BMJ Open

Investigating asthma co-morbidities: a systematic scoping review protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2015-010548
Article Type:	Protocol
Date Submitted by the Author:	13-Nov-2015
Complete List of Authors:	El Ferkh, Karim; University of Edinburgh, Centre for Population Health Sciences Nwaru, Bright; The University Of Edinburgh, Allergy & Respiratory Research Group, Centre for Population Health Sciences Griffiths, Chris; Queen Mary University of London, Centre for Primary Care and Public Health Sheikh, Aziz; University of Edinburgh, Division of Community Health Sciences
Primary Subject Heading:	Immunology (including allergy)
Secondary Subject Heading:	Immunology (including allergy), Respiratory medicine, Epidemiology
Keywords:	Asthma < THORACIC MEDICINE, Allergy < THORACIC MEDICINE, Epidemiology < THORACIC MEDICINE, Immunology < THORACIC MEDICINE

Investigating asthma co-morbidities: a systematic scoping review protocol

Karim El Ferkh,[1] Bright Nwaru,[1,2] Chris Griffiths,[3] Aziz Sheikh A.[1]

[1]Asthma UK Centre for Applied Research, Centre for Medical Informatics, Usher Institute for Population Health Sciences, The University of Edinburgh

[2]School of Health Sciences, University of Tampere, Finland

[3]Asthma UK Centre for Applied Research, Centre for Primary Care and Public Health, Blizard Institute, Queen Mary, University of London

Correspondence to: Karim El Ferkh

Asthma UK Centre for Applied Research,

Usher Institute of Population Health Sciences and Informatics

The University of Edinburgh,

Rm 815, Doorway 3, Medical School,

Teviot Place, EH8 9AG

Edinburgh, United Kingdom

Tel: +44 (0)131 650 3232

Email: k.firikh@ed.ac.uk

Keywords: Asthma, co-morbidity, asthma phenotypes, systematic scoping review, global health.

Abstract

Introduction: Asthma is a common long-term disorder with a number of related co-morbid conditions, which may impact asthma outcomes. There is a need for greater appreciation for understanding how these comorbidities interact with asthma in order to improve asthma outcomes.

Objectives: To systematically identify key asthma comorbidities, and describe how these vary in terms of different asthma phenotypes and developmental trajectories.

Methods: We will systematically search the following electronic databases: Medline, EMBASE, ISI Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycINFO, and Google Scholar. Additional literature will be identified by searching the reference list of identified eligible studies and by searching the repositories of international conference proceedings, including ISI Conference Proceeding Citation Index, and ZETOC (British Library).

Dissemination: The findings from this systematic scoping review will be reported at scientific meetings and published in a peer-reviewed journal.

Strengths and limitations:

- To our knowledge this is the first review undertaken to map out the full-spectrum of asthma co-morbidity hence evidence generated from the review will be important in shaping the direction of the field.
- The scoping review will be limited to the past 5 years only, but aimed to map the most contemporaneous evidence on asthma co-morbidity.
- As a scoping review, formal quality assessment and risk of bias will not be undertaken on studies to be included in the review.

Background

Asthma is typically a life-long disease and affects over 300 million people worldwide.[32] It is responsible for considerable morbidity, mortality and substantial healthcare costs.[32,33] Effective self-management and pharmacotherapy leading to well controlled asthma is the key management goal.[1-3] Key indicators of successful asthma control include minimal or no symptoms, no restrictions on activities, optimal pulmonary function, and minimal or no side-effects of treatment.[1-4] Poor asthma control is believed mainly to result from inadequate / suboptimal treatment and problems with adherence to recommended treatments.[2,3] An important and hitherto largely ignored consideration however is the impact of co-morbid diseases.[2,3,5-8] A number of conditions (e.g., allergic rhinitis, gastro-oesophageal reflux disease (GORD), obesity, and depression) may occur more frequently in people with asthma than in those without, leading to potential additional difficulties in asthma management.[9,10] These co-morbid conditions may be associated with poor asthma control, impaired health-related quality of life (HRQoL) and increased health and social care utilisation.[9-16] The systematic identification and mapping of these co-morbid conditions may lead to customised targeted treatment, which in turn offers the potential to substantially improve outcomes in patients with asthma, and thereby reduce the need for health and social care.[2,9,14,17]

There are a number of international studies investigating asthma co-morbidity, impact on asthma control and HRQoL, and consequent healthcare and societal burden, but their results vary depending on the populations studied and the particular co-morbid conditions that are the focus of these investigations.[34-36] There is a need therefore for a systematic investigation into the range of asthma comorbidities and how these vary with different asthma phenotypes and endotypes. This scoping review aims to fill this need and in addition identify important research gaps in understanding the relationship between asthma and its co-morbidities.

Specifically, we aim to:

- Systematically search the relevant literature to produce a comprehensive account of asthma co-morbidities;
- Describe how these co-morbidities vary with different asthma phenotypes and endotypes;
- Understand the trajectories for the development of these co-morbidities;

- Identify gaps in our current knowledge in relation to understanding patterns of asthma-related co-morbidities.

Methods

Eligibility criteria

Types of studies

Cohort studies, case-control studies and cross-sectional studies will be eligible for inclusion. We will exclude editorials, animal studies, reviews, randomised controlled trials (RCTs), quasi-RCTs, case studies, and case-series.

Participants

We are interested in studies on participants of any age with a clinical diagnosis of asthma.

Asthma co-morbidities of interest

We are interested in studies on asthma co-morbidities; these are likely to include, but are not limited to: allergic diseases, chronic obstructive pulmonary disease (COPD), autoimmune disorders (e.g. type 1 diabetes), metabolic disorders (e.g. type 2 diabetes, obesity), psychological dysfunction (anxiety, depression), hypertension, cardiovascular diseases and GORD.

Search methods

Databases

We will identify published studies from the following databases: Medline, EMBASE, ISI Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycINFO, and Google Scholar. Additional literature will be identified by searching the reference list of identified eligible studies and by searching the repositories of international conference proceedings, including ISI Conference Proceeding Citation Index, and ZETOC (British Library). Unpublished literature and ongoing studies will be identified by searching the following registries: ISI Conference Proceedings Citation Index via Web of Knowledge.

Search strategy

A highly sensitive search strategy has been developed in each of the six databases to capture the broad literature on the topic (see appendix). Using bibliographic databases and health-oriented search engines, the search will encompass the two main concepts of our scoping review: asthma comorbidities and asthma phenotypes/endotypes.

The databases will be searched from 2011 until October 2015. Although it is well known for a long time now that researchers have been studying asthma as a heterogeneous disease affected by multiple co-morbidities, however the evidence on asthma and co-morbidities increased exponentially in the past five years. In addition, any past evidence of substantial permanence would have definitely been identified and picked up in studies in the past five years.

Study Selection

The articles retrieved from the search strategy will be screened according to the review inclusion and exclusion criteria. The titles and abstracts will be independently screened by two investigators for potentially eligible studies, and when there is a difference in opinions, discussions will be undertaken to reach a consensus on each paper. If an agreement is not reached, a third reviewer will arbitrate. Full text of potentially relevant studies will be retrieved and screened independently by two reviewers, consensus will be done through discussions, and arbitration by a third reviewer if no agreement reached on any study. All the studies not meeting the inclusion criteria will be excluded. Study screening will be undertaken and reported according to the Preferred Reporting Items for Systematics Reviews and Meta-analyses' (PRISMA) recommendation.[23]

Data Extraction

A customised data extraction form will be constructed to extract all relevant data from each study. The data extraction form will be piloted on a few of the eligible studies to evaluate its reliability in capturing the study data of interest. Data extraction will be undertaken independently by two reviewers. Any disagreements will be resolved by discussion or arbitration by a third reviewer. Descriptive summary tables will be produced to recapitulate the evidence base. The following data will be extracted:

- Author(s) and date

- Geographical location
- Research design
- Aims
- Research questions
- Methods
- Settings
- Participants (N, mean age, gender if available)
- Co-morbidities studied
- Key findings
- Research gaps identified

An initial map will be developed to explore the main comorbidities associated with asthma and describe their development trajectories. This mapping will also try to display groups of asthma phenotypes and endotypes categorised by different comorbidities. Additional narrative summaries will be conducted for each phenotype group. The scoping review reporting will follow the PRISMA checklist.[23]

Conclusions

This systematic scoping review will provide a comprehensive overview of asthma co-morbidities, the strengths of the relationships, the trajectories of development, and how these vary by different phenotypes and endotypes of asthma. We expect to report in the summer of 2016.

Ethics and Dissemination

As there are no primary data collected, there will be need for formal NHS ethical review. The systematic scoping review will presented at a relevant conference and be published in a peer-reviewed journal.

Footnotes

Funding:

This work is supported by the Chief Scientist's Office of the Scottish Government and Asthma UK as part of the Asthma UK Centre for Applied Research [AUK-AC-2012-01]. BN is supported by the Farr Institute and Asthma UK Centre for Applied Research.

Conflicts of interest:

None declared.

Contributorship:

All authors have made substantive intellectual contributions to the development of this protocol. KF was involved in writing this protocol. AS, CG and BN commented critically on several drafts of the manuscript. KF, AS, BN were involved in conceptualising this review.

Appendix

Search Strategy

I. Medline

1. asthma.mp. or exp Asthma/
2. exp Comorbidity/ or co-morbidity.mp.
3. multimorbidity.mp.
4. exp Hypersensitivity/ or Allergens/ or Hypersensitivity, Immediate/ or atopy.mp. or exp Immunoglobulin E/ or exp Dermatitis, Atopic/
5. allergic rhinitis.mp. or exp Rhinitis, Allergic/
6. food allergy.mp. or exp Food Hypersensitivity/
7. exp Anaphylaxis/ or anaphylaxis.mp.
8. exp Urticaria/ or urticaria.mp.
9. exp Celiac Disease/ or Autoantibodies/ or exp Autoimmune Diseases/ or autoimmune disorder.mp. or exp Diabetes, Type 1/
10. Thymus Neoplasms/ or endocrine disorder.mp. or Thyroid Gland/ or exp Endocrine System Diseases/ or Thyroid Diseases/
11. exp Obesity/ or exp Diabetes, Type 2/ or metabolic disorder.mp.
12. exp Depression/ or exp Mental Disorder/ or exp Stress, Psychological/ or psychological dysfunction.mp. or Stress Disorder, Post-Traumatic/
13. panic disorders.mp. or exp Panic Disorder/
14. exp Anxiety/ or anxiety.mp.
15. chronic obstructive pulmonary disease.mp. or exp Pulmonary Disease, Chronic Obstructive/
16. exp Hypertension/ or hypertension.mp.
17. exp Gastroesophageal Reflux/ or gastro-oesophageal reflux disease.mp.
18. exp Sleep Apnea, Obstructive/ or exp Sleep Disorder/ or Sleep Apnea Syndromes/ or obstructive sleep apnoea.mp. or Apnea/
19. cardiovascular disease.mp. or exp Cardiovascular Diseases/
20. 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. 1 and 20
22. cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or retrospective studies/ or cohort.ti,ab. or longitudinal.ti,ab. or prospective.ti,ab. or retrospective.ti,ab.
23. Case-Control Studies/ or Control Groups/ or Matched-Pair Analysis/ or ((case* adj5 control*) or (case adj3 comparison*) or control group*).ti,ab.
24. Cross-Sectional Studies/ or cross-sectional.ti,ab. or ("prevalence study" or "incidence study" or "prevalence studies" or "incidence studies" or "transversal studies" or "transversal study").ti,ab.
25. 22 or 23 or 24
26. 21 and 25
27. limit 26 to yr="2011 -Current"

