more senior librarian and another one of the authors.

This systematic review protocol has been prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) and the PRISMA flow diagram from Moher *et al*[22] can be found in figure 1 and the search strategy can be found in the online supplementary file. The PRISMA flow diagram will allow for more transparent flow of information through the different phases of our systematic review. This protocol has been published in the PROSPERO International Prospective Register of Systematic Reviews with registration number CRD42018087472.

Inclusion criteria

Any full-text, peer-reviewed articles published in English before October 2018, that validated the recording of asthma COPD overlap in a healthcare database will be considered for` inclusion. We aim to focus on healthcare databases, in which the diagnosis of asthma-COPD overlap is primarily based on clinical features, spirometry results, prescription data, radiography and laboratory data. The included studies will be considered if the validated algorithm is compared with an external reference standard such as questionnaires completed by patients or physicians, medical charts review, medical notes, manual review or an independent second database. For each study, we require the presence of at least one study measure such as specificity, sensitivity, positive predictive value or negative predictive value. Also, for our

inclusion criteria, we will include algorithms developed from single codes, algorithms formed of multiple case characteristics (e.g. disease code plus spirometry code plus prescription code) and algorithms generated by natural language processing (NLP) or machine-learning (e.g. Read code, ICD-9 or ICD-10).

Exclusion criteria

Studies without validation of asthma-COPD overlap recording, conference abstracts, surveys and disease registries will be excluded. In addition, studies involving pharmacovigilance databases (spontaneous reporting, signal detection) will be excluded.

Selection Processes

Two independent reviewers will scan titles and abstracts of identified articles and relevant articles will be retrieved based on our research questions and inclusion/exclusion criteria. Discrepancies in determining whether the study met our inclusion criteria during the full-text review will be resolved by consensus between the reviewers. If a consensus could not be reached, arbitration will be decided by a third reviewer.

Data Extraction

The following information will be extracted from each of the included studies by two reviewers independently.

1. Study characteristics (including title, year, country, journal of publication, date of publication and information on the author);
2. Data source, population;

3. Type of healthcare database used (including electronic health record, hospitalization discharge data, etc);
4. Sample characteristics;
5. Clinical outcome;
6. Algorithms; the modality of algorithm development (eg, using logistic regression, Classification and Regression Trees, expert opinion etc.,);
7. Reference standard of validation;
8. Characteristic of the test measure(s) used to determine validity;

Risk of bias assessment

Quality assessment of the design and methods on all included primary studies will be assessed using a checklist developed by Benchimol *et al*. [23] Using Standards for Reporting of Diagnostic accuracy (STARD) [24] criteria as a guide, they created a 40-item checklist of items with which to assess the quality of validation studies of health administrative data and to report studies that validated algorithms or codes for identifying patients with different health states (diseases and conditions).

Two reviewers will independently assess the quality of these studies and report potential bias(es) in a descriptive form. Disagreements will be resolved by discussion or arbitration with a third reviewer. However, no subgroup analysis or publication bias assessment is anticipated.

Data synthesis

All records will be de-duplicated and screened using Covidence (https://www.covidence.org); a web-based software platform that streamlines the production of

systematic reviews and EndNote (Version X7, Thomson Reuters) software will be used to manage the study articles and references. An overview for the validation of asthma-COPD overlap recording will be summarized in narrative composition and in tables describing the methods and results of the included studies. Possibly, validation statistics will be aggregated and stratified by the kind of healthcare database, the type of EHR coding and the country of origin. However, no formal meta-analysis is planned. These results may include specificity, sensitivity, PPV and NPV of studies that met our inclusion criteria. Where they are not reported, these test results such as 95% Confidence Interval (CI), PPV and NPV will be calculated if possible.

Patient and public involvement

No patient will be involved in this review.

ETHICS AND DESSIMINATION

This review protocol will use previously published studies publicly available without directly involving human participants; hence no ethical approval is required. This protocol was published in the PROSPERO International Prospective Register of Systematic Reviews in February 2018 with registration number CRD42018087472. Findings of this review will be presented at epidemiology and pharmacoepidemiology scientific conferences and disseminated through publication in a peer-reviewed journal.

