BMJ Open

Screening tools for work-related asthma and their diagnostic accuracy: a systematic review protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-058054
Article Type:	Protocol
Date Submitted by the Author:	05-Oct-2021
Complete List of Authors:	Kongsupon, Ngamjit; University of Birmingham College of Medical and Dental Sciences, Institue of Applied Health Research Walters, Gareth I.; University of Birmingham College of Arts and Law, Institute of Applied Health Research; Birmingham Chest Clinic, Birmingham Regional NHS Occupational Lung Disease Service Adab, Peymane; University of Birmingham College of Medical and Dental Sciences, Institute of Applied Health Research Jordan, Rachel; University of Birmingham College of Medical and Dental Sciences, Institute of Applied Health Research
Keywords:	Asthma < THORACIC MEDICINE, OCCUPATIONAL & INDUSTRIAL MEDICINE, PREVENTIVE MEDICINE

1

Screening tools for work-related asthma and their diagnostic accuracy: a systematic review protocol

Corresponding author:
Ngamjit Kongsupon
Institute of Applied Health Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK, B152TT. Email: nxk798@student.bham.ac.uk.

All co-authors:
Ngamjit Kongsupon[1], Gareth I. Walters[1, 2], Peymane Adab[1], Rachel E. Jordan[1]

[1]Institute of Applied Health Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK, B15 2TT

[2] Birmingham Regional NHS Occupational Lung Disease Service, Birmingham Chest Clinic, 151 Great Charles Street, Birmingham, UK, B3 3HX

Word count 2,514 words

ABSTRACT

Words=300

Introduction

Work-related asthma (WRA) refers to asthma caused by exposures at work (occupational asthma) and asthma made worse by work conditions (work-exacerbated asthma). WRA is common amongst working-age adults with asthma and impacts on individual health, work-life and income, but is often not detected by healthcare services. Earlier identification can lead to better health and employment outcomes. However, the optimal tool for screening and its effectiveness in practice is not well established. Screening tools may include whole questionnaires, questionnaire items, physiological measurements and/or immunological tests. Since publication of the most contemporary WRA or occupational asthma-specific guidelines, further studies evaluating tools for identifying WRA have been performed. Our systematic review aims to summarise and compare the performance of screening tools for identifying WRA in both clinical and workplace settings.

Methods and analysis

We will conduct a systematic review of observational and experimental studies (1975-2021) using MEDLINE, EMBASE, CINAHL Plus, Web of Science, CDSR, DARE, HTA, CISDOC databases, and grey literature. Two independent reviewers will screen the studies using predetermined criteria, extract data according to a schedule, and assess study quality using the Quality Assessment of Diagnostic Test Accuracy 2 (QUADAS-2) tool. Screening tools and test accuracy measures will be summarised. Paired forest plots and summary receiver operating characteristic (SROC) curves of sensitivities and specificities will be evaluated for heterogeneity between studies, using sub-group analyses, where possible. If the studies are sufficiently homogenous, we will use a bivariate random effects model for meta-analysis. A narrative summary and interpretation will be provided if meta-analysis is not appropriate.

Ethics and dissemination

As this is a systematic review and does not involve primary data collection, formal ethical review is not required. We will disseminate our findings through open access peer-reviewed publication, as well as through other academic and social media.

PROSPERO registration number

CRD42021246031

Strengths and limitations of this study

- This will be a review of experimental, observational and workplace surveillance studies from a comprehensive list of bibliographic databases and the grey literature, to summarise screening tools used for early identification of work-related asthma.
- The methods will adhere to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.
- The quality of eligible studies will be assessed using an objective risk-of-bias tool (Quality Assessment of Diagnostic Test Accuracy 2; QUADAS-2).
- Likely variation and inconsistency in screening tools may limit collation of findings.

INTRODUCTION

Definition and burden

Work-related asthma (WRA) is classified as (1) occupational asthma (OA), which refers to *new-onset* asthma *caused* by inhaled exposures at work; and (2) work-exacerbated asthma (WEA; or work-aggravated asthma), which refers to *pre-existing* asthma *made worse* by conditions at work.[1] Most OA occurs through an immunological mechanism, following a latent period of respiratory sensitisation to an allergen encountered in the workplace (e.g. wheat flour in the bakery process, isocyanates in paint spraying). Less commonly OA is caused by acute exposures to high levels of irritating vapours, dust, or fumes, so-called acute irritant induced asthma (e.g. chlorine gas, diesel exhaust fume).[2] WEA may be triggered by inhaled exposures to airway irritants, usually at airborne levels above workplace exposure limits, or by physical or psychological factors such as heat, humidity, exercise, or emotional stress.[3,4]

Worldwide, around 16% of new asthma diagnoses in adults is attributed to work[5] and OA costs the UK economy £1.1 billion per decade in direct healthcare and other social costs.[6] When compared with non-WRA, individuals with WRA have more severe symptoms and utilise more healthcare resources, which is associated with up to 10 fold higher societal cost.[7] Individuals with WRA also are more likely to experience impaired quality of life, mental disorders, work disruption and economic loss.[8,9]

Early diagnosis and removal from the cause, or exacerbating factor, provide the best prognosis in both OA and WEA.[2,4] A longer duration of exposure prior to diagnosis is associated with poor physiological outcomes,[10] whilst removal from the exposure (compared to reduction or continuation of exposure) improves symptoms and lung function.[11] Nevertheless, data from primary and secondary care suggest that WRA (specifically OA) is under-recognised and the diagnosis is often delayed.[12,13] Studies from UK and Canada suggest a mean delay from symptom onset to specialist referral and diagnosis, of 4 years.[12,14] Workplace respiratory health surveillance programmes may also miss WRA, with one study demonstrating that only 1 in 5 of those with an eventual diagnosis of WRA having been recognised through their surveillance programme.[15]

Clinical pathway for WRA

Establishing a diagnosis of asthma is based on the presence of respiratory symptoms (wheeze, dyspnoea, chest tightness and cough, diurnal variation in symptoms, triggers) and physiological abnormalities, including presence of atopy, high fractional exhaled nitric oxide (FENO) and reversible airflow obstruction on spirometry. Where diagnostic uncertainty remains, second-line investigation including peak expiratory flow (PEF) variability and non-specific bronchial reactivity (NSBR; usually only available in secondary care) may be required.[16]

Guidelines recommend that individuals with new-onset, reactivated or unexplained worsening of asthma symptoms presenting to primary or secondary healthcare services, or their workplace occupational health provider, should be asked about the nature of their work and whether asthma symptoms are better away from work.[1,16-18] Those with a positive

response (and especially those in high-risk occupations for OA) should be further investigated and seen by a clinician with expertise in diagnosing WRA.

Specialist investigation and categorisation as OA or WEA comprises: (1) physiological confirmation of the diagnosis of asthma, where doubt exists, (2) objective demonstration of work-relatedness of the symptoms, usually through the analysis of workplace serial peak expiratory flow (PEF) measurements, and (3) evaluation of workplace exposures to airway allergens and irritants, and demonstration of respiratory sensitisation either by immunological testing (skin prick testing or specific Immunoglobulin E) or specific inhalation challenge (SIC). The gold standard for a diagnosis of OA is generally considered to be a positive SIC to a respiratory sensitiser.[1,18] However, this investigation is only available in certain centres and is not always possible (e.g. if workplace exposures cannot be reproduced in laboratory conditions). Thus, a combination of objective physiological tests can be utilised to diagnose WRA, and differentiate between OA and WEA.

Screening tools

Tools used for screening and identifying WRA may vary depending upon the setting (primary or secondary healthcare, workplace, or specific workplace exposures). In healthcare settings, screening aims to identify individuals with asthma or asthma symptoms who are at high risk of WRA, in terms of their work tasks and exposures. Questions regarding work-relatedness of asthma symptoms (an improvement on days away from work, or on longer periods e.g. holidays) have sensitivities of 58-100% and specificities of 45-100% for the diagnosis of OA. However, these measures of accuracy were obtained primarily in specialist tertiary clinic patients rather than in general populations, leading to low confidence in recommending these in guidelines.[2] Workplace respiratory health surveillance is mandated by UK Health and Safety law, where workers are exposed to respiratory sensitising agents, as demonstrated through the risk assessment process.[19] Surveillance is usually carried out annually by an occupational health provider and generally comprises a respiratory symptom questionnaire and spirometry. Immunological testing is used in certain circumstances (e.g. platinum refining, bakers, laboratory animal workers). Surveillance using screening questionnaires has the benefit of distinguishing low-risk workers who are unlikely to need further investigation, whilst a combination of different tests (such as a sensitisation prediction model in bakers and laboratory animal workers) may better predict OA.[1] However, there has been no agreement or recommendation on the content of screening questionnaires for WRA. This is further complicated by workers sometimes being less willing to answer screening questionnaires honestly due to a fear of losing a job and the employer's judgement.[1]

The most recent International consensus and guidelines on assessment and management of WRA were published in 2012, with recommendations for screening based upon medical literature published before 2010.[1] Similarly, a UK-based systematic review with recommendations for prevention, diagnosis and management of OA was updated in 2012 and based upon literature published up until 2009.[18] Other than a systematic review of immunological testing in immunoglobulin E-mediated asthma in 2019,[20] there have been no systematic reviews or meta-analyses of screening tools used for identifying WRA. Since 2010, further detailed questionnaires and screening tools have been developed and evaluated for use in clinical settings and workplaces. These have included questionnaire

items on allergic symptoms, patient's characteristics (e.g. age, nasal rhinitis), and possible exposures, and also diagnostic or prediction models for workplace surveillance.[21-26]

Aim

The aim of this systematic review is to identify and summarise the characteristics of existing screening tools and their accuracy, and provide evidence for primary and secondary healthcare professionals and occupational health providers.

Objectives

Primary objectives: to identify, describe and compare the performance of published tools for identifying WRA, that could be used for screening in primary and secondary healthcare settings, and for WRA surveillance in occupational settings.

1) What are the existing screening tools evaluated for detecting WRA in clinical and occupational settings?
2) What is the test accuracy of the screening tools for the diagnosis of WRA in clinical settings?
3) What is the test accuracy of the screening tools used in respiratory health surveillance of WRA in occupational settings?

Secondary objective: to investigate heterogeneity in sensitivity and specificity of the screening tools in each setting.

METHODS AND ANALYSIS

This systematic review protocol is based upon the recommended method from the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy.[27] The protocol is registered on the PROSPERO database and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidance for systematic review protocols (PRISMA-P)[28] and the PRISMA statement for diagnostic test accuracy studies[29] (see online supplementary material 1). The start date for this systematic review is 13th September 2021, and it is envisaged that it will take up to 6 months until submission for peer review.

Inclusion and exclusion criteria:

Studies will be included if they meet the following criteria:

Participants

1) *Clinical settings*: include studies where the majority of individuals were aged 16 and over, with asthma or suspected asthma, and were identified from any clinical settings (i.e. primary, secondary or tertiary care) for the investigation of WRA
2) *Workplace surveillance*: include studies where individuals were aged 16 and over, from any workplace setting

Index test

1) *Clinical settings*: structured screening questionnaires and prediction models which may comprise questions about respiratory symptom status, work-relatedness of the symptoms, employment history and exposure to causative antigens, participant

characteristics, or self-report of results of objective tests. We will exclude expert histories and non-structured questionnaires.

2) *Workplace surveillance*: questionnaires, prediction models and any physiological tests. We will exclude studies (i) using prediction models for exposure assessment or pre-employment screening for sensitisation to allergens but not WRA, and (ii) using serum specific immunoglobulin E alone in screening.

Target conditions

Work-related asthma: either occupational asthma, or work-exacerbated asthma, or uncharacterized.