II. EMBASE

1. asthma.mp. or exp Asthma/
2. exp Comorbidity/ or co-morbidity.mp.
3. multimorbidity.mp.
4. exp Hypersensitivity/ or Allergens/ or Hypersensitivity, Immediate/ or atopy.mp. or exp Immunoglobulin E/ or exp Dermatitis, Atopic/
5. allergic rhinitis.mp. or exp Rhinitis, Allergic/
6. food allergy.mp. or exp Food Hypersensitivity/
7. exp Anaphylaxis/ or anaphylaxis.mp.
8. exp Urticaria/ or urticaria.mp.
9. exp Celiac Disease/ or Autoantibodies/ or exp Autoimmune Diseases/ or autoimmune disorder.mp. or exp Diabetes, Type 1/
10. Thymus Neoplasms/ or endocrine disorder.mp. or Thyroid Gland/ or exp Endocrine System Diseases/ or Thyroid Diseases/
11. exp Obesity/ or exp Diabetes, Type 2/ or metabolic disorder.mp.
12. exp Depression/ or exp Mental Disorder/ or exp Stress, Psychological/ or psychological dysfunction.mp. or Stress Disorder, Post-Traumatic/
13. panic disorders.mp. or exp Panic Disorder/
14. exp Anxiety/ or anxiety.mp.
15. chronic obstructive pulmonary disease.mp. or exp Pulmonary Disease, Chronic Obstructive/
16. exp Hypertension/ or hypertension.mp.
17. exp Gastroesophageal Reflux/ or gastro-oesophageal reflux disease.mp.
18. exp Sleep Apnea, Obstructive/ or exp Sleep Disorder/ or Sleep Apnea Syndromes/ or obstructive sleep apnoea.mp. or Apnea/
19. cardiovascular disease.mp. or exp Cardiovascular Diseases/
20. 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. 1 and 20
22. cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or retrospective studies/ or cohort.ti,ab. or longitudinal.ti,ab. or prospective.ti,ab. or retrospective.ti,ab.
23. Case-Control Studies/ or Control Groups/ or Matched-Pair Analysis/ or ((case* adj5 control*) or (case adj3 comparison*) or control group*).ti,ab.
24. Cross-Sectional Studies/ or cross-sectional.ti,ab. or ("prevalence study" or "incidence study" or "prevalence studies" or "incidence studies" or "transversal studies" or "transversal study").ti,ab.
25. 22 or 23 or 24
26. 21 and 25
27. limit 26 to yr="2011 -Current"

III. Web of Science

#4 #3 AND #2 AND #1
Timespan=2011-2015
Search language=Auto
#3 TOPIC: ("cohort study") OR TOPIC: ("longitudinal study") OR TOPIC: ("follow-up study") OR TOPIC: ("prospective study") OR TOPIC: ("retrospective study") OR TOPIC: (cohort) OR TOPIC: (longitudinal) OR TOPIC: (prospective) OR TOPIC: (retrospective) OR TOPIC: ("Case-Control") OR TOPIC: ("Matched-Pair Analysis") OR TOPIC: ("Cross-Sectional") OR TOPIC: ("prevalence study") OR TOPIC: ("incidence study")
Timespan=2011-2015
Search language=Auto
#2 TOPIC: (TOPIC: (Comorbidit*) OR TOPIC: (multimorbidit*) OR TOPIC: (Hypersensitivity) OR TOPIC: (Allerg*) ORTOPIC: ("allergic rhinitis") OR TOPIC: ("Food Hypersensitivity") OR TOPIC: ("food allerg*") ORTOPIC: (Anaphylaxis) OR TOPIC: (Urticaria) OR TOPIC: ("Autoimmune Disease") OR TOPIC:("Autoimmune disorder") OR TOPIC: ("Diabetes") OR TOPIC: ("endocrine disorder") ORTOPIC: ("Thyroid disorder") OR TOPIC: ("metabolic disorder") OR TOPIC: (obesity) OR TOPIC:("Psychological disorder") OR TOPIC: ("Panic Disorder") OR TOPIC: (Anxiety) OR TOPIC: ("chronic obstructive pulmonary disease") OR TOPIC: ("Pulmonary Disease") OR TOPIC: (Hypertension) ORTOPIC: ("gastro-oesophageal reflux disease") OR TOPIC: ("cardiovascular disease") OR TOPIC:("Sleep Apnea"))
Timespan=2011-2015
Search language=Auto
#1 TOPIC: (asthma)
Timespan=2011-2015
Search language=Auto

IV. CINAHL

Query Limiters/Expanders Last Run Via ResultsAction
S30 S27 AND S28 Limiters - Publication Year: 2011-2015
Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 1,391 Edit S30
S29 S27 AND S28 Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 3,845 Edit S29
S28 S23 OR S24 OR S25 Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 411,852 Edit S28
S27 S1 AND S26 Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 27,111 Edit S27
S26 S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 748,799 Edit S26
S25 (MH "Cross Sectional Studies") OR "Cross-Sectional Studies" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 108,137 Edit S25
S24 (MH "Case Control Studies") OR "Case-Control Studies" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 51,374 Edit S24
S23 (MH "Prospective Studies") OR "cohort studies" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 277,306 Edit S23
S22 (MH "Cardiovascular Diseases+") OR "cardiovascular disease" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 386,904 Edit S22
S21 (MH "Sleep Apnea Syndromes+") OR (MH "Sleep Apnea, Obstructive") OR "Sleep Apnea" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 10,336 Edit S21
S20 (MH "Gastroesophageal Reflux") OR "Gastroesophageal Reflux" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 5,683 Edit S20

S19 (MH "Hypertension+") OR "Hypertension" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 65,449 Edit S19
S18 (MH "Pulmonary Disease, Chronic Obstructive+") OR "chronic obstructive pulmonary disease" OR (MH "Lung Diseases, Obstructive+") Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 43,363 Edit S18
S17 (MH "Anxiety+") OR "Anxiety" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 52,157 Edit S17
S16 (MH "Panic Disorder") OR "panic disorder" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 1,682 Edit S16
S15 (MH "Depression+") OR "Depression" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 98,022 Edit S15
S14 (MH "Diabetes, Type 2") OR (MH "Diabetes, Type 1+") OR (MH "Diabetes +") OR "Diabetes" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 112,269 Edit S14
S13 (MH "Obesity+") OR "Obesity" OR (MH "Obesity, Morbid") Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 73,423 Edit S13
S12 "metabolic disorder" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 304 Edit S12
S11 "endocrine disorder" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 117 Edit S11
S10 (MH "Thyroid Diseases+") OR "Thyroid Diseases" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 10,471 Edit S10
S9 (MH "Autoimmune Diseases") OR "Autoimmune Diseases" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 5,816 Edit S9
S8 (MH "Celiac Disease") OR "Celiac Disease" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 3,248 Edit S8

S7 (MH "Urticaria") OR "Urticaria" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 1,505 Edit S7
S6 (MH "Anaphylaxis") OR "Anaphylaxis" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 3,208 Edit S6
S5 (MH "Food Hypersensitivity") OR "food allergy" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 3,880 Edit S5
S4 (MH "Rhinitis, Allergic, Perennial") OR (MH "Rhinitis, Allergic, Seasonal") OR (MH "Dermatitis, Atopic") Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 4,023 Edit S4
S3 (MH "Hypersensitivity+") OR (MH "Hypersensitivity, Immediate") Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 49,092 Edit S3
S2 (MH "Comorbidity") Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 38,672 Edit S2
S1 (MH "Asthma+") OR "asthma" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 29,402

V. PsycINFO

1. asthma.mp. or exp Asthma/
2. exp Comorbidity/ or co-morbidity.mp.
3. multimorbidity.mp.
4. exp Hypersensitivity/ or Allergens/ or Hypersensitivity, Immediate/ or atopy.mp. or exp Immunoglobulin E/ or exp Dermatitis, Atopic/
5. allergic rhinitis.mp. or exp Rhinitis, Allergic/
6. food allergy.mp. or exp Food Hypersensitivity/
7. exp Anaphylaxis/ or anaphylaxis.mp.
8. exp Urticaria/ or urticaria.mp.
9. exp Celiac Disease/ or Autoantibodies/ or exp Autoimmune Diseases/ or autoimmune disorder.mp. or exp Diabetes, Type 1/
10. Thymus Neoplasms/ or endocrine disorder.mp. or Thyroid Gland/ or exp Endocrine System Diseases/ or Thyroid Diseases/
11. exp Obesity/ or exp Diabetes, Type 2/ or metabolic disorder.mp.
12. exp Depression/ or exp Mental Disorder/ or exp Stress, Psychological/ or psychological dysfunction.mp. or Stress Disorder, Post-Traumatic/
13. panic disorder.mp. or exp Panic Disorder/
14. exp Anxiety/ or anxiety.mp.
15. chronic obstructive pulmonary disease.mp. or exp Pulmonary Disease, Chronic Obstructive/
16. exp Hypertension/ or hypertension.mp.
17. exp Gastroesophageal Reflux/ or gastro-oesophageal reflux disease.mp.
18. exp Sleep Apnea, Obstructive/ or exp Sleep Disorder/ or Sleep Apnea Syndromes/ or obstructive sleep apnoea.mp. or Apnea/
19. cardiovascular disease.mp. or exp Cardiovascular Disease/
20. 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. 1 and 20
22. cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or retrospective studies/ or cohort.ti,ab. or longitudinal.ti,ab. or prospective.ti,ab. or retrospective.ti,ab.
23. Case-Control Studies/ or Control Groups/ or Matched-Pair Analysis/ or ((case* adj5 control*) or (case adj3 comparison*) or control group*).ti,ab.
24. Cross-Sectional Studies/ or cross-sectional.ti,ab. or ("prevalence study" or "incidence study" or "prevalence studies" or "incidence studies" or "transversal studies" or "transversal study").ti,ab.
25. 22 or 23 or 24
26. 21 and 25
27. limit 26 to yr="2011 -Current"

