THE RELEVANCE OF PHYSIOLOGICAL SMALL AIRWAYS FUNCTION IN DIAGNOSING ASTHMA AND ASSESSING BRONCHODILATOR RESPONSE.

by

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ABSTRACT

Asthma is a common, chronic and heterogenous disease that is characterised by variable flow rate. Objectively assessing and diagnosing asthma can be difficult due to disease variability. Testing bronchodilator response (BDR) is one of the objective assessments for asthma, however, BDR can be found in other diseases such as chronic obstructive pulmonary disease (COPD) patients. Small airways dysfunction (SAD) is common in asthma and COPD, however the utility or standards of small airways function is new well described in asthma guidelines.

The aim of this thesis was to evaluate the current evidence for the use of physiological small airways function in the diagnosis of asthma. Furthermore, the thesis aimed to evaluate the current evidence for small airways BDR compared to larger airways. It also aimed to understand the relationship between large and small airways indices using spirometry and the prevalence and risk factors of SAD.

Firstly, a systematic review was conducted to review the current evidence for using physiological small airways tests in diagnosing asthma which includes spirometry (MMEF and FEF50) and Oscillometry (R5, R5-20, Ax, and X5). Ten studies were included in the review. Overall, studies were small, heterogeneous and were not standardised, however, differences were found in small airways measurements compared to healthy controls.

Secondly, a retrospective analysis of real-world data assessed the physiological measurements of SAD, its prevalence in asthma and in those with airflow obstruction (AO), and risk factors for SAD. SAD was prevalent in asthma and although a strong relation was found between small and large airways indices, some patients had evidence of SAD without AO. This highlighted the potential importance of assessing

the small airways, especially in smokers, which was found to be associated with SAD in asthma.

Thirdly, a systematic review was conducted to assess the BDR in the small airways compared to large airways (forced expiratory volume in the 1st second (FEV_1)) in asthmatics patients. The studies were small, with diverse methodologies used to conduct the BDR assessment. However, greater BDR was reported for small airways indices compared to FEV_1 and approximately 25% of patients demonstrated BDR in the small airways tests but not in FEV_1.

Finally, a retrospective analysis of real-world data was conducted to assess the BDR for the large and the small airways and their relation to SAD. A greater improvement was found in small airways indices and SAD at baseline was found to be a predictor for a positive BDR for both FEV_1 and MMEF, whereas AO was not.

Overall, this thesis suggests there might be utility in assessing the small airways in asthma, but that standardisation is needed in order to enable definitive research studies.

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LIST OF ABBREVIATIONS

GINA	Global Initiative For Asthma
WHO	World Health Organisation
FEV_1	Forced Expiratory Volume In The First Second
FVC	Forced Vital Capacity
SAD	Small Airways Dysfunction
BDR	Bronchodilator Response
FEF_{50}	Forced Expiratory Flow At 50% Of FVC
FEF_{75}	Forced Expiratory Flow When 75% Of FVC
MMEF	Maximal Mid-Expiratory Flow
FOT	Forced Oscillation Techniques
IOS	Impulse Oscillometry
Zrs	Lung Impedance
Xrs	Lung Reactance
Rrs	Lung Resistance
X5	Reactance At 5 Hertz
Fres	Resonant Frequency
AX	Area Of Reactance
R5	Total Lung Resistance (At 5 Hertz)
R20	Large Airways Resistance (At 20 Hertz)
R5-R20	Resistance Between R5 And R20
MBW	Multiple Breath Washout
LCI	Lung Clearance Index
FRC	Functional Residual Capacity
SF6	Sulphur Hexafluoride
S_{acin}	Ventilation Heterogeneity Peripheral To The Acinar Entrance
S_{cond}	Ventilation Heterogeneity At The Conductive Lung Zone
RV	Residual Volume
TLC	Total Lung Capacity
FEF_{25-75}	Forced Expiratory Flow Between The 25% And 75% Of FVC
SABA	Short Acting $Beta^2$ Agonist Bronchodilators

NHS	National Health Service
ED	Emergency Department
COPD	Chronic Obstructive Pulmonary Disease
GERD	Gastro-Oesophageal Reflux Disease
NICE	National Institute Of Clinical Excellence
BTS	British Thoracic Society/
SIGN	Scottish Intercollegiate Guidelines Network
SINA	Saudi Initiative For Asthma
ATS	American Thoracic Society
ERS	European Respiratory Society
DL_{CO}	Diffusing Capacity For Carbon Monoxide
ICS	Inhaled Corticosteroid
ATLANTIS	Assessment Of Small Airways Involvement In Asthma
BHR	Bronchial Hyper-Responsiveness
SVN	Small-Volume Nebulizers
pMDI	Pressurised Metered-Dose Inhalers
MMAD	Mass Mean Aerodynamic Diameter
DTA	Diagnostic Test Accuracy
ROB	Risk Of Bias
ACT	Asthma Control Test
PROSPERO	International Registry Of Systematic Reviews
PRISMA	Preferred Reporting Items For Systematic Reviews And Meta-Analyses
AHRQ	Agency For Healthcare Research And Quality
QUADAS-2	Quality Assessment Of Diagnostic Accuracy Studies 2
BMI	Body Mass Index
NR	Not Reported
Sen	Sensitivity
Spe	Specificity
MCT	Methacholine Challenge Test
ILD	Interstitial Lung Diseases
AATD	Alpha-1 Antitrypsin Deficiency

AO	Airflow Obstruction
OR	Odds Ratio
LLN	Lower Limit Of Normal
ARTP	Association For Respiratory Technology And Physiology
FEV_3	Forced Exhaled Volume In The First 3seconds
LABA	Long-Acting Beta-Agonist,
LAMA	Long-Acting Muscarinic Antagonists,
SAMA	Short-Acting Muscarinic Antagonists,
CS	Corticosteroid,
HTN	Hypertension,
DM	Diabetes Mellitus.
SAF	Small Airways Function
SBW	Single Breath Washout
PICO	Population, Intervention, Comparator, Outcome
RCT	Randomised Controlled Trials
NIH	National Institute Of Health
GOLD	Global Initiative For Chronic Obstructive Lung Disease
GLI	Global Lung Initiative
VIF	Variance Inflation Factor

CHAPTER 1

1. INTRODUCTION

Part of this chapter has been published as a narrative review in the Chronic Respiratory Disease Journal under the Creative Commons licence (CC-BY 3.0), entitled "**The Diagnosis of Asthma. Can Physiological Tests of Small Airways Function Help?**" (Almeshari et al., 2021c) (see appendix 8.1.1). The authors list and contributions for the published work are listed below.

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M.A.A and E.S. conceived and designed the review. M.A.A wrote the review with E.S. and J.A.S. contributed to the revision of the manuscript.

1.1 BACKGROUND

Asthma is a highly heterogeneous, chronic respiratory disease with variations in inflammatory processes, clinical course, severity, and response to treatment. Inflammation of the airways leads to both clinical symptoms such as chest tightness, wheezing, coughing (classically worse at night or early morning (Kaufman, 2011)) and variable expiratory airflow limitation that changes with time and intensity, becoming fixed in a proportion of cases.

The Global INitiative for Asthma (GINA), is a group of multiple stakeholders for asthma, including scientists, patient representatives, and public health officials. The initiative was started in 1993 with collaboration of the World Health Organisation (WHO) and the National Heart, Lung, and Blood Institute in the United States to provide a unifying framework to diagnose and manage asthma. According to GINA, “Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms, such as wheeze, shortness of breath, chest tightness and cough, that vary over time and in intensity, together with variable expiratory airflow limitation” (Global Initiative for Asthma (GINA), 2022).

This GINA definition emphasises the variable nature of asthma symptoms, airway hyperresponsiveness, and inflammation that could develop during any point in life and the lack of any specific diagnostic test to identify the disease. The risk of developing asthma includes a variety of factors, from genetics to environmental, and asthma is able to manifest in a variety of potentially distinct phenotypes (Martinez and Holt, 1999).

Although asthma has been described centuries ago, there is still a paucity of understanding of the disease in most clinical settings. The diagnosis is often made without objective assessment either physiologically or biologically and the traditional treatment of asthma has been fairly simple (bronchodilators and inhaled corticosteroids) (To et al., 2015). However, recognition of the importance of asthma and the advent of new treatments, including biological therapies, and treatments which have greater dispersion in the lungs (such as ultra-fine particles) have increased the interest in diagnosing asthma accurately and finding treatable traits to stratify therapies for patients.

Asthma is a disease that mainly affects the airways, and the small airways comprise 98% of the lungs cross-sectional area (Carr et al., 2017). Studies of transbronchial biopsies have found evidence of small airways inflammation in severe asthmatics (Balzar et al., 2002) and when comparing small airways in post mortem studies of fatal asthma, the small airways had a significantly higher numbers of inflammatory cells compared to controls (those who had died due to non-pulmonary related diseases) (de Magalhães Simões et al., 2005). Yet, in asthma, the small airways are often not evaluated or reported. The hallmark of asthma, airflow variability, is assessed by the Forced Expiratory Volume in the first second (FEV_1) of the Forced Vital Capacity (FVC). However, this does not measure small airways specifically.

Symptomatology, exacerbations, airways inflammation and airway remodelling can be reduced with an appropriate diagnosis and treatments. However, there is still a significant burden of undiagnosed, and hence untreated asthma in both children and adults (Kavanagh et al., 2019). Case-finding studies suggest under-diagnosis is common, with study describing undiagnosed asthma in 50% of all cases (Nolte et al.,

2006). There is also significant diagnostic delay, with one study describing a median delay between meeting symptom-based criteria and a physician diagnosis of 1.7 years (Ali et al., 2016). Undiagnosed asthma and diagnostic delay are critical, as both are linked to poor clinical outcomes (Accordini et al., 2011, Backer et al., 2007).

Misdiagnosis is also common, with studies describing approximately 30% of patients who are diagnosed with asthma having no objective evidence of asthma when tested more thoroughly (Aaron et al., 2017, Shaw et al., 2012). Over-diagnosis is also problematic, as potentially alternative diagnoses may be missed and patients might take long term therapy which is not required.

Some of this diagnostic uncertainty reflects the fact that there is no gold standard test to diagnose asthma. Guidelines suggest the diagnosis to be based on suggestive symptoms and a detailed medical history and examination, as well as objective measures, most commonly spirometry with reversibility and serial peak flows (Global Initiative for Asthma (GINA), 2022, NICE, 2017, BTS/SIGN, 2019). However, symptoms can be variable and intermittent as well as being common across a variety of respiratory and non-respiratory medical conditions.

Performing spirometry can be challenging as measurements require significant patient effort and an ability to follow the instructions of healthcare specialists (Schneider et al., 2009, Sivan et al., 2009). Exhaling forcefully through a mouthpiece is not a natural breathing manoeuvre, which can make it challenging to obtain accurate results (Motamedi-Fakhr et al., 2017). Results are interpreted in comparison with predicted values based on height, age, sex, and race. However, the “normal” reference ranges are wide and differentiating between health and disease is not always straightforward. Furthermore, the observable differences in lung size across ethnic

groups are not all represented sufficiently in reference populations (Quanjer et al., 2012), just as the extremes of age are under-represented.

Traditionally reported spirometric parameters such as the FEV_1, FVC and FEV_1/FVC may not reflect dysfunction in the small airways (van den Berge et al., 2011). Indeed, asthma was classically considered a disease of the large airways but there has been an increasing awareness that the small airways are also affected . Autopsy specimens from fatal cases of asthma have demonstrated inflammation in the small airways compared to controls died without respiratory diseases (Kuyper et al., 2003). Small airways dysfunction (SAD) has been described in children with mild or intermittent asthma symptoms with a normal FEV_1, suggesting small airways involvement as an early manifestation of the disease (Singer et al., 2013). In a study of transbronchial biopsies, the inflammatory cell infiltrate in the small airways was greater than that in the medium and large airways in patients with poorly controlled asthma symptoms (Balzar et al., 2002). Furthermore, there are now inhaled treatments with extra-fine particles that can target the small airways, leading to increased symptomatic benefit and improved clinical outcomes for asthma patients (van der Molen et al., 2016). All these studies suggest the small airways might be important in asthma and an important therapeutic target. In theory, physiological assessment of small airways function could also provide the means to diagnose asthma with greater certainty and monitor response to treatment.

In this chapter, the pathological basis for small airways involvement in asthma will be discussed alongside the current tools available to assess small airways function. The current evidence to support whether tests of small airways (including the

bronchodilator response (BDR) test in small airways) could diagnose asthma or the response to treatments, which can now target small airway function, will be reviewed.

1.2 THE ANATOMY OF THE SMALL AIRWAYS

The lungs has been described to have approximately 23 airways generations (Weibel, 1963). In figure 1.1, the lungs airways generations are outlined with the small airways starting at approximately the 8th generation (adapted from (McNulty and Usmani, 2014)). Studies suggest that lungs with a volume of 5 litres contain approximately 30,000 small airways and that most small airways are 0.51 mm to 1.0 mm in diameter (Matsuba and Thurlbeck, 1971). The small airways are anatomically defined as bronchial passages less than 2 mm in diameter. The small airways are known to be a major site for pathology in various inflammatory diseases, including asthma (McNulty and Usmani, 2014). The small airways account for more than 98% of the cross-sectional area of the lung, terminate within the alveolar sacs, contain no cartilage to support their structure and are, therefore, more prone to collapsing (Usmani et al., 2016a). However, the large cross-sectional surface area of the small airways also means that they only account for 10% of the total airway resistance (Macklem and Mead, 1967). This led to the small airways being described as the “quiet zone” as extensive small airways disease can be present with little abnormality in conventional pulmonary function tests, which are insensitive to small airways function (Mead, 1970).

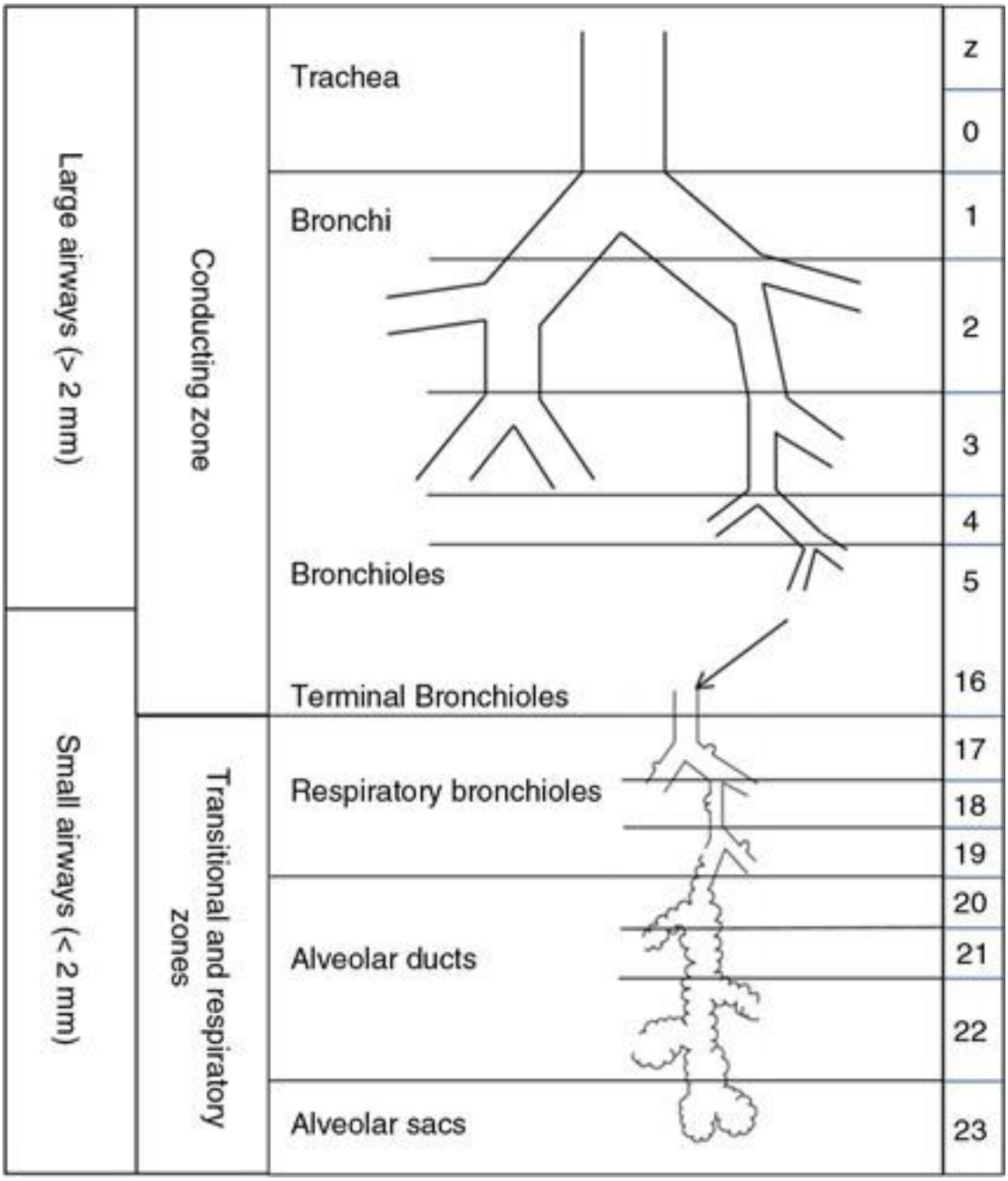


Figure 1.1. Illustration of airways generations.
Adapted from (McNulty and Usmani, 2014).
Legend: The large airways (> 2 mm in diameter) consists of conducting airways and the small airways (< 2 mm in diameter) consisted of some conducting airways, transitional and respiratory airways. The small airways begin at approximately the 8th generation.

1.2 THE PREVLANCE, BURDEN AND COST OF ASTHMA

Asthma is a common chronic and non-communicable disease that affects more than 339 million people globally (Global Initiative for Asthma (GINA), 2022). The number of people suffering from asthma was projected to increase to more than 400 million by 2025 (Masoli et al., 2004). This was partially explained by the effect of global urbanisation (To et al., 2012). Asthma incidence rates are higher in children than adults (Winer et al., 2012) with asthma listed as the most common chronic respiratory disease in childhood (Zwitserloot et al., 2014).

Asthma is a serious condition with the WHO estimating 255,000 asthma-associated deaths each year (Webley and Hahn, 2017), but the death rate is variable globally. Although asthma is more prevalent in high-income countries, asthma related deaths are higher in low to middle income countries, which was attributed to under-diagnosis and medication availability in low and middle-income countries (WHO, 2022). Indeed, it was reported that 96% of the global asthma-related deaths were in low and middle income countries (Meghji et al., 2021). This level of mortality has been reported to be preventable, albeit challenging to address. The updated GINA report in 2019 describe many risk factor associated with asthma deaths, including low adherence to medications, a lack of a written action plan, and over use of short acting beta^2 agonist bronchodilators (SABA) (Global Initiative for Asthma (GINA), 2022).

There are more than 5 million people with asthma in the United Kingdom, most of whom are adults, and asthma care costs the UK National Health Service (NHS) one billion pounds per year in direct health costs(Asthma UK, 2017). The British Lung Foundation (BLF) states that asthma is the most diagnosed pulmonary condition with more than 160 thousand new diagnosis per year, with an incidence rate of 10%

between the years 2008-2012(British Lung Foundation, 2016). In 2014, The Royal College of Physicians published a review of asthma deaths in the UK. The review concluded that on average, someone with asthma is having a life threatening attack every 10 seconds and three patients die daily due to the condition, with most deaths being preventable (Royal College of Physicians, 2014).

As well as significant mortality, asthma is associated with substantial morbidity, including hospitalisations, disability, missing work/school days and decreased quality of life. In 1996, there were 474,000 hospital admission related to asthma in the US alone. A study conducted on elderly asthmatic patients in the US found that 5.7% (n=14,076) had been hospitalised once or more in the past year due to asthma and 32% had to visit the Emergency Department (ED) or urgent care clinic due to asthma symptoms(Hsu et al., 2018). Poverty impacts on asthma outcomes. Children with asthma living in a poor socio-economic urban areas have higher hospitalisations than other children with asthma (Keet et al., 2017b) and 22.5% of patients hospitalised for asthma stated they were unable to buy their medications(Hsu et al., 2018). Asthma is also associated with co-morbidities that include chronic obstructive pulmonary disease (COPD), depression, obesity and gastro-oesophageal reflux disease (GERD)(Keet et al., 2017b).

1.3 PHYSIOLOGICAL TECHNIQUES TO ASSESS SMALL AIRWAYS FUNCTION

1.3.1 Spirometry

Spirometry can provide information about small airways function, including measures of the forced expiratory flow when 50% (FEF_{50}) and 75% (FEF_{75}) of FVC

has been expired as well as the average flow over 25-75% range (FEF_{25-75}). The FEF_{25-75} is also referred to as the maximal mid-expiratory flow (MMEF). This measurement was first described in the 1955 by Leuallen and Fowler (Leuallen and Fowler, 1955). The MMEF has been used to assess small airways limitation in certain patient groups such as those with Alpha-1 antitrypsin deficiency or pre-COPD (Stockley et al., 2017, Kwon et al., 2020). However, the FVC can affect test results and it is recommended that MMEF is corrected for FVC, particularly in bronchodilator response testing (McNulty and Usmani, 2014, Cockcroft and Berscheid, 1980, Hansen et al., 2006). As MMEF is a highly variable measure, current spirometry guidelines only utilise FEV_1 and FVC as the clinically important measurements (Gold and Koth, 2016). In 2014, a large, retrospective study suggested there was little value in reporting MMEF where FEV_1 and FVC was available (Quanjer et al., 2014b), which questioned the use of this test in clinical care. However, the participants included in this study were extremely heterogeneous, and not representative of a specific disease population, thereby limiting the interpretation of the analysis for specific groups of patients. Studies in highly selected populations show that MMEF can be a useful physiological marker of small airways function that relates to different aspects of disease and its progression (Stockley et al., 2017, Kwon et al., 2020).

1.3.2 Oscillometry

To overcome the limitations of maximal forced breathing manoeuvres, other tests that do not rely on such effort-dependent manoeuvres have been developed. These include forced oscillation techniques (FOT) and impulse oscillometry (IOS). The FOT was first developed in the 1950s and uses sinusoidal pressure oscillations (Dubois et al., 1956, Komarow et al., 2011). The IOS utilises the same concept,

however, square wave pressure oscillations (“pulses”) of multiple frequencies at the same time. Both FOT and IOS are easy to perform, but the outcomes can be complex, The oscillation technique describes the lung impedance (Zrs; defined as the spectral relationship between volume and pressure) from which lung reactance (Xrs; defined as the amount of airway recoil against the oscillating pressure wave) and resistance (Rrs; defined as the amount of energy required for the oscillating pressure wave to move through the airways) are derived (Oostveen et al., 2003).

All oscillometry devices generate oscillating sound waves between 3-35 Hz, with higher frequencies traveling shorter distances (measuring larger airways) and lower frequencies traveling further (measuring “total” airway function). The use of multiple frequencies enables the assessment of most of the airway tree (Komarow et al., 2011, Starczewska-Dymek et al., 2019) and although oscillometry is primarily used to assess SAD, it can also be used to assess the large airways (Bickel et al., 2014). Higher resistance within the airways (for example, in the presence of bronchoconstriction) will cause Rrs to increase. In contrast, in emphysema, where there is an increase in compliance, Xrs will decrease, becoming more negative (Crim et al., 2011). In figure 1.2 is a graphical representation of the resistance and reactance curves, with all indices highlighted.