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Authors' contributions

JEA was responsible for drafting the protocol and registering it in PROSPERO. JEA, OB, JMG, MW, JF, BJ, KS, MH and ZG drafted the manuscript and contributed to the development of the research questions, literature search, selection criteria, data extraction criteria, the risk of bias assessment and data synthesis. JEA, OB, JMG, MW, JF, BJ, KS, MH and ZG have critically read, commented on and approved the final version of the manuscript. ZG is responsible for the study management and coordination.

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Disclaimer

The study funder was not involved in the study design or the writing of the protocol.

Competing Interest

None declared.

Figure 1 Study Screening Process: PRISMA flow diagram from Moher *et al*. [22]

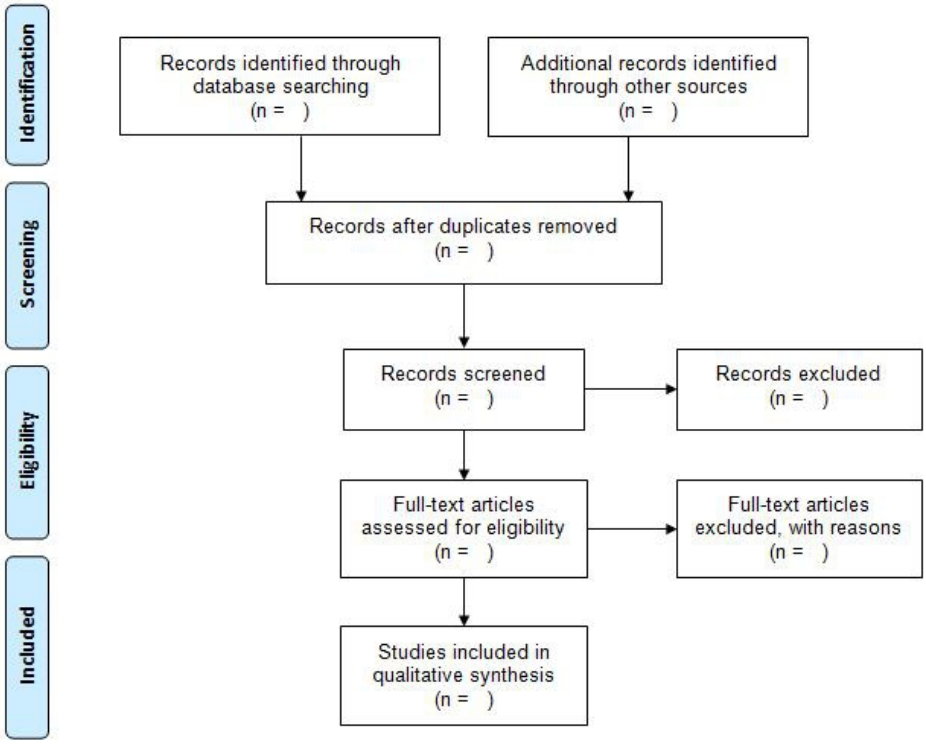

Figure 1 Study Screening Process: PRISMA flow diagram from Moher et al.

173x142mm (96 x 96 DPI)