VI. Google Scholar (first 500 results will be considered)

1. Asthma and comorbidit*

References

1. Global Strategy for Asthma Management and Prevention. Global Initiative for Asthma (GINA), 2012. Www.ginasthma.org. Date last accessed September 2, 2013.
2. Boulet LP. 2009. Influence of comorbid conditions on asthma. *Eur Respir J*; 33: 897-906.
3. Boulet LP, Boulay ME. 2011. Asthma-related comorbidities. *Expert Rev Respir Med*; 5: 377-393.
4. Bateman ED, Boushey HA, Bousguet J, et al. 2004. Can guideline-defined asthma control be achieved? The gaining optimal asthma control study. *Am J Respir Crit Care Med*; 170: 836-844.
5. De Groot EP, Duiverman EJ, Brand PLP. 2010. Comorbidities of asthma during childhood: possibly important, yet poorly studied. *Eur Respir J*; 36. 671-678.
6. Cazzola M, Segreti A, Calzetta L, et al. 2013. Comorbidities of asthma: current knowledge and future research needs. *Curr Opin Pulm Med*; 19: 36-41.
7. Ledford DK, Lockey RF. 2013. Asthma and comorbidities. *Curr Opin Allergy Clin Immunol*; 13: 78-86.
8. Cazzola M, Calzetta L, Gettoncelli G. 2011. Asthma and comorbid medical illness. *Eur Respir J*; 38: 42-49.
9. Gershon AS, Wang C, Guan J, et al. 2010. Burden of comorbidity in individuals with asthma. *Thorax*; 65: 612-618.
10. Zhang T, Carleton BC, Prosser RJ, et al. 2009. The added burden of comorbidity in patients with asthma. *J Asthma*; 46: 1021-1026.
11. Grupp-Phelan J, Lozano P, Fishman P. 2001. Healthcare utilization and cost in children with asthma and selected comorbidities. *J Asthma*; 38: 363-373.
12. Blanchette CM, Gutierrez B, Ory C, et al. 2008. Economic burden in direct costs of concomitant chronic obstructive pulmonary disease and asthma in a medicare advantage population. *J Manag Care Pharm*; 14: 176-185.
13. Soriano JB, Visick GT, Muellerova H, et al. 2005. Patterns of comorbidities in newly diagnosed COPD and asthma in primary care. *Chest*; 128: 2099-2107.
14. Wijnhoven HA, Kriegsman DM, Hesselink AE, et al. 2003. The influence of co-morbidity on health-related quality of life in asthma and COPD patients. *Respir Med*; 97: 468-475.
15. Lehrer PM, Karavidas MK, Lu SE, et al. 2008. Psychological treatment of comorbid asthma and panic disorder: a pilot study. *J Anxiety Disord*; 22: 671-683.
16. Deshmukh VM, Toelle BG, Usherwood T, et al. 2008. The association of comorbid anxiety and depression with asthma-related quality of life and symptom perception in adults. *Respirology*; 13: 695-702.
17. Gershon AS, Guan J, Wang C, et al. 2012. Describing and quantifying asthma comorbidity: a population study. *Plos One*; 7: e34967.
18. Corren, J. (2013) Asthma Phenotypes and Endotypes: An evolving paradigm for classification. *Discovery Medicine*
19. Ben-Noun L (2001) Characteristics of comorbidity in adult asthma. *Public Health Rev:29*(1) pp:49-61.
20. Centre for Disease Control (CDC) (2015), Child Development. http://www.cdc.gov/ncbddd/childdevelopment/positiveparenting/middle.html
21. Liberatos P, Link BG, Kelsey JL. The measurement of social class in epidemiology. Epidemiol Rev 1988;10:87–121.
22. National Institute of Health. Drummond Checklist. Health Economics Information Resources: A Self-Study Course http://www.nlm.nih.gov/nichsr/edu/healthecon/drummond_list.html

23. PRISMA-P Checklist (2015) http://www.systematicreviewsjournal.com/content/4/1/1
24. Begg CB, Mazumdar M.(1994). Operating characteristics of a rank correlation test for publication bias. Biometrics: *50,* pp:1088-101.
25. Egger M, Smith GD, Schneider M, Minder C. (1997) Bias in meta-analysis detected by a simple Graphical test. *BMJ*: *315*, pp:629-34.
26. Cazzola, M., Calzetta, L., Bettoncelli, G.,Novelli, L., Cricelli & Rogliani P. (2011) Asthma and comorbid medical illness. *European Respiratory Journal: 38*(1) pp:42-49
27. Zhang, T., Carleton, B.C., Prosser, R.J & Smith, A.M (2009) *Journal of Asthma: 46*(10) pp:1021-1026
28. Patel, M.R., Leo, H.L., Baptist, A.P., Cao, Y., & Brown, R.W. (2015) *Journal of Allergy and Clinical Immunology: 135*(6) pp:1444-1449
29. Yeh, K, Yu, C, Horng, J, Huang J. (2011) Trend of Asthma Comorbidities of Sleep Apnea, Obesity, and Gastroesophageal Reflux - A 5-year Population Survey. *The Journal of Allergy and Clinical Immunology: 129*(2) pp:AB147
30. Sapra, S, Nielsen, K, Martin, B.C. (2005) The Net Cost of Asthma to North Carolina Medicaid and the Influence of Comorbidities that Drive Asthma Costs. *Journal of Asthma*(42) pp:469–477
31. Sveum R, Bergstrom J, Brottman G, Hanson M, Heiman M, Johns K, Malkiewicz J, Manney S, Moyer L, Myers C, Myers N, O'Brien M, Rethwill M, Schaefer K, Uden (2012) D. Diagnosis and management of asthma. *Institute for Clinical Systems Improvement (ICSI)*. 86 p.
32. Global Asthma Report 2014. The Global Asthma Network (GAN).
33. World Health Organization (WHO) 2013. Asthma Fact Sheet
34. Walker S, Sheikh A. (2005) Self-reported rhinitis is a significant problem for patients with asthma. *Primary Care Respiratory Journal: 14*(2) pp: 83-87.
35. Punekar YS, Sheikh A. (2009) Establishing the sequential progression of multiple allergic diagnoses in a UK birth cohort using the General Practice Research Database. *Clinical & Experimental Allergy: 39*(12) pp:1889-1895
36. Bousquet J, Schünemann HJ, Samolinski B et al (2012). Allergic Rhinitis and its Impact on Asthma (ARIA): achievements in 10 years and future needs. *Journal of Allergy and Clinical Immunology: 130*(5) pp:1049-1062

University of Edinburgh,
Centre for Population Health Sciences
RESEARCH ETHICS SUBGROUP

Proposed Project *(State research question and topic area, and briefly describe method/ data. Specify also countries in which data will be collected.):*

Asthma is typically a life-long disease and affects over 300 million people worldwide. It is responsible for considerable morbidity, mortality and substantial healthcare costs. Effective self-management and pharmacotherapy leading to well controlled asthma is the key management goal. Key indicators of successful asthma control include minimal or no symptoms, no restrictions on activities, optimal pulmonary function, and minimal or no side-effects of treatment. Poor asthma control is believed mainly to result from inadequate / suboptimal treatment and problems with adherence to recommended treatments. An important and hitherto largely ignored consideration however is the impact of co-morbid diseases. A number of conditions (e.g., allergic rhinitis, gastro-oesophageal reflux disease (GORD), obesity, and depression) may occur more frequently in people with asthma than in those without, leading to potential additional difficulties in asthma management. These co-morbid conditions may be associated with poor asthma control, impaired health-related quality of life (HRQoL) and increased health and social care utilisation. The systematic identification and mapping of these co-morbid conditions may lead to customised targeted treatment, which in turn offers the potential to substantially improve outcomes in patients with asthma, and thereby reduce the need for health and social care.
There are a number of international studies investigating asthma co-morbidity, impact on asthma control and HRQoL, and consequent healthcare and societal burden, but their results vary depending on the populations studied and the particular co-morbid conditions that are the focus of these investigations. There is a need therefore for a systematic investigation into the range of asthma comorbidities and how these vary with different asthma phenotypes and endotypes. This scoping review aims to fill this need and in addition identify important research gaps in understanding the relationship between asthma and its co-morbidities.
Specifically, we aim to:

- Systematically search the relevant literature to produce a comprehensive account of asthma co-morbidities;
- Describe how these co-morbidities vary with different asthma phenotypes and endotypes;
- Understand the trajectories for the development of these co-morbidities;
- Identify gaps in our current knowledge in relation to understanding patterns of asthma-related co-morbidities.

Methods and analysis
Undertake a scoping review to synthesise the evidence on the co-morbid conditions associated with asthma and asthma phenotypes and describe the trajectories of development.
We will systematically search the following electronic databases: Medline, EMBASE, ISI Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycINFO, and Google Scholar. Additional literature will be identified by searching the reference list of identified eligible studies and by searching the repositories of international conference proceedings, including ISI Conference Proceeding Citation Index, and ZETOC (British Library).

Self-Audit Checklist for Level 1 Ethical Review for PGR projects

See **Intra** website for further information: http://www.cphs.mvm.ed.ac.uk/intra/research/ethicalReview.php

NOTE to student: *Completion of this form should be under the **oversight** of your supervisor. A good strategy would be to complete a draft as best you can, then discuss with your supervisor before completing a final copy for your supervisor to sign.*

1. Bringing the University into disrepute

Is there any aspect of the proposed research which might bring the University into disrepute? **NO**

2. Data protection and consent

Are there any issues of DATA PROTECTION or CONSENT which are NOT adequately dealt with via established procedures? **NO**

These include well-established sets of undertakings. For example, a 'No' answer is justified *only if*:

(a) There is compliance with the University of Edinburgh's Data Protection procedures (see www.recordsmanagement.ed.ac.uk);

(b) Respondents give consent regarding the collection, storage and, if appropriate, archiving and destruction of data;

(c) Identifying information (eg consent forms) is held separately from data;

(d) There is Caldicott Guardian approval for (or approval will be obtained prior to) obtaining/ analysing NHS patient-data.

(e) There are no other special issues arising about confidentiality/consent.

3. Study participants

Will a study researcher be in direct contact with participants to collect data, whether face-to-face, or by telephone, electronic means or post, or by observation? (eg interviews, focus groups, questionnaires, assessments) **NO**

4. Duty to disseminate research findings

Are there issues which will prevent all relevant stakeholders having access to a clear, understandable and accurate summary of the research findings if they wish?* **NO**

** If, and only if, you answered 'yes' to 3 above, 'stakeholders' includes participants in the research*

5. Moral issues and Researcher/Institutional Conflicts of Interest

Are there any SPECIAL MORAL ISSUES/CONFLICTS OF INTEREST? **NO**

(a) An example of conflict of interest for a researcher would be a financial or non-financial benefit for him/herself or for a relative of friend.

(b) Particular moral issues or concerns could arise, for example where the purposes of research are concealed, where respondents are unable to provide informed consent, or where research findings could impinge negatively/ differentially upon the interests of participants.

(c) Where there is a dual relationship between researcher and participant (eg where research is undertaken by practitioners so that the participant might be unclear as to the distinction between 'care' and research)

6. Potential physical or psychological harm, discomfort or stress

(a) Is there a FORSEEABLE POTENTIAL for PSYCHOLOGICAL HARM or STRESS for participants? **NO**

(b) Is there a FORSEEABLE POTENTIAL for PHYSICAL HARM or DISCOMFORT for participants? **NO**

(c) Is there a FORSEEABLE RISK to the researcher? **NO**

Examples of issues/ topics that have the potential to cause psychological harm, discomfort or distress and should lead you to answer 'yes' to this question include, but are not limited to:

relationship breakdown; bullying; bereavement; mental health difficulties; trauma / PTSD; violence or sexual violence; physical, sexual or emotional abuse in either children or adults.

7. Vulnerable participants

Are any of the participants or interviewees in the research considered to be vulnerable? e.g. children and young people under age of 16, people who are in custody or care, marginalised/stigmatised groups **NO**

8. Protection of research subject confidentiality

Are there any issues of CONFIDENTIALITY which are NOT adequately handled by normal tenets of confidentiality for academic research? **NO**

These include well-established sets of undertakings that should be agreed with collaborating and participating individuals/organisations. For example, a 'No' answer is justified *only if*:

(a) There will be no attribution of individual responses;

(b) Individuals (and, where appropriate, organisations) are anonymised in stored data, publications and presentation;

(c) There has been specific agreement with respondents regarding feedback to collaborators and publication.