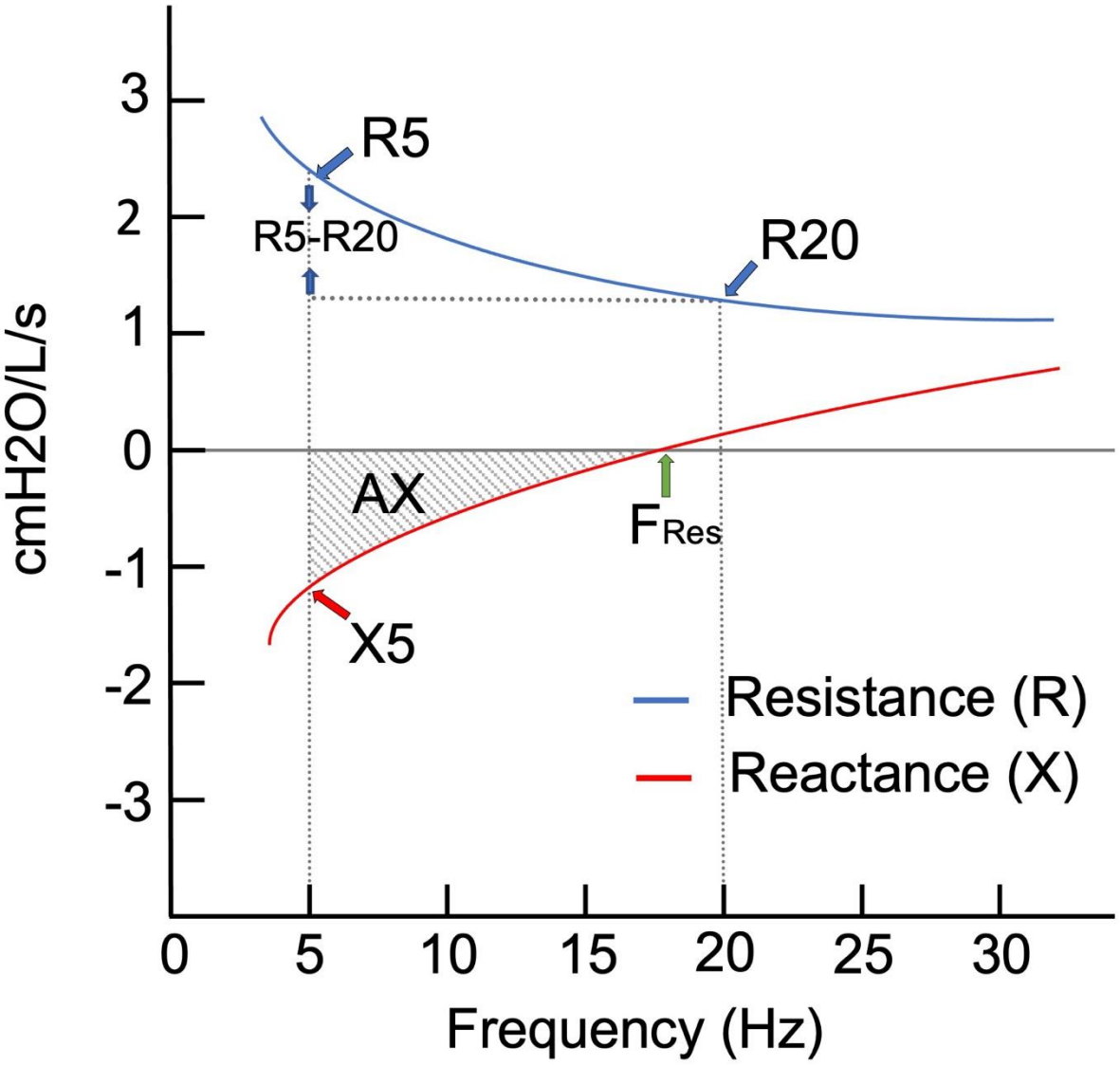


Figure 1.2. Illustration of oscillometry technique indices locations in resistance and reactance curves.
Legend: The red line is the reactance line, and oscillation at 5 Hz is (X5). When reactance pressure reaches 0, this is the point of Resonant Frequency (Fres). The area under the curve between X5 and Fres is the Area of Reactance (AX). The Blue line is the resistance line, and resistance at 5 Hz is the total lung resistance (R5). Resistance at 20 Hz is the large airways resistance (R20). The difference in resistance between R5 and R20 is considered as the small airways resistance (R5-R20).

The main indices reported in oscillometry are the total airway resistance measured at 5 Hz (R5), large airways resistance, measured at 20 Hz (R20) and small airways resistance (R5-R20), which is simply the difference between R5 and R20,

reactance at 5 Hz (X5) and AX, which is the area under the Xrs curve. Figure 1.3 is an illustration of how waveforms travel and how resistance is assessed.

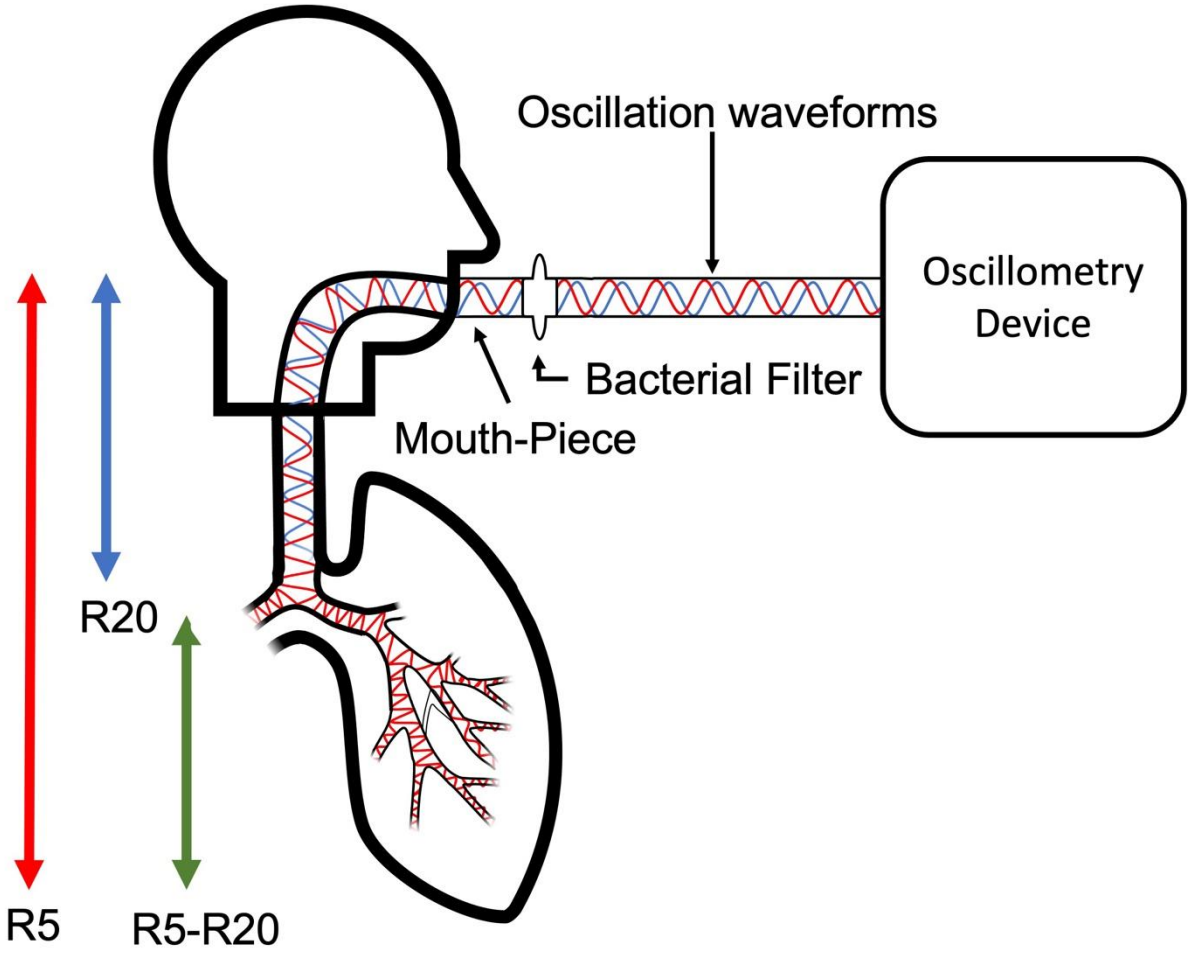


Figure 1.3. A diagrammatic representation of oscillometry.
Legend: Higher frequencies travel shorter than lower frequencies. Resistance at 20 Hz (R20) (blue wave) is considered as a measure of larger airways, and resistance at 5 Hz (R5)(red wave), where waveforms travel further and considered as a measure of the total airways, therefore R5-R20 is considered as a measurement of smaller airways.

For patients, oscillation techniques are simple and non-invasive. It involves the patient making a seal around the mouthpiece of the device, holding their cheeks and breathing normally and quietly. When switched on, the device sends oscillatory pressure waves through the mouth into the airways. The test is short, with

measurements recorded in under 20 seconds. The use of tidal breathing makes this measurement particularly useful in patients who have difficulty understanding or performing forced manoeuvres. However, the use of oscillation techniques has been limited by several factors. First, there is a need for large population-based studies to produce predicted values for a broader group of patients globally (Brashier and Salvi, 2015). Second, different oscillometry devices have been shown to produce different values, limiting the ability to compare results across studies and to form large oscillometry databases that can be used in calculating reference values (Dandurand et al., 2019). Despite this, there is some evidence that oscillometry can identify different asthma phenotypes (Descatha et al., 2005), which makes the test worthy of further investigation and development.

1.3.3 Multiple Breath Washout

Ventilation heterogeneity is defined as the non-uniform distribution of inspired gas within the lung, which can be caused by luminal inflammation, mucus, variable thickening of the airway walls, smooth muscle hyperplasia/hypertrophy, and mucous cell metaplasia. The multiple breath washout (MBW) was first introduced in the 1950s to calculate ventilation heterogeneity using the lung clearance index (LCI). The test can be conducted using two techniques; intrinsic and extrinsic methods. In the intrinsic method, with air within the lungs and airways is “washout out” as the patient breathes 100% oxygen and the measured volume of nitrogen is used to calculate the functional residual capacity (FRC) (Robinson et al., 2009). . With the extrinsic technique, a tracer gas such is sulphur hexafluoride (SF6) is initially washed in and then washed out of the airways, which may be useful in overcoming the effects of high concentration of oxygen on breathing pattern in some populations (Gustafsson et al., 2016). The MBW

test has also been considered in the assessment of small airway function. Although MBW is a simple, submaximal, and non-invasive assessment, it is time consuming (Robinson et al., 2013) and interpretation of the results can sometimes be difficult (McNulty and Usmani, 2014). S_{acin} and S_{cond} are used as the two main indices to determine ventilation heterogeneity. The S_{acin} is the ventilation heterogeneity peripheral to the acinar entrance, while S_{cond} is the ventilation heterogeneity at the conductive lung zone(Verbanck et al., 2012). Figure 1.4 provides a representation of how MBW is conducted.

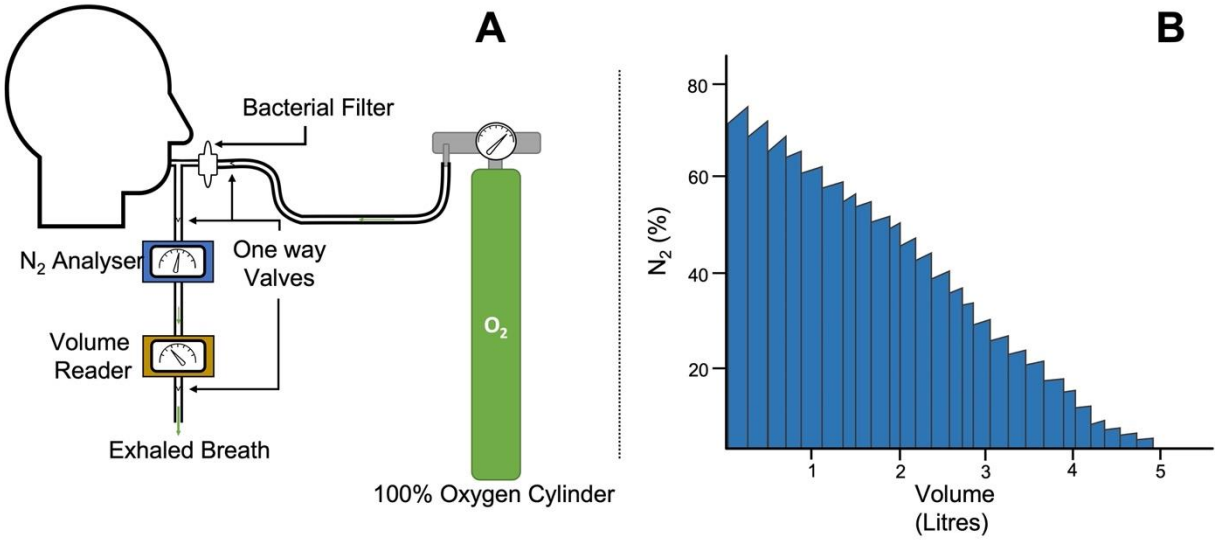


Figure 1.4. A diagrammatic representation of how intrinsic MBW is conducted.
Legend: In (A) subjects breathe 100% of oxygen to washout nitrogen within the lungs and the amount of exhaled air is calculated. In (B) the amount of nitrogen exhaled nitrogen is analysed, and volume is quantified. LCI is calculated by dividing the Cumulative Exhaled Volume by the FRC.

1.3.4 Lung Volumes

By using body plethysmography or gas dilution techniques, specific lung volumes and capacities can be obtained including Residual Volume (RV), FRC and Total Lung Capacity (TLC). An increased RV could be linked to small airways obstruction due to air trapping caused by narrowing of the airways. The RV/TLC ratio

has been used to assess the presence SAD (Postma et al., 2019, Usmani et al., 2016a). Moreover, RV/TLC is considered a more specific index of air trapping in asthma (McNulty and Usmani, 2014). Similar to spirometry, lung volume parameters have robust reference ranges for most populations (Criée et al., 2011, Pellegrino et al., 2005, Hall et al., 2021). The disadvantage of lung volumes is mainly around their specificity to small airways obstruction (McNulty and Usmani, 2014), as elevated values can be due to other disease processes causing hyperinflation (such as emphysema). Table 1.1 provides a summary of physiological small airways function tests, their advantages and disadvantages, and the availability of reference ranges.

Table 1.1. Summary of advantages and disadvantages of small airways function tests

Small airways function test	Advantages	Disadvantages/Limitation	Reference Range
FOT/IOS*	Easy to perform	There are differences among different devices Difficult to interpret due to lack of training Lack of agreed reference ranges	Limited to some populations
MBW†	Easy to perform	Relatively time consuming Difficult to interpret	Available
FEF_{25-75}‡ (MMEF§) **FEF_{50}‖**	Highly available Easy to interpret Widely implemented	Patient dependent Highly variable	Available

* FOT/IOS:	Forced Oscillation Technique/Impulse Oscillometry
† MBW:	Multiple Breath Washout technique
‡ FEF_{25-75}:	The mean Forced Expiratory Flow between the 25% and 75% of the forced vital capacity
§ MMEF:	The mean mid-maximal expiratory flow
‖ FEF_{50}:	The Forced Expiratory Flow in the middle of the forced vital capacity

1.4 ASTHMA DIAGNOSIS

The lack of an objective gold standard test makes diagnosing asthma challenging in some circumstances and, although most guidelines include similar steps to confirm a diagnosis, there are some differences. In table 1.2, the current objective tests used by various guidelines are listed alongside their limitations. Of note, current guidelines do not include tests of small airways function in the diagnostic process. Studies have emphasised that the uptake and implementation of asthma guidelines remain suboptimal globally (Yousef et al., 2015, Luna-Pech et al., 2019, Fitzpatrick et al., 2010), with some suggestion that the lack of objective measures to diagnose asthma (rather than support a diagnosis) are hindering patient care. Therefore, improving diagnostic criteria could improve patient outcomes.

Table 1.2 Summary of objective tests used in diagnosing asthma by various organisation

Objective Test	Recommended by which organization	Recognised limitations of test
Spirometry	NICE*[(NICE, 2017)]	FEV_1† limitation may not be a marker for asthma as it is found in other obstruction diseases.[(Al-Moamary et al., 2019)] The test is effort dependent.
Reversibility	GINA‡[(GINA, 2022)], BTS/SIGN§,[(BTS/SIGN, 2019)] SINA‖,[(Al-Moamary et al., 2019)] NICE, ATS/ERS¶ (Severe)	Not only asthmatic patients have reversibility.[(Tse et al., 2013)] Effort dependent.
Peak Flow monitoring	GINA, BTS/SIGN, SINA, NICE	Effort dependent. Different PEF meters may have different results.
Bronchial Challenge	GINA, BTS/SIGN, SINA	Not as widely available, can be time consuming.
DL_{CO}**	Not recommended, Only in severe asthma (ATS/ERS), and not all cases.	
Biomarkers of inflammation in sputum (Eosinophilic & neutrophilic)	BTS/SIGN, SINA	Not all patients produce sputum No "normal" ranges for cytokines. May be present with other diseases. [(GINA, 2022)] Needs technical expertise and time consuming. [(Lex et al., 2005)]

* **NICE:**	National Institute of Clinical Excellence UK
† **FEV_1:**	Forced Expiratory Volume in the first second
‡ **GINA:**	Global Initiative for Asthma

§ **BTS/SIGN:**	British Thoracic Society/Scottish Intercollegiate Guidelines Network
‖ **SINA:**	Saudi Initiative for Asthma
¶ **ATS/ERS:**	American Thoracic Society/European Respiratory Society
** **DL**$_{CO}$:	Diffusing Capacity for Carbon Monoxide

1.5 ASTHMA PENOTYPES

A phenotype can be defined as any observable clinical characteristic or trait of a disease that stratifies its presentation, outcomes or response to treatment, without any implication of a mechanism (Duffey and Anderson, 2019). Asthma is now stratified into clinical phenotypes, with the aim of providing treatment pathways based on the likelihood of response (Bostantzoglou et al., 2015). Cluster analyses have identified asthma phenotypes using several different features, including the age of symptom onset, the presence of atopy, the severity of airways obstruction, the presence of co-morbidities such as obesity and the requirement and response to medication (Keet et al., 2017a). One notable analysis of 439 patients described several asthma phenotypes: early-onset atopic asthma, obesity-associated asthma, non-eosinophilic asthma, benign asthma, early symptom predominant asthma, and inflammation predominant asthma, with treatment recommendations for each phenotype (Haldar et al., 2008). Several trials have been proposed to classify phenotypes of asthma by observing the response to triggers or clinical characteristics (Pavord, 2012).

1.6 ASTHMA TREATMENTS

According to GINA, the goal of asthma treatment is to gain control of symptoms that may prevent patients from making their activities of daily living, reduce the risk of exacerbation, mortality, persistent airflow limitation, and limit the side effect of treatment (Global Initiative for Asthma (GINA), 2022). In GINA's report, treatments are

given in steps, in which to gain control of the symptoms (with a higher step of treatment) and then adjusting the treatment and maintain control. The severity of asthma in GINA's report is classified based on the treatment the patients are in rather than symptoms or objective measure or a combination of symptoms and objective measures. However, treatments steps are based on symptoms. The GINA report includes a 5 steps system in 2 tracks. The main difference between the tracks is the reliver medication. In track 1, the reliver medication is a low dose inhaled corticosteroid (ICS) with formoterol. In track 2, the reliver is a SABA. In figure 1.5 is the treatment steps as reported in GINA's report. Of note, all guidelines and reports do not elaborate on how inhaled medication is delivered (e.g., small volume nebuliser, vibrating mesh nebuliser, or ultra-fine inhalers).

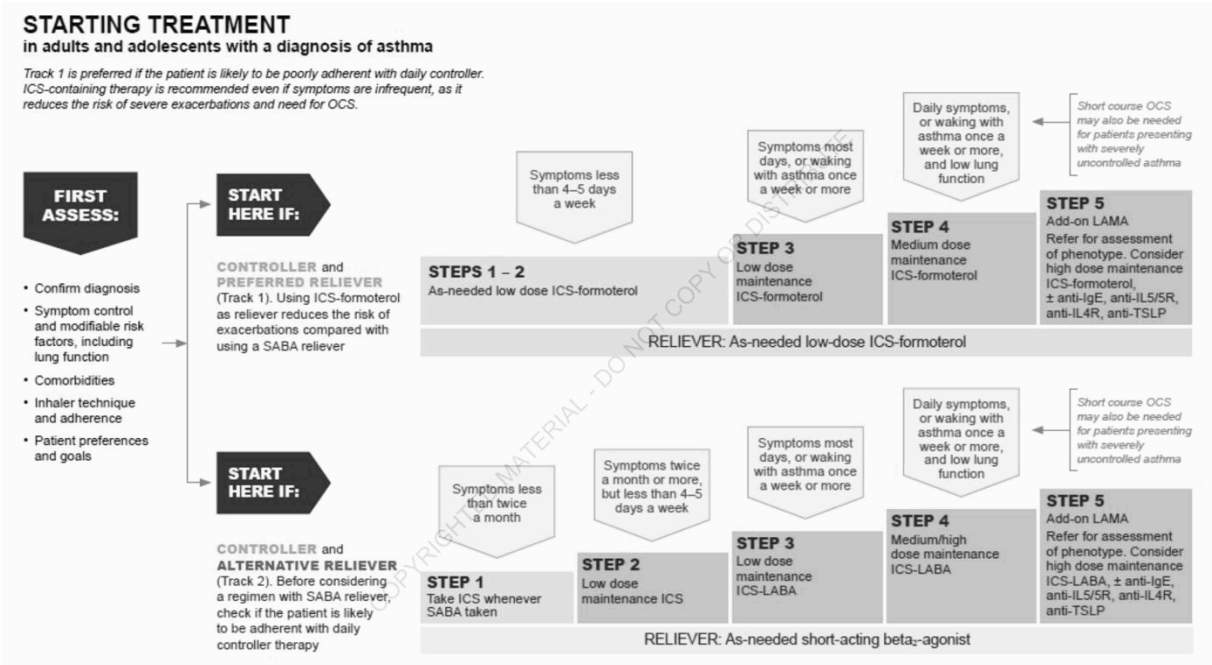


Figure 1.5. GINA's treatment steps for adults with asthma.
Reproduced with permission from GINA (appendix 8.1.2)
Legend: ICS: inhaled corticosteroid; LABA: long-acting beta»-agonist; LAMA: long-acting muscarinic antagonist; OCS: oral corticosteroids; SABA: short-acting beta-agonist.

In the UK, NICE guidelines are normally implemented in clinical practice. The NICE treatment guidelines for adults with newly diagnosed asthma include a reliver therapy (SABA) as a first line of therapy and the only therapy for those with infrequent wheeze with normal lung function. However, those who are symptomatic and uncontrolled with SABA, a low dose of ICS is recommended. If low dose ICS with SABA as reliver remain not efficifnt to control asthma, a leukotriene receptor antagonist (LTRA) should be added. If this remains ineffective adding a LABA is recommended and reviewing LTRA should then be considered with the patient. If the combination of low dose ICS, LABA with or without LTRA is not controlling the asthma, a Maintenance and Reliever Therapy (MART) is recommended. If this does not control asthma within four to eight weeks, an increase in the dose of ICS should then be considered to a moderate dose. If this does not control asthma within four to eight weeks, an increase in the ICS dose should be considered to a high dose. A consultation with a physician with asthma experise should be considered at that point.

1.7 THE SMALL AIRWAYS AND THE EVIDENCE FOR THEIR INVOLVEMENT IN ASTHMA

There is increasing evidence that small airways involvement is present in asthma and that it is associated with both worse symptoms and poorer clinical outcomes (Cottini et al., 2015, Usmani et al., 2016a). Pathological post-mortem studies have demonstrated inflammation and airway remodelling in the small airways of asthmatic patients, especially those of an eosinophilic phenotype, which traditionally can often be reduced with appropriate treatment (Johnson and Hamid, 2012, Dolhnikoff et al., 2009). Biopsy studies in asthma have also confirmed the presence of

small airways inflammation and alveolar eosinophils, the burden of which correlated with lung function decline (Kraft et al., 1996). An increase in airway smooth muscle mass, mucus plugging, and goblet cell hyperplasia have all been described in the large and small airways in asthma (Saetta et al., 1991) but there appear to be differences in the distribution of inflammation. Post-mortem studies in fatal asthma suggest that inflammation is mainly contained within the inner wall of the large airways. In contrast, inflammation tends to occur in the outer airway wall of the small airways (Dolhnikoff et al., 2009), extending to the perivascular region of the pulmonary arteries and the peribronchiolar alveoli (Shiang et al., 2009).

