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

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ABSTRACT

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 among working-age adults with asthma and impacts 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 the 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 tool. Screening tools and test accuracy measures will be summarised. Paired forest plots and summary receiver operating characteristic curves of sensitivities and specificities will be evaluated for heterogeneity between studies, using subgroup analyses, where possible. If the studies are sufficiently homogenous, we will use a bivariate random effect 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 guidelines.
⇒ The quality of eligible studies will be assessed using an objective risk-of-bias tool (Quality Assessment of Diagnostic Test Accuracy 2).
⇒ Likely variation and inconsistency in screening tools may limit the 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 (eg, 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 (eg, 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 use 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] while removal from the exposure (compared with 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 the 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 one in five 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 on high clinical suspicion, with strongly supportive results 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 comprise: (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 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 (eg, if workplace exposures cannot be reproduced in laboratory conditions). Thus, a combination of objective physiological tests can be used to diagnose WRA and differentiate between OA and WEA.

Screening tools

Tools used for screening and identifying WRA may vary depending on 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, for example, 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 (eg, 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, while 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 on 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 on 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 (eg, age, nasal rhinitis) and possible exposures, and also diagnostic or prediction models for workplace surveillance.[22–27]

Aim

This systematic review aims 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, which 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 on 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 13 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 (ie, primary, secondary or tertiary care) for the investigation of WRA
2. *Workplace surveillance*: includes studies where individuals 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 (1) using prediction models for exposure assessment, (2) pre-employment screening for sensitisation to allergens but not WRA and (3) using skin prick test and/or serum-specific immunoglobulin E alone in screening.

Target conditions

WRA: either OA, or WEA or uncharacterised.

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 SIC test in laboratory or workplace challenge, serial PEF measurements at and away from work, NSBR at and away from work, immunologic tests (ie, 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 s) 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 an objective demonstration of sensitisation (ie, 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, that is, 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 and (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 1 January 1975 (the year SIC was introduced as a clinical diagnostic test) until 13 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 X V.9 (Clarivate, Philadelphia) 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 X V.9 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); 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[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, the 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 V.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 subgroup analyses where possible. The subgroups considered will be subsettings (primary care/secondary or tertiary care) and high-risk 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 V.16 software (StataCorp LLC, Texas). Where a bivariate model cannot be fitted (eg, 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 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 on reasonable request.

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Contributors NK conceptualised, designed the protocol, planned the data extraction and analysis. PA, RJ 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.

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Competing interests None declared.

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