Appendix 1: Algorithm used for literature review

PubMed

1. ("Asthma"[Mesh]) AND "Pulmonary Disease, Chronic Obstructive"[Mesh]
2. asthma[tiab] AND (COPD[tiab] OR chronic obstructive pulmonary disease[tiab])
3. 1 OR 2
4. ("Smoking"[Mesh]) OR ("Smoke"[Mesh] AND "Tobacco Smoke Pollution"[Mesh]) OR (smoking exposure[tiab])
5. ("Asthma"[Mesh] OR asthma[tiab]) AND "Pulmonary Disease, Chronic Obstructive"[Mesh]
6. 4 AND 5
7. 3 OR 6
8. "Validation Studies" [Publication Type] OR "Validation Studies as Topic"[Mesh] OR Validation [tiab]
9. validat* OR verif* OR verificat* OR valid* OR identif* OR definition* OR define* OR evaluat*
10. "algorithms"[MeSH Terms] OR algorithm[Text Word]
11. ("sensitivity and specificity"[MeSH Terms]) OR (sensitivity[Text Word]) OR (specificity [tiab]) OR PPV OR PNV OR NPV OR (positive predictive value[tiab]) OR (negative predictive value[tiab]) OR (predictive positive value[tiab]) OR (predictive negative value[tiab]) OR (likelihood ratio) OR precision OR accuracy OR (receiver operating characteristic[tiab]) OR ROC OR kappa
12. 8 OR 9 OR 10 OR 11

13. ("Database Management Systems"[Mesh]) OR (Medical Records Systems, Computerized [Mesh])
14. (health administrative) OR (administrative data) OR (administrative database) OR (claim administrative) OR (electronic[tiab]) OR (digital[tiab]) OR computerized OR programmed OR automated OR database OR data base
15. 13 OR 14
16. 7 AND 12 AND 15

EMBASE

1. asthma AND chronic obstructive pulmonary disease
2. (asthma:ab,ti) AND (COPD:ab,ti OR chronic obstructive pulmonary disease:ab,ti)
3. 1 OR 2
4. smoking OR (smoke AND tobacco smoke pollution) OR (smoking exposure:ab,ti)
5. (asthma OR asthma:ab,ti) AND (chronic obstructive pulmonary disease)
6. 4 AND 5
7. 3 OR 6
8. validation study OR validation process OR validation:ab,ti
9. validat* OR verif* OR verificat* OR valid* OR identif* OR definition* OR define* OR evaluat*
10. algorithm OR algorithm:ab,ti
11. (sensitivity OR specificity) OR (sensitivity:ab,ti) OR (specificity:ab,ti) OR PPV OR PNV OR NPV OR (positive predictive value:ab,ti) OR (negative predictive value:ab,ti) OR (predictive positive value:ab,ti) OR (predictive negative value:ab,ti) OR (likelihood ratio)

OR precision OR accuracy OR (receiver operating characteristic:ab,ti) OR ROC OR kappa

12. 8 OR 9 OR 10 OR 11
13. (Database Management Systems:ab,ti) OR (Medical Records Systems OR computerized)
14. (health administrative) OR (administrative data) OR (administrative database) OR (claim administrative) OR (electronic:ab,ti) OR (digital:ab,ti) OR programmed OR automated OR database OR data base
15. 13 OR 14
16. 7 AND 12 AND 15

Web of Science

1. asthma AND chronic obstructive pulmonary disease
2. (asthma) AND (COPD OR chronic obstructive pulmonary disease)
3. 1 OR 2
4. smoking OR (smoke AND tobacco smoke pollution) OR (smoking exposure)
5. asthma AND (chronic obstructive pulmonary disease)
6. 4 AND 5
7. 3 OR 6
8. validation study OR validation process OR validation
9. algorithm
10. validat* OR verif* OR verificat* OR valid* OR identif* OR definition* OR define* OR evaluat*

11. (positive predictive value) OR (negative predictive value) OR (likelihood ratio) OR (receiver operating characteristic) OR kappa
12. sensitivity or "Sensitivity and Specificity"
13. specificity
14. 8 OR 9 OR 10 OR 11 OR 12 OR 13
15. (health administrative) OR (administrative database) OR (administrative data) OR (medical records system) OR (database management systems) OR (computerized) OR (factual databases) OR (geographic information systems) OR (national practitioner data bank)
16. 7 AND 14 AND 15

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	10
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☐	NA
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	10
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	16
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☐	NA
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	16
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	16
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	16
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	8
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	9

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	10 - 11
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	9, 10
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	Supplementary file
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	12
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	11
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	11, 12
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	12
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	12
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☐	☐	NA
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☐	☐	NA
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☐	☐	NA
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	12

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☐	☒	NA
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐	☐	NA