Reference standards

1) A confirmed diagnosis of asthma by evidence of reversible airflow limitation and/or airway inflammation, non-specific bronchial hyper-reactivity, or positive trial of treatment. Tests may include spirometry, pre- and post-bronchodilator reversibility, PEF variability, NSBR, and FENO.

AND

2) A combination of objective tests showing a relationship between asthma and suspected causative agents in the workplace

   These may include specific inhalation challenge test (SIC) in laboratory or workplace challenge, serial PEF measurements at and away from work, NSBR at and away from work, immunologic tests (i.e. skin prick test and serum specific immunoglobulin E), a trial of return to work with PEF or FEV_1 (forced expiratory volume in 1 second) monitoring.

Individuals who have a confirmed diagnosis of asthma and objective evidence of a relationship between asthma and work will be defined as having WRA. Among these, OA will be distinguished as being those with objective demonstration of sensitisation (i.e. having a positive result from SIC or identification of sensitisers as a cause from immunological tests). Individuals defined as having WEA will be those who have documented prior or concurrent-onset asthma, with a history of exposure to airway irritants, common allergens or other physical factors, with or without evidence of normal sensitisation tests (either SIC or immunological test).

Types of studies included

Cross-sectional studies, workplace surveillance studies and any types of test accuracy studies i.e. randomised comparison, cohort, or case-control type studies will be considered for inclusion in the review.

Outcomes

The main outcomes for this study are: (1) characterisation of tools used for identifying WRA in either clinical settings or during respiratory health surveillance in occupational settings; (2) the performance of included tools (sensitivity, specificity, positive and negative predictive values, area under the receiver operating characteristic (ROC) curve) in identifying WRA.

Search strategy

A systematic search of the medical literature will be undertaken using the following databases: MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health (CINAHL) Plus, Web of Science, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment database, CISDOC database (International Occupational Safety and Health Information Centre). Databases for ongoing studies and grey literature will be ProQuest, and Open Grey. Conference proceedings and electronic publications (ahead of print) will also be included. Any article published from 1st January 1975 (the year SIC introduced as a clinical diagnostic test) until 13th September (start date) 2021 are eligible, and there will be no language restriction. Reference lists from existing guidelines, key position papers and review articles will also be checked for relevant citations not included in the main search. Authors of included studies may be contacted for clarity or any missing information.

Search terms

The search terms have been developed with support from University of Birmingham Library Services' Research Skills Team. Words and index terms synonymous with the target condition (WRA) or with identified index tests, will be included, using Boolean linkage 'OR' within the group and 'AND' between the groups. A pilot search in MEDLINE (Ovid) using the search terms has been included in online supplementary material 2.

Selection of studies

All search results will be imported to EndNote X9 (Clarivate, Philadelphia, USA) and duplicates will be removed. Where multiple publications of the same or a part of the same participants are identified, the most recent or the largest study will be selected, and relevant supplementary information from the other publications will be gathered. The remaining articles will be exported to the web-based application Rayyan[30] for abstract and subsequently full-text article screening. Two reviewers will independently screen titles and abstracts for relevance, then identify eligible studies from their full text using the predetermined inclusion and exclusion criteria. Disagreement will be discussed and a third reviewer sought for consensus. Eligible studies will be imported to EndNote X9 software and grouped by setting (clinical or workplace).

Data extraction

Data will be extracted independently by two reviewers, blinded to each other, using a predetermined data extraction form and kept in a Microsoft Excel spreadsheet (Washington, USA); see online supplementary material 3). Data gathered will include year of publication, author, country of origin, study design, healthcare (primary, secondary or tertiary) or workplace setting, sample population summary, reference standard, index tests and test accuracy measures. Where possible, occupational exposures will be further coded as being high or low risk for OA, according to a list of 20 high-risk occupations.[18] The data extraction form will be pilot tested on at least two studies before formal use.

Quality assessment

The Quality Assessment of Diagnostic Test Accuracy 2 tool (QUADAS-2)[31] will be used to assess the quality of included articles, in terms of risk of bias, and designated as low, high or unclear risk. Assessment will be undertaken independently by two reviews, with a third reviewer involved if any disagreement cannot be resolved by discussion. The risk of bias for each included article will be displayed in a table with a narrative summary and the designated score. Articles with a high risk of bias may be excluded from the data analysis where appropriate.

Data analysis

The target conditions will be categorised as WRA (uncharacterised), OA, WEA, or non-WRA in the analysis. The characteristics of the included studies outlined above will be described, performance (test accuracy) of each index tool evaluated, and a summary will be displayed in a table. Test accuracy metrics will be grouped by index test, and by setting (primary, secondary or tertiary clinical, workplace). Paired forest plots and summary receiver-operating characteristic (SROC) curves of sensitivities and specificities will be performed using RevMan 5 software (Cochrane Collaboration, 2020). Heterogeneity between studies will be examined initially by visual inspection of the paired forest plot and SROC curves, and explored using sub-group analyses where possible. The sub-groups considered will be sub-settings (primary care/secondary or tertiary care) and high- or low-risk occupations. Where clinical and methodological characteristics of the included studies are sufficiently homogeneous, a bivariate random effect model will be performed using STATA 16 software (StataCorp LLC, Texas, USA). Where a bivariate model cannot be fitted (e.g. few studies available or zero cells in the table), a univariate random effects logistic regression model for sensitivity and specificity will be performed.[32] A narrative summary will be considered if meta-analysis is not appropriate. If feasible, we will aim to summarise the evidence and make recommendations using the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) approach.[33]

ETHICS AND DISSEMINATION

As this is a systematic review and does not involve primary data collection from patients, formal ethical review and approval are not required. We will seek to publish our findings in an open access peer-reviewed medical journal and disseminate findings through other academic and social media. Data will be made available upon reasonable request.

REFERENCES

1. Baur X, Sigsgaard T, Aasen TB, et al. Guidelines for the management of work-related asthma. *European Respiratory Journal* 2012;39(3):529-45. doi: 10.1183/09031936.00096111
2. Nicholson PJ, Cullinan P, Burge PS, et al. Occupational asthma: Prevention, identification & management: Systematic review & recommendations. London: British Occupational Health Research Foundation, 2010.
3. Maestrelli P, Henneberger PK, Tarlo S, et al. Causes and phenotypes of work-related asthma. *International Journal of Environmental Research and Public Health* 2020;17(13):1-10. doi: http://dx.doi.org/10.3390/ijerph17134713

4. Henneberger PK, Redlich CA, Callahan DB, et al. An Official American Thoracic Society Statement: Work-Exacerbated Asthma. *American Journal of Respiratory and Critical Care Medicine* 2011;184(3):368-78. doi: 10.1164/rccm.812011ST
5. Blanc PD, Annesi-Maesano I, Balmes JR, et al. The Occupational Burden of Nonmalignant Respiratory Diseases. An Official American Thoracic Society and European Respiratory Society Statement. *American Journal of Respiratory and Critical Care Medicine* 2019;199(11):1312-34. doi: 10.1164/rccm.201904-0717ST
6. Ayres JG, Boyd R, Cowie H, et al. Costs of occupational asthma in the UK. *Thorax* 2011;66(2):128-33. doi: 10.1136/thx.2010.136762
7. Lemiere C, Boulet LP, Chaboillez S, et al. Work-exacerbated asthma and occupational asthma: Do they really differ? *Journal of Allergy and Clinical Immunology* 2013;131(3):704. doi: http://dx.doi.org/10.1016/j.jaci.2012.08.024
8. Karvala K, Nordman H, Luukkonen R, et al. Asthma related to workplace dampness and impaired work ability. *Int Arch Occup Environ Health* 2014;87(1):1-11. doi: 10.1007/s00420-012-0830-0 [published Online First: 2012/12/05]
9. Moullec G, Lavoie KL, Malo JL, et al. Long-term socioprofessional and psychological status in workers investigated for occupational asthma in quebec. *J Occup Environ Med* 2013;55(9):1052-64. doi: 10.1097/JOM.0b013e31829904ab [published Online First: 2013/08/24]
10. Maestrelli P, Schlünssen V, Mason P, et al. Contribution of host factors and workplace exposure to the outcome of occupational asthma. *European Respiratory Review* 2012;21(124):88-96. doi: 10.1183/09059180.00004811
11. Henneberger PK, Patel JR, de Groene GJ, et al. Workplace interventions for treatment of occupational asthma. *Cochrane Database Syst Rev* 2019;10(10):Cd006308. doi: 10.1002/14651858.CD006308.pub4 [published Online First: 2019/10/09]
12. Fishwick D, Bradshaw L, Davies J, et al. Are we failing workers with symptoms suggestive of occupational asthma? *Primary Care Respiratory Journal* 2007;16(5):304-10. doi: 10.3132/pcrj.2007.00064
13. Walters GI, McGrath EE, Ayres JG. Audit of the recording of occupational asthma in primary care. *Occup Med (Lond)* 2012;62(7):570-3. doi: 10.1093/occmed/kqs114 [published Online First: 2012/07/28]
14. Lemière C, To T, de Olim C, et al. Outcome of work-related asthma exacerbations in Quebec and Ontario. *European Respiratory Journal* 2015;45(1):266-68. doi: 10.1183/09031936.00096114
15. Suojalehto H, Karvala K, Haramo J, et al. Medical surveillance for occupational asthma-how are cases detected? *Occup Med (Lond)* 2017;67(2):159-62. doi: 10.1093/occmed/kqw101 [published Online First: 2016/08/06]
16. National Institute For Health And Care Excellence. Ashtma: diagnosis, monitoring and chronic asthma management (NG80) 2017 [Available from: https://www.nice.org.uk/guidance/ng80 accessed 10 May 2021.
17. British Thoracic Society and Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma A national clinical guideline, 2019.
18. Fishwick D, Barber CM, Bradshaw LM, et al. Standards of care for occupational asthma: an update. *Thorax* 2012;67(3):278-80. doi: 10.1136/thoraxjnl-2011-200755
19. Health and Safety Executive. G402 Health surveillance for occupational asthma Buxton, UK2006 [Available from: https://www.hse.gov.uk/pubns/guidance/g402.pdf accessed 4 August 2021.
20. Baur X, Akdis CA, Budnik LT, et al. Immunological methods for diagnosis and monitoring of IgE-mediated allergy caused by industrial sensitizing agents (IMExAllergy). *Allergy* 2019;74(10):1885-97. doi: 10.1111/all.13809 [published Online First: 2019/06/27]
21. Hannu T, Lindström I, Palmroos P, et al. Prediction of obeche wood-induced asthma by specific skin prick testing. *Occup Med (Lond)* 2013;63(6):429-31. doi: 10.1093/occmed/kqt050 [published Online First: 2013/06/19]