Overall assessment

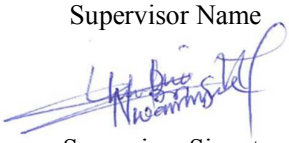
➢ If every answer above is a definite NO, the self-audit has been conducted and confirms the ***ABSENCE OF REASONABLY FORESEEABLE ETHICAL RISKS*** – *please tick box* [X]

This means that regarding this study, as currently self-audited, no further ethical review actions are required within CPHS. However, if in the coming weeks/months there is any change to the

*research plan envisaged now (and outlined above), the study should be **re-audited** against a Level 1 form, because it may be that the change made negates the absence of ethical risks signed off here.*

- If one or more answers are YES, then risks have been identified and prior to commencing any data collection **formal ethical review** is required - either:
  - ~ by NHS REC (NB copy of ethics application and decision letter to be sent to CPHS Ethics); or
  - ~ if not to be formally reviewed by NHS REC, then CPHS level 2/3 ethical review required. *[If either of 5 or 7 are answered 'yes' then almost certainly level 3 is required.]*

Two copies of this form should be taken for inclusion in the final dissertation and the original should be returned to the CPHS Ethics administrator.

Karim El Ferkh	Professor Bright Nwaru
Student Name	Supervisor Name
	
Student Signature	Supervisor Signature *

*** NOTE to supervisor:** *The CPHS Ethics Subgroup will not check this form (the light touch Level 1 form means we have insufficient detail to do so). By counter-signing this check-list as truly warranting all 'No' answers, **you** are taking responsibility, on behalf of CPHS and UoE, that the research proposed truly poses no potential ethical risks. Therefore, if there is any doubt on any issue, it would be a wise precaution to mark it as 'uncertain' and contact the Ethics Subgroup as to whether a level 2 form might be required as well. (See Intra Ethics website – URL at top of form)*

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page number
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
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 (such as PROSPERO) and registration number	NA
Authors:			
Contact	3a	Provide name, institutional affiliation, 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	7
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	7
Sponsor	5b	Provide name for the review funder and/or sponsor	7
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	3-4
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	4-5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5

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	8-14
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	5-6
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	5-6
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	5
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	NA
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	4
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	NA
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	6
	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 (such as I^2, Kendall's τ)	6
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	6
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	6
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as 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 (such as GRADE)	NA

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

Investigating asthma co-morbidities: a systematic scoping review protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2015-010548.R1
Article Type:	Protocol
Date Submitted by the Author:	21-Apr-2016
Complete List of Authors:	El Ferkh, Karim; University of Edinburgh, Centre for Population Health Sciences Nwaru, Bright; The University Of Edinburgh, Allergy & Respiratory Research Group, Centre for Population Health Sciences Griffiths, Chris; Queen Mary University of London, Centre for Primary Care and Public Health Sheikh, Aziz; University of Edinburgh, Division of Community Health Sciences
Primary Subject Heading:	Immunology (including allergy)
Secondary Subject Heading:	Immunology (including allergy), Respiratory medicine, Epidemiology
Keywords:	Asthma < THORACIC MEDICINE, Allergy < THORACIC MEDICINE, Epidemiology < THORACIC MEDICINE, Immunology < THORACIC MEDICINE

Investigating asthma co-morbidities: a systematic scoping review protocol

Karim El Ferkh,[1] Bright Nwaru,[1,2] Chris Griffiths,[3] Aziz Sheikh A.[1]

[1]Asthma UK Centre for Applied Research, Centre for Medical Informatics, Usher Institute for Population Health Sciences, The University of Edinburgh

[2]School of Health Sciences, University of Tampere, Finland

[3]Asthma UK Centre for Applied Research, Centre for Primary Care and Public Health, Blizard Institute, Queen Mary, University of London

Correspondence to: Karim El Ferkh

Asthma UK Centre for Applied Research,

Usher Institute of Population Health Sciences and Informatics

The University of Edinburgh,

Rm 815, Doorway 3, Medical School,

Teviot Place, EH8 9AG

Edinburgh, United Kingdom

Tel: +44 (0)131 650 3232

Email: k.firikh@ed.ac.uk

Keywords: Asthma, co-morbidity, systematic scoping review, global health.

Abstract

Introduction: Asthma is a common long-term disorder with a number of related co-morbid conditions, which may impact asthma outcomes. There is a need for greater appreciation for understanding how these comorbidities interact with asthma in order to improve asthma outcomes.

Objectives: To systematically identify and map out key asthma comorbidities.

Methods: We will systematically search the following electronic databases: Medline, EMBASE, ISI Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycINFO, and Google Scholar. Additional literature will be identified by searching the reference list of identified eligible studies and by searching the repositories of international conference proceedings, including ISI Conference Proceeding Citation Index, and ZETOC (British Library).

Dissemination: The findings from this systematic scoping review will be reported at scientific meetings and published in a peer-reviewed journal.

Strengths and limitations:

- To our knowledge this is the first review undertaken to map out the full-spectrum of asthma co-morbidity hence evidence generated from the review will be important in shaping the direction of the field.
- The scoping review will be limited to the past 5 years only, but aimed to map the most contemporaneous evidence on asthma co-morbidity.
- As a scoping review, formal quality assessment and risk of bias will not be undertaken on studies to be included in the review.

Background

Asthma is typically a life-long disease and affects over 300 million people worldwide [1]. It is responsible for considerable morbidity, mortality and substantial healthcare costs[1, 2]. Effective self-management and pharmacotherapy leading to well controlled asthma is the key management goal [3-5]. Key indicators of successful asthma control include minimal or no symptoms, no restrictions on activities, optimal pulmonary function, and minimal or no side-effects of treatment [3-6]. Poor asthma control is believed mainly to result from inadequate / suboptimal treatment and problems with adherence to recommended treatments [4, 5]. An important consideration as well is the impact of co-morbid diseases on asthma [4, 5, 7-10]. Many definitions exist for asthma as there is a significant proportion of heterogeneity; the definition adopted here is a doctor-diagnosed or patient-reported asthma ever.

The presence of more than one different condition in a person is the widely suggested concept for co-morbidity [11]. The doctor-diagnosed diseases should be linked to the International Classification of Diseases (ICD) regardless of their chronological occurrence (before or after the index condition: asthma). The importance of co-morbidities lies not only in their presence but also in their severity that can be used to convey the concept of "burden of disease" [11]. The Charlson Index is commonly used to compare and understand the complexity of co-existing diseases. A number of conditions (e.g., allergic rhinitis, gastro-oesophageal reflux disease (GORD), obesity, and depression) may occur more frequently in people with asthma than in those without, leading to potential additional difficulties in asthma management [12, 13]. These co-morbid conditions may be associated with poor asthma control, impaired health-related quality of life (HRQoL) and increased health and social care utilisation [12-19]. The systematic identification and mapping of these co-morbid conditions

may lead to customised targeted treatment, which in turn offers the potential to substantially improve outcomes in patients with asthma, and thereby reduce the need for health and social care [4, 12, 19, 20].

There are a number of international studies investigating asthma co-morbidity, impact on asthma control and HRQoL, and consequent healthcare and societal burden, but their results vary depending on the populations studied and the particular co-morbid conditions that are the focus of these investigations [21-23]. There is a need therefore for a systematic investigation into the range of asthma comorbidities. This scoping review aims to fill this need and in addition identify important research gaps in understanding the relationship between asthma and its co-morbidities. It will not focusing on studies that have looked at the association between asthma and other diseases and vice versa but on studies that have investigated the impact of other disease conditions on asthma outcomes.

Methods

Eligibility criteria

Types of studies

Cohort studies, case-control studies and cross-sectional studies will be eligible for inclusion. We will exclude editorials, animal studies, reviews, randomised controlled trials (RCTs), quasi-RCTs, case studies, and case-series.

Participants

We are interested in studies on participants of any age with a clinical diagnosis of asthma.

Asthma and the co-morbidities of interest

As this is only a scoping review, our aim is to uncover the various approaches that have been employed including the definition of asthma that authors have employed. Therefore, restricting ourselves to a specific definition of asthma may also be restrictive to our objective of the scoping systematic review.

The comorbidities that we are interested in are those which are an impact of asthma that exacerbate its management and prognosis (e.g effect of asthma), regardless of whether they develop before or after asthma. We will also group comorbidities according to the Charlson Comorbidity Index; a method of categorizing comorbidities of patients based on the ICD

diagnosis codes. We are interested in studies on asthma co-morbidities; these are likely to include, but are not limited to: allergic diseases, cardiovascular diseases chronic obstructive pulmonary disease (COPD), autoimmune disorders (e.g. type 1 diabetes), metabolic disorders (e.g. type 2 diabetes, obesity), cardiovascular diseases, eosinophilic diseases, psychological dysfunction (anxiety, depression), hypertension, cardiovascular diseases and GORD.

Search methods

Databases

We will identify published studies from the following databases: Medline, EMBASE, ISI Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycINFO, and Google Scholar. Additional literature will be identified by searching the reference list of identified eligible studies and by searching the repositories of international conference proceedings, including ISI Conference Proceeding Citation Index, and ZETOC (British Library). Unpublished literature and ongoing studies will be identified by searching the following registries: ISI Conference Proceedings Citation Index via Web of Knowledge.

Search strategy

A highly sensitive search strategy has been developed in each of the six databases to capture the broad literature on the topic (see appendix). Using bibliographic databases and health-oriented search engines,

In order to maximise the sensitivity of our search, we are not restricting our overall strategy to topic searches in literature databases, but are also taking these steps: consulting with experts in the field; looking in clinical trials registers; looking in conference proceedings; looking in grey literature such as PhD theses; doing forward and backward citation tracking; interrogating the websites of key organisations; hand-searching journals. We will search from March 2014 until March 2016. Although it is well known for a long time now that researchers have been studying asthma as a heterogeneous disease affected by multiple co-morbidities, however the evidence on asthma and co-morbidities increased exponentially in the past years. In addition, our preliminary search provided over 20,000 records from one database; this 2-year time frame will enable us to achieve our objectives in a pragmatic manner.

Study Selection

The articles retrieved from the search strategy will be screened according to the review inclusion and exclusion criteria. The titles and abstracts will be independently screened by two investigators for potentially eligible studies, and when there is a difference in opinions, discussions will be undertaken to reach a consensus on each paper. If an agreement is not reached, a third reviewer will arbitrate. Full text of potentially relevant studies will be retrieved and screened independently by two reviewers, consensus will be done through discussions, and arbitration by a third reviewer if no agreement reached on any study. All the studies not meeting the inclusion criteria will be excluded. Study screening will be undertaken and reported according to the Preferred Reporting Items for Systematics Reviews and Meta-analyses' (PRISMA) recommendation [24].

Data Extraction

A customised data extraction form will be constructed to extract all relevant data from each study. The data extraction form will be piloted on a few of the eligible studies to evaluate its reliability in capturing the study data of interest. Data extraction will be undertaken independently by two reviewers. Any disagreements will be resolved by discussion or arbitration by a third reviewer. Descriptive summary tables will be produced to recapitulate the evidence base. The following data will be extracted:

- Author(s) and date
- Geographical location
- Research design
- Aims
- Research questions
- Methods
- Settings
- Participants (N, mean age, gender if available)
- Co-morbidities studied
- Key findings

- Research gaps identified

An initial map will be developed to explore the main comorbidities associated with asthma. Then the findings will be synthesized in a descriptive and a narrative review and summarized in a concise table to facilitate the comparisons of different co-morbidities. The replication of results and discrepancies will be investigated. The results will be then stratified according to different age groups, gender, and other relevant indicators of interest. The scoping review designed will be developed according to the Levac's et al framework [25] and the reporting will follow the PRISMA checklist [24].