Children with asthma have been shown to have greater disease involvement in the peripheral as opposed to the central airways (Gelfand and Kraft, 2009), and SAD has been described in children with mild or intermittent asthma symptoms, often in the absence of an abnormal FEV_1 (Singer et al., 2013). This might lead to the assumption that SAD is an early feature of asthma. However, SAD is not universal in asthma, and it appears to affect only a sub-set of patients. In the previously discussed study of small airways function in children, only one third had abnormalities in tests of small airways function (Singer et al., 2013). A systematic review conducted in 2016 suggested that SAD could be measured in approximately 50-60% of patients with asthma and that SAD could occur in asthma patients without any evidence of larger airway obstruction (Usmani et al., 2016a). A multinational study called AssessmenT of smalL Airways involvemeNT In aSthma (ATLANTIS) in 2019 assessed the presence of SAD in 773 adults with asthma using multiple tests of small airway function (Postma et al., 2019). In this group, SAD was also common but, crucially, different SAD techniques and devices altered the detected prevalence of SAD, suggesting that different tests

identified different groups of patients. This highlights the critical nature of test selection when comparing studies (discussed in more detail later).

1.8 SMALL AIRWAYS DYSFUNCTION AS A PHENOTYPE OF ASTHMA

Given the SAD is only present in a proportion of asthma patients, it is possible that this too could be considered a phenotype. Studies comparing asthma patients with and without small airways disease (measured using physiological tests) have described clinical differences between the groups. These include a reduced FEV_1 in combination with a history of smoking, raised blood eosinophils, and poorly controlled asthma (Kjellberg et al., 2016). Bronchial hyper-responsiveness (BHR) has also been shown to be a feature of those with SAD. In one study of 94 patients with asthma, those with small airways obstruction had more severe BHR as well as lower FEV_1, FVC and FEV_1/FVC values and higher levels of reversibility (Telenga et al., 2013). In the same study, patients with small airways obstruction using ICS had a significantly higher daily dose of ICS than patients without small airways obstruction (800 versus 500 µg per day beclomethasone dipropionate equivalent).

There are also specific therapies that may be more beneficial to those with SAD, particularly inhalers with extra and ultra-fine particles that are more likely to reach the small airways. Inhaler devices that have been routinely used in clinical practice may not effectively deliver ICS into small airways. Conventional aerosol-generating devices such as small-volume nebulizers (SVN) or pressurised metered-dose inhalers (pMDI) generate fine, aerosolized particles with a mass mean aerodynamic diameter (MMAD) of 2-5 µm. Although other factors contribute to drug deposition in the lungs (including

inhaler technique and flow rates), particles of this size may not efficiently reach small airways compared to extra fine inhalers (1-2 μm) (Leach et al., 1998, Busse et al., 1999).

Particle size is a major determinant in the deposition and distribution of inhaled drug within the lungs. In a study of 12 asthmatic subjects, the lung distribution of inhaled technetium-99m-labeled monodisperse albuterol aerosols was assessed by planar gamma-scintigraphy. Here, smaller particles achieved greater total lung deposition but bronchodilation (assessed by FEV_1 and MMEF) was greatest with the larger particle size (Usmani et al., 2005). Ciclesonide is an extra-fine particle ICS (with a mass median aerodynamic diameter (MMAD) of 1.0 μm) that shows both high overall lung deposition and peripheral lung distribution in healthy volunteers and patients with asthma (Leach et al., 2006, Newman et al., 2006). Moreover, ciclesonide has been associated with improved asthma outcomes in patients, including a reduction in exacerbation frequency, better asthma control and improved tests of small airways function (Postma et al., 2017, van der Molen et al., 2016). This highlights the need of more research with an emphasis on small airways response in asthmatic subjects.

There has been a move to develop extra-fine particles (defined as particles less than 2 μm in MMAD) for inhalation to address this limitation. These particles have shown higher deposition rates in the lung periphery and a better response to treatment, especially when patients have evidence of SAD (Allegra et al., 2012). Currently, the EU Clinical Trials Registry (EudraCT, 2019) and the USA Clinical Trials Registry collectively report 151 studies on treating small airways in asthma (clinicaltrials.gov, 2021), highlighting the interest in this area.

Endotypes are defined as subtypes of a disease or condition which share pathophysiological feature at the molecular and/or cellular level (Kuruvilla et al., 2019). A number of asthma endotypes have been proposed but currently it is unclear if SAD is associated with a separate endotype, or if SAD is present across several endotypes (Contoli et al., 2012). The limited studies to date have not found a “small airways specific” inflammatory endotype but, in common with the larger airways, have described higher numbers of activated eosinophils in the small airways of patients with asthma (Hamid et al., 1997). In addition, alveolar inflammation has been specifically implicated in nocturnal symptoms, perhaps reflecting a symptom-based phenotype (Kraft et al., 1999).

In summary, current evidence suggests that small airways involvement could be a phenotype of asthma, which may be associated with clinical traits and a treatment response. Evidence to support SAD reflecting a specific endotype is currently lacking, but SAD has been associated with a predominance of eosinophilic inflammation.

1.9 SMALL AIRWAYS FUNCTION IN ASTHMA ASSESSMENT AND DIAGNOSIS

As stated (section 1.5), current guidelines do not include tests of small airways function in the diagnosis of asthma. However, this may represent a missed opportunity given that patients with SAD and asthma tend to have poorer symptom control (Riley et al., 2016) and that there are now treatments available to target the smaller airways.

Perhaps tests of small airways could offer an opportunity to improve the diagnosis of asthma and identify patients who may benefit most from specific therapies, such as ultra-fine inhaled medicines. There are several methodologies that

can assess small airways function. Unfortunately, there is currently no agreed gold standard and specific small airways tests are often selected over others with no clear rationale. The most commonly used tests of small airways function and the current evidence to support their use in asthma are discussed below.

1.9.1 MMEF

The MMEF has been used to help exclude cough variant asthma from chronic cough of other causes (Chen et al., 2019) and has been found to be abnormal in patients with mild asthma and bronchodilator reversibility (Telenga et al., 2013). Compared to the FEV_1, the % predicted of MMEF has consistently been lower in multiple groups with asthma, despite a normal or near-normal % predicted FEV_1 (Almeshari et al., 2020b). Nevertheless, high variability and poor reproducibly are the major drawbacks of using MMEF in diagnosis.

1.9.2 Oscillometry

Previous diagnostic test accuracy (DTA) studies have described that R5 had a sensitivity of 69-72% and specificity of 61-86% in diagnosing asthma when a positive bronchodilator response in FEV_1 was used as a reference standard (Li et al., 2015, Nikkhah et al., 2011), comparing favourably to FEV_1. A systematic review and meta-analysis reviewing the DTA of BDR using FEV_1 found a sensitivity of 38.9% (95%CI: 18.3-65.6) and specificity of 94.6 (95%CI: 85.7-99.7) (Sano et al., 2019). Also, these tests might be able to differentiate whether respiratory symptoms relate to active asthma or another disease process. One study suggested small airways evaluated by IOS indices, R5-R20 and X5 and AX correlated more strongly with clinical symptoms (assessed by the asthma control test (ACT) score) than spirometry (Sharshar, 2018).

1.9.3 MBW

There are several studies of MBW in asthma, of which only a few discuss or reference SAD. In patients with asthma, an abnormally high S_{acin} has been associated with an increased likelihood of responsiveness to inhaled corticosteroids and was considered suggestive of SAD (Verbanck et al., 2006). S_{cond} is a predictor of airway hyper-responsiveness in adults with asthma (Downie et al., 2007).

Despite the potential of MBW test in assessing small airways function and the advantages of a test which allows tidal breathing, the software for calculating S_{acin} and S_{cond} is not widely available and limited to specialist centres. MBW also lacks robust, universally accepted reference ranges (Robinson et al., 2009).

1.9.4 Lung volumes

In one study of 321 physician diagnosed subjects with asthma, 52% and 57% had an abnormal residual volume and abnormal RV/TLC ratio, respectively. There was a negative correlation between RV and FEF_{25-75}. The authors described a significant proportion of asthmatic patients having an elevated residual volume and an abnormal RV/TLC ratio in the presence of normal FEV_1/FVC ratio and absence of significant BDR (Jain et al., 2013). A second study also found a high prevalence of RV dysfunction in asthma patients with a normal FEV_1/FVC ratio but with symptoms (Perez et al., 2013), highlighting the potential for this test to identify patients with active lung disease.

1.10 THE USE OF SMALL AIRWAYS IN THE CLINICAL DIAGNOSIS OF ASTHMA

The evidence presented suggest that tests of small airways function can be altered in some patients with asthma, but to be adopted into clinical practice, these

differences must have clinical significance in terms of diagnosis, pathology, progression or treatment response.

Head-to-head studies have reported that some patients with symptoms of or inflammation consistent with asthma, have altered small airways test results, even without objective evidence of airflow obstruction (Riley et al., 2016). Since asthma remains a clinical diagnosis, and a patient can have asthma without measurable airflow obstruction at the time of testing, the combination of symptoms and SAD could be sufficient to diagnose asthma and may help identify specific groups of patients to inform treatment approaches. Studies to date have not shown major differences in the inflammatory endotype of patients with SAD and those without, but SAD is commonly associated with eosinophilic inflammation (Riley et al., 2016), which points towards a specific group of therapies. Ultrafine aerosol particles can reach the small airways, and therefore it would make sense to target these therapies with people with measurable SAD and use SAD to track the response to therapy.

Next to consider is which tests to deploy. There are no gold standard recommended tests of SAD. Of the tests of small airways discussed above, only MMEF has well validated predicted ranges, although these are wide. With other tests, there would be uncertainty as to what represented an abnormal result. MMEF is routinely captured during normal spirometry, and therefore has no extra equipment or resource costs, and does not lengthen the time to perform tests. A disadvantage of MMEF is the forced nature of the manoeuvre. IOS, FOT and MBW use tidal breathing, but MBW is a lengthy test and requires specialised equipment. IOS and FOT also require specific devices, but the test is quick to perform and can be used by the bedside. MBW, IOS

and FOT can be difficult to interpret, and with IOS and FOT, the exact device used alters results, meaning results are not comparable across centres.

The on-going COVID-19 pandemic has significantly impacted the provision of pulmonary function tests, leading to delays in the assessment of pulmonary diseases. Infection control measures in lung function laboratories aim to prevent the transmission of diseases between health care providers and patients or participants (Miller et al., 2005a). The evidence for the transmission of infections is limited (Kendrick et al., 2003) but pulmonary function testing is considered an aerosol generating procedure. During the COVID-19 pandemic many laboratories reduced or stopped providing these tests. There is some evidence that FVC manoeuvres produce more and larger droplet particles than tidal breathing (Greening et al., 2021, Helgeson et al., 2020) and so it might be the case that submaximal assessments such as oscillometry or MBW, may be safer in terms of aerosol generation. However, this would need to be specifically tested.

In summary, these tests appear to be telling us something about certain groups of people with asthma, and the expansion of ultrafine inhaled therapies and strategies to target eosinophilic asthma may provide a clinical rationale to assess small airways. However, there are still barriers to deploying these tests in the clinic.

1.11 BRONCHODILATOR RESPONSE TESTS FOR THE SMALL AIRWAYS

As stated earlier, one of asthma's manifestations is the variability and of airflow limitation. Thus, airflow reversibility is considered the hallmark of asthma. Variability is assessed by administering a SABA, usually through an pMDI. The pre and post FEV_1

is the main index in evaluating BDR. According to the latest ATS/ERS spirometry guidelines, the term reversibility was replaced to BDR, as the term reversibility may indicate the return of lung function to normal ranges (Graham et al., 2019). Moreover, the previously recommended cut-off for a significant improvement in lung function (i.e. increase of >12% and at least 200 mL in FEV_1) was removed. Instead, the guideline recommended the level of significance to be evaluated at the discretion of the clinical team, as there are many variances in the assessment methods that may alter the level of the significance level (e.g. SABA dose, method of delivery, type of inhaler (particles sizes), time between manoeuvre). Nevertheless, in the supplementary materials, a cut-off of >12% and >200mL of FEV_1 was reported as an example for evaluating BDR. Indeed, it was previously reported that a change between >8-12% is an appropriate level of significance for assessing BDR (Ward et al., 2015, Pellegrino et al., 2005).

Assessing and reporting the BDR in small airways in not well defined (Almeshari et al., 2021b). As mentioned earlier, there are a wide range of dependencies in the assessment of BDR and no clear guidance as to a standardised approach. This may limit the utility of BDR in small airways. Moreover, BDR is a hallmark of asthma, yet it is not a distinctive feature of it as it is found in other disease processes such as COPD (Borrill et al., 2005). Assessing for small airways dysfunction at baseline and the BDR in both small airways and conventional large airways (i.e. FEV_1) could be clinically important and a distinct phenotype of asthma.

1.12 KNOWLEDGE GAPS THAT LIMIT THE UTILITY OF SMALL AIRWAYS TESTING IN ASTHMA

Although studies have aimed to stratify asthma by small airways function, comparing study results is complex. The lack of a gold standard to assess SAD has resulted in studies varying in testing protocols, equipment used, and accepted cut-offs for identifying diseased and non-diseased states. Even within a specific methodology (such as oscillometry), different devices capture different measurements, which has prevented the development of common reference ranges (Dandurand et al., 2019). These constraints have considerably limited our ability to draw firm conclusions from data published to date, despite promising results from smaller studies.

More research is urgently needed. First, to understand the importance of inflammation within the small airways in asthma and to identify if this requires specific treatment. Second, to clarify which tests of small airways function are most useful in identifying pathological change in asthma. This includes assessing when each test becomes abnormal and to decipher if certain tests are identifying different cohorts or subsets of patients. This will evaluate their diagnostic accuracy to determine if they might be of use in all cases of asthma (which current evidence suggests is unlikely) or a subset of patients (a phenotype). Third, to assess the variability of repeat testing and the accuracy of SAD tests in identifying disease severity and treatment response. Forth, to determine if there is a relationship between measured SAD and inflammatory signals. If so, this could be used to stratify treatment decisions by inflammatory pathway and degree, potentially improving patient outcomes. However, this approach requires a consensus on the methods for assessing small airways to interpret insights from different studies. Lastly, to evaluate the relevance of small airways to

bronchodilator response. Indeed, the small airways makes up most of the bronchial tree, therefore, assessing the small airways BDR and the small airways at baseline is clinically important and relevant.

1.13 CONCLUSION

Asthma is a common and increasingly prevalent condition associated with poor patient outcomes, including mortality and morbidity. There is an ongoing need to adequately diagnose, manage, and control asthma more effectively. Asthma is heterogeneous, comprising several clinical phenotypes and cellular endotypes with different responses to treatment. We need specific tools to identify the subsets of patients most likely to benefit from specific and stratified therapeutic approaches and to monitor treatment response.

Studies over time have highlighted the involvement of the small airways in asthma pathology and recent advances in treatments that now reach the small airways offer a new therapeutic paradigm for asthma. Multiple physiological tests of small airways exist, which could be used to identify SAD and measure the response to treatment. However, currently there is no universally accepted approach to choosing a specific test for a specific population or clinical question and there still needs to be significant expansion of reference ranges to aid interpretation. Further research is needed but this is still an area of great promise that could potentially improve patient care and outcomes.

1.14 HYPOTHESES, AIMS AND OBJECTIVES

In the presented thesis, two main hypotheses were tested.

First, small airways function are a reliable method for assessing and diagnosing asthma.

Second, in asthma, the small airways have higher response to bronchodilators than conventional large airways and particularly in those with SAD.

To test the hypotheses of this thesis the following aims were outlined:

Aims for the first hypothesis:

- To summarise and evaluate the body of evidence on what small airways function tests were used in the diagnosis of asthma.
- To analyse the prevalence of SAD in asthma and the relationship of small airways indices to conventional large airways indices.

To achieve the aims of the first hypothesis of this thesis, the following objectives were set:

- Conducted a comprehensive systematic review on the small airways function use in the diagnosis of asthma.
- Conducted a retrospective analysis of prevalence of SAD in subjects being evaluated for asthma and assessed the risk factors of SAD.

Aims for the second hypothesis:

- To summarise and evaluate the body of evidence on the small airways bronchodilator response in patients with asthma in comparison to conventional large airways.

- To analyse the BDR in the small airways and in patients with SAD and how it relates to BDR in conventional large airways.

To achieve the aims of the second hypothesis of this thesis, the following objectives were set:

- Conducted a comprehensive systematic review on BDR response in small airways of patients with asthma
- Conducted a retrospective analysis on the BDR in asthmatics with and without SAD and analysed the BDR in small airways function in comparison to conventional large airways

CHAPTER 2

2. PHYSIOLOGICAL TESTS OF SMALL AIRWAYS FUNCTION IN DIAGNOSING ASTHMA: A SYSTEMATIC REVIEW

2.1 INTRODUCTION

There is increasing interest in using physiological tests of small airways function to diagnose and monitor asthma. This systematic review was performed to assess which physiological tests of small airways function have been used in studies which include diagnosing asthma. This work has been published in abstract form at the 2020 European Respiratory Society Congress and published in the European Respiratory Journal (Almeshari et al., 2020a) (see appendix 8.2.1).

This chapter has also been published in full in the BMJ Open Respiratory Research Journal, entitled "**Physiological Tests Of Small Airways Function In Diagnosing Asthma: A Systematic Review**" (Almeshari et al., 2020b) (see appendix 8.2.2). The paper is presented in full, below and author contributions, as published, are given.

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Authors Contribution:

M.A.A and E.S. conceived, planned, analysed the data, and made a major contribution in writing the manuscript. M.A.A., N.Y.A. and R.G.E. performed abstract screening, full-text screening and quality assessment. M.A.A. and R.G.E. planned and performed searching strategy and data synthesis. R.G.E. and J.A.S. contributed to data analysis and revision of the manuscript.

2.2 ABSTRACT

Background: Asthma is a common, heterogeneous disease that is characterized by chronic airway inflammation and variable expiratory airflow limitation. Current guidelines use spirometric measures for asthma assessment. This systematic review aimed to assess whether the most commonly reported tests of small airways function could contribute to the diagnosis of asthma.

Methods: Standard systematic review methodology was used, and a range of electronic databases was searched (Embase, MEDLINE, CINAHL, CENTRAL, Web of Science, DARE). Studies that included physiological tests of small airways function to diagnose asthma in adults were included, with no restrictions on language or date. The risk of bias and quality assessment tools used were AHRQ tool for cross-sectional studies and QUADAS-2 for diagnostic test accuracy (DTA) studies.

Results: 7072 studies were identified, and 10 studies met review criteria. 7 included oscillation techniques and 5 included maximal mid-expiratory flow (MMEF). Studies were small and of variable quality. In oscillometry, total resistance (R5) and reactance at 5 Hz (X5) was altered in asthma compared to healthy controls. The % predicted of MMEF was lower in patients with asthma compared to controls in all studies and lower than the % predicted FEV_1. In DTA of oscillometry, R5 showed a sensitivity between 69-72% and specificity between 61-86%.

Conclusion: There were differences in the results of physiological tests of small airway function in patients with asthma compared to controls. However, studies are small and heterogeneous. Further studies are needed to assess the effectiveness of these tests

on a larger scale, including studies to determine which test methodology is the most useful in asthma.

2.3 BACKGROUND

Asthma is a common but heterogeneous disease characterised by chronic airway inflammation and clinically defined by the presence of respiratory symptoms that vary over time and in intensity. Physiologically, asthma is characterised by variable expiratory airflow limitation which may become persistent over time (Global Initiative for Asthma (GINA), 2022). Symptoms and airflow limitation can be extremely variable, including the age of onset, triggers for symptoms, the decline in lung function and therapeutic response.

It is estimated that 339 million people are affected by asthma globally (Global Initiative for Asthma (GINA), 2022) but diagnosing asthma is often challenging as there is no gold standard test. This has led to a high burden of undiagnosed disease, especially in children and older adults (Wilson et al., 2005, Coffman et al., 2008). According to current guidelines (Global Initiative for Asthma (GINA), 2022), (NICE, 2017), a diagnosis of asthma should be objectively supported with an assessment of FEV_1 reversibility. However, some patients with asthma have no evidence of reversibility or airflow obstruction (Janson et al., 2019a, Marcon et al., 2009) and airflow obstruction and reversibility are seen in patients with alternative diagnoses such as Chronic Obstructive Pulmonary Disease (COPD) (Schneider et al., 2009, Ozarek-Hanc et al., 2012). Furthermore, the forced manoeuvres required for spirometry requires effort and coordination, which can be difficult for some individuals (Jain et al., 2006).

In the past, asthma was thought to only affect larger airways (Kaufman, 2011) but current evidence suggests that small airways (defined as airways of $\leq$2 mm in diameter) are affected as well. The small airways may form a site of active disease,

even in the absence of airflow obstruction (Bourdin et al., 2006). If the small airways are the first to be affected in asthma, identifying small airways dysfunction may help identify asthma earlier, enabling treatment. However, there are several tests that report small airways function. Some of these are being used as secondary outcomes in experimental studies of asthma, to determine asthma phenotype and assess the response to new therapies (NIH US National Library of Medicine, 2020). The evidence to support the use of any physiological test of small airways function in the diagnosis of asthma is unclear.

This systematic review aimed to assess the evidence to support the use of commonly reported physiological tests of small airways function to diagnose asthma in adults and assess if the selected tests should be included in future clinical studies of the disease.

2.4 METHODS

The protocol was prospectively registered in the international registry of systematic reviews (PROSPERO) with registration number CRD42019133239, complete protocol is found in appendix 8.2.3. The review was prepared in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al., 2009) and the PRISMA checklist is provided in appendix 8.2.4. Meta-analysis was considered where homogenous results were provided, otherwise data was pooled for graphical presentational purposes.

Through both scoping searches and discussion with experts, the following test were selected to be included in the search, FOT, IOS, and MMEF also known as Forced expiratory flow between 25-75% of FVC (FEF_{25-75}), and multiple breath

washout test (MBW). These tests were selected as they represented some of the most reported physiological tests of small airways function in obstructive lung disease in adults. Figure 8.2.5 of the appendices is the PICO chart with the studies selection criteria.

2.4.1 Eligibility Criteria

Studies were considered for inclusion if they used one of the proposed physiological small airways function tests (FOT/IOS, MBW, MMEF) in diagnosing asthma in adults aged >18 years old. Patients with either a physician diagnosis or a suspected diagnosis of asthma were considered for inclusion. FEV_1 was used as the comparator as it is the current standard in physiological airway assessment. Studies were excluded if they included only children (<18 years), patients with respiratory infections within 2 months of the assessment, did not assess FEV_1, included patients with Asthma-COPD overlap, were laboratory-based studies, animal-based studies or case series of less than ten participants. There were no language or publication date restrictions.

Search queries were carried out in May 2019 (and the detailed search strategy is found in the appendix 8.2.6) on the following electronic databases: Embase, MEDLINE, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science (Abstracts & Proceedings) up to 5 years and DARE database for grey literature. Clinicaltrials.gov and EudraCT were also searched for active trials or published data. Hand searching of references listed in the selected articles was included. Search terms contained subject heading and terms for the selected test (IOS/FOT, MBW, and MMEF) combined with terms of asthma and small airways function.

2.4.2 Study selection

Search results were imported into EndNote 9.1 (Clarivate Analytics) where duplicates were removed and data was uploaded to Rayyan (Ouzzani et al., 2016) (a webapp tool used for screening titles and abstracts). Abstracts were screened blindly and independently by the authors MAA and NYA using the predefined inclusion and exclusion criteria. Disagreements were resolved by discussion, otherwise by the third reviewer, whose initials were RGE. Full-text articles were acquired and imported into EndNote 9.1 by author MAA and similar abstract screening methodology was used in screening full texts for eligibility.

2.4.3 Data extraction

Data was extracted by author MAA and checked by author NYA for consistency and accuracy using a custom, piloted data extraction form. Diagnostic criteria used to identify asthma, tests used to aid the diagnosis such as airway reversibility, asthma severity, phenotype, medications, the device used, and comorbidities were extracted to aid narrative review and provide clinical context. Studies were categorized based on the small airways test used. In Diagnostic Test Accuracy (DTA) studies, sensitivity and specificity values were extracted and a 2x2 contingency table was calculated.