22. Jonaid BS, Rooyackers J, Stigter E, et al. Predicting occupational asthma and rhinitis in bakery workers referred for clinical evaluation. *Occup Environ Med* 2017;74(8):564-72. doi: 10.1136/oemed-2016-103934 [published Online First: 2017/03/21]
23. Killorn KR, Dostaler SM, Groome PA, et al. The use of a work-related asthma screening questionnaire in a primary care asthma program: an intervention trial. *J Asthma* 2015;52(4):398-406. doi: 10.3109/02770903.2014.971966 [published Online First: 2014/10/08]
24. Lipinska-Ojrzanowska AA, Wiszniewska M, Walusiak-Skorupa JM. Work-related asthma among professional cleaning women. *Arch Environ Occup Health* 2017;72(1):53-60. doi: 10.1080/19338244.2016.1156046 [published Online First: 2016/02/20]
25. Paraskevaidou K, Porpodis K, Kontakiotis T, et al. Asthma and rhinitis in Greek furniture workers. *J Asthma* 2019:1-10. doi: 10.1080/02770903.2019.1674328 [published Online First: 2019/10/18]
26. Pralong JA, Moullec G, Suarthana E, et al. Screening for occupational asthma by using a self-administered questionnaire in a clinical setting. *J Occup Environ Med* 2013;55(5):527-31. doi: 10.1097/JOM.0b013e3182851790 [published Online First: 2013/04/27]
27. Cochrane Diagnostic Test Accuracy Working Group. Cochrane Handbook for systematic reviews of diagnostic test accuracy: The Cochrane Collaboration 2010.
28. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ : British Medical Journal* 2015;350:g7647. doi: 10.1136/bmj.g7647
29. McInnes MDF, Moher D, Thombs BD, et al. Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies: The PRISMA-DTA Statement. *Jama* 2018;319(4):388-96. doi: 10.1001/jama.2017.19163 [published Online First: 2018/01/25]
30. Ouzzani M, Hammady H, Fedorowicz Z, et al. Rayyan—a web and mobile app for systematic reviews. *Systematic Reviews* 2016;5(1):210. doi: 10.1186/s13643-016-0384-4
31. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011;155(8):529-36. doi: 10.7326/0003-4819-155-8-201110180-00009 [published Online First: 2011/10/19]
32. Takwoingi Y, Guo B, Riley RD, et al. Performance of methods for meta-analysis of diagnostic test accuracy with few studies or sparse data. *Statistical Methods in Medical Research* 2017;26(4):1896-911. doi: 10.1177/0962280215592269
33. Schünemann HJ, Oxman AD, Brozek J, et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. *BMJ* 2008;336(7653):1106-10. doi: 10.1136/bmj.39500.677199.AE

AUTHORS' CONTRIBUTION

NK conceptualised, designed the protocol, planned the data extraction and analysis. PA, REJ and GIW refined the research concept, search terms, and data analysis plan. GIW provided clinical insights. NK drafted the initial manuscript. All authors edited, reviewed and approved the final version of the written protocol.

ACKNOWLEDGEMENT

We would like to thank Vicky Wallace, the research skill librarian, University of Birmingham, for support in developing the search strategy.

FUNDING STATEMENT

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

COMPETING INTERESTS STATEMENT

The authors have no competing interest to declare that are relevant to the content of this article.

Supplementary material 1

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist:
Screening tools for work-related asthma and their diagnostic accuracy: a systematic review – Kongsupon et al, 2021

Section and topic	Item No	Checklist item	Reported	
ADMINISTRATIVE INFORMATION				
Title:				
Identification	1a	Identify the report as a protocol of a systematic review	Yes	In the title
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Yes	
Authors:				
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Yes	Tile page
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Yes	Author's contribution
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	N/A	
Support:				
Sources	5a	Indicate sources of financial or other support for the review	Yes	Funding statement
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A	No funding
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A	No funding
INTRODUCTION				
Rationale	6	Describe the rationale for the review in the context of what is already known	Yes	Introduction

Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Yes	Introduction
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	Yes	Methods and analysis
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	Yes	Methods and analysis
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	Yes	Methods and analysis
Study records:				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Yes	Methods and analysis
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)	Yes	Methods and analysis
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	Yes	Methods and analysis
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	Yes	Methods and analysis
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Yes	Methods and analysis
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	Yes	Methods and analysis
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Yes	Methods and analysis
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining	Yes	Methods and analysis

		data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)		
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Yes	Methods and analysis
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Yes	Methods and analysis
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	N/A	
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Yes	Methods and analysis

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.

Supplementary material 2

Screening tools for work-related asthma and their diagnostic accuracy: a systematic review – Kongsupon et al, 2021

Search terms and a pilot search results (MEDLINE-OVID)

	Target Conditions	Index tests
Free texts	Asthma *AND*	Screening Surveillance Question
	Occupation Occupational Work related Workplace Worker Work exacerbated Work aggravated	Diagnosis Test accuracy Diagnostic accuracy
Index terms	Asthma Occupational exposures Occupational Diseases	Surveys and questionnaires Sensitivity and specificity Diagnosis Medical surveillance Secondary prevention

Pilot search results

Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations <1946 to July 16, 2021>

#	Query	Results from 18 Jul 2021
1	screening.ti,ab.	555,955
2	surveillance.ti,ab.	189,449
3	question*.ti,ab.	1,012,503
4	diagnos*.ti,ab.	2,591,966
5	test accuracy.ti,ab.	2,584
6	diagnostic accuracy.ti,ab.	47,498
7	exp "Sensitivity and Specificity"/	612,147
8	exp "Surveys and Questionnaires"/	1,105,623
9	exp Diagnosis/	8,881,364
10	exp Immunologic Surveillance/ or exp Population Surveillance/	73,924
11	exp Secondary Prevention/	21,434
12	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	11,609,670
13	(asthma* adj3 (work related or occupation* or work exacerbated or work aggravated or worker* or workplace)).ti,ab.	3,790
14	Asthma/di, ep, sn [Diagnosis, Epidemiology, Statistics & Numerical Data]	32,027
15	exp "Occupations"/	35,147
16	exp "Occupational Exposure"/	65,980
17	14 and (15 or 16)	916
18	Asthma, Occupational/	614
19	13 or 17 or 18	4,334
20	12 and 19	2,999

21	limit 20 to case reports	552
22	20 not 21	2,447
23	limit 22 to yr="1975 -Current"	2,397

Supplementary material 4

Screening tools for work-related asthma and their diagnostic accuracy: a systematic review – Kongsupon et al, 2021

Data extraction form

Data extraction form	**Date:**	**Reviewer initials:**
Study ID		
First author's last name		Year of publication:
Objective	□ clinical diagnosis □ occupational surveillance	
Study Characteristics		
Study design		
Country/region		
Setting	□ primary/secondary/ tertiary care □ occupation_____	
Population	_____	
Index tests	□ questionnaire □ prediction model □ spirometry □ PEF □ SPT □ Specific IgE	
Target condition	□ WRA □ WEA □ OA □ Specific OA: _____	
Reference standards	□ SIC □ serial PEF □ NSBR □ Specific IgE □ SPT □ workplace challenge □ Trial of RTW	
Participants characteristics		
Age (mean and SD)		
Male %		
Occupation		
Exposures	□ HMW_____ □ LMW_____ □ Irritant_____ □ others_____	
Allergy %		
Rhinitis symptoms%		
No. of targeted participants		
No. of participants received index tests		
No. of participants received reference standard		
Index test		
□ Questionnaire	Title	
Self-reported	Y/N	
No of domains and items		
Included questions	Respiratory symptoms	Y/N
	Work-relatedness of the symptoms	Y/N
	Occupational history	Y/N
	Exposure	Y/N
	Other tests_____	
□ Prediction model		
Components		

□ Spirometry □ PEF □ SPT □ Specific IgE Cut-off value Threshold for referral				
Test accuracy measured Y/N				
		WRA/OA/WEA	Non-disease	total
Index test outcome	positive			
	negative			
	total			
Sensitivity Specificity Area under the curve		Positive predictive value Negative predictive value		
Comments				

BMJ Open

Screening tools for work-related asthma and their diagnostic accuracy: a systematic review protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-058054.R1
Article Type:	Protocol
Date Submitted by the Author:	20-May-2022
Complete List of Authors:	Kongsupon, Ngamjit; University of Birmingham College of Medical and Dental Sciences, Institue of Applied Health Research Walters, Gareth I.; University of Birmingham College of Medical and Dental Sciences, Institute of Applied Health Research; Birmingham Chest Clinic, Birmingham Regional NHS Occupational Lung Disease Service Adab, Peymane; University of Birmingham College of Medical and Dental Sciences, Institute of Applied Health Research Jordan, Rachel; University of Birmingham College of Medical and Dental Sciences, Institute of Applied Health Research
Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	General practice / Family practice, Occupational and environmental medicine
Keywords:	Asthma < THORACIC MEDICINE, OCCUPATIONAL & INDUSTRIAL MEDICINE, PREVENTIVE MEDICINE

1

Screening tools for work-related asthma and their diagnostic accuracy: a systematic review protocol

Corresponding author:
Ngamjit Kongsupon
Institute of Applied Health Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK, B152TT. Email: nxk798@student.bham.ac.uk.

All co-authors:
Ngamjit Kongsupon[1], Gareth I. Walters[1, 2], Peymane Adab[1], Rachel E. Jordan[1]

[1]Institute of Applied Health Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK, B15 2TT

[2] Birmingham Regional NHS Occupational Lung Disease Service, Birmingham Chest Clinic, 151 Great Charles Street, Birmingham, UK, B3 3HX

Word count 2,588 words

ABSTRACT

Words=300

Introduction

Work-related asthma (WRA) refers to asthma caused by exposures at work (occupational asthma) and asthma made worse by work conditions (work-exacerbated asthma). WRA is common amongst working-age adults with asthma and impacts on individual health, work-life and income, but is often not detected by healthcare services. Earlier identification can lead to better health and employment outcomes. However, the optimal tool for screening and its effectiveness in practice is not well established. Screening tools may include whole questionnaires, questionnaire items, physiological measurements and/or immunological tests. Since publication of the most contemporary WRA or occupational asthma-specific guidelines, further studies evaluating tools for identifying WRA have been performed. Our systematic review aims to summarise and compare the performance of screening tools for identifying WRA in both clinical and workplace settings.

Methods and analysis

We will conduct a systematic review of observational and experimental studies (1975-2021) using MEDLINE, EMBASE, CINAHL Plus, Web of Science, CDSR, DARE, HTA, CISDOC databases, and grey literature. Two independent reviewers will screen the studies using predetermined criteria, extract data according to a schedule, and assess study quality using the Quality Assessment of Diagnostic Test Accuracy 2 (QUADAS-2) tool. Screening tools and test accuracy measures will be summarised. Paired forest plots and summary receiver operating characteristic (SROC) curves of sensitivities and specificities will be evaluated for heterogeneity between studies, using sub-group analyses, where possible. If the studies are sufficiently homogenous, we will use a bivariate random effects model for meta-analysis. A narrative summary and interpretation will be provided if meta-analysis is not appropriate.

Ethics and dissemination

As this is a systematic review and does not involve primary data collection, formal ethical review is not required. We will disseminate our findings through open access peer-reviewed publication, as well as through other academic and social media.

PROSPERO registration number

CRD42021246031

Strengths and limitations of this study

- This will be a review of experimental, observational and workplace surveillance studies from a comprehensive list of bibliographic databases and the grey literature, to summarise screening tools used for early identification of work-related asthma.
- The methods will adhere to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.
- The quality of eligible studies will be assessed using an objective risk-of-bias tool (Quality Assessment of Diagnostic Test Accuracy 2; QUADAS-2).
- Likely variation and inconsistency in screening tools may limit collation of findings.

