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Spirometry parameters used to define small airways obstruction in population-based studies: systematic review protocol

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ABSTRACT

Introduction In recent years, there has been increasing interest in the use of spirometry for the assessment of small airways obstruction (SAO) driven by the idea that these changes occur prior to development of established obstructive lung disease. Maximal mid-expiratory and distal flow rates have been widely used despite a lack of agreement regarding parameter selection or definition of an abnormal result. We aim to provide evidence from population-based studies, describing the different parameters, definitions of normal range and the resulting impact on prevalence estimates for SAO. Summarising this evidence is important to inform development of future studies in this area.

Methods and analysis A systematic review of population-based studies will be conducted. MEDLINE, Web of Science and Google Scholar will be searched from database inception to May 2021. Primary outcomes will include the spirometry parameter used to define SAO, and the definition of an abnormal result. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines will be followed for study selection. Study methods will be assessed using the Newcastle-Ottawa scale and the Grading of Recommendations Assessment, Development and Evaluation working group methodology. Narrative synthesis will be conducted for all included studies. Meta-analysis will also be conducted for prevalence estimates and associated risk factors where data quality and availability allow. Random effects models will be used to conduct the meta-analysis and I^2 statistics will be used to assess heterogeneity across studies. Where appropriate subgroup analysis will be conducted to explore heterogeneity.

Ethics and dissemination There is no requirement for ethical approval for this project. Findings will be disseminated via peer-reviewed publications and other formats, for example, conferences, congresses or symposia.

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Strengths and limitations of this study

- This protocol provides a reproducible and transparent methodology to review the literature on spirometry parameters used to define small airways obstruction (SAO) in population-based studies.
- This systematic review will provide the highest level of evidence to inform the development of future large epidemiological studies where spirometry is used to assess SAO.
- The qualitative nature of the primary outcomes and the likely heterogeneity of secondary outcomes are the main limitations of this study.

INTRODUCTION

The small airways are those of less than 2 mm in diameter, have no cartilage and arise between the 4th and 14th generation of airway branching.[1] The small conducting airways are not normally a site of significant airway resistance, however have been shown to cause significant airflow limitation in conditions such as chronic obstructive pulmonary disease (COPD).[2] Key features of small airway obstruction (SAO) in COPD include hypersecretion of mucus, airway remodelling and inflammation, which have been shown to precede emphysematous changes and reduction in traditional spirometric markers.[3]

There is currently no gold standard method to assess SAO non-invasively.[4] In 1972 it was proposed that maximum mid-expiratory flow rate (MMEF) derived from spirometry could be used in the assessment of SAO, especially in the presence of a normal forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) ratio.[5] MMEF or as it is sometimes called $FEF_{25–75}$ refers to the maximum forced expiratory flow between 25% and 75% of the FVC. McFadden and Linden[5] hypothesised that excessive narrowing and collapse of the small airways in COPD is exacerbated by the increase in small airway resistance at lower lung volumes, as such the mid-late portion of the FVC is reflective of air flow through the small airways. Other spirometry parameters that have been used to assess SAO include the forced expiratory flow at 50% and 75% (FEF_{50}, FEF_{75}), the forced expiratory flow

between 75% and 85% of the FVC ($FEF_{75–85}$), the MMEF as a ratio of the FVC (MMEF/FVC), the forced expiratory volume in 3 s (FEV_3) as a ratio of the FVC (FEV3/FVC), the FEV_3 as a ratio of the forced expiratory volume in 6 s (FEV_3/FEV6) and the 1–FEV_3/FVC.

Mid-expiratory and distal flow indices are volume dependant. Therefore, accurate interpretation of results relies on both the accuracy of measurement of the FVC and whether an individual's lungs are a normal size for their age, height and sex, and for this reason it is not routinely used in clinical practice.[6] However, many published studies have demonstrated associations between these parameters and clinical outcomes, including prognosis in early obstructive lung disease,[7] lung damage from exposure to fine particulate matter ($PM_{2.5}$),[8] small airways impairment in allergic rhinitis,[9] long term asthma symptoms and exacerbation risk,[10] early lung damage in alpha 1 antitrypsin deficiency[11] and risk of acute bronchitis, pneumonia and hospitalisation in elderly populations.[12]