2.4.4 Quality and risk of bias assessment

Quality and risk of bias were assessed using validated tools based on study design. Cross-sectional studies were assessed using the Agency for Healthcare Research and Quality (AHRQ) checklist tool (Rostom et al., 2004). The Quality Assessment of Diagnostic Accuracy Studies 2 (Whiting et al., 2011) (QUADAS-2) was used in DTA. The QUADAS-2 tool assesses the risk of bias of studies over four domains: flow and timing, reference standard, Index test and patient selection. The

tool also assesses for applicability concerns under three domains: reference standard, index test and patient selection.

2.4.5 Descriptions of the tests of small airways function included in the reported studies

Here, only tests included in the analysed studies are described.

2.4.5.1 Oscillometry

Oscillometry can be assessed using either the Forced Oscillation Technique (FOT) or Impulse Oscillometry (IOS). Oscillometry transmits oscillating sound signals of various frequencies along the bronchial tree, providing a measure of the total airway resistance (resistance at 5 Hz (R5)) and the proximal airway resistance (resistance at 20 Hz (R20)), which allows for the derivation of small airways resistance (R5-R20). Reactance at 5 Hz (X5) relates to physical properties of the lung parenchyma and its ability to expand and facilitate alveolar filling. Resonant Frequency (Fres) is the point at which reactance is zero (when forces of inertia and capacitance are equal). The area of reactance (AX) is the sum of area under the reactance curve between X5 and Fres (Komarow et al., 2011, Starczewska-Dymek et al., 2019). Limitations with this technique include the lack of universal normal ranges for all populations and variance of results between different devices, which can impede interpretation (Shirai and Kurosawa, 2016).

2.4.5.2 MMEF

The maximal mid-expiratory flow (MMEF) is the mean forced expiratory flow between 25% and 75% of the FVC (FEF_{25-75}) and is taken from the spirometric blow with the largest sum of FEV_1 and FVC. The MMEF is highly dependent on the validity of the FVC measurement and the level of expiratory effort(McNulty and Usmani, 2014,

Hansen et al., 2006). MMEF is commonly reported in studies of small airways as it is readily accessible from spirometry reports.

2.5 RESULTS

2.5.1 Study selection

Initial searches identified 7072 abstracts. After the removal of duplicates, 5764 abstracts were screened of which 469 abstracts included for full text screening. Ten articles ultimately met the inclusion criteria (figure 2.1 shows the PRISMA flow diagram). Articles excluded in the full-text screening phase are listed in appendix 8.2.7 with reasons given. All included studies were cross-sectional in design and 3/10 of the included studies were diagnostic test accuracy (DTA) studies.

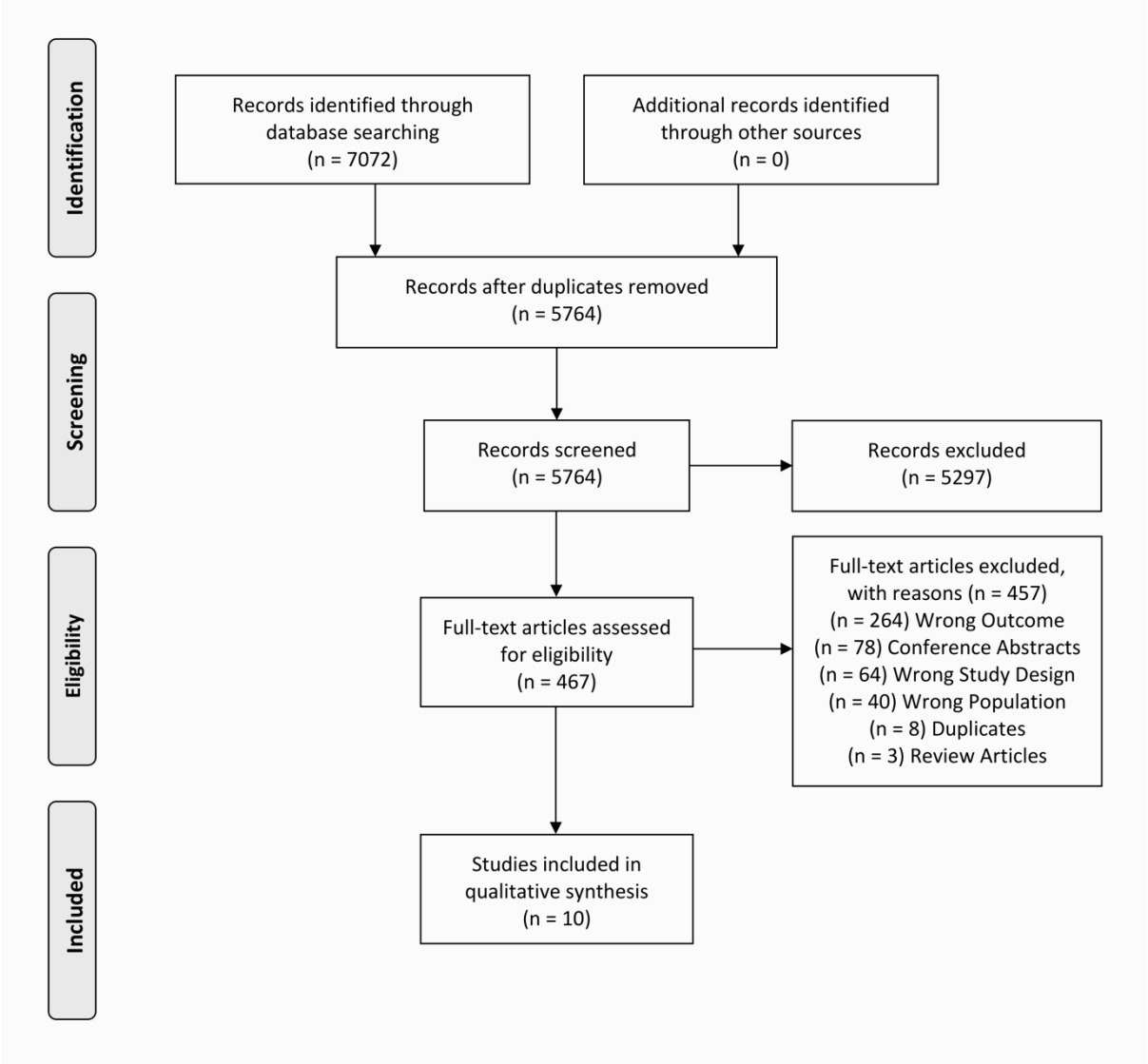


Figure 2.1. PRISMA flow chart of included studies.
This figure was adapted from (Moher et al., 2009)

2.5.2 Study characteristics

Seven of the included articles reported oscillometry (IOS/FOT)(Koruga et al., 2017, Mendonça et al., 2011, Mori et al., 2011, Mousa and Kamal, 2018, Nair et al., 2011b, Li et al., 2015, Nikkhah et al., 2011) and five reported MMEF (Yartsev, 2006, Gulden Pasaoglu et al., 2008, Mendonça et al., 2011, Son et al., 2009). None of the included studies reported MBW use in diagnosing asthma. Seven studies were not designed as DTA studies and are presented in table 1. Three studies were designed

as DTA studies, and these are presented in table 2. The diagnostic criteria used to confirm a diagnosis of asthma differed among studies. Four studies used GINA guidelines (Gulden Pasaoglu et al., 2008, Mori et al., 2011, Mousa and Kamal, 2018, Nikkhah et al., 2011), one ATS guidelines(Li et al., 2015) and one the Global Strategy: Joint Report of the National Institute for Heart, Lungs, and Blood and World Health Organization(Yartsev, 2006). Three studies recruited patients based on a previous diagnosis of asthma, without reporting the diagnosis criteria used (Koruga et al., 2017, Mendonça et al., 2011, Nair et al., 2011b). One study reported that patients with symptoms of asthma were included without any formal diagnosis (Son et al., 2009). All included studies were based in different countries (USA, UK, Japan, Korea, Turkey, Egypt, Russia, Serbia, Iran and China) from 4 different continents (North America, Europe, Asia and Africa) making the ethnicity of participants heterogeneous. Body Mass Index (BMI) was only reported in three of the included studies (Mendonça et al., 2011, Mori et al., 2011, Mousa and Kamal, 2018). Meta-analysis of the data was inappropriate due to the variety and scope of methodological design. Where appropriate, data was displayed graphically to aid the representation of results. No MMEF studies explicitly corrected for FVC, which can potentially affect interpretation

Table 2.1. The characteristics of included studies without a Diagnostic test accuracy (DTA) analysis.

ID	Sample Size	Age	BMI	SA Device	SA Function	FEV_1	Diagnosis Criteria
(Mendonça et al., 2011) USA Cross-sectional	Asthma 35 Control 34	21(3) 22(2)	66Kg(12)*	NR	**Asthma**: MMEF% 69(20) R8 cmH2O 2.91(0.99) **Control**: MMEF 93%(20) R8 cmH2O 2.21(0.48)	88(11) 95(10)	Previous diagnosis of asthma.
(Mori et al., 2011) Japan Cross-sectional	Asthma 49 Control 13	53(15) 42(16)	23.9(6.3) 21.2(3.3)	FOT-MostGraph-01	**Asthma**: MMEF% 49.9(27.7) X5 cmH2O -0.96(1.03) R5-R20 cmH2O 0.86(0.62) R5 cmH2O 4.2(1.43) **Control**: MMEF 88.9(22.1) X5 cmH2O -0.05(0.27) R5-R20 cmH2O 0.32(0.44) R5 cmH2O 3.29(1.17)	80.5(20.2) 105.4(17.8)	GINA 2009
(Mousa and Kamal, 2018) Egypt Cross-sectional	Asthma 25 Control 20	45(13) 34(13)	29.27(6.03) 26.6(4.97)	IOS-Masterscreen	**Asthma**: R5% 245.24(109.18) X5 (Unit NR) -2.87(1.84) **Control**: R5% 109.25(19.40) X5 (Unit NR) -0.28(0.10)	59.68(23.73) 89.75(8.70	GINA 2017
(Koruga et al., 2017) Serbia Cross-sectional	Asthma 31	23(5)	NR	IOS-Masterscreen	**Asthma**: X5 kPa -0.09(0.05) AX kPa 0.23(0.16) R5 kPa 0.34(0.09)	4.47L(0.64)	Previous diagnosis of asthma.

(Nair et al., 2011b) UK Cross-sectional	Asthma 82 Control 61	49(17) 28(10)	NR	IOS-Masterscreen	**Asthma**: X5% 441.72(137.86) R5% 162.22(7.5) **Control**: X5% -229.8(125.75) R5% 111.01(3.96)	83.99(2.23) 99.25(1.72)	Previous diagnosis of asthma.
(Gulden Pasaoglu et al., 2008) Turkey Cross-sectional	Asthma 443	37(15)	NR	Vmax 229	MMEF L/s 3.17(5.8)	2.99(0.9)	GINA 2006
(Son et al., 2009)† Korea Cross-sectional	Asthma 125	43(1)	NR	NR	1.MMEF% 97.67(3.48) 2.MMEF% 95.08(5.74) 3.MMEF% 70.16(4.64)	1. 107.84(1.79) 2. 105.2(3.43) 3. 96.16(2.71)	Clinical suspicion of asthma

Values reported in mean (SD)
* Weight in Kilograms
† Values reported in mean (SEM)
ID= study identification (authors, year) country, research type. BMI= Body Mass Index. SA=Small Airways. NR= Not Reported. FOT= Forced Oscillation Technique. IOS=Impulse Oscillometry. GINA= Global Initiative for Asthma.

Table 2.2. The characteristics of included studies with a DTA analysis.

ID	Sample Size	Age	SA Device	FEV_1	SA Test	Cut-off	TP	FN	FP	TN	Sen .%	Spc . %	Diagnosis Criteria
(Li et al., 2015) China Cross-sectional	Asthma 561 Control 205	50.5(18.8) *	Master Lab-IOS	NR	R5 X35	NR	404 297	157 264	80 49	125 156	72 53	61 76	ATS Guidelines
(Nikkhah et al., 2011) Iran Cross-sectional	Asthma 87 Control 87	41.4(15.5) 37.6(17.8)	Master Screen-IOS	2.2(0.6) L 3.2(0.9) L	R5 X5	>0.51 ≤-0.2	60 36	27 51	12 8	75 79	69 41	86 91	GINA 2008
(Yartsev, 2006) Russia Cross-sectional	1-Asthma 209 2-Asthma 75 3-Asthma 81 Control 216	1-47.4(0.8) 2-47.4(0.9) 3-54.4(1.6) 43.8(0.8)	Jaeger Master Screen	1-101(0.9) 2-70(0.73) 3-53.1(1.6) 102.6(1.4)	MMEF All Groups	90% 70% 50%	138 74 80	71 1 1	19 0 0	197 216 216	66 99 99	91 100 100	Global Strategy: Joint Report of the NHLBI and WHO 1993

*For both groups
ID= study identification (authors, year) country, research type. SA=Small Airways. NR= Not Reported. TP=True Positive. FN=False Negative. FP=False Positive. TN=True Negative. Sen=Sensitivity. Spc=Specificity. ATS= American Thoracic Society. GINA= Global Initiative for Asthma.

2.5.3 Risk of bias

Two risks of bias and quality assessment tools were used in this systematic review, based on the design of the included studies. Seven studies were assessed using the AHRQ tool for cross-sectional studies (Rostom et al., 2004) (See figure 2.2a). This highlighted potential methodological issues around subject selection and quality assurance concerns, which may have impacted on the reliability of results and the reporting of study follow up. There was an overall low risk of bias around patient recruitment (including the source of subjects), the inclusion/exclusion criteria and time periods when patients were identified. Response rates and completeness of results were all reported. A summary of all included studies using both tools is available in the appendix 8.2.8.

Three studies were assessed using QUADAS-2 tool for DTA studies (See figure 2.2b). One study had a high risk of bias and applicability concern in the patient selection phase. Two studies had a high risk of bias in the index test.

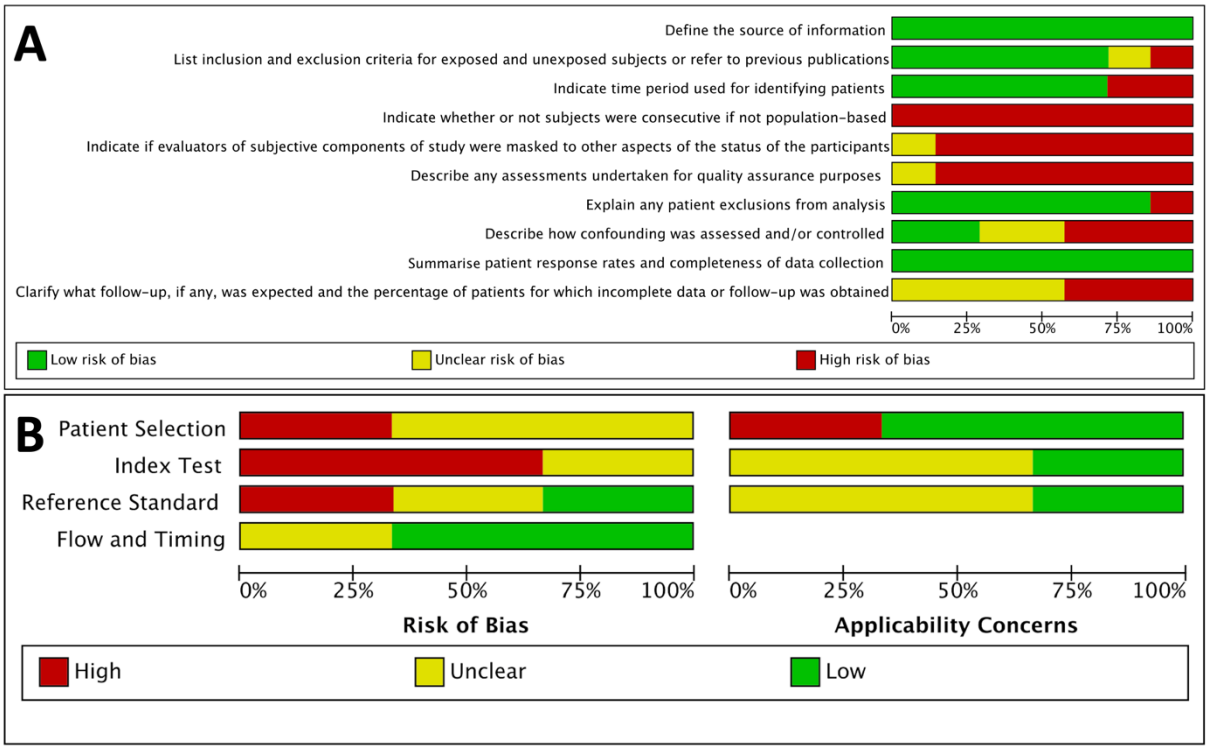


Figure 2.2. (A) Graph of AHRQ tool for quality/risk of bias of cross-sectional studies. (B) Graph of QUADAS-2 tool for DTA studies

2.5.4 Results of individual studies

2.5.4.1 Oscillometry

Seven studies used oscillometry. One study used FOT (Mori et al., 2011), five studies used IOS (Koruga et al., 2017, Mousa and Kamal, 2018, Nair et al., 2011b, Li et al., 2015, Nikkhah et al., 2011) and one study did not reported which type of oscillometry was used (Mendonça et al., 2011). Five studies reported R5 (Mousa and Kamal, 2018, Koruga et al., 2017, Mendonça et al., 2011, Mori et al., 2011, Nair et al., 2011b), which represent the total lung resistance. Only one study reported R5-R20 (Mori et al., 2011). The values of the test were reported in different units with Mori et al. and Mendonca et al. reporting results in $cmH_2O/L/s$, Nair et al. and Mousa & Kamal the % predicted values and Koruga et al. and Nikkhah et al. in kPa/L/s.

Mori et al.(Mori et al., 2011) reported R5, R5-R20, X5 and MMEF in 49 asthmatic patients,13 controls and 51 COPD patients. They described differences in MMEF, R5-R20, and X5 when comparing asthma to control subjects but not R5. In addition, they reported that the coloured 3-Dimensional model provided by the FOT device could differentiate between asthma, COPD and healthy subjects, with a higher resistance and lower reactance observed in asthma. Asthma severity was not reported and 24 of the asthmatic subjects were ex-smokers.

Mendonca et al.(Mendonça et al., 2011) studied 35 asthmatic and 34 non-asthmatic participants but used a different technique and frequency than the commonly reported value. Oscillometry values were reported in $cmH_2O/L/s$. The whole breath resistance at 8 Hz (R8) and the minimum resistance at maximum inhalation R_{min} were both different when comparing the asthmatic (R8=2.91±0.99) and non-asthmatic group (R8=2.21±0.48). In the asthmatic patients, both the MMEF % predicted value was lower (69%±20) than healthy controls (93%±20) and a higher R_{min} was observed. They also conducted a methacholine challenge test (MCT) in all participants and found that (31/35) asthmatic subject and (8/34) non-asthmatic group had a positive result. A subgroup analysis was reported including asthmatics with positive MCT (31/35) and non-asthmatic with a negative MCT (26/34) and similar results were reported to the overall analysis with a higher R_{min} in positive MCT (1.41±0.42) compared to (1.02±0.24) in negative MCT. Moreover, MMEF was lower in the MCT positive group (68%±18) compared to (99%±18) in negative MCT group. The mean FEV_1 was 88%±11 predicted in the asthmatic group and 95%±10 predicted in the non-asthmatic group, both within the normal range. The authors examined the ability of MMEF, R_{min}, and FEV_1 to predict airway hyperresponsiveness to methacholine by producing a

Receiver Operating Characteristic (ROC) curve which showed that MMEF had the highest area under the curve (AUC) of 0.87, while R_{min} and FEV_1 had AUC of 0.85 and 0.78 respectively. R8 was not reported in the ROC curve.

Mousa & Kamal (Mousa and Kamal, 2018) recruited 25 asthmatic patients and 20 healthy controls (with differences in the mean ages of the groups: asthmatic =45 years and the controls =34 years). Mean BMI did not differ between groups. The severity of the asthmatic group was not reported. IOS was used to assess asthma, with X5 and R5 being reported. R5 was reported in % predicted, but the X5 was reported in absolute values, but did not indicate the unit used. X5 and R5 were different between the two groups (Asthma: mean X5 -2.87±1.84 and R5% 245.24±109.18. Healthy controls mean X5 -0.28±0.10 and R5% 109.25±19.40). FEV_1 was lower in the asthmatic group with a mean of 59.68%±23.73 predicted compared to the healthy controls mean of 89.75%±8.70 predicted.

Koruga et al. (Koruga et al., 2017) included 31 male military recruits in Serbia with a previous diagnosis of asthma. Histamine was used to assess bronchial hyperreactivity (BHR), recording the dose that decreased FEV_1 by 20% predicted value (PD20). X5, R5 and Ax was reported at baseline and after PD20. They found that the overall change in FEV_1 after PD20 was 25.66%, while the R5 and X5 had a change of 66.64±62.91and 132.18±148.13 respectively. No controls were included in the study.

Similar to Koruga et al. and Mousa & Kamal, Nair et al.(Nair et al., 2011b) used a Masterscreen-IOS device, but reported X5 and R5 as % predicted values. Nair et al. included 82 patients with previous diagnosis of asthma and 61 healthy subjects. The asthma group was older (mean age 49 years versus mean age 28 years in the control group). Weight was not reported in either group. Nineteen percent of the asthma

patients were current or previous smokers, but the controls were all never smokers. All inhaled drugs such as short acting beta-agonists (SABA) and long acting beta-agonists (LABA) were withheld before reversibility testing except inhaled corticosteroids (ICS). Asthma severity and co-morbidities were not reported. Airways reversibility was assessed using 400 mcg of salbutamol via a pressurised metered dose inhaler (pMDI) and spacer and reported a mean change of 6.34% of FEV_1 in the asthma group and 2.25% in the healthy controls. The mean percentage of change after administering salbutamol was -33.78±4.43 and -72.93±88.73 in R5 and X5, respectively in the asthma group. In the control group, the mean change was -14.91±2.48 in R5 and 40.09±65.64 in X5.

2.5.4.2MMEF

Guldent et al. (Gulden Pasaoglu et al., 2008) recruited 433 asthmatic patients (mean age 37 years) and 152 patients with COPD (mean age 54 years), aiming to assess differences in clinical and spirometric features of asthma and COPD. 29% of the asthma group and 64% of the COPD group were current smokers. Reversibility was assessed in both groups using 200 mcg of salbutamol and defined by an increase of more than 12% and 200 mL of the FEV_1 value. 62.1% of the asthma group met criteria for reversibility compared to 39.5% in the COPD group. MMEF was the only parameter that was below the normal range in non-smoking asthmatic patients with normal auscultation, suggesting that MMEF was a physiological marker of asthma in non-smoking asymptomatic patients. Although bronchodilator responses were measured, these were not reported.

Son et al. (Son et al., 2009) conducted a retrospective study of 125 patients with a clinical suspicion of asthma who had undergone an MCT. Patients were stratified into

three groups based on their FEV_1 and MMEF response to MCT. The positive response to MCT was considered if there was a decline of 20% in FEV_1 and for MMEF, as well. Group 1 included patients with negative MCT tests for both parameters. Group 2 included patients with a negative FEV_1 and a positive MMEF. Group 3 included patients with positive test to both parameters. The mean ages of the included subjects were 45 years in group 1, 39 years in group 2 and 43 years in group 3. Eight subjects had a previous diagnosis of asthma, three in group 1 and five in group 3. Allergic rhinitis was reported in 34 subjects, 16 of them were positive to MCT in both spirometric indices, therefore included in group 3. Mean baseline MMEF in groups 1 and 2 was 97.67%±3.48 predicted and 95.08%±5.74 predicted respectively. In group 3, mean MMEF was 70.16%±4.64 predicted. The authors suggested that MMEF may be a more sensitive marker of asthma than FEV_1 in patients with otherwise normal spirometry results.