Conclusions

This systematic scoping review will provide a comprehensive overview of asthma co-morbidities. We expect to report in the summer of 2016.

Ethics and Dissemination

As there are no primary data collected, there will be need for formal NHS ethical review. The systematic scoping review will presented at a relevant conference and be published in a peer-reviewed journal.

Footnotes

Funding:

This work is supported by the Chief Scientist's Office of the Scottish Government and Asthma UK as part of the Asthma UK Centre for Applied Research [AUK-AC-2012-01]. BN is supported by the Farr Institute and Asthma UK Centre for Applied Research.

Conflicts of interest:

None declared.

Contributorship:

All authors have made substantive intellectual contributions to the development of this protocol. KF was involved in writing this protocol. AS, CG and BN commented critically on several drafts of the manuscript. KF, AS, BN were involved in conceptualising this review.

References

1. (GAN), G.A.N., *Global Asthma Report 2014.* 2014.
2. Organization, W.H., *Asthma Fact Sheet.* 2013.
3. (GINA), G.I.f.A., *Global Strategy for Asthma Management and Prevention.* 2012.
4. Boulet, L., *Influence of comorbid conditions on asthma.* European Respiratory Journal, 2009. **33**(4): p. 897-906.
5. Boulet, L. and M. Boulay, *Asthma-related comorbidities. Expert Rev Respir Med 2011; 5: 377-393.* External Resources Pubmed/Medline (NLM) CrossRef (DOI).
6. Bateman, E.D., et al., *Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma ControL study.* American journal of respiratory and critical care medicine, 2004. **170**(8): p. 836-844.
7. Cazzola, M., et al., *Asthma and comorbid medical illness.* European Respiratory Journal, 2011. **38**(1): p. 42-49.
8. Cazzola, M., et al., *Comorbidities of asthma: current knowledge and future research needs.* Current opinion in pulmonary medicine, 2013. **19**(1): p. 36-41.
9. De Groot, E., E. Duiverman, and P. Brand, *Comorbidities of asthma during childhood: possibly important, yet poorly studied.* European Respiratory Journal, 2010. **36**(3): p. 671-678.
10. Ledford, D.K. and R.F. Lockey, *Asthma and comorbidities.* Current opinion in allergy and clinical immunology, 2013. **13**(1): p. 78-86.
11. Valderas, J.M., et al., *Defining comorbidity: implications for understanding health and health services.* The Annals of Family Medicine, 2009. **7**(4): p. 357-363.
12. Gershon, A.S., et al., *Burden of comorbidity in individuals with asthma.* Thorax, 2010. **65**(7): p. 612-618.
13. Zhang, T., et al., *The added burden of comorbidity in patients with asthma.* Journal of Asthma, 2009. **46**(10): p. 1021-1026.
14. Blanchette, C.M., et al., *Economic burden in direct costs of concomitant chronic obstructive pulmonary disease and asthma in a Medicare Advantage population.* Journal of Managed Care Pharmacy, 2008. **14**(2): p. 176-185.
15. Deshmukh, V.M., et al., *The association of comorbid anxiety and depression with asthma-related quality of life and symptom perception in adults.* Respirology, 2008. **13**(5): p. 695-702.
16. Grupp-Phelan, J., P. Lozano, and P. Fishman, *Health care utilization and cost in children with asthma and selected comorbidities.* Journal of Asthma, 2001. **38**(4): p. 363-373.
17. Lehrer, P.M., et al., *Psychological treatment of comorbid asthma and panic disorder: a pilot study.* Journal of anxiety disorders, 2008. **22**(4): p. 671-683.
18. Soriano, J.B., et al., *Patterns of comorbidities in newly diagnosed COPD and asthma in primary care.* Chest Journal, 2005. **128**(4): p. 2099-2107.
19. Wijnhoven, H., et al., *The influence of co-morbidity on health-related quality of life in asthma and COPD patients.* Respiratory medicine, 2003. **97**(5): p. 468-475.
20. Gershon, A.S., et al., *Correction: Describing and Quantifying Asthma Comorbidity: A Population Study.* PloS one, 2013. **8**(1).
21. Punekar, Y. and A. Sheikh, *Establishing the sequential progression of multiple allergic diagnoses in a UK birth cohort using the General Practice Research Database.* Clinical & Experimental Allergy, 2009. **39**(12): p. 1889-1895.
22. ROMANO, A., *Allergic Rhinitis and its Impact on Asthma (ARIA): Achievements in 10 years and future needs.* JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, 2012(Ottobre): p. N/A-N/A.

23. Walker, S. and A. Sheikh, *Self reported rhinitis is a significant problem for patients with asthma.* Primary Care Respiratory Journal, 2005. **14**(2): p. 83-87.
24. Moher, D., et al., *Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement.* Systematic reviews, 2015. **4**(1): p. 1.
25. Levac, D., H. Colquhoun, and K.K. O'Brien, *Scoping studies: advancing the methodology.* Implement Sci, 2010. **5**(1): p. 1-9.

Appendix

Search Strategy

I. Medline

1. asthma.mp. or exp Asthma/
2. exp Comorbidity/ or co-morbidity.mp.
3. multimorbidity.mp.
4. exp Hypersensitivity/ or Allergens/ or Hypersensitivity, Immediate/ or atopy.mp. or exp Immunoglobulin E/ or exp Dermatitis, Atopic/
5. allergic rhinitis.mp. or exp Rhinitis, Allergic/
6. food allergy.mp. or exp Food Hypersensitivity/
7. exp Anaphylaxis/ or anaphylaxis.mp.
8. exp Urticaria/ or urticaria.mp.
9. exp Celiac Disease/ or Autoantibodies/ or exp Autoimmune Diseases/ or autoimmune disorder.mp. or exp Diabetes, Type 1/ or exp eosinophilic disorder
10. Thymus Neoplasms/ or endocrine disorder.mp. or Thyroid Gland/ or exp Endocrine System Diseases/ or Thyroid Diseases/
11. exp Obesity/ or exp Diabetes, Type 2/ or metabolic disorder.mp.
12. exp Depression/ or exp Mental Disorder/ or exp Stress, Psychological/ or psychological dysfunction.mp. or Stress Disorder, Post-Traumatic/
13. panic disorders.mp. or exp Panic Disorder/
14. exp Anxiety/ or anxiety.mp.
15. chronic obstructive pulmonary disease.mp. or exp Pulmonary Disease, Chronic Obstructive/
16. exp Hypertension/ or hypertension.mp.
17. exp Gastroesophageal Reflux/ or gastro-oesophageal reflux disease.mp.
18. exp Sleep Apnea, Obstructive/ or exp Sleep Disorder/ or Sleep Apnea Syndromes/ or obstructive sleep apnoea.mp. or Apnea/
19. cardiovascular disease.mp. or exp Cardiovascular Diseases/
20. 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. 1 and 20
22. cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or retrospective studies/ or cohort.ti,ab. or longitudinal.ti,ab. or prospective.ti,ab. or retrospective.ti,ab.
23. Case-Control Studies/ or Control Groups/ or Matched-Pair Analysis/ or ((case* adj5 control*) or (case adj3 comparison*) or control group*).ti,ab.
24. Cross-Sectional Studies/ or cross-sectional.ti,ab. or ("prevalence study" or "incidence study" or "prevalence studies" or "incidence studies" or "transversal studies" or "transversal study").ti,ab.
25. 22 or 23 or 24
26. 21 and 25
27. limit 26 to yr="2011 -Current"

II. EMBASE

1. asthma.mp. or exp Asthma/
2. exp Comorbidity/ or co-morbidity.mp.
3. multimorbidity.mp.
4. exp Hypersensitivity/ or Allergens/ or Hypersensitivity, Immediate/ or atopy.mp. or exp Immunoglobulin E/ or exp Dermatitis, Atopic/
5. allergic rhinitis.mp. or exp Rhinitis, Allergic/
6. food allergy.mp. or exp Food Hypersensitivity/
7. exp Anaphylaxis/ or anaphylaxis.mp.
8. exp Urticaria/ or urticaria.mp.
9. exp Celiac Disease/ or Autoantibodies/ or exp Autoimmune Diseases/ or autoimmune disorder.mp. or exp Diabetes, Type 1/
10. Thymus Neoplasms/ or endocrine disorder.mp. or Thyroid Gland/ or exp Endocrine System Diseases/ or Thyroid Diseases/
11. exp Obesity/ or exp Diabetes, Type 2/ or metabolic disorder.mp.
12. exp Depression/ or exp Mental Disorder/ or exp Stress, Psychological/ or psychological dysfunction.mp. or Stress Disorder, Post-Traumatic/
13. panic disorders.mp. or exp Panic Disorder/
14. exp Anxiety/ or anxiety.mp.
15. chronic obstructive pulmonary disease.mp. or exp Pulmonary Disease, Chronic Obstructive/
16. exp Hypertension/ or hypertension.mp.
17. exp Gastroesophageal Reflux/ or gastro-oesophageal reflux disease.mp.
18. exp Sleep Apnea, Obstructive/ or exp Sleep Disorder/ or Sleep Apnea Syndromes/ or obstructive sleep apnoea.mp. or Apnea/
19. cardiovascular disease.mp. or exp Cardiovascular Diseases/
20. 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. 1 and 20
22. cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or retrospective studies/ or cohort.ti,ab. or longitudinal.ti,ab. or prospective.ti,ab. or retrospective.ti,ab.
23. Case-Control Studies/ or Control Groups/ or Matched-Pair Analysis/ or ((case* adj5 control*) or (case adj3 comparison*) or control group*).ti,ab.
24. Cross-Sectional Studies/ or cross-sectional.ti,ab. or ("prevalence study" or "incidence study" or "prevalence studies" or "incidence studies" or "transversal studies" or "transversal study").ti,ab.
25. 22 or 23 or 24
26. 21 and 25
27. limit 26 to yr="2011 -Current"

III. Web of Science

#4 #3 AND #2 AND #1
Timespan=2011-2015
Search language=Auto
#3 TOPIC: ("cohort study") OR TOPIC: ("longitudinal study") OR TOPIC: ("follow-up study") OR TOPIC: ("prospective study") OR TOPIC: ("retrospective study") OR TOPIC: (cohort) OR TOPIC: (longitudinal) OR TOPIC: (prospective) OR TOPIC: (retrospective) OR TOPIC: ("Case-Control") OR TOPIC: ("Matched-Pair Analysis") OR TOPIC: ("Cross-Sectional") OR TOPIC: ("prevalence study") OR TOPIC: ("incidence study")
Timespan=2011-2015
Search language=Auto
#2 TOPIC: (TOPIC: (Comorbidit*) OR TOPIC: (multimorbidit*) OR TOPIC: (Hypersensitivity) OR TOPIC: (Allerg*) ORTOPIC: ("allergic rhinitis") OR TOPIC: ("Food Hypersensitivity") OR TOPIC: ("food allerg*") ORTOPIC: (Anaphylaxis) OR TOPIC: (Urticaria) OR TOPIC: ("Autoimmune Disease") OR TOPIC:("Autoimmune disorder") OR TOPIC: ("Diabetes") OR TOPIC: ("endocrine disorder") ORTOPIC: ("Thyroid disorder") OR TOPIC: ("metabolic disorder") OR TOPIC: (obesity) OR TOPIC:("Psychological disorder") OR TOPIC: ("Panic Disorder") OR TOPIC: (Anxiety) OR TOPIC: ("chronic obstructive pulmonary disease") OR TOPIC: ("Pulmonary Disease") OR TOPIC: (Hypertension) ORTOPIC: ("gastro-oesophageal reflux disease") OR TOPIC: ("cardiovascular disease") OR TOPIC:("Sleep Apnea"))
Timespan=2011-2015
Search language=Auto
#1 TOPIC: (asthma)
Timespan=2011-2015
Search language=Auto