Despite a wealth of small and medium size studies, predominantly in clinical populations, large population-based studies investigating the prevalence and risk factors associated with SAO are limited. A recent cross-sectional study from China with 58 000 participants showed SAO to be associated with cigarette smoking, $PM_{2.5}$ exposure and elevated body mass index.[13] The diagnostic criteria used to define SAO was two of MMEF, FEF_{50} or FEF_{75} less than 65% of predicted. They found up to 25% of the study population had evidence of SAO. Other studies using MMEF have reported similar results, with prevalence of SAO being 29.6% and 23.6% using <65% and <lower limit of normal (LLN) to define abnormality.[7 14] A smaller North American study reported the prevalence of SAO to be just 6.3% using lone FEV_3/FVC<LLN as a diagnostic criterion.[15] In addition to a lack of agreement in the literature as to which spirometry parameter is best for measuring SAO, there is also lack of consensus as to what defines an abnormal result, with both per cent predicted cut-offs and LLN being used. Mid-expiratory flow indices have been shown to have a wide range of normal values and within-subject variability, while LLN varies greatly among different populations.[16] Conversely, the relatively novel measure of FEV_3/FVC has established reference equations that demonstrate narrow confidence limits of normal.[17 18]

While the importance of spirometric indices of SAO for clinical decision making is still is up for debate,[19 20] there is an argument that identification of those with SAO in the general population and associated risk factors may assist in key policy decision making regarding preventable lung disease. We therefore propose a systematic review to evaluate the literature regarding the different spirometry parameters used to define SAO, the definition of normal range, prevalence estimates and associated risk factors in population-based studies. To the best of our knowledge, no previous review has investigated this topic.

Aim and research questions

The aim of this review is to systematically evaluate all available reports of population-based studies where spirometry has been used to define SAO. The proposed systematic review will answer the following research questions.

Primary question

- Which spirometry parameter and which cut-off are used in the assessment of SAO in population-based studies?

Secondary questions

- How do prevalence estimates for SAO compare across population-based studies, especially where different spirometry parameters and different definitions of normal range are used?
- What are the risk factors associated with SAO in population-based studies?
- Can SAO be used as a prognostic marker of obstructive lung disease in population-based studies?

METHODS AND ANALYSIS

This protocol was made following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) checklist[21] to ensure methodological transparency and search reproducibility. The planned start date of the review is 4 May 2021 with completion anticipated by 4 October 2021.

Study selection criteria

Table 1 shows both the inclusion and exclusion criteria using the modified PICOS (Population, Intervention, Comparison, Outcome(s), Study design) tool to include study designs.[22] The modified PICOS tool will assist in limiting the number of irrelevant articles.

Information sources

Original research published in peer review journals will be retrieved using two established databases: Medline (PubMed) and Web of Science. Google Scholar will also be used to identify grey literature which falls outside of mainstream journals. Both qualitative and quantitative studies will be sought. To ensure the inclusion of important early publications, a literature search from inception of the databases to May 2021 will be performed. Study inclusion will not be limited by language, all attempts will be made to translate and extract information from non-English publications. Non-primary literature, such as literature reviews, editorials, case-studies, protocol studies and clinical guidelines will not be included. The reference lists of key publications returned by the search will also be reviewed to ensure that additional relevant articles are not missed and to evaluate the robustness of the search criteria.

The International Prospective Register of Systematic Reviews (PROSPERO) record of this protocol is available online (https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=250206).

Table 1 Inclusion and exclusion criteria

PICO strategy	Inclusion criteria	Exclusion criteria
P—Population	Population-based studies in adults (≥18 years)	Not in humans
I—Intervention	N/A	N/A
C—Comparison	N/A	N/A
O—Outcome(s)	Spirometry parameters reported: Measured at least one spirometry parameter used to define small airways obstruction: FEF_{50}, FEF_{75}, $FEF_{25–75}$, MMEF, FEV_3, FEV_3/FVC, MMEF/FVC or 1–FEV_3/FVC	Spirometry parameters not used to define SAO
S—Study design	Observational cross-sectional, case–cohort or cohort studies	Longitudinal studies with less than 1-year follow-up

FEF_{50} and FEF_{75}, forced expiratory flow at 50% and 75%; FEV_3, forced expiratory volume in 3 s; FVC, forced vital capacity; MMEF, maximum mid-expiratory flow rate; SAO, small airway obstruction.