2.5.5 DTA Studies

2.5.5.1 IOS

Li et al.(Li et al., 2015) and Nikkhah et al. (Nikkhah et al., 2011) assessed the DTA of IOS for asthma. The majority of participants in Nikkhah et al. study were females, while Li et al. had a majority of male participants. Neither study reported participants' weight or BMI. Nikkhah et al. cut-offs were not pre-specified, but were proposed after plotting a ROC curve. Li et al. did not report a cut-off value. They both studied resistance at 5 Hz, but reactance was studied at different frequencies with Li et al. at 35 Hz, and Nikkhah et al. at 5 Hz. The sensitivity of R5 was reported as 72% by Li et al. and 69% by Nikkhah et al. while specificity reported by Li et al. at 61% and Nikkhah et al. at 86%. Reactance had lower sensitivity in both studies. Both studies did not

report the asthma severity of the participants or clinical co-morbidities and Li et al. did not report the FEV_1 results, although they performed bronchodilator response tests on all participants. Figure 2.3(A) shows the pooled data of R5 of the two studies.

2.5.5.2 MMEF

There was only one DTA study which used MMEF in asthma compared to controls (Yartsev, 2006). The asthma group was older than the control group. Both the asthma and control groups had a majority of female participants. Asthma severity and co-morbidities of participants were not reported. The author stratified asthma patients into three groups based on the baseline FEV_1. Group 1 included participants with FEV_1 of >80% predicted value, group 2 with FEV_1 60-80% predicted and group 3 with FEV_1 25-60% predicted. In MMEF tests, the cut-off used was 90% predicted in group 1, 70% predicted in group 2, and 50% predicted in group 3. The DTA of MMEF in group 1 was a sensitivity of 66% and specificity of 91%. Identical results were found in groups 2 and 3 with a sensitivity of 99% and specificity of 100%. The accuracy of MMEF was assessed on all groups with a cut-off value of 70% showed a sensitivity of 88% and specificity 97%. Using FEV_1, cut-off was set at 120% predicted in group 1, 90% predicted in group 2, 70% predicted in group 3. The DTA of FEV_1 in group 1 was a sensitivity of 77% and specificity of 65%. In groups 2 and 3, identical sensitivity of 100% and specificity of 100% was reported. All groups were assessed for accuracy using FEV_1, with a 70% predicted cut-off, showing a sensitivity of 92% and specificity of 88%. Diagnostic test accuracy data was pooled into the forest plot shown in figure

2.3(B).

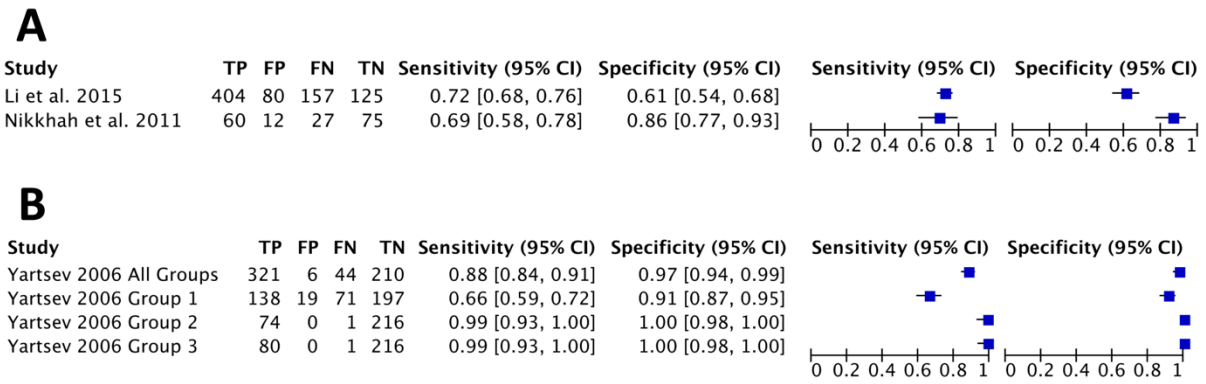


Figure 2.3. (A) DTA forest plot of R5. (B) DTA forest plot of MMEF.
FN, false negative; FP, false positive; TN, true negative; TP, true positive.

2.5.6 Synthesis of results

Small airways function in asthma were found to be different when compared to healthy controls. The % predicted MMEF value appeared consistently lower than the % predicted FEV_1, as shown in figure 2.4. In oscillometry, R5 was also found to be consistently higher in asthmatic when compared to healthy controls as shown in figure 2.5. These results highlight the presence of small airways limitation in asthmatic patients with heterogeneous characteristics including age, ethnicity and weight.

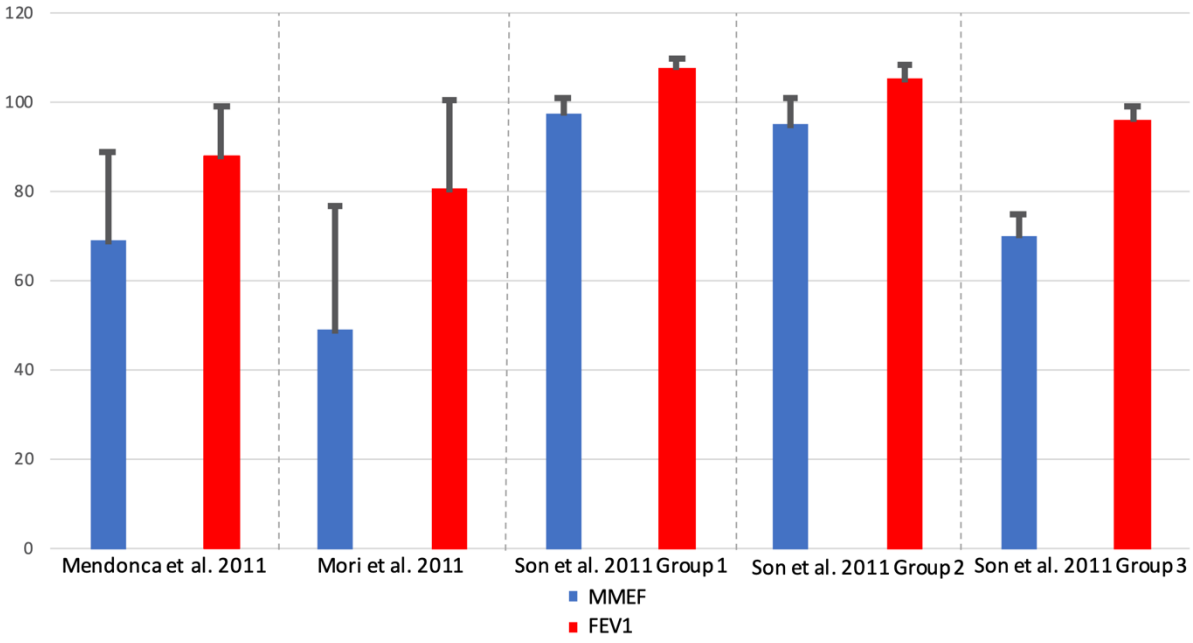


Figure 2.4. Comparison of % predicted of MMEF to FEV_1 in asthmatic patients.

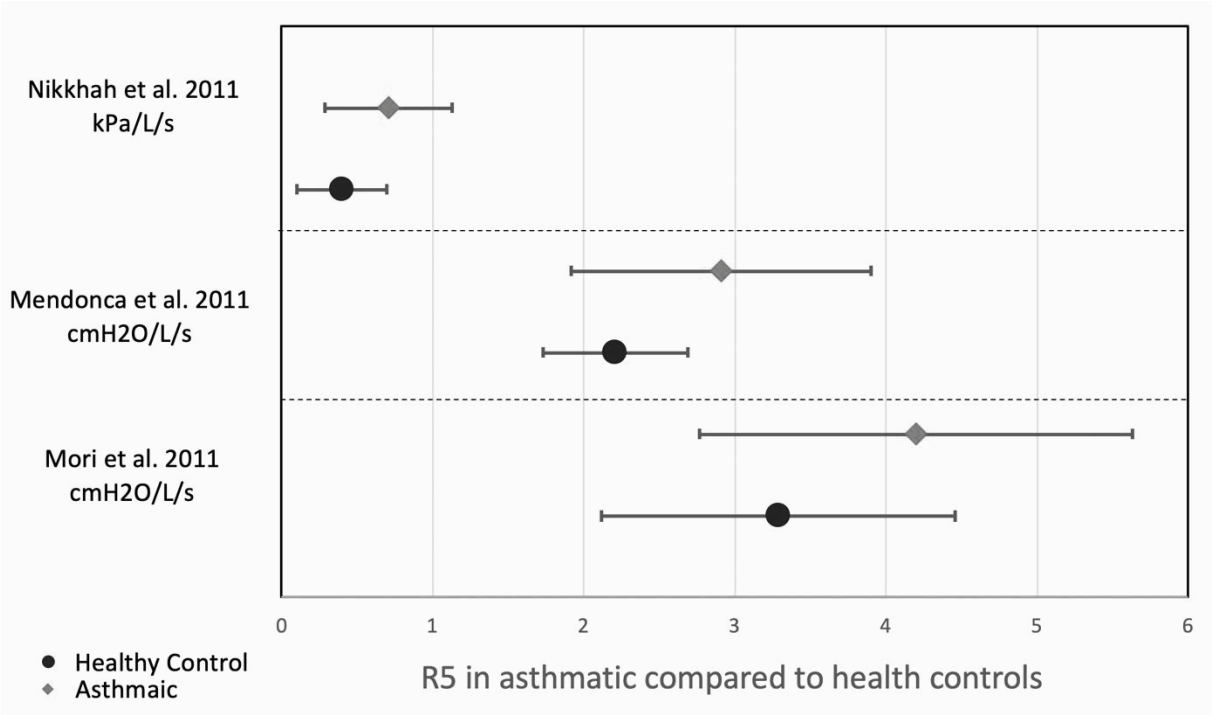


Figure 2.5. Comparison of R5 between asthmatic patients to healthy controls.

2.5.7 ROB across studies

There were some concerns of bias in regard to reporting outcomes. Kamal & Mousa(Mousa and Kamal, 2018) reported R5 as the % predicted value while X5 was reported without a unit of measurement. Yartsev(Yartsev, 2006) did not report how the cut-offs were determined or how subjects were recruited.

2.6 DISCUSSION

To the authors' knowledge, this is the first systematic review to assess the use of physiological tests of small airways function in the diagnosis of asthma. Previous work has suggested that small airways dysfunction (SAD) is associated with asthma and that the prevalence of SAD increases with the severity of asthma (Usmani et al., 2016b,

Postma et al., 2019). This review suggests that most published studies of small airways function tests in asthma are heterogeneous, of varying methodological quality and have primarily identified SAD rather than using measures of small airways to diagnose asthma. No studies reported the severity of asthma in the participants and participants groups were often poorly matched or characterised in terms of other co-morbidities and weight.

This review focuses on MMEF and oscillometry and does not explore all potential measures to assess small airways function. MMEF and oscillometry were chosen as these represented the most commonly cited small airways measures. The clinical utility of oscillometry techniques has been described in asthma and other lung conditions such as interstitial lung diseases (ILD) and COPD (Shirai and Kurosawa, 2016). Oscillometry has been suggested as a useful tool in diagnosing asthma in children (Starczewska-Dymek et al., 2018). However, there remains a lack of universal reference ranges, especially in adults. Height (Mendonça et al., 2011) and sex (Oostveen et al., 2013) appear to alter values. Oostveen et al., conducted a multicentre study on healthy subjects in an effort to produce reference ranges for oscillometry in adults, but only one ethnicity was studied (Oostveen et al., 2013). Another study was also conducted in Japan to establish reference ranges for Japanese adults (Furuie et al., 2017). Understanding and interpreting oscillometry remains challenging. In this review, it was unclear if oscillometry studies provided the most robust measure of small airways function. The R5-R20 (often referred to as resistance of the small airways) was only reported by Mori et al. Airways reversibility, a hallmark of asthma, was only assessed using oscillometry by Nair et al and, here, the mean percentage of change

in the FEV_1 in the asthma group was 6.34%, which is less than the standard reversibility change of 12%.

The MMEF is an effort-dependent test and guidelines for reproducibility of the manoeuvre is based on FVC and FEV_1 (Miller et al., 2005b). In all the included articles that studies MMEF, the % predicted of MMEF was found to be lower in asthmatic groups compared to control groups. Moreover, the % predicted value of MMEF was lower than the % predicted FEV_1 in the asthmatic group, suggesting that small airways limitation might be an early marker of airways obstruction. The potential utility of MMEF in early disease was described in one study of patients with alpha-1 antitrypsin deficiency (AATD), where an MMEF less than 80% predicted, with a normal FEV_1/FVC ratio, was associated with increased respiratory symptoms and a faster decline in FEV_1 compared to those with an MMEF of 80% or greater and normal spirometry, suggesting a role for MMEF in early disease monitoring (Stockley et al., 2017).

There are significant limitations to the evidence base described in this review including study heterogeneity, poor patient characterisation, and differences in reported values. Not all tests of small airways function have been assessed in asthma (for example, MBW). There are no universally accepted predicted values for oscillometry, especially in adults, making the interpretation of the results more difficult. Oscillation techniques produce many parameters in both inspiratory and expiratory phases and the differences in reported values limits comparisons between studies. MMEF was not corrected for FVC in any study, and this is a limitation as MMEF is a timed/flow measurement and FVC exhalation curve changes may affect the results (Mirsadraee et al., 2013). Nevertheless, most studies provide at least some signal of SAD in asthma suggesting these indices could be helpful in diagnosing and monitoring

asthma. To take this field forward, further research is needed. This should include standardising the assessment of small airways tests (although different tests may have greater or lesser utility in different diseases) and forming normal reference ranges to aid interpretation. Studies in asthma need to pre-define how asthma was diagnosed, and report clearly which small airways tests have been measured, by what device, what units are reported and what would be considered an abnormal result or clinically meaningful change in a specified value.

2.7 CONCLUSION

Physiological tests of small airways function are feasible in diagnosing asthma and have been shown to be altered in asthma when compared to healthy adults. However, a lack of robust reference ranges and the heterogeneity of approach complicate their use.

Further studies are needed to assess small airways function in asthma, especially in early disease. Larger studies are needed to assess the impact of demographic characteristics and co-morbidities such as obesity or allergic rhinitis. This systematic review of current literature suggests these tests may have promise as part of the future diagnostic criteria of asthma, but more work is needed before they can be embedded into clinical care.

2.8 SUMMARY OF THE CHAPTER

This systematic review demonstrated that physiological tests of small airways function are altered in asthma and could be feasibly used in the diagnosis of this variable disease. However, more studies are needed which address some of the

limitations in the current literature. Bronchodilator responsiveness is also used to diagnose asthma, and the use of tests of small airways function in bronchodilator responsiveness will be assessed in chapters 4 and 5.

CHAPTER 3

3. THE PREVELANCE AND RISK FACTORS OF SMALL AIRWAYS DYSFUNCTION IN ASTHMA: A REAL-WORLD RETROSPECTIVE ANALYSIS

3.1 INTRODUCTION

Small airways dysfunction (SAD) is prevalent in asthma, but the relationship between SAD and airflow obstruction (AO) in asthma is less clear. Identifying patients with SAD may be clinically important, as those with SAD and asthma have been found to have worse symptom control and more severe asthma according to GINA (Global Initiative for Asthma (GINA), 2022) criteria. In this chapter, the prevalence of small airways dysfunction and demographic and physiological parameters associated with SAD are explored using a commonly reported physiological index, the Maximal Mid-Expiratory Flow rate (MMEF). This work has been partly published in abstracts form at the 2022 CHEST Congress and published in the CHEST Journal (Almeshari et al., 2022b, Almeshari et al., 2022a) (see appendices 8.3.1 and 8.3.2).

Part of this chapter is being prepared to be submitted in a peer-reviewed journal with a title "**Physiological small airways function and the bronchodilator response in adults with asthma: a retrospective analysis**". Below are authors list, affiliation, and contributions.

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Authors Contribution:

M.A.A designed and planned the study, analysed the data and wrote the manuscript. N.Y.A. assisted in analysing the data. J.A.S. and R.A.S. reviewed the data and revised the manuscript. E.S. designed and planned the study, reviewed the data, and revised the manuscript.

3.2 ABSTRACT

Background: Physiological evidence of Small airways dysfunction (SAD) is present in some patients with asthma. It is unclear if this represents a distinct phenotype of asthma or is an early manifestation of disease and how it relates to airflow obstruction (AO).

Methods: A retrospective analysis of routinely collected health data obtained from adults with asthma or clinical suspicion of asthma referred for routine spirometric assessment. Demographic data and pre-bronchodilator data assessed the prevalence and associated factors for SAD (categorised using Maximal Mid-Expiratory Flow (MMEF) z-scores). The AO was evaluated using the pre-bronchodilator FEV_1/FVC z-scores.

Results: A total of 2328 records were screened, of which 1829 unique patients records were included. Overall, 486 (26.6%) had evidence of SAD of whom 337 (69.3%) also had AO. The prevalence of SAD increased with the severity of AO based on FEV_1 z-score. A higher FEV_1 and FEV_1/FVC z-scores was found to be associated with a lower chance of having SAD with an Odds Ratio (OR) of 0.17 (95%CI:0.13–0.2), and 0.17 (95%CI: 0.14–0.21), respectively. Although a univariate regression model found that current smokers (OR: 2.33; 95%CI: 1.75-3.10) and previous smoker (OR: 1.27; 95%CI: 1.00-1.62) were at increased risk of SAD, in a multivariate analysis, only lower FEV_1 z scores and FEV_1/FVC ratio predicted the presence of SAD.

Conclusion: In asthma, SAD is related to baseline AO and increases with obstruction severity. Smoking asthmatics are at an increased risk of having SAD.

Keywords: Small airways, Asthma, Spirometry, Lung function.

3.3 BACKGROUND

Asthma is a common chronic disease, with more than 300 million people thought to be affected globally; 20 million in the United States (Olin and Wechsler, 2014) and 9.8 million in the United Kingdom (Mukherjee et al., 2016). Asthma is a heterogeneous disease with different clinical presentations and several asthma phenotypes have been proposed (Weatherall et al., 2009, Haldar et al., 2008). Spirometry is the most commonly used instrument for objectively assessing and diagnosing asthma and a significant Bronchodilator Response (BDR) is considered the hallmark of asthma (Kudo et al., 2013). One of the main goals of asthma therapy is to achieve good disease control, with minimal symptoms and rescue inhaler use (Global Initiative for Asthma (GINA), 2022). However, despite this, real world studies have shown poor control in a significant proportion of patients (Braido et al., 2016).

Small airways dysfunction (SAD) is prevalent in patients with asthma (Usmani et al., 2016a) and there is evidence to suggest that inflammation in the small airways and the resultant SAD may be a contributory factor in poor disease control (Cottini et al., 2021). Cigarette smoking has already been implicated as a risk factor for SAD in asthma (Abdo et al., 2021) as it is a major indicator of the early development of Chronic Obstructive Pulmonary Disease (COPD) (Kwon et al., 2020).

Recently, the AssessmenT of smalL Airways involvemeNT In aSthma (ATLANTIS) Study (Postma et al., 2019) found that SAD was more common in patients with more severe asthma (as defined by the Global Initiative for Asthma (GINA) and associated with poor asthma control and increased exacerbation frequency (Kraft et

al., 2022), However, this comprehensive study used multiple techniques to assess SAD and identified that different physiological tests characterised different cohorts of patients with SAD, suggesting that the assessment tool has impact on identifying patients with SAD (7). It is currently unclear which physiological test should be used to measure SAD (Almeshari et al., 2020b) but in clinical practice, it is likely that only one assessment tool could be used.

The Forced Vital Capacity (FVC) and forced expiration volume in the 1st second (FEV_1) are used to classify airflow obstruction (AO), its severity, and the response to bronchodilators. These are considered to predominantly reflect the function of the larger airways. While many other indices can be used to assess the function of the small airways, the Maximal Mid-Expiratory Flow (MMEF; also referred to as the forced expiratory flow between 25-75% (FEF_{25-75}) of the FVC) is one of the most widely reported, as it forms a part of spirometric testing and is readily available.

Identifying the presence of SAD in asthma is increasingly of clinical importance. Small airways now form a therapeutic target with the development of inhaled treatments with smaller aerosol particles (Manoharan et al., 2016) and more recent evidence of biologics having an effect in the small airways (Farah et al., 2019, Sposato et al., 2020).

This current real-world study sought to assess the prevalence of SAD using a commonly deployed methodology (namely MMEF measured as part of routine spirometry) in an unselected cohort of patients with asthma, and determine the relationship of SAD to AO, and smoking.

3.3.1 Hypothesis and aims

We hypothesised that physiological evidence of SAD, as assessed by MMEF, would only be present in a proportion of patients with a diagnosis of asthma and may not always co-exist with conventional AO but would be a feature of those with established FEV_1/FVC defined AO. We further hypothesised that the presence of SAD and AO would reflect cigarette smoking exposure in asthma.

The study had three main aims:

1. To investigate the prevalence of SAD in patients with a clinical diagnosis of asthma or suspected as having asthma by a clinician.
2. To determine the relationship between both the presence of and severity of SAD and conventional airflow obstruction in asthma.
3. To assess the relationship between demographic features and smoking behaviors and the likelihood of SAD.

3.4 METHODS

3.4.1 Study design and setting

The study is a cross-sectional, retrospective analysis of patients referred to lung functions laboratory for asthma assessment. The data were obtained from the lung function department in a tertiary hospital in the West Midlands of the UK. The study and all study activities were approved by the Health Research Authority (HRA IRAS number 274729; REC Reference: 20/HRA/0203).

All routine lung function records of adults, tested between 1st January 2016 and 30th April 2021. The data was collected and compiled by the lung function department and anonymised prior to analysis.

3.4.2 Participants

Patients with either a diagnosis or a clinical suspicion of asthma were considered for inclusion. The following inclusion and exclusion criteria were applied:

3.4.2.1 Inclusion Criteria

- Adults (aged 18 or over)
- A clinical diagnosis or clinical suspicion of asthma that was referred for lung function testing by a physician.
- Report of primary spirometry indices (FEV_1, FVC, MMEF).

3.4.2.2 Exclusion Criteria

- The presence of other respiratory diagnoses including Chronic Obstructive Pulmonary Disease (COPD), bronchiectasis and lung malignancy
- Any previous lung surgery likely to impact lung function parameters
- Entries with missing key parameters (FEV_1, FVC, MMEF).

- Paediatric patients (<18 years of age)

3.4.3 Outcomes

The study had the following outcomes:

3.4.3.1 Primary outcomes

- The proportion of and characteristics of patients with evidence of SAD.

3.4.3.2 Secondary outcomes

- Relationship of smoking to SAD.

3.4.4 Lung function testing

Participants were assessed using spirometry (MasterScreen Pro lung function system (Jaeger Ltd, Hochberg, Germany)), which was performed according to the Association for Respiratory Technology and Physiology (ARTP)/British Thoracic Society guidelines (Sylvester et al., 2020).

The categorisation was based on z-scores of the FEV_1/FVC (Quanjer et al., 2014a) for AO and MMEF for SAD. The z-score was calculated from the raw data provided using the Global Lung Initiative (GLI) 2012 formula. An FEV_1/FVC z-score of <-1.645 was taken to indicate the presence of AO, and the severity was classified by FEV_1 z-scores as follow: >-1.645: Mild, <-2: Moderate, <-2.5 Moderately severe, <-3: Severe, <-4: Very severe (Sylvester et al., 2020). The lower limit of normal (LLN) of MMEF was used to define SAD using a z-score of <-1.645.

3.4.5 Demographics definitions

The data did not contain body mass index (BMI) and it was calculated using the following equation:

$$\mathrm{BMI} = \frac{\mathrm{Weight\ (kg)}}{\mathrm{Height\ (m)}^2}$$

The smoking status was defined as those who reported to be smoking as current smoker, and those who were smoking but quitted as previous smoker, whereas those who reported that the never smoked as never smokers.