IV. CINAHL

Query Limiters/Expanders Last Run Via Results Action
S30 S27 AND S28 Limiters - Publication Year: 2011-2015
Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 1,391 Edit S30
S29 S27 AND S28 Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 3,845 Edit S29
S28 S23 OR S24 OR S25 Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 411,852 Edit S28
S27 S1 AND S26 Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 27,111 Edit S27
S26 S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 748,799 Edit S26
S25 (MH "Cross Sectional Studies") OR "Cross-Sectional Studies" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 108,137 Edit S25
S24 (MH "Case Control Studies") OR "Case-Control Studies" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 51,374 Edit S24
S23 (MH "Prospective Studies") OR "cohort studies" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 277,306 Edit S23
S22 (MH "Cardiovascular Diseases+") OR "cardiovascular disease" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 386,904 Edit S22
S21 (MH "Sleep Apnea Syndromes+") OR (MH "Sleep Apnea, Obstructive") OR "Sleep Apnea" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 10,336 Edit S21
S20 (MH "Gastroesophageal Reflux") OR "Gastroesophageal Reflux" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 5,683 Edit S20

S19 (MH "Hypertension+") OR "Hypertension" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 65,449 Edit S19
S18 (MH "Pulmonary Disease, Chronic Obstructive+") OR "chronic obstructive pulmonary disease" OR (MH "Lung Diseases, Obstructive+") Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 43,363 Edit S18
S17 (MH "Anxiety+") OR "Anxiety" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 52,157 Edit S17
S16 (MH "Panic Disorder") OR "panic disorder" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 1,682 Edit S16
S15 (MH "Depression+") OR "Depression" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 98,022 Edit S15
S14 (MH "Diabetes, Type 2") OR (MH "Diabetes, Type 1+") OR (MH "Diabetes +") OR "Diabetes" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 112,269 Edit S14
S13 (MH "Obesity+") OR "Obesity" OR (MH "Obesity, Morbid") Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 73,423 Edit S13
S12 "metabolic disorder" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 304 Edit S12
S11 "endocrine disorder" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 117 Edit S11
S10 (MH "Thyroid Diseases+") OR "Thyroid Diseases" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 10,471 Edit S10
S9 (MH "Autoimmune Diseases") OR "Autoimmune Diseases" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 5,816 Edit S9
S8 (MH "Celiac Disease") OR "Celiac Disease" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 3,248 Edit S8

S7 (MH "Urticaria") OR "Urticaria" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 1,505 Edit S7
S6 (MH "Anaphylaxis") OR "Anaphylaxis" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 3,208 Edit S6
S5 (MH "Food Hypersensitivity") OR "food allergy" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 3,880 Edit S5
S4 (MH "Rhinitis, Allergic, Perennial") OR (MH "Rhinitis, Allergic, Seasonal") OR (MH "Dermatitis, Atopic") Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 4,023 Edit S4
S3 (MH "Hypersensitivity+") OR (MH "Hypersensitivity, Immediate") Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 49,092 Edit S3
S2 (MH "Comorbidity") Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 38,672 Edit S2
S1 (MH "Asthma+") OR "asthma" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 29,402

V. PsycINFO

1. asthma.mp. or exp Asthma/
2. exp Comorbidity/ or co-morbidity.mp.
3. multimorbidity.mp.
4. exp Hypersensitivity/ or Allergens/ or Hypersensitivity, Immediate/ or atopy.mp. or exp Immunoglobulin E/ or exp Dermatitis, Atopic/
5. allergic rhinitis.mp. or exp Rhinitis, Allergic/
6. food allergy.mp. or exp Food Hypersensitivity/
7. exp Anaphylaxis/ or anaphylaxis.mp.
8. exp Urticaria/ or urticaria.mp.
9. exp Celiac Disease/ or Autoantibodies/ or exp Autoimmune Diseases/ or autoimmune disorder.mp. or exp Diabetes, Type 1/
10. Thymus Neoplasms/ or endocrine disorder.mp. or Thyroid Gland/ or exp Endocrine System Diseases/ or Thyroid Diseases/
11. exp Obesity/ or exp Diabetes, Type 2/ or metabolic disorder.mp.
12. exp Depression/ or exp Mental Disorder/ or exp Stress, Psychological/ or psychological dysfunction.mp. or Stress Disorder, Post-Traumatic/
13. panic disorder.mp. or exp Panic Disorder/
14. exp Anxiety/ or anxiety.mp.
15. chronic obstructive pulmonary disease.mp. or exp Pulmonary Disease, Chronic Obstructive/
16. exp Hypertension/ or hypertension.mp.
17. exp Gastroesophageal Reflux/ or gastro-oesophageal reflux disease.mp.
18. exp Sleep Apnea, Obstructive/ or exp Sleep Disorder/ or Sleep Apnea Syndromes/ or obstructive sleep apnoea.mp. or Apnea/
19. cardiovascular disease.mp. or exp Cardiovascular Disease/
20. 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. 1 and 20
22. cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or retrospective studies/ or cohort.ti,ab. or longitudinal.ti,ab. or prospective.ti,ab. or retrospective.ti,ab.
23. Case-Control Studies/ or Control Groups/ or Matched-Pair Analysis/ or ((case* adj5 control*) or (case adj3 comparison*) or control group*).ti,ab.
24. Cross-Sectional Studies/ or cross-sectional.ti,ab. or ("prevalence study" or "incidence study" or "prevalence studies" or "incidence studies" or "transversal studies" or "transversal study").ti,ab.
25. 22 or 23 or 24
26. 21 and 25
27. limit 26 to yr="2011 -Current"

VI. Google Scholar (first 500 results will be considered)

1. Asthma and comorbidit*

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page number
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
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 (such as PROSPERO) and registration number	NA
Authors:			
Contact	3a	Provide name, institutional affiliation, 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	7
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	7
Sponsor	5b	Provide name for the review funder and/or sponsor	7
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	3-4
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	4-5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5

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	8-14
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	5-6
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	5-6
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	5
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	NA
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	4
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	NA
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	6
	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 (such as I^2, Kendall's τ)	6
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	6
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	6
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as 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 (such as GRADE)	NA

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

Investigating asthma co-morbidities: a systematic scoping review protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2015-010548.R2
Article Type:	Protocol
Date Submitted by the Author:	30-Jun-2016
Complete List of Authors:	El Ferkh, Karim; University of Edinburgh, Centre for Population Health Sciences Nwaru, Bright; The University Of Edinburgh, Allergy & Respiratory Research Group, Centre for Population Health Sciences Griffiths, Chris; Queen Mary University of London, Centre for Primary Care and Public Health Sheikh, Aziz; University of Edinburgh, Division of Community Health Sciences
Primary Subject Heading:	Immunology (including allergy)
Secondary Subject Heading:	Immunology (including allergy), Respiratory medicine, Epidemiology
Keywords:	Asthma < THORACIC MEDICINE, Allergy < THORACIC MEDICINE, Epidemiology < THORACIC MEDICINE, Immunology < THORACIC MEDICINE

Investigating asthma co-morbidities: a systematic scoping review protocol

Karim El Ferkh,[1] Bright Nwaru,[1,2] Chris Griffiths,[3] Aziz Sheikh A.[1]

[1]Asthma UK Centre for Applied Research, Centre for Medical Informatics, Usher Institute for Population Health Sciences, The University of Edinburgh

[2]School of Health Sciences, University of Tampere, Finland

[3]Asthma UK Centre for Applied Research, Centre for Primary Care and Public Health, Blizard Institute, Queen Mary, University of London

Correspondence to: Karim El Ferkh

Asthma UK Centre for Applied Research,

Usher Institute of Population Health Sciences and Informatics

The University of Edinburgh,

Rm 815, Doorway 3, Medical School,

Teviot Place, EH8 9AG

Edinburgh, United Kingdom

Tel: +44 (0)131 650 3232

Email: k.firikh@ed.ac.uk

Keywords: Asthma, co-morbidity, systematic scoping review, global health.

Abstract

Introduction: Asthma is a common long-term disorder with a number of related co-morbid conditions, which may impact asthma outcomes. There is a need for greater appreciation for understanding how these comorbidities interact with asthma in order to improve asthma outcomes.

Objectives: To systematically identify and map out key asthma comorbidities.

Methods: We will systematically search the following electronic databases: Medline, EMBASE, ISI Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycINFO, and Google Scholar. Additional literature will be identified by searching the reference list of identified eligible studies and by searching the repositories of international conference proceedings, including ISI Conference Proceeding Citation Index, and ZETOC (British Library).

Dissemination: The findings from this systematic scoping review will be reported at scientific meetings and published in a peer-reviewed journal.

Strengths and limitations:

- To our knowledge this is the first review undertaken to map out the full-spectrum of asthma co-morbidity hence evidence generated from the review will be important in shaping the direction of the field.
- The scoping review will be limited to the past 5 years only, but aimed to map the most contemporaneous evidence on asthma co-morbidity.
- As a scoping review, formal quality assessment and risk of bias will not be undertaken on studies to be included in the review.

Background

Asthma is typically a life-long disease and affects over 300 million people worldwide [1]. It is responsible for considerable morbidity, mortality and substantial healthcare costs[1, 2]. Effective self-management and pharmacotherapy leading to well controlled asthma is the key management goal [3-5]. Key indicators of successful asthma control include minimal or no symptoms, no restrictions on activities, optimal pulmonary function, and minimal or no side-effects of treatment [3-6]. Poor asthma control is believed mainly to result from inadequate / suboptimal treatment and problems with adherence to recommended treatments [4, 5]. An important consideration as well is the impact of co-morbid diseases on asthma [4, 5, 7-10]. Many definitions exist for asthma as there is a significant proportion of heterogeneity; the definition adopted here is a doctor-diagnosed or patient-reported asthma ever.

The presence of more than one condition in a person is the widely suggested concept for co-morbidity [11]. The doctor-diagnosed diseases should be linked to the International Classification of Diseases (ICD) regardless of their chronological occurrence (before or after the index condition: asthma). The importance of co-morbidities lies not only in their presence but also in their severity that can be used to convey the concept of "burden of disease" [11]. The Charlson Index is commonly used to compare and understand the complexity of co-existing diseases. A number of conditions (e.g., allergic rhinitis, gastro-oesophageal reflux disease (GORD), obesity, and depression) may occur more frequently in people with asthma than in those without, leading to potential additional difficulties in asthma management [12, 13]. These co-morbid conditions may be associated with poor asthma control, impaired health-related quality of life (HRQoL) and increased health and social care utilisation [12-19]. The systematic identification and mapping of these co-morbid conditions may lead to

customised, targeted treatment, which in turn offers the potential to substantially improve outcomes in patients with asthma, and thereby reduce the need for health and social care [4, 12, 19, 20].