Search strategy

A preliminary search for MeSH (medical subject headings) terms was conducted. MeSH search terms were combined with key words using the Boolean operators AND and OR.[23] MeSH terms were only found for definitions of mid-expiratory flow rate. No MeSH terms were identified for any derivation of SAO or disease, therefore in these instances key words were identified after thorough review of relevant literature. Search terms will be kept consistent across all databases. When searching in Google Scholar, quotation marks will be used to confine the search to exact terms only – this is to limit the number of irrelevant articles.

The following search strategy was constructed: ((Maximal midexpiratory flow rate OR FEF 25-75 Percent OR 25-75 Percent, FEF OR 25-75 Percent* FEF OR FEF 25 75 Percent OR FEF 25-75 Percent OR Percent, FEF 25-75 OR Percent*, FEF 25-75 OR MMFR OR Forced Expiratory Flow 025-075 Percent OR Forced Expiratory Flow 025 075 Percent) OR (forced expiratory flow OR mid-expiratory flow rate OR MMEF OR MMEF/FVC OR MEF50 OR MEF 50 OR MEF75 OR MEF 75 OR FEF25-75 OR FEF 50 OR FEF50 OR FEF 75 OR FEF75 OR FEV3/FVC OR FEV3 OR FEV3/FEV6) AND (Small airway* OR small airway* obstruction OR small airway* disease OR small airway* narrowing OR peripheral airway OR peripheral airway* disease OR peripheral airway* obstruction OR SAD OR small airway* dysfunction OR small airway* function OR small airway* limitation OR distal airway* OR distal airway* disease) AND (alladult[Filter])). FEV3/FVC, FEV3/FEV6 and FEV3 will also be entered as lone search terms due to the expectation of very few publications for these novel measurements. This strategy was built for Medline (PubMed) and will be adapted for Web of Science and Google Scholar search fields.

Study records

Literature search results will be imported into the Covidence web-based software for systematic review management (www.covidence.org). Covidence automatically screens for duplicates and removes them from the review list. Each reviewer will have access to the project via Covidence. Initially, blinded screening of titles and abstracts will be done by independent reviewers BK-B and OM; this requires a 'yes', 'no' or 'maybe' response to be selected. Studies with two 'yes' votes, 'yes/maybe' or 'maybe/maybe' will be progressed for review of full text, two 'no' votes will be discarded, and conflicts will be moved to a resolve conflicts list. Project supervisor (AFSA) will resolve conflicts after discussion via the settings menu in Covidence. Prior to full text review, inclusion and exclusion criteria will be entered into Covidence and full text PDFs will be imported. Two reviewers will then screen the full text articles for inclusion, selecting appropriate inclusion and exclusion reasons from dropdown menus. The project supervisor will be notified of any conflicts requiring resolution. We will contact study authors for additional information where necessary to resolve questions regarding eligibility.

The Covidence software will be used for the creation of data extraction forms. The following domains will be used: (1) study identification, (2) methods, (3) participant demographic information and (4) relevant study outcomes. Data extraction will be done independently and in duplicate by BK-B and OM. Inconsistencies highlighted by Covidence will be resolved after discussion with AFSA. We will make every attempt to contact study authors to obtain missing information, or to resolve uncertainties regarding data extraction. We will extract the following information in relation to the above domains: (1) article title, journal title, authors, country, language, publication year and institution; (2) study design, objectives/hypothesis, length of any follow-up, statistical analysis; (3) number of participants, gender/sex, age, race, groups and controls, if appropriate and (4) spirometry parameter used to define SAO, definition of abnormal result, prevalence of SAO, associated risk factors and, for longitudinal studies, prediction of lung function decline, development of COPD, morbidity and mortality (ORs and HRs where applicable).

Outcomes and prioritisation

The primary purpose of this review is to evaluate how different spirometric measures have been used in

population-based studies to define SAO. Not only do we need to know the selected parameter, but we also need to know the criteria for defining an abnormal result. For this reason, there are two primary outcomes: (1) spirometry parameter used to define SAO and (2) definition of an abnormal result. Secondary outcomes for this study include the prevalence of SAO (percentage of population with SAO), the risk factors associated with SAO and the ability of SAO at baseline to predict future lung function decline, morbidity and mortality during longitudinal follow-up. While not the priority of this review, population-based studies tend to collect this information, and it is important to give context to the prevalence estimates.