INTRODUCTION

Definition and burden

Work-related asthma (WRA) is classified as (1) occupational asthma (OA), which refers to *new-onset* asthma *caused* by inhaled exposures at work; and (2) work-exacerbated asthma (WEA; or work-aggravated asthma), which refers to *pre-existing* asthma *made worse* by conditions at work.[1] Most OA occurs through an immunological mechanism, following a latent period of respiratory sensitisation to an allergen encountered in the workplace (e.g. wheat flour in the bakery process, isocyanates in paint spraying). Less commonly OA is caused by acute exposures to high levels of irritating vapours, dust, or fumes, so-called acute irritant induced asthma (e.g. chlorine gas, diesel exhaust fume).[2] WEA may be triggered by inhaled exposures to airway irritants, usually at airborne levels above workplace exposure limits, or by physical or psychological factors such as heat, humidity, exercise, or emotional stress.[3,4]

Worldwide, around 16% of new asthma diagnoses in adults is attributed to work[5] and OA costs the UK economy £1.1 billion per decade in direct healthcare and other social costs.[6] When compared with non-WRA, individuals with WRA have more severe symptoms and utilise more healthcare resources, which is associated with up to 10 fold higher societal cost.[7] Individuals with WRA also are more likely to experience impaired quality of life, mental disorders, work disruption and economic loss.[8,9]

Early diagnosis and removal from the cause, or exacerbating factor, provide the best prognosis in both OA and WEA.[2,4] A longer duration of exposure prior to diagnosis is associated with poor physiological outcomes,[10] whilst removal from the exposure (compared to reduction or continuation of exposure) improves symptoms and lung function.[11] Nevertheless, data from primary and secondary care suggest that WRA (specifically OA) is under-recognised and the diagnosis is often delayed.[12,13] Studies from UK and Canada suggest a mean delay from symptom onset to specialist referral and diagnosis, of 4 years.[12,14] Workplace respiratory health surveillance programmes may also miss WRA, with one study demonstrating that only 1 in 5 of those with an eventual diagnosis of WRA having been recognised through their surveillance programme.[15]

Diagnosis and clinical pathway for WRA

Establishing a diagnosis of asthma is based on the presence of respiratory symptoms (wheeze, dyspnoea, chest tightness and cough, diurnal variation in symptoms, triggers) and physiological abnormalities, including presence of atopy, high fractional exhaled nitric oxide (FENO) and reversible airflow obstruction on spirometry. Where diagnostic uncertainty remains, second-line investigation including peak expiratory flow (PEF) variability and non-specific bronchial reactivity (NSBR; usually only available in secondary care) may be required.[16] Confirming asthma is an important step in the investigation of WRA, however no single gold standard physiological test exists for its diagnosis. The sensitivity and specificity of physiological tests are less well described in general populations.[17] Current clinical recommendations are based upon high clinical suspicion, with strongly supportive- or a combination of physiological test results.[16, 18]

Guidelines recommend that individuals with new-onset, reactivated or unexplained worsening of asthma symptoms presenting to primary or secondary healthcare services, or their workplace occupational health provider, should be asked about the nature of their work and whether asthma symptoms are better away from work.[1,16,18-19] Those with a positive response (and especially those in high-risk occupations for OA) should be further investigated and seen by a clinician with expertise in diagnosing WRA.

Specialist investigation and categorisation as OA or WEA comprises: (1) physiological confirmation of the diagnosis of asthma, where doubt exists, (2) objective demonstration of work-relatedness of the symptoms, usually through the analysis of workplace serial peak expiratory flow (PEF) measurements, and (3) evaluation of workplace exposures to airway allergens and irritants, and demonstration of respiratory sensitisation either by immunological testing (skin prick testing or specific Immunoglobulin E) or specific inhalation challenge (SIC). The gold standard for a diagnosis of OA is generally considered to be a positive SIC to a respiratory sensitiser.[1,19] However, this investigation is only available in certain centres and is not always possible (e.g. if workplace exposures cannot be reproduced in laboratory conditions). Thus, a combination of objective physiological tests can be utilised to diagnose WRA, and differentiate between OA and WEA.

Screening tools

Tools used for screening and identifying WRA may vary depending upon the setting (primary or secondary healthcare, workplace, or specific workplace exposures). In healthcare settings, screening aims to identify individuals with asthma or asthma symptoms who are at high risk of WRA, in terms of their work tasks and exposures. Questions regarding work-relatedness of asthma symptoms (an improvement on days away from work, or on longer periods e.g. holidays) have sensitivities of 58-100% and specificities of 45-100% for the diagnosis of OA. However, these measures of accuracy were obtained primarily in specialist tertiary clinic patients rather than in general populations, leading to low confidence in recommending these in guidelines.[2] Workplace respiratory health surveillance is mandated by UK Health and Safety law, where workers are exposed to respiratory sensitising agents, as demonstrated through the risk assessment process.[20] Surveillance is usually carried out annually by an occupational health provider and generally comprises a respiratory symptom questionnaire and spirometry. Immunological testing is used in certain circumstances (e.g. platinum refining, bakers, laboratory animal workers). Surveillance using screening questionnaires has the benefit of distinguishing low-risk workers who are unlikely to need further investigation, whilst a combination of different tests (such as a sensitisation prediction model in bakers and laboratory animal workers) may better predict OA.[1] However, there has been no agreement or recommendation on the content of screening questionnaires for WRA. This is further complicated by workers sometimes being less willing to answer screening questionnaires honestly due to a fear of losing a job and the employer's judgement.[1]

The most recent International consensus and guidelines on assessment and management of WRA were published in 2012, with recommendations for screening based upon medical literature published before 2010.[1] Similarly, a UK-based systematic review with recommendations for prevention, diagnosis and management of OA was updated in 2012 and based upon literature published up until 2009.[19] Other than a systematic review of immunological testing in immunoglobulin E-mediated asthma in 2019,[21] there have been no

systematic reviews or meta-analyses of screening tools used for identifying WRA. Since 2010, further detailed questionnaires and screening tools have been developed and evaluated for use in clinical settings and workplaces. These have included questionnaire items on allergic symptoms, patient's characteristics (e.g. age, nasal rhinitis), and possible exposures, and also diagnostic or prediction models for workplace surveillance.[22-27]

Aim

The aim of this systematic review is to identify and summarise the characteristics of existing screening tools and their accuracy, and provide evidence for primary and secondary healthcare professionals and occupational health providers.

Objectives

Primary objectives: to identify, describe and compare the performance of published tools for identifying WRA, that could be used for screening in primary and secondary healthcare settings, and for WRA surveillance in occupational settings.

1) What are the existing screening tools evaluated for detecting WRA in clinical and occupational settings?
2) What is the test accuracy of the screening tools for the diagnosis of WRA in clinical settings?
3) What is the test accuracy of the screening tools used in respiratory health surveillance of WRA in occupational settings?

Secondary objective: to investigate heterogeneity in sensitivity and specificity of the screening tools in each setting.

METHODS AND ANALYSIS

This systematic review protocol is based upon the recommended method from the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy.[28] The protocol is registered on the PROSPERO database and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidance for systematic review protocols (PRISMA-P)[29] and the PRISMA statement for diagnostic test accuracy studies[30] (see online supplementary material 1). The start date for this systematic review is 13th September 2021, and it is envisaged that it will take up to 12 months (September 2022) to complete the study.

Inclusion and exclusion criteria:

Studies will be included if they meet the following criteria:

Participants

1) *Clinical settings*: include studies where the majority of individuals were aged 16 and over, with asthma or suspected asthma, and were identified from any clinical settings (i.e. primary, secondary or tertiary care) for the investigation of WRA
2) *Workplace surveillance*: include studies where individuals were aged 16 and over, from any workplace setting

Index test

1) *Clinical settings*: structured screening questionnaires, questionnaire items or prediction models which may comprise questions about respiratory symptom status, work-relatedness of the symptoms, employment history and exposure to causative antigens, participant characteristics, or the results of objective tests. We will exclude expert histories.
2) *Workplace surveillance*: screening questionnaires, questionnaire items or prediction models, and/or any physiological tests. We will exclude studies (i) using prediction models for exposure assessment, (ii) pre-employment screening for sensitisation to allergens but not WRA, and (iii) using skin prick test and/or serum specific immunoglobulin E alone in screening.

Target conditions

Work-related asthma: either occupational asthma, or work-exacerbated asthma, or uncharacterized.

Reference standards

1) A confirmed diagnosis of asthma by evidence of reversible airflow limitation and/or airway inflammation, non-specific bronchial hyper-reactivity, or positive trial of treatment. Tests may include spirometry, pre- and post-bronchodilator reversibility, PEF variability, NSBR, and FENO.

AND

2) A combination of objective tests showing a relationship between asthma and suspected causative agents in the workplace

   These may include specific inhalation challenge test (SIC) in laboratory or workplace challenge, serial PEF measurements at and away from work, NSBR at and away from work, immunologic tests (i.e. skin prick test and serum specific immunoglobulin E) to suspected work exposure agent, a trial of return to work with PEF or FEV_1 (forced expiratory volume in 1 second) monitoring.

Individuals who have a confirmed diagnosis of asthma and objective evidence of a relationship between asthma and work will be defined as having WRA. Among these, OA will be distinguished as being those with objective demonstration of sensitisation (i.e. having a positive result from SIC or identification of sensitisers as a cause from immunological tests). Individuals defined as having WEA will be those who have documented prior or concurrent-onset asthma, with a history of exposure to airway irritants, common allergens or other physical factors, with or without evidence of normal sensitisation tests (either SIC or immunological test).

Types of studies included

Cross-sectional studies, workplace surveillance studies and any types of test accuracy studies i.e. randomised comparison, cohort, or case-control type studies will be considered for inclusion in the review.

Outcomes

The main outcomes for this study are: (1) the performance of included tools (sensitivity, specificity, positive and negative predictive values, area under the receiver operating characteristic (ROC) curve) in identifying WRA; (2) characterisation of the included tools used for identifying WRA in either clinical settings or during respiratory health surveillance in occupational settings.

Search strategy

A systematic search of the medical literature will be undertaken using the following databases: MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health (CINAHL) Plus, Web of Science, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment database, CISDOC database (International Occupational Safety and Health Information Centre). Databases for ongoing studies and grey literature will be ProQuest, and Open Grey. Conference proceedings and electronic publications (ahead of print) will also be included. Any article published from 1st January 1975 (the year SIC introduced as a clinical diagnostic test) until 13th September (start date) 2021 are eligible, and there will be no language restriction. Reference lists from existing guidelines, key position papers and review articles will also be checked for relevant citations not included in the main search. Authors of included studies may be contacted for clarity or any missing information.

Search terms

The search terms have been developed with support from University of Birmingham Library Services' Research Skills Team. Words and index terms synonymous with the target condition (WRA) or with identified index tests, will be included, using Boolean linkage 'OR' within the group and 'AND' between the groups. A pilot search in MEDLINE (Ovid) using the search terms has been included in online supplementary material 2.

Selection of studies

All search results will be imported to EndNote X9 (Clarivate, Philadelphia, USA) and duplicates will be removed. Where multiple publications of the same or a part of the same participants are identified, the most recent or the largest study will be selected, and relevant supplementary information from the other publications will be gathered. The remaining articles will be exported to the web-based application Rayyan[31] for abstract and subsequently full-text article screening. Two reviewers will independently screen titles and abstracts for relevance, then identify eligible studies from their full text using the predetermined inclusion and exclusion criteria. Disagreement will be discussed and a third reviewer sought for consensus. Eligible studies will be imported to EndNote X9 software and grouped by setting (clinical or workplace).

Data extraction

Data will be extracted independently by two reviewers, blinded to each other, using a predetermined data extraction form and kept in a Microsoft Excel spreadsheet (Washington, USA); see online supplementary material 3). Data gathered will include year of publication, author, country of origin, study design, healthcare (primary, secondary or tertiary) or

workplace setting, sample population summary, reference standard, index tests and test accuracy measures. Where possible, occupational exposures will be further coded as being high or low risk for OA, according to a list of 20 high-risk occupations.[19] The data extraction form will be pilot tested on at least two studies before formal use.

Quality assessment

The Quality Assessment of Diagnostic Test Accuracy 2 tool (QUADAS-2)[32] will be used to assess the quality of included articles, in terms of risk of bias, and designated as low, high or unclear risk. Assessment will be undertaken independently by two reviews, with a third reviewer involved if any disagreement cannot be resolved by discussion. The risk of bias for each included article will be displayed in a table with a narrative summary and the designated score. Articles with a high risk of bias may be excluded from the data analysis where appropriate.