3.4.6 Statistical analysis

Data analysis was performed using Rstudio (based on R, from the R Core Team, version 4.2.0) software. Predicted values and z-scores were calculated using IBM SPSS (version 27) software. Normality of data was assessed using the Shapiro test, then normality of variance was assessed using Levene's test in normally distributed data. For normally distributed data, unpaired t-tests were used to compare two continuous variables and ANOVA was used to compare more than two. For non-normally-distributed data, unpaired Wilcoxon rank tests were used to compare two continuous variables and the Kruskal-Wallis test to compare more than two such variables. P-values were adjusted using the Bonferroni method (Bland and Altman, 1995) for multiple comparisons. For categorical variables, Chi-square tests were used for both parametric and non-parametric analyses. Correlations were assessed using either Pearson's or Spearman's as appropriate. Backward stepwise logistic regression models were used for SAD and AO. Univariate logistic regression models were initially used to assess predictors individually and multivariate logistic models were then used to assess the significant predictors after adjusting the factors.

3.5 RESULTS

A total of 2328 lung function tests were performed during the study period for patients with a confirmed or suspected diagnosis of asthma. The records were screened as per the inclusion and exclusion criteria. A total of 1829 unique patient records were included in the baseline analysis. Figure 3.1 describes the number of records and reasons for exclusion in a flowchart.

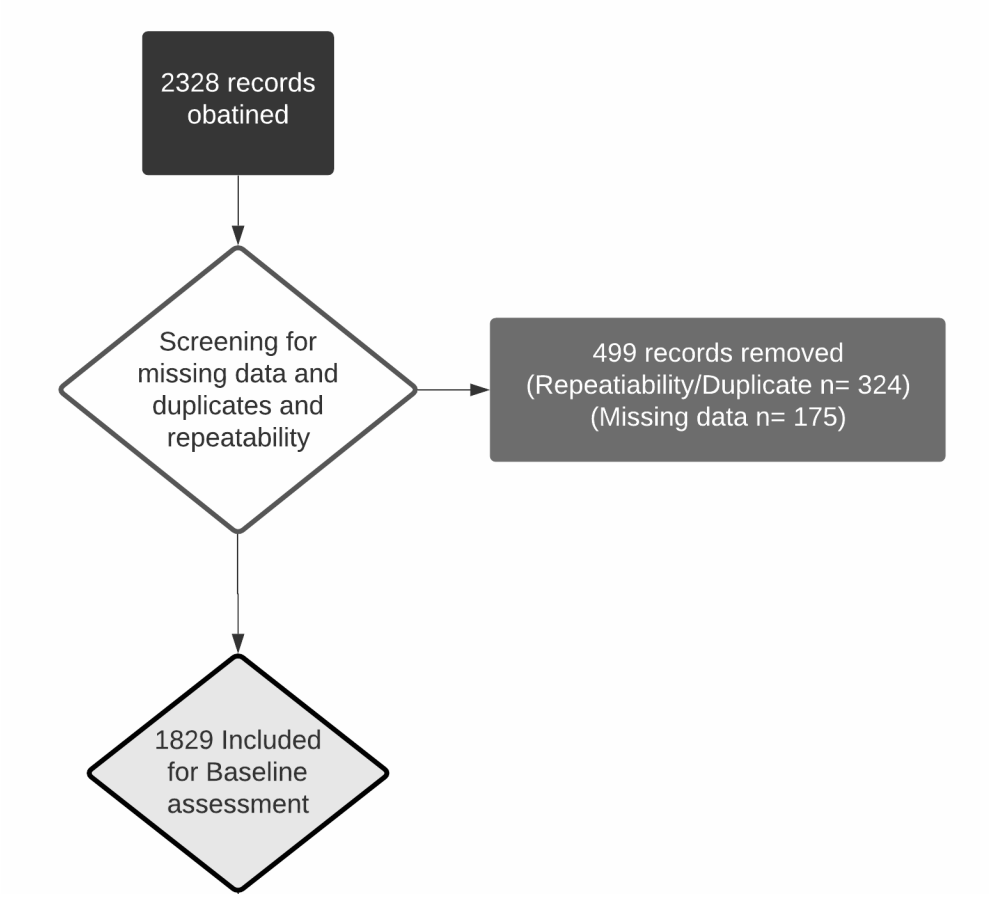


Figure 3.1. Flowchart of the screened records that shows the number that were assessed based on the inclusion/exclusion criteria.
Abbreviations: BDR, Bronchodilator Response.

3.5.1 Baseline characteristics

The largest proportion of patients 1285 (70.3%) had neither SAD nor AO (SAD-/AO-). Four hundred and eighty-six (26.6%) participants had evidence of SAD, of whom

149 (30.7%) had isolated SAD with no AO (SAD+/AO-) and 337 (69.3%) had both SAD and AO (SAD+/AO+). Of the whole cohort, 395 (21.6%) patients had AO, with 337 (85.3%) of these having both AO and SAD. The smallest group (58 people (14.7 %)) was those with AO but no SAD (SAD-/AO+) .

The SAD+/AO- group was younger than SAD-/AO- group, but did not differ from the other groups. Most of the patients were never smokers (63.1%) and 23.8% were previous smokers. The only statistical difference in smoking status was between SAD-/AO- and SAD+/AO+ groups, with SAD+/AO+ group having a higher percentage of previous and current smokers.

Most participants were receiving:- Short-Acting Beta-2 Agonist (SABA) 1192 (65.2%), Inhaled corticosteroids/Long-Acting Beta-2 Agonist combination (ICS/LABA) 706 (38.6%), or ICS alone 425 (23.2%). There was no difference in medication use between the groups.

Table 3.1 summarises the demographics, table 3.2 summarises the lung function measurements, and table 3.3 summarises medications used in each group.

Table 3.1. Demographics of patients based on physiological characteristics

	Overall (N=1829)	SAD-/AO- **(N=1285)**	SAD+/AO- **(N=149)**	SAD+/AO+ **(N=337)**	SAD-/AO+ **(N=58)**	**P-value**
Age (Years)	47.0 (33.0 to 60.0)	48.0 (34.0 to 60.0)	41.0 (32.0 to 52.0)*	46.0 (33.0 to 61.0)	50.0 (31.8 to 69.0)	**0.004**
Sex						
Female	1124 (61.5%)	827 (64.4%)	106 (71.1%)	171 (50.7%)*,†	20 (34.5%)*,†	**<0.001**
Race						
Asian	377 (20.6%)	273 (21.2%)	49 (32.9%)	49 (14.5%)	6 (10.3%)	**<0.001**
Black	98 (5.4%)	66 (5.1%)	18 (12.1%)	14 (4.2%)	0 (0%)	
White	1338 (73.2%)	938 (73.0%)	78 (52.3%)	270 (80.1%)	52 (89.7%)	
Unspecified	16 (0.9%)	8 (0.6%)	4 (2.7%)	4 (1.2%)	0 (0.0%)	
BMI	28.5 (24.8 to 33.0)	29.0 (25.2 to 33.2)	29.0 (24.8 to 35.3)	27.4 (23.6 to 31.2)*,†	27.1 (24.4 to 30.6)	**<0.001**
Smoking Status						
Never Smoker	1154 (63.1%)	855 (66.5%)	90 (60.4%)	179 (53.1%)	30 (51.7%)	**<0.001**
Previous Smoker	435 (23.8%)	302 (23.5%)	27 (18.1%)*	87 (25.8%)	19 (32.8%)†	
Current Smoker	240 (13.1%)	128 (10.0%)	32 (21.5%)*	71 (21.1%)*	9 (15.5%)	
Pack Years	10.0 (4.0 to 23.0)	10.0 (4.0 to 20.0)	13.0 (5.0 to 21.8)	11.0 (5.0 to 30.0)	9.00 (4.00 to 21.5)	0.148

Legend: Groups were based on the type of obstruction and labelled accordingly.
Abbreviation: SAD: small airways dysfunction, AO: airflow obstruction, BMI: Body mass index.
Values are in Median (Q1 to Q3), or n (%).

Kruskal Wallis test was used to assess the statistical difference between the continuous groups. Pairwise statistical analysis was assessed using the Wilcoxon rank test for continuous variables. The Chi-square test assessed the statistical difference between the categorical and pairwise groups.
* Statistically different from (SAD-/AO-) group; †, Statistically different from (SAD+/AO-) group; ‡ Statistically different from (SAD+/AO+) group.

Table 3.2. Baseline lung function of patients based on physiological characteristics.

	Overall (N=1829)	SAD-/AO- **(N=1285)**	SAD+/AO- **(N=149)**	SAD+/AO+ **(N=337)**	SAD-/AO+ **(N=58)**	**P-value**
FEV_1						
% Predicted	88.5 (76.4 to 99.7)	94.2 (84.8 to 103)	70.8 (59.6 to 79.5)*	64.2 (52.9 to 76.8)*	94.7 (88.8 to 100)†,‡	**<0.001**
Z-score	-1.05 (-1.97 to -0.17)	-0.61 (-1.29 to -0.10)	-2.46 (-2.98 to -1.95)*	-2.65 (-3.34 to -1.84)*	-0.50 (-0.87 to -0.05)†,‡	**<0.001**
FVC						
% Predicted	92.7 (81.8 to 103)	94.9 (86.3 to 104)	77.7 (65.5 to 88.7)*	86.2 (73.7 to 98.7)*,†	114 (107 to 122)*,†,‡	**<0.001**
Z-score	-0.69 (-1.57 to 0.09)	-0.59 (-1.29 to 0.15)	-2.10 (-2.74 to -1.20)*	-1.24 (-2.06 to -0.23)*,†	0.97 (0.46-1.49)*,†,‡	**<0.001**
FEV_1/FVC (Ratio)	77.9 (70.5 to 83.0)	80.7 (76.4 to 84.9)	75.0 (71.9 to 78.0)*	62.2 (55.2 to 66.1)*,†	66.2 (60.6 to 70.3)*,†	**<0.001**
FEV_1/FVC Z-score	-0.52 (-1.46 to 0.25)	-0.08 (-0.64 to 0.48)	-1.18 (-1.45 to -0.89)	-2.52 (-3.12 to -2.05)	-1.87 (-2.10 to -1.77)	
MMEF						
% Predicted	78.1 (55.6 to 100)	90.4 (76.3 to 109)	52.7 (44.3 to 58.7)*	36.0 (26.4 to 45.3)*,†	62.6 (52.7 to 67.6)*,‡	**<0.001**
Z-score	-0.86 (-1.71 to -0.09)	-0.42 (-0.94 to 0.20)	-1.97 (-2.25 to -1.78)	-2.58 (-3.17 to -2.15)	-1.44 (-1.55 to -1.33)	
FEV_3/FVC (Ratio)	94.8 (90.9 to 97.6)	96.1 (93.7 to 98.3)	94.6 (92.1 to 96.7)*	86.4 (81.0 to 90.0)*,†	88.6 (84.2 to 91.8)*,†	**<0.001**

Legend: Groups were based on the physiological characteristics and labelled accordingly.

Abbreviations: SAD: small airways dysfunction, AO: airflow obstruction, FEV_1: forced exhaled volume in the 1^{st} second, FVC: Forced vital capacity, MMEF: Mid-maximal expiratory flow, FEV_3: forced exhaled volume in the first 3seconds.
Values are in Median (Q1 to Q3), or n (%).
Kruskal Wallis test was used to assess the statistical difference between the continuous groups. Pairwise statistical analysis was assessed using the Wilcoxon rank test for continuous variables. The Chi-square test assessed the statistical difference between the categorical and pairwise groups.
* Statistically different from SAD-/AO- group; †, Statistically different from SAD+/AO- group; ‡ Statistically different from SAD+/AO+ group.

Table 3.3. Medication use in participants based on groups.

	Overall (N=1829)	(SAD-/AO-) **(N=1285)**	(SAD+/AO-) **(N=149)**	(SAD+/AO+) **(N=337)**	(SAD-/AO+) **(N=58)**	**P-value**
SABA	1192 (65.17%)	853 (66.4%)	93 (62.4%)	216 (64.1%)	30 (51.7%)	0.106
ICS	425 (23.24%)	293 (22.8%)	29 (19.5%)	92 (27.3%)	11 (19.0%)	0.169
LABA	28 (1.53%)	18 (1.4%)	3 (2.0%)	6 (1.8%)	1 (1.7%)	0.913
LAMA	188 (10.28%)	136 (10.6%)	11 (7.4%)	34 (10.1%)	7 (12.1%)	0.637
SAMA	19 (1.04%)	16 (1.2%)	0 (0%)	2 (0.6%)	1 (1.7%)	0.39
ICS/LABA	706 (38.60%)	505 (39.3%)	63 (42.3%)	115 (34.1%)	23 (39.7%)	0.262
Montelukast	233 (12.74%)	166 (12.9%)	17 (11.4%)	44 (13.1%)	6 (10.3%)	0.896
Antihistamine	104 (5.69%)	64 (5.0%)	14 (9.4%)	23 (6.8%)	3 (5.2%)	0.119
Nasal CS	41 (2.24%)	33 (2.6%)	4 (2.7%)	4 (1.2%)	0 (0%)	0.284
HTN Meds	282 (15.24%)	198 (15.4%)	18 (12.1%)	56 (16.6%)	10 (17.2%)	0.617
DM Meds	76 (4.16%)	56 (4.4%)	5 (3.4%)	14 (4.2%)	1 (1.7%)	0.745
Oral CS	58 (3.17%)	37 (2.9%)	4 (2.7%)	15 (4.5%)	2 (3.4%)	0.516

SABA: short-acting beta-agonist, ICS: Inhaled corticosteroids, LABA: Long-acting beta-agonist, LAMA: Long-acting muscarinic antagonists, SAMA: Short-acting muscarinic antagonists, CS: Corticosteroid, HTN: Hypertension, DM: Diabetes mellitus. Values are in n (%).

3.5.2 Lung function characteristics

Those in the SAD+/AO- group had lower FEV_1 values than those in the SAD-/AO- and SAD-/AO+ groups, which was within the normal range. The median FEV_1 was lowest in the SAD+/AO+ group (both for % predicted and z-score).

While the FEV_1/FVC ratio was within the normal range in the SAD+/AO- group, it was lower than the SAD-/AO- group. Although the SAD-/AO+ group had lower values of FEV_1/FVC and were statistically different from the SAD-/AO- and the SAD+/AO- groups the median z-score for FEV_1 and FVC were within normal range (-1.87; IQR -2.10 to -1.77). Detailed lung functions indices are reported in table 3.2.

There was a strong correlation between MMEF and FEV_1/FVC z-scores (R^2=0.76, p <0.001), as shown in figure 3.2.

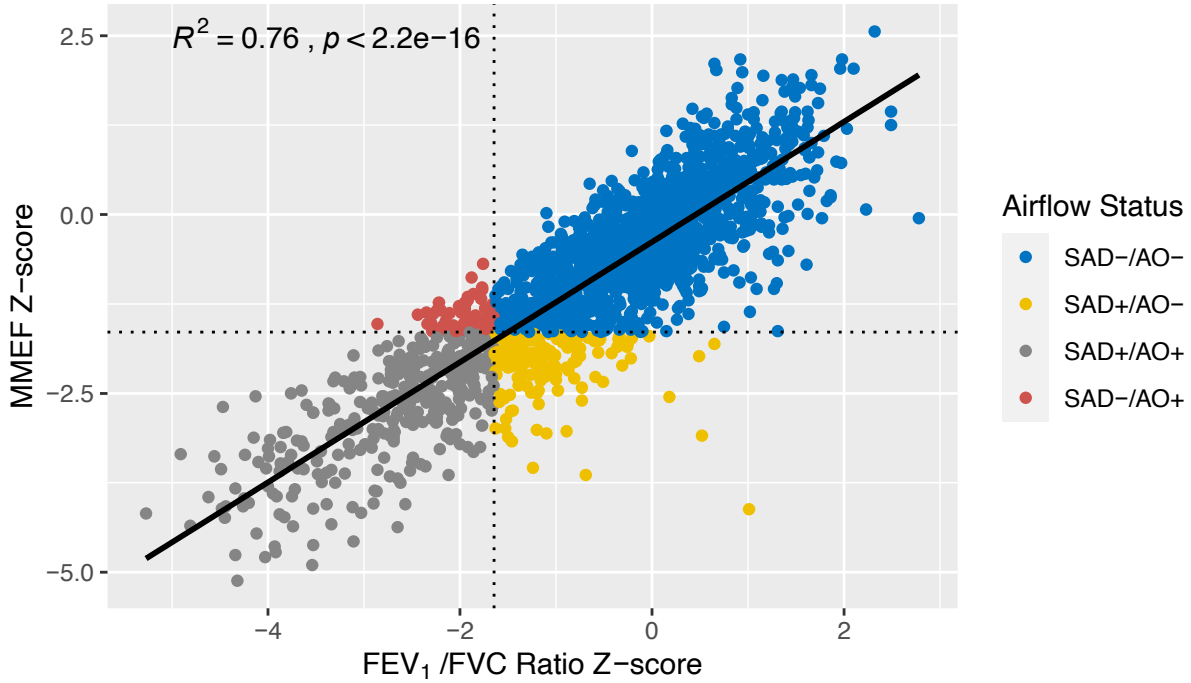


Figure 3.2. Scatter plot of MMEF and FEV_1/FVC z-scores with regression line and R^2.
A cut-off of -1.645 was used to categorise SAD and AO using MMEF and FEV_1/FVC
Legend: MMEF, Maximal mid-expiratory flow; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; SAD, small airways dysfunction; AO, airflow obstruction. Abbreviations: SAD: small airways dysfunction, AO: airflow obstruction,

The MMEF z-score declined in a stepwise fashion with increasing AO severity (p >0.001), see figure 3.3.

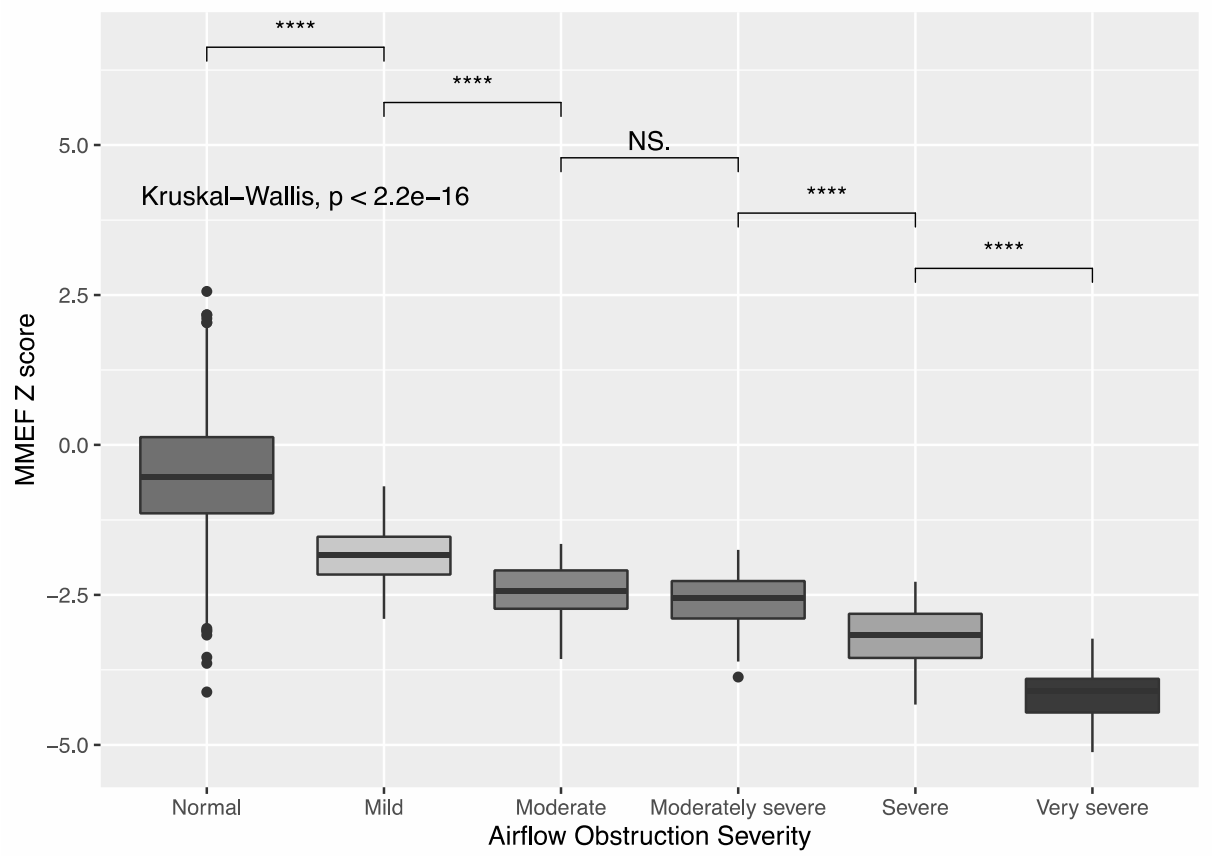


Figure 3.3. Box plot of MMEF z-scores and across AO severities as defined in methods.
Legend: MMEF, Maximal mid-expiratory flow; AO, airflow obstruction.
("****"= p < .0001, "***"= p < .001, "**"= p < .01, "*"= p < .05, NS.= Not significant)

3.5.3 Relationship

To evaluate the relationships between parameters, a correlation model was evaluated. The MMEF z-score was positively correlated with the FEV_1, FEV_1/FVC, and the FVC, however, the FVC had a weak correlation coefficient value (r=0.34) compared to strong corelation with FEV_1 (r=0.77) and FEV_1/FVC (r=0.87). All spirometric indices were negatively correlated and statically significant with the pack years history of smoking. Age and BMI are minimally corelated with spirometric indices.

In table 3.4, the correlation matrix is reported.

Table 3.4. Correlation coefficient matrix for the baseline value and continuous demographics.

Characteristic	Age	BMI	Pack Years	MMEF z-score	FEV_1 z-score	FEV_1/FVC z-score
Age						
BMI	0.17*					
Pack Years	0.45*	0.16*				
MMEF z-score	0.07*	0.06*	-0.09*			
FEV_1 z-score	-0.05*	-0.08*	-0.16*	0.77*		
FEV_1/FVC z-score	0.02	0.13*	-0.09*	0.87*	0.44*	
FVC z-score	-0.10*	-0.18*	-0.15*	0.34*	0.82*	-0.07*

Abbreviation: BMI: Body mass index, FEV_1: forced exhaled volume in the 1st second, FVC: Forced vital capacity, MMEF: Mid-maximal expiratory flow. Values are the Spearman's correlation co-efficient (r). * Statistically significant.

3.5.4 Predictors of SAD

To explore the predictors of SAD in asthmatic patients a univariate regression model was developed that included the whole cohort (n=1829) and the Odds Ratios (OR) were calculated. Sex, age, BMI, smoking status, FEV_1 z-score and FEV_1/FVC z-scores were assessed. The OR of SAD was increased in current smokers (2.33; 95% CI: 1.75-3.10) and previous smokers (1.27; 95% CI: 1.00-1.62) compared to never-smokers ($p<0.001$). The OR of SAD was decreased for people with a higher FEV_1 (0.17 (95% CI: 0.14-0.20)) and FEV_1/FVC (0.16: (95% CI: 0.14-0.19)), $p<0.001$ all comparisons. No other factor was significant in the model.

These factors were entered into a multivariate analysis. In this model, smoking status no longer predicted SAD but the relationship with FEV_1 and FEV_1/FVC ratio remained, with a higher FEV_1 and FEV_1/FVC ratio associated with a lower likelihood or developing SAD (OR 0.17 (95% CI: 0.13-0.21) and OR 0.17 (95% CI: 0.14-0.21)

respectively, p<0.001 for both). In table 3.5, the univariate and multivariate regression is reported.

Table 3.5. The univariate and multivariate logistic regression for SAD.

Characteristic	Univariate			Multivariate		
	OR	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
Age	1.00	0.99-1.01	0.84			
Sex			0.069			
Female (Ref)	–	–		–	–	
Male	1.21	0.99-1.48				
BMI Groups			0.080			
Underweight (Ref)	–	–		–	–	
Healthy Weight	0.52	0.27-0.99				
Overweight	0.43	0.23-0.82				
Obese	0.44	0.23-0.84				
Severely Obese	0.52	0.26-1.05				
Smoking Status			**<0.001**			
Never Smoker (Ref)	–	–		–	–	
Previous Smoker	1.27	1.00-1.62		0.96	0.63-1.44	0.8
Current Smoker	2.33	1.75-3.10		1.20	0.74-1.94	0.5
FEV_1 z-score	0.17	0.14-0.20	**<0.001**	0.17	0.13-0.21	**<0.001**
FEV_1/FVC	0.16	0.14-0.19	**<0.001**	0.17	0.14-0.21	**<0.001**

Abbreviation: OR: Odds ratio, BMI: Body mass index, FEV_1: forced exhaled volume in the 1st second, FVC: Forced vital capacity, MMEF: Mid-maximal expiratory flow.