Quality assessment

Study quality will be assessed using the Newcastle-Ottawa scale.[24] This scale is widely used in the assessment of the quality of non-randomised studies, and is recommended by the Cochrane Collaboration for observational studies.[25] The scale contains three quality parameters (selection, comparability and outcome), which are subdivided into eight items. Each Item is worth one point except for comparability, which is worth two. Studies will be assigned a score from 0 to 9 with <5 indicating a high risk of bias. Assessments will be completed in duplicate by BK-B and OM using the Covidence review management software. Where there is disagreement a third reviewer (AFSA) will have the final decision.

Data synthesis

The two primary outcomes (spirometry parameter used to measure SAO and definition of an abnormal result) are categorical and therefore cannot be quantitatively synthesised. To summarise data, a systematic narrative synthesis will be conducted. This will include information in the form of both text and tables. Narrative synthesis will be conducted in line with previous guidance.[26] Text will be used to summarise relationships and findings within and between included studies and act as a commentary to tabulated information. Tables will be constructed to summarise and allow visual comparison of study characteristics. It is anticipated that the following tables will be constructed: (1) study characteristics, participant demographics and primary outcomes; (2) risk factors associated with SAO; (3) outcomes from longitudinal studies and (4) risk of bias assessment. Studies will only be included in tables if there is a low or moderate risk of bias. Studies with a Newcastle-Ottawa score <5 will not be included.

Depending on data availability and quality, the prevalence of SAO, associations with risk factors and longitudinal outcomes will be meta-analysed. Heterogeneity between estimates will be assessed via visual inspection of forest plots and by I^2 statistics.[27] Prior to meta-analysis, prevalence estimates will be transformed using the double arcsine method,[28] which accounts for overestimation of result weight caused by the variance drifting towards zero in the presence of prevalence estimates at either extreme (0 or 100%). To account for heterogeneity, random effects models will be used to conduct the meta-analyses, giving pooled estimates and 95% CI for prevalence, associated risk factors (ORs) and longitudinal outcomes (HRs). Sensitivity analysis will be performed by incorporating risk of bias scores into the synthesis, secondary analysis will include studies with low-moderate risk of bias only. Where possible subgroup analysis will be performed on prevalence estimates to explore heterogeneity considering age, gender/sex and location.

Confidence in cumulative evidence

Quality of evidence will be assessed using the Grading of Recommendations Assessment, Development and Evaluation working group methodology (GRADE). As this review will be based on observational studies, we will use an adapted form of the GRADE methodology, where observational studies are a priori assigned as moderate certainty.[29] Five categories will then be considered when rating down: risk of bias, imprecision, inconsistency, indirectness and publication bias. The final grade will be given once these five categories have been considered.

Patient and public involvement

No patient involved.

DISCUSSION

The purpose of this protocol is to provide a reproducible and transparent methodology for this review. This protocol provides a detailed background to the subject area, clearly outlines the review objectives, inclusion/exclusion criteria, outcome measures, data sources, search strategy, data extraction and procedures for assessing study bias and quality. Publication of this protocol will minimise the risk of bias and clearly set out the intentions of this review to the scientific community.

The physiological assessment of SAO is contentious but rapidly increasing in popularity. To date reviews have not been specific to spirometry and have had a, mainly, clinical focus. The strength of this proposed review is that it will summarise the evidence in population-based studies, hopefully informing the development of future large epidemiological studies where spirometry is used to assess pulmonary function. A potential limitation of this review is the qualitative nature of the primary outcomes and the likely heterogeneity of the secondary outcomes.

In conclusion, the intention of this review is to explore the value of the assessment of SAO in population-based studies, while also summarising the methodological differences in studies to date. Highlighting the strengths and weaknesses of available evidence is important prior to further research in this area.

Ethics and dissemination

This is a protocol for a systematic review and no participant recruitment will take place. The results of this review will be published in an open access, peer-review journal.

Results will also be disseminated via other methods, such as conferences, seminars, congresses or symposia where appropriate.

Contributors BK-B and AFSA were responsible for the conception, design and drafting of the protocol manuscript. OM provided version review and critical insights into the methodology. All authors have approved and contributed to the final written manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

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