There are a number of international studies investigating asthma co-morbidity, impact on asthma control and HRQoL, and consequent healthcare and societal burden, but their results vary depending on the populations studied and the particular co-morbid conditions that are the focus of these investigations [21-23]. There is a need therefore for a systematic investigation into the range of asthma comorbidities. This scoping review aims to fill this need and in addition identify important research gaps in understanding the relationship between asthma and its co-morbidities. It will not focus on studies that have looked at the association between asthma and other diseases and vice versa but on studies that have investigated the impact of other conditions on asthma outcomes.

Methods

Eligibility criteria

Types of studies

Cohort studies, case-control studies and cross-sectional studies will be eligible for inclusion. We will exclude editorials, animal studies, reviews, randomised controlled trials (RCTs), quasi-RCTs, case studies, and case-series.

Participants

We are interested in studies on participants of any age with a clinical diagnosis of asthma.

Outcome

Clinical diagnosis of asthma: doctor-diagnosed asthma ever or current assessed subjectively (patient reported) or objectively (health/medical records).

Asthma and the co-morbidities of interest

As this is only a scoping review, our aim is to uncover the various approaches that have been employed including the definition of asthma that authors have employed. Therefore, restricting ourselves to a specific definition of asthma may also be restrictive to our objective of the scoping systematic review.

The comorbidities that we are interested in are those that exacerbate asthma's management and prognosis (e.g effect of asthma), regardless of whether they develop before or after asthma. We will also group comorbidities according to the Charlson Comorbidity Index; a method of categorizing comorbidities of patients based on the ICD diagnosis codes. We are interested in studies on asthma co-morbidities; these are likely to include, but are not limited to: allergic diseases, cardiovascular diseases, chronic obstructive pulmonary disease (COPD), autoimmune disorders (e.g. type 1 diabetes), metabolic disorders (e.g. type 2 diabetes, obesity), eosinophilic diseases, psychological dysfunction (anxiety, depression), hypertension, cardiovascular diseases and GORD.

Search methods

Databases

We will identify published studies from the following databases: Medline, EMBASE, ISI Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycINFO, and Google Scholar. Additional literature will be identified by searching the reference list of identified eligible studies and by searching the repositories of international conference proceedings, including ISI Conference Proceeding Citation Index, and ZETOC (British Library). Unpublished literature and ongoing studies will be identified by searching the following registries: ISI Conference Proceedings Citation Index via Web of Knowledge.

Search strategy

A highly sensitive search strategy has been developed in each of the six databases to capture the broad literature on the topic (see appendix). Using bibliographic databases and health-oriented search engines,

In order to maximise the sensitivity of our search, we are not restricting our overall strategy to topic searches in literature databases, but are also taking these steps: consulting with experts in the field; looking in clinical trials registers; looking in conference proceedings; looking in grey literature such as PhD theses; doing forward and backward citation tracking; interrogating the websites of key organisations; hand-searching journals. We will search from March 2014 until March 2016. Although it is well known that researchers have been studying asthma as a heterogeneous disease affected by multiple co-morbidities, however the evidence

on asthma and co-morbidities increased exponentially in the past years. In addition, our preliminary search provided over 20,000 records from one database; this 2-year time frame will enable us to achieve our objectives in a pragmatic manner.

Study Selection

The articles retrieved from the search strategy will be screened according to the review inclusion and exclusion criteria. The titles and abstracts will be independently screened by two investigators for potentially eligible studies, and when there is a difference in opinions, discussions will be undertaken to reach a consensus on each paper. If an agreement is not reached, a third reviewer will arbitrate. Full text of potentially relevant studies will be retrieved and screened independently by two reviewers, consensus will be done through discussions, and arbitration by a third reviewer if no agreement reached on any study. All the studies not meeting the inclusion criteria will be excluded. Study screening will be undertaken and reported according to the Preferred Reporting Items for Systematics Reviews and Meta-analyses' (PRISMA) recommendation [24].

Data Extraction

A customised data extraction form will be constructed to extract all relevant data from each study. The data extraction form will be piloted on a few of the eligible studies to evaluate its reliability in capturing the study data of interest. Data extraction will be undertaken independently by two reviewers. Any disagreements will be resolved by discussion or arbitration by a third reviewer. Descriptive summary tables will be produced to recapitulate the evidence base. The following data will be extracted:

- Author(s) and date
- Geographical location
- Research design
- Aims
- Research questions
- Methods
- Settings

- Participants (N, mean age, gender if available)
- Co-morbidities studied
- Key findings
- Research gaps identified

An initial map will be developed to explore the main comorbidities associated with asthma. Then the findings will be synthesized in a descriptive and a narrative review and summarized in a concise table to facilitate the comparisons of different co-morbidities. The replication of results and discrepancies will be investigated. The results will be then stratified according to different age groups, gender, and other relevant indicators of interest. The scoping review designed will be developed according to the Levac's et al framework [25] and the reporting will follow the PRISMA checklist [24].

Conclusions

This systematic scoping review will provide a comprehensive overview of asthma co-morbidities. We expect to report in the summer of 2016.

Ethics and Dissemination

As there are no primary data collected, there will be need for formal NHS ethical review. The systematic scoping review will presented at a relevant conference and be published in a peer-reviewed journal.

Footnotes

Funding:

This work is supported by the Chief Scientist's Office of the Scottish Government and Asthma UK as part of the Asthma UK Centre for Applied Research [AUK-AC-2012-01]. BN is supported by the Farr Institute and Asthma UK Centre for Applied Research.

Conflicts of interest:

None declared.

Contributorship:

All authors have made substantive intellectual contributions to the development of this protocol. KF was involved in writing this protocol. AS, CG and BN commented critically on several drafts of the manuscript. KF, AS, BN were involved in conceptualising this review.

References

1. (GAN), G.A.N., *Global Asthma Report 2014.* 2014.
2. Organization, W.H., *Asthma Fact Sheet.* 2013.
3. (GINA), G.I.f.A., *Global Strategy for Asthma Management and Prevention.* 2012.
4. Boulet, L., *Influence of comorbid conditions on asthma.* European Respiratory Journal, 2009. **33**(4): p. 897-906.
5. Boulet, L. and M. Boulay, *Asthma-related comorbidities. Expert Rev Respir Med 2011; 5: 377-393.* External Resources Pubmed/Medline (NLM) CrossRef (DOI).
6. Bateman, E.D., et al., *Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma ControL study.* American journal of respiratory and critical care medicine, 2004. **170**(8): p. 836-844.
7. Cazzola, M., et al., *Asthma and comorbid medical illness.* European Respiratory Journal, 2011. **38**(1): p. 42-49.
8. Cazzola, M., et al., *Comorbidities of asthma: current knowledge and future research needs.* Current opinion in pulmonary medicine, 2013. **19**(1): p. 36-41.
9. De Groot, E., E. Duiverman, and P. Brand, *Comorbidities of asthma during childhood: possibly important, yet poorly studied.* European Respiratory Journal, 2010. **36**(3): p. 671-678.
10. Ledford, D.K. and R.F. Lockey, *Asthma and comorbidities.* Current opinion in allergy and clinical immunology, 2013. **13**(1): p. 78-86.
11. Valderas, J.M., et al., *Defining comorbidity: implications for understanding health and health services.* The Annals of Family Medicine, 2009. **7**(4): p. 357-363.
12. Gershon, A.S., et al., *Burden of comorbidity in individuals with asthma.* Thorax, 2010. **65**(7): p. 612-618.
13. Zhang, T., et al., *The added burden of comorbidity in patients with asthma.* Journal of Asthma, 2009. **46**(10): p. 1021-1026.
14. Blanchette, C.M., et al., *Economic burden in direct costs of concomitant chronic obstructive pulmonary disease and asthma in a Medicare Advantage population.* Journal of Managed Care Pharmacy, 2008. **14**(2): p. 176-185.
15. Deshmukh, V.M., et al., *The association of comorbid anxiety and depression with asthma-related quality of life and symptom perception in adults.* Respirology, 2008. **13**(5): p. 695-702.
16. Grupp-Phelan, J., P. Lozano, and P. Fishman, *Health care utilization and cost in children with asthma and selected comorbidities.* Journal of Asthma, 2001. **38**(4): p. 363-373.
17. Lehrer, P.M., et al., *Psychological treatment of comorbid asthma and panic disorder: a pilot study.* Journal of anxiety disorders, 2008. **22**(4): p. 671-683.
18. Soriano, J.B., et al., *Patterns of comorbidities in newly diagnosed COPD and asthma in primary care.* Chest Journal, 2005. **128**(4): p. 2099-2107.
19. Wijnhoven, H., et al., *The influence of co-morbidity on health-related quality of life in asthma and COPD patients.* Respiratory medicine, 2003. **97**(5): p. 468-475.
20. Gershon, A.S., et al., *Correction: Describing and Quantifying Asthma Comorbidity: A Population Study.* PloS one, 2013. **8**(1).
21. Punekar, Y. and A. Sheikh, *Establishing the sequential progression of multiple allergic diagnoses in a UK birth cohort using the General Practice Research Database.* Clinical & Experimental Allergy, 2009. **39**(12): p. 1889-1895.
22. ROMANO, A., *Allergic Rhinitis and its Impact on Asthma (ARIA): Achievements in 10 years and future needs.* JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, 2012(Ottobre): p. N/A-N/A.

23. Walker, S. and A. Sheikh, *Self reported rhinitis is a significant problem for patients with asthma.* Primary Care Respiratory Journal, 2005. **14**(2): p. 83-87.
24. Moher, D., et al., *Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement.* Systematic reviews, 2015. **4**(1): p. 1.
25. Levac, D., H. Colquhoun, and K.K. O'Brien, *Scoping studies: advancing the methodology.* Implement Sci, 2010. **5**(1): p. 1-9.