3.6 DISCUSSION

In this retrospective data analysis of 1829 patients with a diagnosis or a clinical suspicion of asthma, SAD as measured by MMEF was prevalent and associated with AO and smoking. There was a strong correlation between MMEF and FEV_1/FVC with the severity of SAD increasing as airflow obstruction worsened, defined by the FEV_1 z-score as described in the ARTP statement (Sylvester et al., 2020). These results are consistent with other studies, including the ATLANTIS study(Postma et al., 2019, Usmani et al., 2016a) where the prevalence of SAD also increased with asthma

severity (defined by GINA, but here have been applied in a real-world setting and with a larger cohort of patients.

This is likely to be of clinical relevance. Studies have shown that SAD is associated with clinical symptoms and poor control (Riley et al., 2016, Siroux et al., 2016). There are treatments which can target the small airways and there is increasing evidence that biological therapies impact positively on small airways inflammation (Zinellu et al., 2019). Measuring SAD should provide a means to objectively track small airways responses to therapies. Assessing the function of small airways provides an opportunity to identify these individuals and evaluate targeting SAD specifically as a therapeutic strategy.

Our study pragmatically chose MMEF as an indicator of SAD as it is readily available on spirometry reporting and hence does not require additional testing methodologies. There is controversy concerning the use of MMEF, with studies highlighting the variability in this test (Hansen et al., 2006, Quanjer et al., 2014b). For example, MMEF was considered not clinically useful in a large multicentre, retrospective analysis of unselected patients referred for lung function tests including those without lung pathology and those with a wide range of lung diseases. However, the analysis did not stratify the participants based on disease or specific clinical presentation (Quanjer et al., 2014b) and just because an indicator is not useful in an unselected cohort, it does not negate its use in a selected group. Recent study showed that MMEF can be a reliable index for assessing SAD, and that MMEF correlates with asthma features such as BDR and airway hyperresponsiveness (Qin et al., 2021). Further, another study of asthma patients reported increased nocturnal and persistent symptoms, more emergency room visits and a higher blood eosinophil count in those

with SAD defined by MMEF but no AO compared to those with normal lung function (Riley et al., 2016) indicating a pathological and therapeutic response association.

Recent studies have found that abnormal MMEF was associated with early disease manifestation in other lung diseases such as COPD (Stockley et al., 2017, Kwon et al., 2020), suggesting it reflects early airways disease. However, more studies will be needed to determine if there are shared inflammatory pathways between disease entities which account for the similar physiological findings.

Furthermore, it appears that females are more likely to develop SAD even in the absence of AO. Indeed, it was previously reported that females had an increased OR to develop SAD (OR 2.27; 95% CI 1.29–4.06) compared to males (Cottini et al., 2021). The majority of the sample was from the white race, however, it appears that Asians and those form the black race are more likely to develop SAD alone. This could be partially explained by a population based study that previously reported that SAD prevalence was 43.5% in people in China (Xiao et al., 2020).

It is possible that other physiological tests of small airways function are better to identify SAD in asthma. However, the reporting of small airways function is not currently well described in relevant guidelines or statements such as the ATS or the ERS (Knox-Brown et al., 2022, Almeshari et al., 2021b). Furthermore, there are differences in the methods for reported measurements, and normal ranges used for the interpretation of SAD which complicates their use. This is also true for MMEF. Some studies report the % predicted of MMEF, but for some patients, the LLN can be below 40% predicted (Quanjer et al., 2014b, Hansen et al., 2006). In general, the ARTP's statement for lung function supports the report of z-scores to prevent sex, age

and height biases and therefore z-scores are recommended as the standard unit and hence have been utilised here.

Our study has strengths, with the use of routinely collected data enabling a large number of patients to be assessed. There were limitations to this study. The pragmatic use of routinely collected data was associated with some missing data fields. The study lacked patient reported outcomes such as the ACT or asthma quality of life questionnaire (AQLQ). Data restrictions also prevented us stratifying severity using GINA criteria. Moreover, the medications data was limited to patient self-report and not by reviewing prescriptions. Nevertheless, the study provides evidence to support the measurement of SAD using small airways functions such as MMEF, especially in future studies with interventions targeting the small airways in asthmatics with symptoms and SAD, even in the absence of AO.

3.7 CONCLUSION

Small airways dysfunction is prevalent in asthma and is present in asthmatics without physiological evidence of AO. The MMEF is a pragmatic physiological tool to assess SAD. The MMEF and FEV_1/FVC are highly associated and should be evaluated along with symptoms and clinical presentation during clinical assessment. SAD prevalence increases with physiological evidence of AO. In asthmatics patients, smoking was associated with SAD. The relation between SAD, respiratory symptoms, patient reported outcomes and therapies that target small airways should be evaluated in future studies.

3.8 SUMMARY OF THE CHAPTER

This retrospective analysis of real-world data demonstrated the prevalence of SAD in asthma and that it is also found in the absence of physiological AO. Smoking was found to be a predictor of SAD. Those with physiological AO were more likely to have SAD. As SAD was demonstrated to be prevalent in asthma, in chapter 4, the bronchodilator repones in the small airways compared to FEV_1 will be evaluated by systematically reviewing the available literature.

CHAPTER 4

4. SMALL AIRWAYS RESPONSE TO BRONCHODILATORS IN ADULTS WITH ASTHMA: A SYSTEMATIC REVIEW

4.1 INTRODUCTION

The previous systematic review highlighted the potential utility of physiological tests of small airways function in the diagnosis of asthma. Bronchodilator responsiveness is also used in the diagnosis of asthma, and it is unclear whether tests of small airways function could be used to further delineate bronchodilator responses. This systematic review was conducted to review the evidence for tests of small airways in bronchodilator responsiveness in asthma and COPD. An abstract of this review was presented at the 2020 Winter meeting of the British Thoracic society and published in Thorax Journal (Almeshari et al., 2021a) (see appendix 8.4.1).

This chapter has also been published in full in the International Journal of Chronic Obstructive Pulmonary Disease, entitled "**Small airways response to bronchodilators in adults with asthma or COPD: a systematic review**" (Almeshari et al., 2021b) (see appendix 8.4.2). An exact copy of the work is provided below.

The work was performed in collaboration with fellow PhD student (Alobaidi NY) with author contributions described below.

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Authors Contribution:

M.A.A. and N.Y.A. designed and planned the study, performed the initial search and data extraction, assessed the eligibility of the included studies, performed the quality assessment for the included studies and wrote the initial manuscript. This was performed equally with tasks shared across authors. E.S. designed and planned the study and revised the manuscript. O.U. assisted in designing and planning the study. R.A.S. and J.A.S. revised the manuscript.

4.2 ABSTRACT

Background: Bronchodilator responsiveness (BDR) is commonly used in the diagnosis of lung disease. Although small airways dysfunction is a feature of asthma and COPD, physiological tests of small airways are not included in guidelines for BDR testing. This systematic review assessed the current evidence of BDR using small airways function in asthma and COPD.

Methods: The systematic review used standard methodology with the protocol prospectively registered on PROSPERO, (CRD42020164140). Electronic medical databases (EMBASE and MEDLINE) were searched using related keywords. Abstracts and full texts were screened independently by two reviewers. Studies that reported the change of physiological small airways function and FEV_1 were included in the review. The revised Cochrane risk of bias tool for RCT and NIH quality assessment tool for cohort and cross-sectional studies were used to evaluate the studies.

Results: 934 articles were identified, with 12 meeting the inclusion criteria. 10 studies included asthma patients, 1 study included COPD patients and 1 study included both asthma and COPD. A total of 1,104 participants were included, of whom 941 were asthmatic, 64 had COPD and 109 were healthy controls. Studies were heterogeneous in design including the device, dose and time intervals for BDR assessment. A small airway BDR was seen for most tests in asthma and COPD, including oscillometry (R5-20, reactance (X5), area of reactance (AX) and resonant frequency (Fres)) and Maximal Mid Expiratory Flow.

Conclusion: There is a measurable BDR in the small airways. However, with no consensus on how to assess BDR, studies were heterogeneous. Further research is

needed to inform how BDR should be assessed, its clinical impact and place in routine clinical practice.

Keywords: Asthma, COPD, bronchodilator, reversibility, small airways function.

4.3 BACKGROUND

Testing for bronchodilator responsiveness is currently included in the diagnosis of asthma and can help in differentiating asthma from other respiratory-related diseases such as Chronic Obstructive Pulmonary Disease (COPD) (Chhabra, 2013). The term ‘reversibility’ is often used but, in the 2019 spirometry standards update by the American Thoracic Society (ATS) and European Thoracic Society (ERS), the term ‘responsiveness’ was recommended, as ‘reversibility’ may imply fully reversing airways obstruction (Graham et al., 2019). The effort-dependent Forced Vital Capacity (FVC) manoeuvre is usually used in a pre- and post-bronchodilator assessment with the forced expiratory volume in the first second (FEV_1) as the index usually reported to assess airways responsiveness.

Evidence suggests that small airways dysfunction is prevalent in both asthma and COPD (Higham et al., 2019, Usmani et al., 2016a). Spirometry is the current gold standard to diagnose airways obstruction and Maximal Mid-Expiratory Flow (MMEF), also known as Forced Expiratory Flow between 25-75% of FVC (FEF_{25-75}), and occasionally called MEF and FEF_{50}, is the index parameter most commonly used to evaluate small airways function by spirometry (BTS/SIGN, 2019, Quanjer et al., 2014b, Graham et al., 2019). However, administering bronchodilators can change both the FEV_1 and the FVC directly so, as FVC influences MMEF, a volume adjustment is needed to accurately evaluate any response when using MMEF (Graham et al., 2019).

Short-acting beta2 agonists (SABA), such as salbutamol, are the most widely used bronchodilators for bronchodilator response (BDR) testing and are commonly delivered using a jet nebulizer or pressurized metered dose inhalers (pMDI) with a

spacer (Graham et al., 2019). However, there are many factors which can impact on the results of BDR testing and, currently, there is no consensus regarding the dose, technique or device used. The latest ATS/ERS guidelines released in 2019 suggest that this should be decided by the healthcare professional providing care (Graham et al., 2019). In a previous guideline of the ATS/ERS task force, it was highlighted that dose standardization was needed to determine reversibility/response cut-off values (Miller et al., 2005b).

The effectiveness of aerosolized medication and the BDR is dependent on the deposition in the lungs which, in turn, is dependent on multiple factors, including the concentration of the drug, technique of delivery and the size of particles (Coates et al., 2001, Newhouse, 1999). There is no gold standard for BDR testing regimens and the type of medication, dosage, and time delay for post-assessment can vary, leading to difficulty in comparing results, although doses between 200-400 mcg of salbutamol via pMDI are suggested (Molimard et al., 2005, Calverley et al., 2003, National Institute for Health Care Excellence (NICE), 2017). There are clear recommendations that patients should omit taking SABA for 4-6 hours before a baseline test; short-acting muscarinic antagonists (SAMA) for 12 hours before the test; long-acting beta2 agonists (LABA) for 24 hours before the test; Ultra-LABA for 36 hours before the test; long-acting muscarinic antagonists (LAMA) for 36-48 hours before the test (Graham et al., 2019).

Different criteria have been suggested to define a “significant” BDR but a change in FEV_1 of at least 160 mL is usually recommended due to the effort-dependent variability of the test especially following repeated measures (Tweeddale et al., 1987). Significant BDR is defined as a change of over 12% from the baseline FEV_1 and an

absolute increase of more than 200 mL by ATS/ERS (Pellegrino et al., 2005), and a change of over 15% from the baseline FEV_1 with an increase of 200 mL in volume by the British Thoracic Society (BTS) (British Thoracic Society, 1997).

Although BDR is thought to be important to differentiate between asthma and COPD, studies have indicated that it may not be discriminatory (Chhabra, 2005, Janson et al., 2019b). A BDR is seen in some patients with COPD, although this can have day-to-day variability (Albert et al., 2012, Tan et al., 2012). BDR may be important in the diagnosis and prognosis of asthma (Denlinger et al., 2016, Galant et al., 2011), but not all patients with diagnosed asthma have BDR. Nonetheless, in asthmatic patients with normal FEV_1, MMEF has been reported below normal values, indicating small airways dysfunction as part of the disease paradigm (Almeshari et al., 2020b). The usefulness of BDR in managing COPD patients is also unclear. Even in the absence of FEV_1 improvement, Vital Capacity and Inspiratory Capacity can increase following inhaled bronchodilator use and these improvements are reflected in reduced dyspnoea and increased exercise performance.(O'DONNELL et al., 2001, Schermer et al., 2007) This suggests that changes in FEV_1 may not be the only marker to capture a treatment response.

Studies using small airway tests to assess BDR have reported improvements in these lung function parameters post-therapy.(Wouters et al., 1989, Borrill et al., 2005) In COPD, there is evidence that small airways dysfunction might be the earliest pathological manifestation of disease (both pathologically and physiologically) and several studies reported a substantial loss of small airways or their function before the development of classical spirometric airflow obstruction.(Bosken et al., 1990, Hogg et al., 1968, Stockley et al., 2017)

In both asthma and COPD, inhaled extra-fine particle treatments have been developed specifically to target the smaller airways (Papi et al., 2018) and more novel treatment trials are in progress. Understanding whether bronchodilator response can be assessed using tests of small airways function (SAF) would be important for clinical trials and assessing patient response to treatments.

The objective of this systematic review was to evaluate the current evidence of small airways response to short-acting inhaled bronchodilators in adults with asthma or COPD. Moreover, to evaluate the effectiveness of methods used in delivering aerosolized bronchodilators to the small airways and their function.

4.4 METHODS

4.4.1 Protocol & sources of information & search strategy

The protocol was registered in PROSPERO (registration number CRD42020164140, complete protocol is found in appendix 8.4.3). The review was written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al., 2009) and the PRISMA checklist is provided in appendix 8.4.4. Through scoping, the following tests were selected to be included in the search, Forced Oscillometry (FOT), Impulse Oscillometry (IOS), Forced Expiratory Flow at 50% of FVC (FEF_{50}), Single Breath Washout (SBW) and Multiple Breath Washout (MBW). A complete searching strategy is provided in appendix 8.4.5.

4.4.2 Eligibility criteria (PICO)

Studies were considered for inclusion to the review if the selected small airways tests were conducted on adults diagnosed with either asthma or COPD, where both

FEV_1 and the change in small airways function due to BDR tests were reported. The eligibility criteria are detailed in table 4.1.

Table 4.1. The PICO (Population, Intervention, Comparator, Outcome) and Study Design for the Systematic Review

PICO	Inclusion criteria	Exclusion criteria
Population	Adult patients aged at least 18 years with a clinical diagnosis of Asthma or COPD	- Other chronic lung diseases such as cystic fibrosis. - Patients younger than 18 years old
Intervention	Small airways function (IOS, FOT, MMEF, FEF_{50}, MBW, SBW) response to BDR using short acting beta2 agonist (SABA) via various aerosol delivery devices.	
Comparator	BDR in conventional lung function (FEV_1)	
Outcome	Change in small airways function after administrating the bronchodilator therapy.	
Study design	Randomised Control Trials (RCT), Cohort, Cross-sectional, Longitudinal, Case-series >10 patients, Systematic reviews	Reviews, Editorials, Case series of <10 Patients, Case reports
Notes: The Systematic review included the following inclusion and exclusion criteria, as described above. **Abbreviations**: IOS, impulse oscillometry; FOT, forced oscillometry; FEV_1, forced expiratory volume in 1 second; MMEF, mean mid-maximal expiratory flow; FEF_{50}, forced expiratory flow at 50% of FVC.		

4.4.3 Study selection and data extraction:

Search results were imported into EndNote 9.1 (Clarivate Analytics) and duplicates were removed. The screening was conducted using Rayyan software(Ouzzani et al., 2016) to facilitate the screening between reviewers. Abstracts

were screened blindly and independently by MAA and NYA using the predefined inclusion and exclusion criteria. Disagreements were resolved through discussion. Full-text articles were obtained and imported into EndNote by MAA and similar abstract screening method was used in screening full texts for suitability.

Using a custom, piloted data extraction form, data were extracted by MAA and NYA and then compared for consistency and accuracy. SAF tests used to assess the BDR, dose of medication, time interval after bronchodilator administration, characteristics of populations, smoking history, and devices used to assess BDR were extracted to aid the narrative synthesis of the studies. The categorization of the studies was based on the SAF test and the disease (asthma and COPD).

4.4.4 Quality Assessment

The quality assessment of included studies was undertaken blindly by two independent reviewers. The revised Cochrane risk of bias tool for randomized controlled trials (RCT) was used to assess the quality and likelihood of bias in the RCT studies included, with the risk of bias classified as high, some concern or low for each study.(Sterne et al., 2019) The National Institute of Health (NIH) tool for quality assessment of cohort and cross-sectional studies was used to assess the quality of cohort and cross-sectional studies, with the quality classified as good, fair or poor. (National Heart and Lung and Blood Institute (NIH))

4.4.5 Data synthesis

Meta-analysis was considered where homogeneous results were provided. Otherwise, data were drawn into figures.

4.5 RESULTS

4.5.1 Study selection

Through the electronic search, a total of 934 abstracts were identified, of which 817 were screened in the full-text phase and a total of 12 studies met the inclusion criteria. A PRISMA flow chart is shown in figure 4.1.

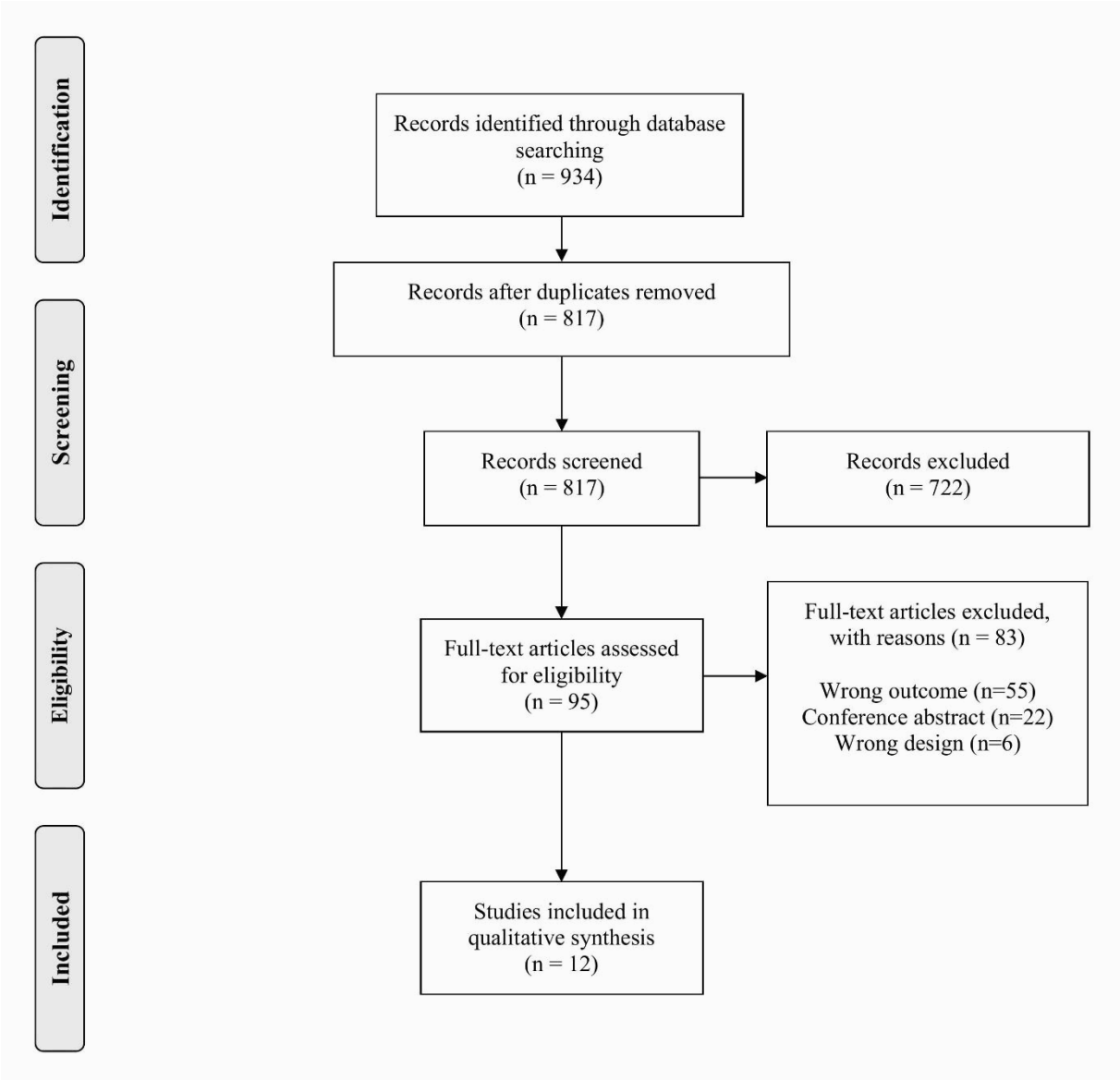


Figure 4.1. PRISMA flow chart showing the studies identification process from EMBASE and Medline databases.
This figure was adapted from (Moher et al., 2009)

4.5.2 Study Characteristics

Ten studies included patients with asthma,(El-Khatib et al., 2014, Fakharian et al., 2008, Lipworth and Clark, 1997, Mariotta et al., 2005, Nair et al., 2011a, Ohwada et al., 2011, Rajkumar et al., 2002, Schecker et al., 1993, Tavares e Castro et al., 2015, Yaegashi et al., 2007) one study included COPD patients,(Borrill et al., 2005) and one study included both asthmatic and COPD patients.(Park et al., 2019) The total number of the participants included from all studies was 1104, of whom 941 were asthmatic, 64 COPD patients and 109 healthy control subjects. Studies were conducted in different countries from three continents. Three studies were conducted in the United Kingdom, two in the United States, and one study in each of the following countries: India, Iran, Italy, Japan, Korea, Lebanon, and Portugal. In table 4.2, the main characteristics of each study are shown.