Data analysis

The target conditions will be categorised as WRA (uncharacterised), OA, WEA, or non-WRA in the analysis. The characteristics of the included tools outlined above will be described, performance (test accuracy) of each index tool will be evaluated, and a summary will be displayed in a table. Test accuracy metrics will be grouped by index test, and by setting (primary, secondary or tertiary clinical, workplace). Paired forest plots and summary receiver-operating characteristic (SROC) curves of sensitivities and specificities will be performed using RevMan 5 software (Cochrane Collaboration, 2020). Heterogeneity between studies will be examined initially by visual inspection of the paired forest plot and SROC curves, and explored using sub-group analyses where possible. The sub-groups considered will be sub-settings (primary care/secondary or tertiary care) and high- or low-risk occupations. Where clinical and methodological characteristics of the included studies are sufficiently homogeneous, a bivariate random effect model will be performed using STATA 16 software (StataCorp LLC, Texas, USA). Where a bivariate model cannot be fitted (e.g. few studies available or zero cells in the table), a univariate random effects logistic regression model for sensitivity and specificity will be performed.[33] A narrative summary will be considered if meta-analysis is not appropriate. If feasible, we will aim to summarise the evidence and make recommendations using the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) approach.[34]

ETHICS AND DISSEMINATION

As this is a systematic review and does not involve primary data collection from patients, formal ethical review and approval are not required. We will seek to publish our findings in an open access peer-reviewed medical journal and disseminate findings through other academic and social media. Data will be made available upon reasonable request.

REFERENCES

1. Baur X, Sigsgaard T, Aasen TB, et al. Guidelines for the management of work-related asthma. *European Respiratory Journal* 2012;39(3):529-45. doi: 10.1183/09031936.00096111
2. Nicholson PJ, Cullinan P, Burge PS, et al. Occupational asthma: Prevention, identification & management: Systematic review & recommendations. London: British Occupational Health Research Foundation, 2010.
3. Maestrelli P, Henneberger PK, Tarlo S, et al. Causes and phenotypes of work-related asthma. *International Journal of Environmental Research and Public Health* 2020;17(13):1-10. doi: http://dx.doi.org/10.3390/ijerph17134713
4. Henneberger PK, Redlich CA, Callahan DB, et al. An Official American Thoracic Society Statement: Work-Exacerbated Asthma. *American Journal of Respiratory and Critical Care Medicine* 2011;184(3):368-78. doi: 10.1164/rccm.812011ST
5. Blanc PD, Annesi-Maesano I, Balmes JR, et al. The Occupational Burden of Nonmalignant Respiratory Diseases. An Official American Thoracic Society and European Respiratory Society Statement. *American Journal of Respiratory and Critical Care Medicine* 2019;199(11):1312-34. doi: 10.1164/rccm.201904-0717ST
6. Ayres JG, Boyd R, Cowie H, et al. Costs of occupational asthma in the UK. *Thorax* 2011;66(2):128-33. doi: 10.1136/thx.2010.136762
7. Lemiere C, Boulet LP, Chaboillez S, et al. Work-exacerbated asthma and occupational asthma: Do they really differ? *Journal of Allergy and Clinical Immunology* 2013;131(3):704. doi: http://dx.doi.org/10.1016/j.jaci.2012.08.024
8. Karvala K, Nordman H, Luukkonen R, et al. Asthma related to workplace dampness and impaired work ability. *Int Arch Occup Environ Health* 2014;87(1):1-11. doi: 10.1007/s00420-012-0830-0 [published Online First: 2012/12/05]
9. Moullec G, Lavoie KL, Malo JL, et al. Long-term socioprofessional and psychological status in workers investigated for occupational asthma in quebec. *J Occup Environ Med* 2013;55(9):1052-64. doi: 10.1097/JOM.0b013e31829904ab [published Online First: 2013/08/24]
10. Maestrelli P, Schlünssen V, Mason P, et al. Contribution of host factors and workplace exposure to the outcome of occupational asthma. *European Respiratory Review* 2012;21(124):88-96. doi: 10.1183/09059180.00004811
11. Henneberger PK, Patel JR, de Groene GJ, et al. Workplace interventions for treatment of occupational asthma. *Cochrane Database Syst Rev* 2019;10(10):Cd006308. doi: 10.1002/14651858.CD006308.pub4 [published Online First: 2019/10/09]
12. Fishwick D, Bradshaw L, Davies J, et al. Are we failing workers with symptoms suggestive of occupational asthma? *Primary Care Respiratory Journal* 2007;16(5):304-10. doi: 10.3132/pcrj.2007.00064
13. Walters GI, McGrath EE, Ayres JG. Audit of the recording of occupational asthma in primary care. *Occup Med (Lond)* 2012;62(7):570-3. doi: 10.1093/occmed/kqs114 [published Online First: 2012/07/28]
14. Lemière C, To T, de Olim C, et al. Outcome of work-related asthma exacerbations in Quebec and Ontario. *European Respiratory Journal* 2015;45(1):266-68. doi: 10.1183/09031936.00096114
15. Suojalehto H, Karvala K, Haramo J, et al. Medical surveillance for occupational asthma-how are cases detected? *Occup Med (Lond)* 2017;67(2):159-62. doi: 10.1093/occmed/kqw101 [published Online First: 2016/08/06]
16. National Institute For Health And Care Excellence. Ashtma: diagnosis, monitoring and chronic asthma management (NG80) 2017 [Available from: https://www.nice.org.uk/guidance/ng80 accessed 10 May 2021.
17. Tuomisto LE, Ilmarinen P, Lehtimäki L, Tommola M, Kankaanranta H. Immediate bronchodilator response in FEV1 as a diagnostic criterion for adult asthma. *European Respiratory Journal*. 2019;53(2):1800904. doi: 10.1183/13993003.00904-2018.
18. British Thoracic Society and Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma A national clinical guideline, 2019.

19. Fishwick D, Barber CM, Bradshaw LM, et al. Standards of care for occupational asthma: an update. *Thorax* 2012;67(3):278-80. doi: 10.1136/thoraxjnl-2011-200755
20. Health and Safety Executive. G402 Health surveillance for occupational asthma Buxton, UK2006 [Available from: https://www.hse.gov.uk/pubns/guidance/g402.pdf accessed 4 August 2021.
21. Baur X, Akdis CA, Budnik LT, et al. Immunological methods for diagnosis and monitoring of IgE-mediated allergy caused by industrial sensitizing agents (IMExAllergy). *Allergy* 2019;74(10):1885-97. doi: 10.1111/all.13809 [published Online First: 2019/06/27]
22. Hannu T, Lindström I, Palmroos P, et al. Prediction of obeche wood-induced asthma by specific skin prick testing. *Occup Med (Lond)* 2013;63(6):429-31. doi: 10.1093/occmed/kqt050 [published Online First: 2013/06/19]
23. Jonaid BS, Rooyackers J, Stigter E, et al. Predicting occupational asthma and rhinitis in bakery workers referred for clinical evaluation. *Occup Environ Med* 2017;74(8):564-72. doi: 10.1136/oemed-2016-103934 [published Online First: 2017/03/21]
24. Killorn KR, Dostaler SM, Groome PA, et al. The use of a work-related asthma screening questionnaire in a primary care asthma program: an intervention trial. *J Asthma* 2015;52(4):398-406. doi: 10.3109/02770903.2014.971966 [published Online First: 2014/10/08]
25. Lipinska-Ojrzanowska AA, Wiszniewska M, Walusiak-Skorupa JM. Work-related asthma among professional cleaning women. *Arch Environ Occup Health* 2017;72(1):53-60. doi: 10.1080/19338244.2016.1156046 [published Online First: 2016/02/20]
26. Paraskevaidou K, Porpodis K, Kontakiotis T, et al. Asthma and rhinitis in Greek furniture workers. *J Asthma* 2019:1-10. doi: 10.1080/02770903.2019.1674328 [published Online First: 2019/10/18]
27. Pralong JA, Moullec G, Suarthana E, et al. Screening for occupational asthma by using a self-administered questionnaire in a clinical setting. *J Occup Environ Med* 2013;55(5):527-31. doi: 10.1097/JOM.0b013e3182851790 [published Online First: 2013/04/27]
28. Cochrane Diagnostic Test Accuracy Working Group. Cochrane Handbook for systematic reviews of diagnostic test accuracy: The Cochrane Collaboration 2010.
29. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ : British Medical Journal* 2015;350:g7647. doi: 10.1136/bmj.g7647
30. McInnes MDF, Moher D, Thombs BD, et al. Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies: The PRISMA-DTA Statement. *Jama* 2018;319(4):388-96. doi: 10.1001/jama.2017.19163 [published Online First: 2018/01/25]
31. Ouzzani M, Hammady H, Fedorowicz Z, et al. Rayyan—a web and mobile app for systematic reviews. *Systematic Reviews* 2016;5(1):210. doi: 10.1186/s13643-016-0384-4
32. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011;155(8):529-36. doi: 10.7326/0003-4819-155-8-201110180-00009 [published Online First: 2011/10/19]
33. Takwoingi Y, Guo B, Riley RD, et al. Performance of methods for meta-analysis of diagnostic test accuracy with few studies or sparse data. *Statistical Methods in Medical Research* 2017;26(4):1896-911. doi: 10.1177/0962280215592269
34. Schünemann HJ, Oxman AD, Brozek J, et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. *BMJ* 2008;336(7653):1106-10. doi: 10.1136/bmj.39500.677199.AE

AUTHORS' CONTRIBUTION

NK conceptualised, designed the protocol, planned the data extraction and analysis. PA, REJ and GIW refined the research concept, search terms, and data analysis plan. GIW provided clinical insights. NK drafted the initial manuscript. All authors edited, reviewed and approved the final version of the written protocol.

ACKNOWLEDGEMENT

We would like to thank Vicky Wallace, the research skill librarian, University of Birmingham, for support in developing the search strategy.

FUNDING STATEMENT

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

COMPETING INTERESTS STATEMENT

The authors have no competing interest to declare that are relevant to the content of this article.

PATIENT AND PUBLIC INVOLVEMENT

Patients were not involved in the design of this systematic review protocol.

Supplementary material 1

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist:
Screening tools for work-related asthma and their diagnostic accuracy: a systematic review – Kongsupon et al, 2022

Section and topic	Item No	Checklist item	Reported	
ADMINISTRATIVE INFORMATION				
Title:				
Identification	1a	Identify the report as a protocol of a systematic review	Yes	Page 1, line 2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Yes	Page 2, line 34
Authors:				
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Yes	Page 1, line 5-17
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Yes	Page 12, line 1-5
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	N/A	
Support:				
Sources	5a	Indicate sources of financial or other support for the review	Yes	Page 12, line 12
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A	No funding
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A	No funding
INTRODUCTION				
Rationale	6	Describe the rationale for the review in the context of what is already known	Yes	Page 4, line 42 to page 6

Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Yes	Page 6 line 14-25
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	Yes	Page 6 line 37 to page 8
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	Yes	Page 8 line 9
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	Yes	Supplementary material 2
Study records:				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Yes	Page 8 line 30, 33-34, 38, 44
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)	Yes	Page 8 line 30-39
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	Yes	Page 8 line 42 to page 9
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	Yes	Page 8 line 44 to page 9 and supplementary material 3
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Yes	Page 8 line 1-5
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	Yes	Page 9 line 7-13
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Yes	Page 9 line 17-22
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining	Yes	Page 9 line22-24, 26-28

		data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)		
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Yes	Page 8, line 24-26 and 28
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Yes	Page 8, line 30
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	N/A	
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Yes	Page 9, line 33

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.