Appendix

Search Strategy

I. Medline

1. asthma.mp. or exp Asthma/
2. exp Comorbidity/ or co-morbidity.mp.
3. multimorbidity.mp.
4. exp Hypersensitivity/ or Allergens/ or Hypersensitivity, Immediate/ or atopy.mp. or exp Immunoglobulin E/ or exp Dermatitis, Atopic/
5. allergic rhinitis.mp. or exp Rhinitis, Allergic/
6. food allergy.mp. or exp Food Hypersensitivity/
7. exp Anaphylaxis/ or anaphylaxis.mp.
8. exp Urticaria/ or urticaria.mp.
9. exp Celiac Disease/ or Autoantibodies/ or exp Autoimmune Diseases/ or autoimmune disorder.mp. or exp Diabetes, Type 1/ or exp eosinophilic disorder
10. Thymus Neoplasms/ or endocrine disorder.mp. or Thyroid Gland/ or exp Endocrine System Diseases/ or Thyroid Diseases/
11. exp Obesity/ or exp Diabetes, Type 2/ or metabolic disorder.mp.
12. exp Depression/ or exp Mental Disorder/ or exp Stress, Psychological/ or psychological dysfunction.mp. or Stress Disorder, Post-Traumatic/
13. panic disorders.mp. or exp Panic Disorder/
14. exp Anxiety/ or anxiety.mp.
15. chronic obstructive pulmonary disease.mp. or exp Pulmonary Disease, Chronic Obstructive/
16. exp Hypertension/ or hypertension.mp.
17. exp Gastroesophageal Reflux/ or gastro-oesophageal reflux disease.mp.
18. exp Sleep Apnea, Obstructive/ or exp Sleep Disorder/ or Sleep Apnea Syndromes/ or obstructive sleep apnoea.mp. or Apnea/
19. cardiovascular disease.mp. or exp Cardiovascular Diseases/
20. 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. 1 and 20
22. cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or retrospective studies/ or cohort.ti,ab. or longitudinal.ti,ab. or prospective.ti,ab. or retrospective.ti,ab.
23. Case-Control Studies/ or Control Groups/ or Matched-Pair Analysis/ or ((case* adj5 control*) or (case adj3 comparison*) or control group*).ti,ab.
24. Cross-Sectional Studies/ or cross-sectional.ti,ab. or ("prevalence study" or "incidence study" or "prevalence studies" or "incidence studies" or "transversal studies" or "transversal study").ti,ab.
25. 22 or 23 or 24
26. 21 and 25
27. limit 26 to yr="2011 -Current"

II. EMBASE

1. asthma.mp. or exp Asthma/
2. exp Comorbidity/ or co-morbidity.mp.
3. multimorbidity.mp.
4. exp Hypersensitivity/ or Allergens/ or Hypersensitivity, Immediate/ or atopy.mp. or exp Immunoglobulin E/ or exp Dermatitis, Atopic/
5. allergic rhinitis.mp. or exp Rhinitis, Allergic/
6. food allergy.mp. or exp Food Hypersensitivity/
7. exp Anaphylaxis/ or anaphylaxis.mp.
8. exp Urticaria/ or urticaria.mp.
9. exp Celiac Disease/ or Autoantibodies/ or exp Autoimmune Diseases/ or autoimmune disorder.mp. or exp Diabetes, Type 1/
10. Thymus Neoplasms/ or endocrine disorder.mp. or Thyroid Gland/ or exp Endocrine System Diseases/ or Thyroid Diseases/
11. exp Obesity/ or exp Diabetes, Type 2/ or metabolic disorder.mp.
12. exp Depression/ or exp Mental Disorder/ or exp Stress, Psychological/ or psychological dysfunction.mp. or Stress Disorder, Post-Traumatic/
13. panic disorders.mp. or exp Panic Disorder/
14. exp Anxiety/ or anxiety.mp.
15. chronic obstructive pulmonary disease.mp. or exp Pulmonary Disease, Chronic Obstructive/
16. exp Hypertension/ or hypertension.mp.
17. exp Gastroesophageal Reflux/ or gastro-oesophageal reflux disease.mp.
18. exp Sleep Apnea, Obstructive/ or exp Sleep Disorder/ or Sleep Apnea Syndromes/ or obstructive sleep apnoea.mp. or Apnea/
19. cardiovascular disease.mp. or exp Cardiovascular Diseases/
20. 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. 1 and 20
22. cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or retrospective studies/ or cohort.ti,ab. or longitudinal.ti,ab. or prospective.ti,ab. or retrospective.ti,ab.
23. Case-Control Studies/ or Control Groups/ or Matched-Pair Analysis/ or ((case* adj5 control*) or (case adj3 comparison*) or control group*).ti,ab.
24. Cross-Sectional Studies/ or cross-sectional.ti,ab. or ("prevalence study" or "incidence study" or "prevalence studies" or "incidence studies" or "transversal studies" or "transversal study").ti,ab.
25. 22 or 23 or 24
26. 21 and 25
27. limit 26 to yr="2011 -Current"

III. Web of Science

#4 #3 AND #2 AND #1
Timespan=2011-2015
Search language=Auto
#3 TOPIC: ("cohort study") OR TOPIC: ("longitudinal study") OR TOPIC: ("follow-up study") OR TOPIC: ("prospective study") OR TOPIC: ("retrospective study") OR TOPIC: (cohort) OR TOPIC: (longitudinal) OR TOPIC: (prospective) OR TOPIC: (retrospective) OR TOPIC: ("Case-Control") OR TOPIC: ("Matched-Pair Analysis") OR TOPIC: ("Cross-Sectional") OR TOPIC: ("prevalence study") OR TOPIC: ("incidence study")
Timespan=2011-2015
Search language=Auto
#2 TOPIC: (TOPIC: (Comorbidit*) OR TOPIC: (multimorbidit*) OR TOPIC: (Hypersensitivity) OR TOPIC: (Allerg*) ORTOPIC: ("allergic rhinitis") OR TOPIC: ("Food Hypersensitivity") OR TOPIC: ("food allerg*") ORTOPIC: (Anaphylaxis) OR TOPIC: (Urticaria) OR TOPIC: ("Autoimmune Disease") OR TOPIC:("Autoimmune disorder") OR TOPIC: ("Diabetes") OR TOPIC: ("endocrine disorder") ORTOPIC: ("Thyroid disorder") OR TOPIC: ("metabolic disorder") OR TOPIC: (obesity) OR TOPIC:("Psychological disorder") OR TOPIC: ("Panic Disorder") OR TOPIC: (Anxiety) OR TOPIC: ("chronic obstructive pulmonary disease") OR TOPIC: ("Pulmonary Disease") OR TOPIC: (Hypertension) ORTOPIC: ("gastro-oesophageal reflux disease") OR TOPIC: ("cardiovascular disease") OR TOPIC:("Sleep Apnea"))
Timespan=2011-2015
Search language=Auto
#1 TOPIC: (asthma)
Timespan=2011-2015
Search language=Auto

IV. CINAHL

Query Limiters/Expanders Last Run Via Results Action
S30 S27 AND S28 Limiters - Publication Year: 2011-2015
Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 1,391 Edit S30
S29 S27 AND S28 Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 3,845 Edit S29
S28 S23 OR S24 OR S25 Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 411,852 Edit S28
S27 S1 AND S26 Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 27,111 Edit S27
S26 S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 748,799 Edit S26
S25 (MH "Cross Sectional Studies") OR "Cross-Sectional Studies" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 108,137 Edit S25
S24 (MH "Case Control Studies") OR "Case-Control Studies" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 51,374 Edit S24
S23 (MH "Prospective Studies") OR "cohort studies" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 277,306 Edit S23
S22 (MH "Cardiovascular Diseases+") OR "cardiovascular disease" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 386,904 Edit S22
S21 (MH "Sleep Apnea Syndromes+") OR (MH "Sleep Apnea, Obstructive") OR "Sleep Apnea" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 10,336 Edit S21
S20 (MH "Gastroesophageal Reflux") OR "Gastroesophageal Reflux" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 5,683 Edit S20

S19 (MH "Hypertension+") OR "Hypertension" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 65,449 Edit S19
S18 (MH "Pulmonary Disease, Chronic Obstructive+") OR "chronic obstructive pulmonary disease" OR (MH "Lung Diseases, Obstructive+") Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 43,363 Edit S18
S17 (MH "Anxiety+") OR "Anxiety" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 52,157 Edit S17
S16 (MH "Panic Disorder") OR "panic disorder" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 1,682 Edit S16
S15 (MH "Depression+") OR "Depression" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 98,022 Edit S15
S14 (MH "Diabetes, Type 2") OR (MH "Diabetes, Type 1+") OR (MH "Diabetes +") OR "Diabetes" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 112,269 Edit S14
S13 (MH "Obesity+") OR "Obesity" OR (MH "Obesity, Morbid") Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 73,423 Edit S13
S12 "metabolic disorder" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 304 Edit S12
S11 "endocrine disorder" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 117 Edit S11
S10 (MH "Thyroid Diseases+") OR "Thyroid Diseases" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 10,471 Edit S10
S9 (MH "Autoimmune Diseases") OR "Autoimmune Diseases" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 5,816 Edit S9
S8 (MH "Celiac Disease") OR "Celiac Disease" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 3,248 Edit S8

S7 (MH "Urticaria") OR "Urticaria" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 1,505 Edit S7
S6 (MH "Anaphylaxis") OR "Anaphylaxis" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 3,208 Edit S6
S5 (MH "Food Hypersensitivity") OR "food allergy" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 3,880 Edit S5
S4 (MH "Rhinitis, Allergic, Perennial") OR (MH "Rhinitis, Allergic, Seasonal") OR (MH "Dermatitis, Atopic") Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 4,023 Edit S4
S3 (MH "Hypersensitivity+") OR (MH "Hypersensitivity, Immediate") Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 49,092 Edit S3
S2 (MH "Comorbidity") Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 38,672 Edit S2
S1 (MH "Asthma+") OR "asthma" Search modes - Find all my search terms Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus 29,402

V. PsycINFO

1. asthma.mp. or exp Asthma/
2. exp Comorbidity/ or co-morbidity.mp.
3. multimorbidity.mp.
4. exp Hypersensitivity/ or Allergens/ or Hypersensitivity, Immediate/ or atopy.mp. or exp Immunoglobulin E/ or exp Dermatitis, Atopic/
5. allergic rhinitis.mp. or exp Rhinitis, Allergic/
6. food allergy.mp. or exp Food Hypersensitivity/
7. exp Anaphylaxis/ or anaphylaxis.mp.
8. exp Urticaria/ or urticaria.mp.
9. exp Celiac Disease/ or Autoantibodies/ or exp Autoimmune Diseases/ or autoimmune disorder.mp. or exp Diabetes, Type 1/
10. Thymus Neoplasms/ or endocrine disorder.mp. or Thyroid Gland/ or exp Endocrine System Diseases/ or Thyroid Diseases/
11. exp Obesity/ or exp Diabetes, Type 2/ or metabolic disorder.mp.
12. exp Depression/ or exp Mental Disorder/ or exp Stress, Psychological/ or psychological dysfunction.mp. or Stress Disorder, Post-Traumatic/
13. panic disorder.mp. or exp Panic Disorder/
14. exp Anxiety/ or anxiety.mp.
15. chronic obstructive pulmonary disease.mp. or exp Pulmonary Disease, Chronic Obstructive/
16. exp Hypertension/ or hypertension.mp.
17. exp Gastroesophageal Reflux/ or gastro-oesophageal reflux disease.mp.
18. exp Sleep Apnea, Obstructive/ or exp Sleep Disorder/ or Sleep Apnea Syndromes/ or obstructive sleep apnoea.mp. or Apnea/
19. cardiovascular disease.mp. or exp Cardiovascular Disease/
20. 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. 1 and 20
22. cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or retrospective studies/ or cohort.ti,ab. or longitudinal.ti,ab. or prospective.ti,ab. or retrospective.ti,ab.
23. Case-Control Studies/ or Control Groups/ or Matched-Pair Analysis/ or ((case* adj5 control*) or (case adj3 comparison*) or control group*).ti,ab.
24. Cross-Sectional Studies/ or cross-sectional.ti,ab. or ("prevalence study" or "incidence study" or "prevalence studies" or "incidence studies" or "transversal studies" or "transversal study").ti,ab.
25. 22 or 23 or 24
26. 21 and 25
27. limit 26 to yr="2011 -Current"

VI. Google Scholar (first 100 results will be considered)

1. Asthma and comorbidit*

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page number
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
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 (such as PROSPERO) and registration number	NA
Authors:			
Contact	3a	Provide name, institutional affiliation, 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	7
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	7
Sponsor	5b	Provide name for the review funder and/or sponsor	7
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	3-4
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	4-5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5

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	8-14
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	5-6
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	5-6
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	5
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	NA
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	4
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	NA
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	6
	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 (such as I^2, Kendall's τ)	6
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	6
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	6
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as 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 (such as GRADE)	NA

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.