Supplementary material 2

Screening tools for work-related asthma and their diagnostic accuracy: a systematic review – Kongsupon et al, 2022

Search terms and a pilot search results (MEDLINE-OVID)

	Target Conditions	Index tests
Free texts	Asthma *AND*	Screening Surveillance Question
	Occupation Occupational Work related Workplace Worker Work exacerbated Work aggravated	Diagnosis Test accuracy Diagnostic accuracy
Index terms	Asthma Occupational exposures Occupational Diseases	Surveys and questionnaires Sensitivity and specificity Diagnosis Medical surveillance Secondary prevention

Pilot search results

Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations <1946 to July 16, 2021>

#	Query	Results from 18 Jul 2021
1	screening.ti,ab.	555,955
2	surveillance.ti,ab.	189,449
3	question*.ti,ab.	1,012,503
4	diagnos*.ti,ab.	2,591,966
5	test accuracy.ti,ab.	2,584
6	diagnostic accuracy.ti,ab.	47,498
7	exp "Sensitivity and Specificity"/	612,147
8	exp "Surveys and Questionnaires"/	1,105,623
9	exp Diagnosis/	8,881,364
10	exp Immunologic Surveillance/ or exp Population Surveillance/	73,924
11	exp Secondary Prevention/	21,434
12	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	11,609,670
13	(asthma* adj3 (work related or occupation* or work exacerbated or work aggravated or worker* or workplace)).ti,ab.	3,790
14	Asthma/di, ep, sn [Diagnosis, Epidemiology, Statistics & Numerical Data]	32,027
15	exp "Occupations"/	35,147
16	exp "Occupational Exposure"/	65,980
17	14 and (15 or 16)	916
18	Asthma, Occupational/	614
19	13 or 17 or 18	4,334
20	12 and 19	2,999

21	limit 20 to case reports	552
22	20 not 21	2,447
23	limit 22 to yr="1975 -Current"	2,397

Supplementary material 3

Screening tools for work-related asthma and their diagnostic accuracy: a systematic review – Kongsupon et al, 2022

Data extraction form

Data extraction form	**Date:**	**Reviewer initials:**
Study ID		
First author's last name		Year of publication:
Objective	□ clinical diagnosis □ occupational surveillance	
Study Characteristics		
Study design		
Country/region		
Setting	□ primary/secondary/ tertiary care □ occupation_____	
Population	_____	
Index tests	□ questionnaire □ prediction model □ spirometry □ PEF □ SPT □ Specific IgE	
Target condition	□ WRA □ WEA □ OA □ Specific OA: _____	
Reference standards	□ SIC □ serial PEF □ NSBR □ Specific IgE □ SPT □ workplace challenge □ Trial of RTW	
Participants characteristics		
Age (mean and SD)		
Male %		
Occupation		
Exposures	□ HMW_____ □ LMW_____ □ Irritant_____ □ others_____	
Allergy %		
Rhinitis symptoms%		
No. of targeted participants		
No. of participants received index tests		
No. of participants received reference standard		
Index test		
□ Questionnaire	Title	
Self-reported	Y/N	
No of domains and items		
Included questions	Respiratory symptoms	Y/N
	Work-relatedness of the symptoms	Y/N
	Occupational history	Y/N
	Exposure	Y/N
	Other tests_____	
Threshold for referral		
□ Prediction model		
Components and Cut-off value		
□ Spirometry ……	□ PEF ……	□ SPT…….. □ Specific IgE ……
Threshold for referral		

□ Other index tests □ Spirometry …… □ PEF ……... □ SPT…… □ Specific IgE ……. □ other…….	Threshold for referral …… …… …… …… …….			
Test accuracy measured Y/N				
		WRA/OA/WEA	Non-disease	total
Index test outcome	positive			
	negative			
	total			
Sensitivity Specificity Area under the curve		Positive predictive value Negative predictive value		
Comments				

BMJ Open

Screening tools for work-related asthma and their diagnostic accuracy: a systematic review protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-058054.R2
Article Type:	Protocol
Date Submitted by the Author:	25-Aug-2022
Complete List of Authors:	Kongsupon, Ngamjit; University of Birmingham College of Medical and Dental Sciences, Institue of Applied Health Research Walters, Gareth I.; University of Birmingham College of Medical and Dental Sciences, Institute of Applied Health Research; Birmingham Chest Clinic, Birmingham Regional NHS Occupational Lung Disease Service Adab, Peymane; University of Birmingham College of Medical and Dental Sciences, Institute of Applied Health Research Jordan, Rachel; University of Birmingham College of Medical and Dental Sciences, Institute of Applied Health Research
Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	General practice / Family practice, Occupational and environmental medicine
Keywords:	Asthma < THORACIC MEDICINE, OCCUPATIONAL & INDUSTRIAL MEDICINE, PREVENTIVE MEDICINE

1

Screening tools for work-related asthma and their diagnostic accuracy: a systematic review protocol

Corresponding author:
Ngamjit Kongsupon
Institute of Applied Health Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK, B152TT. Email: nxk798@student.bham.ac.uk.

All co-authors:
Ngamjit Kongsupon[1], Gareth I. Walters[1, 2], Peymane Adab[1], Rachel E. Jordan[1]

[1]Institute of Applied Health Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK, B15 2TT

[2] Birmingham Regional NHS Occupational Lung Disease Service, Birmingham Chest Clinic, 151 Great Charles Street, Birmingham, UK, B3 3HX

Word count 2,604 words

ABSTRACT

Words=300

Introduction

Work-related asthma (WRA) refers to asthma caused by exposures at work (occupational asthma) and asthma made worse by work conditions (work-exacerbated asthma). WRA is common amongst working-age adults with asthma and impacts on individual health, work-life and income, but is often not detected by healthcare services. Earlier identification can lead to better health and employment outcomes. However, the optimal tool for screening and its effectiveness in practice is not well established. Screening tools may include whole questionnaires, questionnaire items, physiological measurements and/or immunological tests. Since publication of the most contemporary WRA or occupational asthma-specific guidelines, further studies evaluating tools for identifying WRA have been performed. Our systematic review aims to summarise and compare the performance of screening tools for identifying WRA in both clinical and workplace settings.

Methods and analysis

We will conduct a systematic review of observational and experimental studies (1975-2021) using MEDLINE, EMBASE, CINAHL Plus, Web of Science, CDSR, DARE, HTA, CISDOC databases, and grey literature. Two independent reviewers will screen the studies using predetermined criteria, extract data according to a schedule, and assess study quality using the Quality Assessment of Diagnostic Test Accuracy 2 (QUADAS-2) tool. Screening tools and test accuracy measures will be summarised. Paired forest plots and summary receiver operating characteristic (SROC) curves of sensitivities and specificities will be evaluated for heterogeneity between studies, using sub-group analyses, where possible. If the studies are sufficiently homogenous, we will use a bivariate random effects model for meta-analysis. A narrative summary and interpretation will be provided if meta-analysis is not appropriate.

Ethics and dissemination

As this is a systematic review and does not involve primary data collection, formal ethical review is not required. We will disseminate our findings through open access peer-reviewed publication, as well as through other academic and social media.

PROSPERO registration number

CRD42021246031

Strengths and limitations of this study

- This will be a review of experimental, observational and workplace surveillance studies from a comprehensive list of bibliographic databases and the grey literature, to summarise screening tools used for early identification of work-related asthma.
- The methods will adhere to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.
- The quality of eligible studies will be assessed using an objective risk-of-bias tool (Quality Assessment of Diagnostic Test Accuracy 2; QUADAS-2).
- Likely variation and inconsistency in screening tools may limit collation of findings.

INTRODUCTION

Definition and burden

Work-related asthma (WRA) is classified as (1) occupational asthma (OA), which refers to *new-onset* asthma *caused* by inhaled exposures at work; and (2) work-exacerbated asthma (WEA; or work-aggravated asthma), which refers to *pre-existing* asthma *made worse* by conditions at work.[1] Most OA occurs through an immunological mechanism, following a latent period of respiratory sensitisation to an allergen encountered in the workplace (e.g. wheat flour in the bakery process, isocyanates in paint spraying). Less commonly OA is caused by acute exposures to high levels of irritating vapours, dust, or fumes, so-called acute irritant induced asthma (e.g. chlorine gas, diesel exhaust fume).[2] WEA may be triggered by inhaled exposures to airway irritants, usually at airborne levels above workplace exposure limits, or by physical or psychological factors such as heat, humidity, exercise, or emotional stress.[3,4]

Worldwide, around 16% of new asthma diagnoses in adults is attributed to work[5] and OA costs the UK economy £1.1 billion per decade in direct healthcare and other social costs.[6] When compared with non-WRA, individuals with WRA have more severe symptoms and utilise more healthcare resources, which is associated with up to 10 fold higher societal cost.[7] Individuals with WRA also are more likely to experience impaired quality of life, mental disorders, work disruption and economic loss.[8,9]

Early diagnosis and removal from the cause, or exacerbating factor, provide the best prognosis in both OA and WEA.[2,4] A longer duration of exposure prior to diagnosis is associated with poor physiological outcomes,[10] whilst removal from the exposure (compared to reduction or continuation of exposure) improves symptoms and lung function.[11] Nevertheless, data from primary and secondary care suggest that WRA (specifically OA) is under-recognised and the diagnosis is often delayed.[12,13] Studies from UK and Canada suggest a mean delay from symptom onset to specialist referral and diagnosis, of 4 years.[12,14] Workplace respiratory health surveillance programmes may also miss WRA, with one study demonstrating that only 1 in 5 of those with an eventual diagnosis of WRA having been recognised through their surveillance programme.[15]

Diagnosis and clinical pathway for WRA

Establishing a diagnosis of asthma is based on the presence of respiratory symptoms (wheeze, dyspnoea, chest tightness and cough, diurnal variation in symptoms, triggers) and physiological abnormalities, including presence of atopy, high fractional exhaled nitric oxide (FENO) and reversible airflow obstruction on spirometry. Where diagnostic uncertainty remains, second-line investigation including peak expiratory flow (PEF) variability and non-specific bronchial reactivity (NSBR; usually only available in secondary care) may be required.[16] Confirming asthma is an important step in the investigation of WRA, however no single gold standard physiological test exists for its diagnosis. The sensitivity and specificity of physiological tests are less well described in general populations.[17] Current clinical recommendations are based upon high clinical suspicion, with strongly supportive- or a combination of physiological test results.[16, 18]

Guidelines recommend that individuals with new-onset, reactivated or unexplained worsening of asthma symptoms presenting to primary or secondary healthcare services, or their workplace occupational health provider, should be asked about the nature of their work and whether asthma symptoms are better away from work.[1,16,18-19] Those with a positive response (and especially those in high-risk occupations for OA) should be further investigated and seen by a clinician with expertise in diagnosing WRA.

Specialist investigation and categorisation as OA or WEA comprises: (1) physiological confirmation of the diagnosis of asthma, where doubt exists, (2) objective demonstration of work-relatedness of the symptoms, usually through the analysis of workplace serial peak expiratory flow (PEF) measurements, and (3) evaluation of workplace exposures to airway allergens and irritants, and demonstration of respiratory sensitisation either by immunological testing (skin prick testing or specific Immunoglobulin E) or specific inhalation challenge (SIC). The gold standard for a diagnosis of OA is generally considered to be a positive SIC to a respiratory sensitiser.[1,19] However, this investigation is only available in certain centres and is not always possible (e.g. if workplace exposures cannot be reproduced in laboratory conditions). Thus, a combination of objective physiological tests can be utilised to diagnose WRA, and differentiate between OA and WEA.

Screening tools

Tools used for screening and identifying WRA may vary depending upon the setting (primary or secondary healthcare, workplace, or specific workplace exposures). In healthcare settings, screening aims to identify individuals with asthma or asthma symptoms who are at high risk of WRA, in terms of their work tasks and exposures. Questions regarding work-relatedness of asthma symptoms (an improvement on days away from work, or on longer periods e.g. holidays) have sensitivities of 58-100% and specificities of 45-100% for the diagnosis of OA. However, these measures of accuracy were obtained primarily in specialist tertiary clinic patients rather than in general populations, leading to low confidence in recommending these in guidelines.[2] Workplace respiratory health surveillance is mandated by UK Health and Safety law, where workers are exposed to respiratory sensitising agents, as demonstrated through the risk assessment process.[20] Surveillance is usually carried out annually by an occupational health provider and generally comprises a respiratory symptom questionnaire and spirometry. Immunological testing is used in certain circumstances (e.g. platinum refining, bakers, laboratory animal workers). Surveillance using screening questionnaires has the benefit of distinguishing low-risk workers who are unlikely to need further investigation, whilst a combination of different tests (such as a sensitisation prediction model in bakers and laboratory animal workers) may better predict OA.[1] However, there has been no agreement or recommendation on the content of screening questionnaires for WRA. This is further complicated by workers sometimes being less willing to answer screening questionnaires honestly due to a fear of losing a job and the employer's judgement.[1]

The most recent International consensus and guidelines on assessment and management of WRA were published in 2012, with recommendations for screening based upon medical literature published before 2010.[1] Similarly, a UK-based systematic review with recommendations for prevention, diagnosis and management of OA was updated in 2012 and based upon literature published up until 2009.[19] Other than a systematic review of immunological testing in immunoglobulin E-mediated asthma in 2019,[21] there have been no

systematic reviews or meta-analyses of screening tools used for identifying WRA. Since 2010, further detailed questionnaires and screening tools have been developed and evaluated for use in clinical settings and workplaces. These have included questionnaire items on allergic symptoms, patient's characteristics (e.g. age, nasal rhinitis), and possible exposures, and also diagnostic or prediction models for workplace surveillance.[22-27]

Aim

The aim of this systematic review is to identify and summarise the characteristics of existing screening tools and their accuracy, and provide evidence for primary and secondary healthcare professionals and occupational health providers.

Objectives

Primary objectives: to identify, describe and compare the performance of published tools for identifying WRA, that could be used for screening in primary and secondary healthcare settings, and for WRA surveillance in occupational settings.

1) What are the existing screening tools evaluated for detecting WRA in clinical and occupational settings?
2) What is the test accuracy of the screening tools for the diagnosis of WRA in clinical settings?
3) What is the test accuracy of the screening tools used in respiratory health surveillance of WRA in occupational settings?

Secondary objective: to investigate heterogeneity in sensitivity and specificity of the screening tools in each setting.

METHODS AND ANALYSIS

This systematic review protocol is based upon the recommended method from the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy.[28] The protocol is registered on the PROSPERO database and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidance for systematic review protocols (PRISMA-P)[29] and the PRISMA statement for diagnostic test accuracy studies[30] (see online supplementary material 1). The start date for this systematic review is 13th September 2021, and it is envisaged that it will take up to 12 months (September 2022) to complete the study.

Patient and public involvement

Patients were not involved in the design of this systematic review protocol.

Inclusion and exclusion criteria:

Studies will be included if they meet the following criteria:

Participants

1) *Clinical settings*: include studies where the majority of individuals were aged 16 and over, with asthma or suspected asthma, and were identified from any clinical settings (i.e. primary, secondary or tertiary care) for the investigation of WRA

2) *Workplace surveillance*: include studies where individuals were aged 16 and over, from any workplace setting

Index test

1) *Clinical settings*: structured screening questionnaires, questionnaire items or prediction models which may comprise questions about respiratory symptom status, work-relatedness of the symptoms, employment history and exposure to causative antigens, participant characteristics, or the results of objective tests. We will exclude expert histories.
2) *Workplace surveillance*: screening questionnaires, questionnaire items or prediction models, and/or any physiological tests. We will exclude studies (i) using prediction models for exposure assessment, (ii) pre-employment screening for sensitisation to allergens but not WRA, and (iii) using skin prick test and/or serum specific immunoglobulin E alone in screening.

Target conditions

Work-related asthma: either occupational asthma, or work-exacerbated asthma, or uncharacterized.

Reference standards

1) A confirmed diagnosis of asthma by evidence of reversible airflow limitation and/or airway inflammation, non-specific bronchial hyper-reactivity, or positive trial of treatment. Tests may include spirometry, pre- and post-bronchodilator reversibility, PEF variability, NSBR, and FENO.

AND

2) A combination of objective tests showing a relationship between asthma and suspected causative agents in the workplace

   These may include specific inhalation challenge test (SIC) in laboratory or workplace challenge, serial PEF measurements at and away from work, NSBR at and away from work, immunologic tests (i.e. skin prick test and serum specific immunoglobulin E) to suspected work exposure agent, a trial of return to work with PEF or FEV_1 (forced expiratory volume in 1 second) monitoring.

Individuals who have a confirmed diagnosis of asthma and objective evidence of a relationship between asthma and work will be defined as having WRA. Among these, OA will be distinguished as being those with objective demonstration of sensitisation (i.e. having a positive result from SIC or identification of sensitisers as a cause from immunological tests). Individuals defined as having WEA will be those who have documented prior or concurrent-onset asthma, with a history of exposure to airway irritants, common allergens or other physical factors, with or without evidence of normal sensitisation tests (either SIC or immunological test).

Types of studies included

Cross-sectional studies, workplace surveillance studies and any types of test accuracy studies i.e. randomised comparison, cohort, or case-control type studies will be considered for inclusion in the review.

Outcomes

The main outcomes for this study are: (1) the performance of included tools (sensitivity, specificity, positive and negative predictive values, area under the receiver operating characteristic (ROC) curve) in identifying WRA; (2) characterisation of the included tools used for identifying WRA in either clinical settings or during respiratory health surveillance in occupational settings.

Search strategy

A systematic search of the medical literature will be undertaken using the following databases: MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health (CINAHL) Plus, Web of Science, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment database, CISDOC database (International Occupational Safety and Health Information Centre). Databases for ongoing studies and grey literature will be ProQuest, and Open Grey. Conference proceedings and electronic publications (ahead of print) will also be included. Any article published from 1st January 1975 (the year SIC introduced as a clinical diagnostic test) until 13th September (start date) 2021 are eligible, and there will be no language restriction. Reference lists from existing guidelines, key position papers and review articles will also be checked for relevant citations not included in the main search. Authors of included studies may be contacted for clarity or any missing information.

Search terms

The search terms have been developed with support from University of Birmingham Library Services' Research Skills Team. Words and index terms synonymous with the target condition (WRA) or with identified index tests, will be included, using Boolean linkage 'OR' within the group and 'AND' between the groups. A pilot search in MEDLINE (Ovid) using the search terms has been included in online supplementary material 2.

Selection of studies

All search results will be imported to EndNote X9 (Clarivate, Philadelphia, USA) and duplicates will be removed. Where multiple publications of the same or a part of the same participants are identified, the most recent or the largest study will be selected, and relevant supplementary information from the other publications will be gathered. The remaining articles will be exported to the web-based application Rayyan[31] for abstract and subsequently full-text article screening. Two reviewers will independently screen titles and abstracts for relevance, then identify eligible studies from their full text using the predetermined inclusion and exclusion criteria. Disagreement will be discussed and a third reviewer sought for consensus. Eligible studies will be imported to EndNote X9 software and grouped by setting (clinical or workplace).

Data extraction

Data will be extracted independently by two reviewers, blinded to each other, using a predetermined data extraction form and kept in a Microsoft Excel spreadsheet (Washington, USA); see online supplementary material 3). Data gathered will include year of publication, author, country of origin, study design, healthcare (primary, secondary or tertiary) or workplace setting, sample population summary, reference standard, index tests and test accuracy measures. Where possible, occupational exposures will be further coded as being high or low risk for OA, according to a list of 20 high-risk occupations.[19] The data extraction form will be pilot tested on at least two studies before formal use.

Quality assessment

The Quality Assessment of Diagnostic Test Accuracy 2 tool (QUADAS-2)[32] will be used to assess the quality of included articles, in terms of risk of bias, and designated as low, high or unclear risk. Assessment will be undertaken independently by two reviews, with a third reviewer involved if any disagreement cannot be resolved by discussion. The risk of bias for each included article will be displayed in a table with a narrative summary and the designated score. Articles with a high risk of bias may be excluded from the data analysis where appropriate.

Data analysis

The target conditions will be categorised as WRA (uncharacterised), OA, WEA, or non-WRA in the analysis. The characteristics of the included tools outlined above will be described, performance (test accuracy) of each index tool will be evaluated, and a summary will be displayed in a table. Test accuracy metrics will be grouped by index test, and by setting (primary, secondary or tertiary clinical, workplace). Paired forest plots and summary receiver-operating characteristic (SROC) curves of sensitivities and specificities will be performed using RevMan 5 software (Cochrane Collaboration, 2020). Heterogeneity between studies will be examined initially by visual inspection of the paired forest plot and SROC curves, and explored using sub-group analyses where possible. The sub-groups considered will be sub-settings (primary care/secondary or tertiary care) and high- or low-risk occupations. Where clinical and methodological characteristics of the included studies are sufficiently homogeneous, a bivariate random effect model will be performed using STATA 16 software (StataCorp LLC, Texas, USA). Where a bivariate model cannot be fitted (e.g. few studies available or zero cells in the table), a univariate random effects logistic regression model for sensitivity and specificity will be performed.[33] A narrative summary will be considered if meta-analysis is not appropriate. If feasible, we will aim to summarise the evidence and make recommendations using the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) approach.[34]

ETHICS AND DISSEMINATION

As this is a systematic review and does not involve primary data collection from patients, formal ethical review and approval are not required. We will seek to publish our findings in an open access peer-reviewed medical journal and disseminate findings through other academic and social media. Data will be made available upon reasonable request.

REFERENCES

1. Baur X, Sigsgaard T, Aasen TB, et al. Guidelines for the management of work-related asthma. *European Respiratory Journal* 2012;39(3):529-45. doi: 10.1183/09031936.00096111
2. Nicholson PJ, Cullinan P, Burge PS, et al. Occupational asthma: Prevention, identification & management: Systematic review & recommendations. London: British Occupational Health Research Foundation, 2010.
3. Maestrelli P, Henneberger PK, Tarlo S, et al. Causes and phenotypes of work-related asthma. *International Journal of Environmental Research and Public Health* 2020;17(13):1-10. doi: http://dx.doi.org/10.3390/ijerph17134713
4. Henneberger PK, Redlich CA, Callahan DB, et al. An Official American Thoracic Society Statement: Work-Exacerbated Asthma. *American Journal of Respiratory and Critical Care Medicine* 2011;184(3):368-78. doi: 10.1164/rccm.812011ST
5. Blanc PD, Annesi-Maesano I, Balmes JR, et al. The Occupational Burden of Nonmalignant Respiratory Diseases. An Official American Thoracic Society and European Respiratory Society Statement. *American Journal of Respiratory and Critical Care Medicine* 2019;199(11):1312-34. doi: 10.1164/rccm.201904-0717ST
6. Ayres JG, Boyd R, Cowie H, et al. Costs of occupational asthma in the UK. *Thorax* 2011;66(2):128-33. doi: 10.1136/thx.2010.136762
7. Lemiere C, Boulet LP, Chaboillez S, et al. Work-exacerbated asthma and occupational asthma: Do they really differ? *Journal of Allergy and Clinical Immunology* 2013;131(3):704. doi: http://dx.doi.org/10.1016/j.jaci.2012.08.024
8. Karvala K, Nordman H, Luukkonen R, et al. Asthma related to workplace dampness and impaired work ability. *Int Arch Occup Environ Health* 2014;87(1):1-11. doi: 10.1007/s00420-012-0830-0 [published Online First: 2012/12/05]
9. Moullec G, Lavoie KL, Malo JL, et al. Long-term socioprofessional and psychological status in workers investigated for occupational asthma in quebec. *J Occup Environ Med* 2013;55(9):1052-64. doi: 10.1097/JOM.0b013e31829904ab [published Online First: 2013/08/24]
10. Maestrelli P, Schlünssen V, Mason P, et al. Contribution of host factors and workplace exposure to the outcome of occupational asthma. *European Respiratory Review* 2012;21(124):88-96. doi: 10.1183/09059180.00004811
11. Henneberger PK, Patel JR, de Groene GJ, et al. Workplace interventions for treatment of occupational asthma. *Cochrane Database Syst Rev* 2019;10(10):Cd006308. doi: 10.1002/14651858.CD006308.pub4 [published Online First: 2019/10/09]
12. Fishwick D, Bradshaw L, Davies J, et al. Are we failing workers with symptoms suggestive of occupational asthma? *Primary Care Respiratory Journal* 2007;16(5):304-10. doi: 10.3132/pcrj.2007.00064
13. Walters GI, McGrath EE, Ayres JG. Audit of the recording of occupational asthma in primary care. *Occup Med (Lond)* 2012;62(7):570-3. doi: 10.1093/occmed/kqs114 [published Online First: 2012/07/28]
14. Lemière C, To T, de Olim C, et al. Outcome of work-related asthma exacerbations in Quebec and Ontario. *European Respiratory Journal* 2015;45(1):266-68. doi: 10.1183/09031936.00096114
15. Suojalehto H, Karvala K, Haramo J, et al. Medical surveillance for occupational asthma-how are cases detected? *Occup Med (Lond)* 2017;67(2):159-62. doi: 10.1093/occmed/kqw101 [published Online First: 2016/08/06]
16. National Institute For Health And Care Excellence. Ashtma: diagnosis, monitoring and chronic asthma management (NG80) 2017 [Available from: https://www.nice.org.uk/guidance/ng80 accessed 10 May 2021.
17. Tuomisto LE, Ilmarinen P, Lehtimäki L, Tommola M, Kankaanranta H. Immediate bronchodilator response in FEV1 as a diagnostic criterion for adult asthma. *European Respiratory Journal*. 2019;53(2):1800904. doi: 10.1183/13993003.00904-2018.

18. British Thoracic Society and Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma A national clinical guideline, 2019.
19. Fishwick D, Barber CM, Bradshaw LM, et al. Standards of care for occupational asthma: an update. *Thorax* 2012;67(3):278-80. doi: 10.1136/thoraxjnl-2011-200755
20. Health and Safety Executive. G402 Health surveillance for occupational asthma Buxton, UK2006 [Available from: https://www.hse.gov.uk/pubns/guidance/g402.pdf accessed 4 August 2021.
21. Baur X, Akdis CA, Budnik LT, et al. Immunological methods for diagnosis and monitoring of IgE-mediated allergy caused by industrial sensitizing agents (IMExAllergy). *Allergy* 2019;74(10):1885-97. doi: 10.1111/all.13809 [published Online First: 2019/06/27]
22. Hannu T, Lindström I, Palmroos P, et al. Prediction of obeche wood-induced asthma by specific skin prick testing. *Occup Med (Lond)* 2013;63(6):429-31. doi: 10.1093/occmed/kqt050 [published Online First: 2013/06/19]
23. Jonaid BS, Rooyackers J, Stigter E, et al. Predicting occupational asthma and rhinitis in bakery workers referred for clinical evaluation. *Occup Environ Med* 2017;74(8):564-72. doi: 10.1136/oemed-2016-103934 [published Online First: 2017/03/21]
24. Killorn KR, Dostaler SM, Groome PA, et al. The use of a work-related asthma screening questionnaire in a primary care asthma program: an intervention trial. *J Asthma* 2015;52(4):398-406. doi: 10.3109/02770903.2014.971966 [published Online First: 2014/10/08]
25. Lipinska-Ojrzanowska AA, Wiszniewska M, Walusiak-Skorupa JM. Work-related asthma among professional cleaning women. *Arch Environ Occup Health* 2017;72(1):53-60. doi: 10.1080/19338244.2016.1156046 [published Online First: 2016/02/20]
26. Paraskevaidou K, Porpodis K, Kontakiotis T, et al. Asthma and rhinitis in Greek furniture workers. *J Asthma* 2019:1-10. doi: 10.1080/02770903.2019.1674328 [published Online First: 2019/10/18]
27. Pralong JA, Moullec G, Suarthana E, et al. Screening for occupational asthma by using a self-administered questionnaire in a clinical setting. *J Occup Environ Med* 2013;55(5):527-31. doi: 10.1097/JOM.0b013e3182851790 [published Online First: 2013/04/27]
28. Cochrane Diagnostic Test Accuracy Working Group. Cochrane Handbook for systematic reviews of diagnostic test accuracy: The Cochrane Collaboration 2010.
29. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ : British Medical Journal* 2015;350:g7647. doi: 10.1136/bmj.g7647
30. McInnes MDF, Moher D, Thombs BD, et al. Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies: The PRISMA-DTA Statement. *Jama* 2018;319(4):388-96. doi: 10.1001/jama.2017.19163 [published Online First: 2018/01/25]
31. Ouzzani M, Hammady H, Fedorowicz Z, et al. Rayyan—a web and mobile app for systematic reviews. *Systematic Reviews* 2016;5(1):210. doi: 10.1186/s13643-016-0384-4
32. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011;155(8):529-36. doi: 10.7326/0003-4819-155-8-201110180-00009 [published Online First: 2011/10/19]
33. Takwoingi Y, Guo B, Riley RD, et al. Performance of methods for meta-analysis of diagnostic test accuracy with few studies or sparse data. *Statistical Methods in Medical Research* 2017;26(4):1896-911. doi: 10.1177/0962280215592269
34. Schünemann HJ, Oxman AD, Brozek J, et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. *BMJ* 2008;336(7653):1106-10. doi: 10.1136/bmj.39500.677199.AE

AUTHORS' CONTRIBUTION

NK conceptualised, designed the protocol, planned the data extraction and analysis. PA, REJ and GIW refined the research concept, search terms, and data analysis plan. GIW provided clinical insights. NK drafted the initial manuscript. All authors edited, reviewed and approved the final version of the written protocol.

ACKNOWLEDGEMENT

We would like to thank Vicky Wallace, the research skill librarian, University of Birmingham, for support in developing the search strategy.

FUNDING STATEMENT

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

COMPETING INTERESTS STATEMENT

The authors have no competing interest to declare that are relevant to the content of this article.

Supplementary material 1

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist:
Screening tools for work-related asthma and their diagnostic accuracy: a systematic review – Kongsupon et al, 2022

Section and topic	Item No	Checklist item	Reported	
ADMINISTRATIVE INFORMATION				
Title:				
Identification	1a	Identify the report as a protocol of a systematic review	Yes	Page 1, line 2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Yes	Page 2, line 34
Authors:				
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Yes	Page 1, line 5-17
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Yes	Page 12, line 1-5
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	N/A	
Support:				
Sources	5a	Indicate sources of financial or other support for the review	Yes	Page 12, line 12
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A	No funding
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A	No funding
INTRODUCTION				
Rationale	6	Describe the rationale for the review in the context of what is already known	Yes	Page 4, line 42 to page 6

Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Yes	Page 6 line 14-25
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	Yes	Page 6 line 37 to page 8
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	Yes	Page 8 line 9
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	Yes	Supplementary material 2
Study records:				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Yes	Page 8 line 30, 33-34, 38, 44
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)	Yes	Page 8 line 30-39
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	Yes	Page 8 line 42 to page 9
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	Yes	Page 8 line 44 to page 9 and supplementary material 3
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Yes	Page 8 line 1-5
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	Yes	Page 9 line 7-13
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Yes	Page 9 line 17-22
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining	Yes	Page 9 line22-24, 26-28

		data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)		
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Yes	Page 8, line 24-26 and 28
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Yes	Page 8, line 30
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	N/A	
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Yes	Page 9, line 33

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.

Supplementary material 2

Screening tools for work-related asthma and their diagnostic accuracy: a systematic review – Kongsupon et al, 2022

Search terms and a pilot search results (MEDLINE-OVID)

	Target Conditions	Index tests
Free texts	Asthma *AND*	Screening Surveillance Question
	Occupation Occupational Work related Workplace Worker Work exacerbated Work aggravated	Diagnosis Test accuracy Diagnostic accuracy
Index terms	Asthma Occupational exposures Occupational Diseases	Surveys and questionnaires Sensitivity and specificity Diagnosis Medical surveillance Secondary prevention

Pilot search results

Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations <1946 to July 16, 2021>

#	Query	Results from 18 Jul 2021
1	screening.ti,ab.	555,955
2	surveillance.ti,ab.	189,449
3	question*.ti,ab.	1,012,503
4	diagnos*.ti,ab.	2,591,966
5	test accuracy.ti,ab.	2,584
6	diagnostic accuracy.ti,ab.	47,498
7	exp "Sensitivity and Specificity"/	612,147
8	exp "Surveys and Questionnaires"/	1,105,623
9	exp Diagnosis/	8,881,364
10	exp Immunologic Surveillance/ or exp Population Surveillance/	73,924
11	exp Secondary Prevention/	21,434
12	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	11,609,670
13	(asthma* adj3 (work related or occupation* or work exacerbated or work aggravated or worker* or workplace)).ti,ab.	3,790
14	Asthma/di, ep, sn [Diagnosis, Epidemiology, Statistics & Numerical Data]	32,027
15	exp "Occupations"/	35,147
16	exp "Occupational Exposure"/	65,980
17	14 and (15 or 16)	916
18	Asthma, Occupational/	614
19	13 or 17 or 18	4,334
20	12 and 19	2,999

21	limit 20 to case reports	552
22	20 not 21	2,447
23	limit 22 to yr="1975 -Current"	2,397

Supplementary material 3

Screening tools for work-related asthma and their diagnostic accuracy: a systematic review – Kongsupon et al, 2022

Data extraction form

Data extraction form	**Date:**	**Reviewer initials:**
Study ID		
First author's last name		Year of publication:
Objective	□ clinical diagnosis □ occupational surveillance	
Study Characteristics		
Study design		
Country/region		
Setting	□ primary/secondary/ tertiary care □ occupation_____	
Population	_____	
Index tests	□ questionnaire □ prediction model □ spirometry □ PEF □ SPT □ Specific IgE	
Target condition	□ WRA □ WEA □ OA □ Specific OA: _____	
Reference standards	□ SIC □ serial PEF □ NSBR □ Specific IgE □ SPT □ workplace challenge □ Trial of RTW	
Participants characteristics		
Age (mean and SD)		
Male %		
Occupation		
Exposures	□ HMW_____ □ LMW_____ □ Irritant_____ □ others_____	
Allergy %		
Rhinitis symptoms%		
No. of targeted participants		
No. of participants received index tests		
No. of participants received reference standard		
Index test		
□ Questionnaire	Title	
Self-reported	Y/N	
No of domains and items		
Included questions	Respiratory symptoms	Y/N
	Work-relatedness of the symptoms	Y/N
	Occupational history	Y/N
	Exposure	Y/N
	Other tests_____	
Threshold for referral		
□ Prediction model		
Components and Cut-off value		
□ Spirometry ……	□ PEF ……	□ SPT…….. □ Specific IgE ……
Threshold for referral		

□ Other index tests □ Spirometry …… □ PEF ……... □ SPT…… □ Specific IgE ……. □ other…….	Threshold for referral …… …… …… …… …….			
Test accuracy measured Y/N				
		WRA/OA/WEA	Non-disease	total
Index test outcome	positive			
	negative			
	total			
Sensitivity Specificity Area under the curve		Positive predictive value Negative predictive value		
Comments				