Table 4.2. Characteristics of included studies

Study ID	Population	n= (M/F)	Age	SABA /Dose	Aerosol Device	BDR Time	SAF test	SAF change	FEV_1 Change
Ohwada et al., 2011[a]	Asthma	45 (12/33)	36.8±10.2	salbutamol/ 200 mcg	pMDI + Spacer	15 min	MMEF(%)	6.7%±10.5	5.5%±8.1
							FEF_{50}(%)	33.3%±48.9	
Schecker et al., 1993[b]	Asthma	20(16/4)	44±18	Pirbuterol/ 0.4 mg	pMDI	60 min	MMEF(%)	44.6%±8.6	31.1%±4.8
					Autohaler		MMEF(%)	45.6%±7	32%±5.8
Fakharian et al., 2008[a]	Asthma	40(15/25)	43.1±12.99	Salbutamol/ 400 mcg	Asmyar (spacer)	10 min	MMEF(%)	16.3%±12.1	7.7%±5.1
							FEF_{50} (%)	13.5%±11.8	
		40(15/25)	43.1±12.99		Damyar (spacer)	10 min	MMEF(%)	16.1%±13.1	7.1%±5.9
							FEF_{50} (%)	14.4%±11.4	
Mariotta et al., 2005[a]	Asthma (Intermittent)	108(68/40)	29.4±5.22	Salbutamol/ 200 mcg	pMDI	20 min	MMEF(%)	19.3%±17.9	5.03%±4.6
							FEF_{50} (%)	18.65%±16.2	
	Asthma (Persistent)	183(88/95)	31.07±10.48				MMEF(%)	28.9%±23.1	8.65%±5.9
							FEF_{50} (%)	27.1%±20.9	
	Control	38(24/14)	30.9±9.36				MMEF(%)	18.26%±9.3	3.4%±2.8
							FEF_{50} (%)	15.2%±8.9	
Rajkumar et al., 2002[d]	Asthma	15(7/8)	31.8	Salbutamol/ 200 mcg	pMDI (Market Spacer)	NR	MMEF(%)	37.0%	19.0%
					pMDI (Homemade Spacer)		MMEF(%)	47.0%	22.7%
Castro et al., 2015[a]	Asthma (-reversibility)	50(18/32)	61.2±11.9	Salbutamol/ 400 mcg	pMDI + Spacer	10 min	MMEF(%)	5.3%±10.9	3.9%±5.1
	Asthma (+reversibility)	50(28/22)	56.1±15.6				MMEF(%)	39.4%±62.6	18.5%±11.8
El-Khatib et al., 2014[a]	Asthma (Group 1)	44(21/23)	51±14	Salbutamol/ 2.5 mg	SVN	15-30 min	MMEF(L/s)	0.5±0.6	0.2L±0.3
							FEF_{50} (L/s)	0.7±0.9	
	Asthma (Group 2)	44(22/22)	52±13				MMEF(L/s)	0.2±0.4	0.2L±0.3
							FEF_{50} (L/s)	0.3±0.7	
	Asthma (Group 3)	44(23/21)	53±8				MMEF(L/s)	0.1±0.1	0.2L±0.2
							FEF_{50} (L/s)	0.1±0.2	
Lipworth et al., 1997[c, e]	Asthma mild	10	31.7±8.7	Salbutamol/ 40mcg/kg	SVN	30 min	MMEF(L/s)	0.7 (0.0 to 0.1)	0.4L (-0.4 to 0.4)
	Asthma severe	10	52.9±15.2					0.3	0.4

	Control	10	20.6±1					0.7 (0.1 to 0.9)	0. 2 (-0.2 to 0.6)
Yaegashi et al., 2006[a]	Asthma	126(30/96)	45.1±13.9	Pirbuterol/ 0.8mg/	pMDI	30 min	R5(kPa/L/s)	-0.2±0.2	0.2L
							R5-R20(kPa/L/s)	-0.1±0.1	
							R20(kPa/L/s)	-0.1±0.1	
Nair et al., 2011[c]	Asthma	82(28/54)	48.7±16.51	Salbutamol/ 400mcg	Accuhaler DPI	15 min	R5(%)	-33.0% (-42.6 to -25.0)	6.3% (5.0 to 7.6)
							R20(%)	-20.1% (-27.8 to -12.4)	
							X5(%)	-72.9% (-249.6 to 103.8)	
	Control	61(27/34)	28.2±10.13				R5(%)	-14.9% (-19.9 to -9.9)	2.25% (1.6 to 2.9)
							R20(%)	-15.7% (-21.0 to -10.4)	
							X5(%)	40.1% (-91.4 to 171.7)	
Park et al., 2019[b]	COPD	40(36/4)	74.35±4.7	Salbutamol/ 200 mcg	pMDI	15 min	Fres(Hz)	−9.6%±2.1	6.3%±1.0
							R5(kPa/L/s)	−9.3%±1.8	
							R20(kPa/L/s)	−6.8%±1.6	
							R5-20(kPa/L/s)	−8.5%±1.6	
							X5(kPa/L/s)	−13.5%±3.2	
							AX(kPa/L/s)	−22.7%±4.5	
							MMEF(%)	8.3%±3.0	
	Asthma	30 (23/7)	74.70±4.84				Fres(Hz)	−15.3%±2.6	9.2%±1.9
							R5(kPa/L/s)	−12.7%±2.7	
							R20(kPa/L/s)	−6.4%±2.6	
							R5-20 (kPa/L/s)	−10.3%±2.6	
							X5(kPa/L/s)	−5.9%±7.3	
							AX(kPa/L/s)	−22.9%±7.3	

							MMEF(%)	NR	
Borrill et al., 2004[c]	COPD	24 (16/8)	63.6±7.1	Salbutamol/ 20 mcg	Dosimeter	15 min	R5(kPa/L/s)	- 9.0%(-14 to -4)	2.8%(0.8 to 4.9)
							R20(kPa/L/s)	-2.7%(-7 to -1.7)	
							X5(kPa/L/s)	-18.5%(-27.2 to -9.8)	
							Fres(Hz)	-11.1%(-15 to -7.2)	
							MMEF(L/s)	3.6%(-1.8 to 8.9)	
				Salbutamol/ 50 mcg			R5(kPa/L/s)	-16.7%(-22.5 to -10.8)	8%(5.2 to 10.4)
							R20(kPa/L/s)	-5.8%(-10.4 to - 2.2)	
							X5(kPa/L/s)	-32.0%(-47 to -16.9)	
							Fres(Hz)	-19.4%(-25 to -13.7)	
							MMEF(L/s)	12.9%(4.2 to 21.4)	
				Salbutamol/ 100 mcg			R5(kPa/L/s)	-16%(-23.3 to -8.6)	10.2%(7.4 to 12.9)
							R20(kPa/L/s)	-4.6%(-11.6 to 2.3)	
							X5(kPa/L/s)	-26.7%(-42.7 to -10.7)	
							Fres(Hz)	-17.9%(-23.3 to -12.4)	
							MMEF(L/s)	13.6%(5.2 to 22.1)	
				Salbutamol/ 200 mcg			R5(kPa/L/s)	-17.9%(-25.5 to -10.3)	11.9%(8.6 to 15.1)
							R20(kPa/L/s)	-6.2%(-13 to 0.6)	
							X5(kPa/L/s)	-28.6%(-45.9 to -11.3)	

							Fres(Hz)	-20.7%(-25.8 to - 12.4)	
							MMEF(L/s)	21.3%(11.1 to 31.6)	
				Salbutamol/ 400 mcg			R5(kPa/L/s)	-20%(-28.3 to -11.6)	13.7%(10.2 to 17.2)
							R20(kPa/L/s)	-7.4%(-13.9 to -0.9)	
							X5(kPa/L/s)	-32.8%(-48.8 to -16.8)	
							Fres(Hz)	-22.7%(-29.1 to -16.3)	
							MMEF(L/s)	19.3%(7.9 to 30.7)	
				Salbutamol/ 800 mcg			R5(kPa/L/s)	-22.4%(-29.3 to -15.4)	16.3%(12.2 to 20.4)
							R20(kPa/L/s)	-11.0%(-17.4 to -4.6)	
							X5(kPa/L/s)	-36.2%(-49.6 to -22.8)	
							Fres(Hz)	-23.3%(-29.0 to -17.5)	
							MMEF(L/s)	25.0%(11.8 to 38.2)	
							AX(cmH_2O)	−0.10±0.3	
							R15(cmH_2O)	−0.008±0.1	

Notes: For each study, the population, numbers of participants by gender, average age of participant, SABA used, device for BDR, time from delivery to measurement, small airway function test (SAF), change in that test and change in FEV1 is reported. Change in SAF and FEV_1 is reported in % predicted or in units as reported in the table.

[a] Changes reported in mean ± standard deviation (SD)

[b] Changes reported in mean ± standard error of mean (SEM)

[c] Changes reported in mean (95% CI)

[d] Mean was only reported for this study

[e] Measure of variance was not reported for severe asthmatic group

Abbreviations:

FEV_1, forced expiratory volume in 1 second; MMEF, mean mid-maximal expiratory flow; FEF_{50}, forced expiratory flow at 50% of FVC; Fres, resonant frequency; R5, resistance at 5 Hz; R20, resistance at 20 Hz; R5–20, resistance between 5 and 20 Hz; X5, reactance at 5 Hz; AX, area of reactance curve (between X5 and Fres); COPD, chronic obstructive pulmonary disease.

There were differences in the reported diagnostic criteria for asthma. In studies of asthma, four used Global Initiative of Asthma (GINA) guidelines(Mariotta et al., 2005, Ohwada et al., 2011, Tavares e Castro et al., 2015) and one study used a specific criterion (stable asthma who showed at least 15% BDR after SABA inhalation within 12-month prior starting the study).(Schecker et al., 1993) However, six of the studies that included asthmatic patients did not specify the diagnostic criteria.(El-Khatib et al., 2014, Fakharian et al., 2008, Lipworth and Clark, 1997, Nair et al., 2011a, Rajkumar et al., 2002, Yaegashi et al., 2007) In studies of COPD, the Global initiative for chronic obstructive lung disease (GOLD) criteria were used for COPD diagnosis (Borrill et al., 2005, Park et al., 2019). None of the included studies reported correction of MMEF in relation to FVC post-bronchodilation.

Only seven of the included studies defined the criteria for significance of BDR test. Those seven studies used the ATS/ERS criteria for defining significant BDR ($\geq$12% and $\geq$200ml)(El-Khatib et al., 2014, Mariotta et al., 2005, Nair et al., 2011a, Ohwada et al., 2011, Park et al., 2019, Tavares e Castro et al., 2015, Yaegashi et al., 2007) while in five, the criteria were not specified.(Borrill et al., 2005, Fakharian et al., 2008, Lipworth and Clark, 1997, Rajkumar et al., 2002, Schecker et al., 1993)

There were different methods used in delivering aerosolized medications. Eight studies used pMDIs, two used small volume jet nebulizers (SVN), one used dry powder inhalers (DPI) and one used dosimeter. None of the included studies reported the use of extra-fine aerosol delivery devices such as vibrating mesh nebulizers. Only two studies compared modalities of delivering bronchodilators, which was a comparison between spacers.(Fakharian et al., 2008, Rajkumar et al., 2002) One study compared two types of inhalers: a standard pMDI and an Autohaler (a breath-actuated

pMDI).(Schecker et al., 1993) All studies used SABA, of which 10 used salbutamol and 2 used pirbuterol. Dosages were also different between studies but mostly ranged between 200-400 mcg of salbutamol or equivalent. Tests used for assessing SAF were spirometry (MMEF, FEF_{50}) in 10 studies and oscillometry in four. None of the included studies reported using MBW or SBW technique.

There were also differences in reporting the outcomes of BDR response. Absolute change of the parameters was reported in three of the studies(El-Khatib et al., 2014, Lipworth and Clark, 1997, Yaegashi et al., 2007) whereas the change in % predicted in one study.(Nair et al., 2011a) The percentage of change was reported in eight studies,(Borrill et al., 2005, Fakharian et al., 2008, Mariotta et al., 2005, Ohwada et al., 2011, Park et al., 2019, Rajkumar et al., 2002, Schecker et al., 1993, Tavares e Castro et al., 2015) but most did not indicate if the percentage of change was derived from the absolute values or % predicted. Of the studies reporting percentage of a change, only two(Mariotta et al., 2005, Ohwada et al., 2011) reported the method of obtaining % change using absolute values with the following conventional formula: [(post-treatment – pre-treatment)/ pre-treatments] *100.

Meta-analysis was not considered feasible due to non-conformity of studies with respect to demographics, disease severity stages, methods used in delivering bronchodilators, drug type/dose, the time intervals between bronchodilation administration and tests differing between studies. A feature of all the studies, however, was the wide spread of patient responses, with large measures of variance across studies, suggesting marked heterogeneity between individuals and their responses.

4.5.3 Quality assessment

The revised Cochrane risk of bias tool was used for one study, which was the only RCT.(Schecker et al., 1993) Here, there was an overall high risk of bias, but there was a low risk of bias around deviation from the intervention or the measurement of the outcome.

The rest of the studies were assessed with the NIH tool for observational cohort and cross-sectional studies. The questions in all domains (D) of the NIH tool were answerable except that of D8, which relates to exposure to the outcome and was considered not applicable to the included studies. The assessment showed an overall good quality in 6 studies,(Borrill et al., 2005, El-Khatib et al., 2014, Ohwada et al., 2011, Park et al., 2019, Tavares e Castro et al., 2015, Yaegashi et al., 2007) fair quality in two(Mariotta et al., 2005, Nair et al., 2011a) and poor quality in three.(Fakharian et al., 2008, Lipworth and Clark, 1997, Rajkumar et al., 2002) A graph of NIH quality assessment is shown in appendix 8.4.6.

4.5.4 Result of individual studies

4.5.4.1 Spirometry (MMEF, FEF50) for asthma

Eight of the 12 studies reported BDR of MMEF, FEF_{50} or both in asthmatic patients. (El-Khatib et al., 2014, Fakharian et al., 2008, Lipworth and Clark, 1997, Mariotta et al., 2005, Ohwada et al., 2011, Rajkumar et al., 2002, Schecker et al., 1993, Tavares e Castro et al., 2015) Ohwada et al.(Ohwada et al., 2011) recruited 45 non-smoking patients diagnosed with asthma but treatment-naive. The BDR assessment was carried out using 200 mcg of salbutamol via pMDI and spacer. 15 minutes after inhaling the salbutamol, patients were reassessed. All results were reported as mean

and standard deviation (±SD). A non-significant change of 6.7±10.5% change in MMEF was described. In contrast, a significant change in FEF_{50} of 33.3±48.9 % was found and statistically significant (p = 0.001) as well as a 5.7±8.1% change (p = 0.004) in FEV_1. However, the change of FEV_1 did not meet the ATS/ERS criterion for significant BDR.

Schecker et al.(Schecker et al., 1993) assessed two types of inhalers to determine if device influenced the medication deposition or response; the standard pMDI and the Autohaler. Patients were tested on two separate days to assess consistency with both devices. Pirbuterol 0.4 mg was used as the bronchodilator and spirometry results were reported after 60 minutes. Similar changes in both devices were found for MMEF and FEV_1. A mean change in MMEF of 44.6±8.6% was reported using a standard pMDI and 45.6±7.0 using the Autohaler. Mean change in FEV_1 was 31.1±4.8% using a standard pMDI and 32.0±5.8 using the Autohaler, meeting ATS/ERS criteria for significant BDR for both inhalers, although there were no significant differences between the two devices for results for either MMEF or FEV_1.

Fakharian et al.(Fakharian et al., 2008) conducted a study to compare the BDR of 2 spacers (Asmyar and Damyar). The authors reported the change in MMEF and FEF_{50} 10 minutes after administering 400 mcg of salbutamol and included only non-smokers with mild to moderate asthma. The change in MMEF and FEF_{50} using Asmyar was 16.3±12.1% and 13.5±11.8%, respectively whereas, in Damyar, the change was 16.1±13.1% and 14.4±11.4%, respectively. The change in FEV_1 was reported to be 7.7±5.1% in Asmyar and 7.10±5.91% in Damyar. There were no differences between the spacers for any of the indices and subjects did not meet the ATS/ERS criteria for BDR in FEV_1.

Mariotta et al.(Mariotta et al., 2005) reported MMEF and FEF_{50} in asthmatic patients (with either intermittent or persistent symptoms) and control subjects. The 3 groups were tested for BDR with 200 mcg of salbutamol and had spirometry test assessed after 20 minutes. The authors reported a mean change in MMEF of 19.3±17.9%, 28.9±23.1% and 18.3±9.3% in intermittent, persistent and control, respectively. FEF_{50} change was reported to be 18.7±16.2%, 27.1±20.9% and 15.2±8.9% and FEV_1 change was reported to be 5.0±4.6%, 8.7±5.9% and 3.4±2.8% for the same groups. However, once again, the changes of FEV_1 did not meet the ATS/ERS criteria for BDR in any group.

Rajkumar et al.(Rajkumar et al., 2002) studied the difference between commercial and home-made spacers. Percentage of change in MMEF was reported after administering 200 mcg of salbutamol but the time to post-bronchodilator testing was not reported. In this study, although the mean % change was reported, measure of variance was not. The change of MMEF was 37.0% and 47.1% when using commercial spacers versus home-made, respectively. FEV_1 change was 19.0% and 22.7% for commercial and home-made spacers, respectively, which is (on average) above the 12% threshold of the ATS/ERS BDR criterion for both groups. There was no difference in response between the two spacers.

Castro et al.(Tavares e Castro et al., 2015) included asthmatic patients with a confirmed history of airway reversibility consistent with the ATS/ERS 2005 guidelines as well as matched asthmatic patients without evidence of airway reversibility. Smoking patients, those under 20 years of age and patients who had a recent exacerbation of asthma were excluded from the study. Salbutamol (400 mcg) was used to assess BDR, and testing was completed ten minutes post-bronchodilator. The mean

change (±SD) in MMEF in the patients with a history of reversibility was 39.4±62.6% opposed to those without reversibility 5.3±10.9%. The average FEV_1 change (±SD) was 18.5±11.8% and 3.9±5.1% in patients with reversible and non-reversible airflow, respectively, confirming that the group with previously noted reversibility once again met the ATS/ERS criterion for BDR as a % change.

Figure 4.2 summarizes these results by showing the average % change and the absolute change of MMEF and FEF_{50} in comparison to FEV_1 and FVC in asthmatic patients. For all studies, there was a greater average % change in tests of SAD than FEV_1.

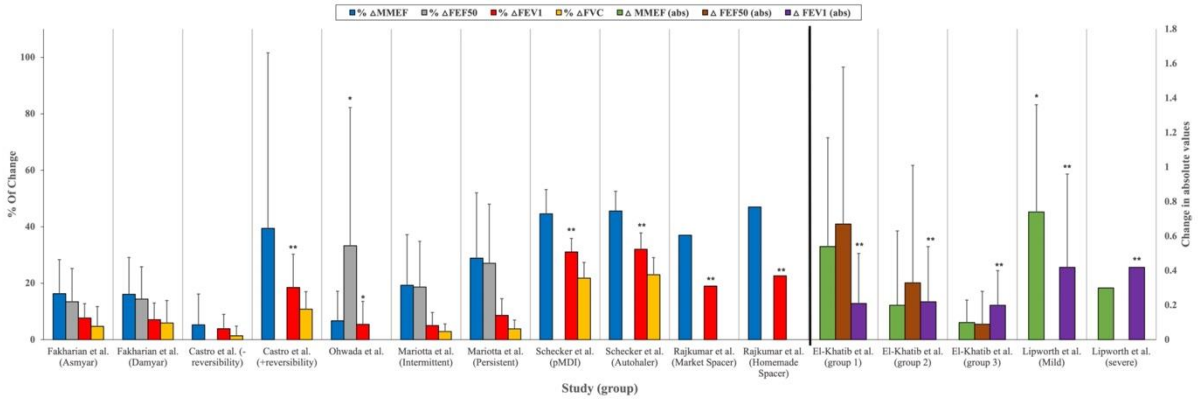


Figure 4.2. The average percentage of change and absolute change in MMEF, FEF_{50}, FEV_1 and FVC across asthma studies.
Legend. Left vertical axis is percentage of change in MMEF, FEF_{50}, FEV_1 and FVC in asthmatic patients. Right Vertical axis is absolute change in MMEF, FEF_{50}, FEV_1. Data presented are means ± standard deviation (SD).
Included data has been taken and adapted from Fakhrian et al., Castro et al., Ohwada et al., Mariotta et al., Schecker et al., Rajkumar et al., Elkhatib et al., and Lipworth et al. Measure of variances is not displayed in the error bars for Rajkumar et al. and severe asthmatic patients in Lipworth et al. because SD was not reported.
* = BDR is statistically significant.
** = BDR is clinically significant according to ATS/ERS criteria.

El-Khatib et al.(El-Khatib et al., 2014) designed a study to compare the effectiveness of using Heliox to reduce viscosity compared to medical air when nebulizing bronchodilators. The authors randomized asthma patients in a cross-over

design so that each patient received albuterol 2.5mg using one or other method for nebulization on 2 different days, (thus acting as their own control). Patients were grouped based on their baseline FEV_1 results (all % predicted: $\geq$80 % (Group 1), <80% to >50 % (Group 2) and $\leq$50 % (Group 3)) and absolute values of change were reported. Using medical air, mean changes of 0.54L/s±0.63 in MMEF and 0.67L/s±0.91 in FEF_{50} were reported in group 1. In group 2, a mean change in MMEF and FEF_{50} were 0.20L/s±0.43 and 0.33L/s±0.68, respectively. In group 3, mean changes in MMEF and FEF_{50} were 0.10L/s±0.13 and 0.09L/s±0.19, respectively. The mean change of FEV_1 was reported to be 0.21L±0.29 in Group 1, 0.22L±0.32 in Group 2 and 0.20L±0.20 in Group 3 which, on average, met the ATS/ERS criteria for significant BDR in all groups.

Lipworth et al.(Lipworth and Clark, 1997) conducted a study to assess the lungs' absorption of nebulized salbutamol (using a weight adjusted dose of 40mcg/kg) with lung physiology measured at baseline and 30 minutes after treatment. The authors recruited participants with mild and severe asthma as well as healthy controls. Thirty participants were included, with 10 in each group. Of note, 95% confidence intervals were only reported for the healthy controls and mild groups, with no explanation as to why these data were omitted in the severe asthma group. The mean change of MMEF in L/s (95% CI) was reported as 0.74 (0.04 to 0.93) in mild patient, 0.30 in severe patients and 0.69 (0.09 to 0.88) in the control group. The mean change in FEV_1 (95% CI) was 0.42L (−0.38 to 0.39) in mild patients, 0.42L in severe patients and 0.22L (−0.18 to 0.59) in the control group, meeting average ATS/ERS criteria for significant BDR in all groups. In figure 4.2, the mean change of MMEF (L/s) and FEF_{50} (L/s) in

comparison to FEV_1 (L) is shown in the asthmatic patients from the studies by El-Khatib et al. and Lipworth et al.

Across all studies in asthma, BDR as measured using small airways tests appeared to show a greater difference than FEV_1 (especially in milder disease) but had higher variability. In studies that assessed BDR in asthmatic subjects, only 5/10 studies met the ATS/ERS criteria for BDR of FEV_1.(El-Khatib et al., 2014, Lipworth and Clark, 1997, Rajkumar et al., 2002, Schecker et al., 1993, Tavares e Castro et al., 2015)

4.5.4.2 Spirometry (MMEF, FEF50) for COPD

Two studies reported BDR using MMEF in COPD patients.(Borrill et al., 2005, Park et al., 2019) Borrill et al.(Borrill et al., 2005) recruited 24 patients with COPD to compare IOS, airway resistance measured by body plethysmography and spirometry (including MMEF) to find the most reliable method for evaluating BDR. In this study, short-acting bronchodilators, long-acting beta2 agonists and tiotropium were withheld for 6 hours, 12 hours and 24 hours, respectively prior to the study day. Salbutamol (administered via dosimeter) was given in ascending doses of 20mcg, 50mcg, 100mcg, 200mcg, 400mcg and 800mcg, to assess the BDR and lung function was reassessed 15 minutes after each dose. In this study, MMEF showed statistically significant improvements ($p < 0.05$) at doses of 200mcg and 400mcg with mean (95% CI) of 21.3% (11.1 to 31.6) and 19.3% (7.9 to 30.7), respectively. In contrast, the mean change of FEV_1 showed statistically significant improvement ($p < 0.05$) starting from a dose of 100mcg, showing % change of 10.2% (7.4 to 12.9) and 11.9% (8.6 to 15.1) after a dose of 100mcg and 200mcg, respectively. However, the ATS/ERS criteria for significant BDR with FEV_1 were only met at a dose of 400mcg and 800mcg: average

13.7% (10.2 to 17.2) and 16.3% (12.2 to 20.4), respectively. Figure 4.4 summarizes these % changes in MMEF and FEV_1 using the different doses of salbutamol.

A recent prospective study by Park et al.(Park et al., 2019) was conducted to assess BDR using IOS compared to spirometry in 40 elderly patients with COPD. In this study, patients were required to have no change in their prescribed medications for at least 4 weeks before the study but there were no details of when or if medications were paused prior to measurements. Albuterol was administered as two puffs of 100mcg via pMDI to assess BDR and the time interval between the inhalation and post-bronchodilator measurements was 15 minutes. The authors performed IOS before spirometry in all patients. In this study, the COPD patients were compared with 30 asthmatic patients and MMEF (referred to in the study as FEF_{25-75}) was also used to assess the BDR. Following administration of albuterol, the mean change in MMEF was 8.6% (SEM 3.0). The mean change in FEV_1 of 6.3% predicted (1.0 SEM) did not reach the ATS/ERS criteria for BDR. It was not reported if any changes reached statistical significance.

4.5.4.3 Oscillometry (R5, R5-20, X5, AX, Fres) for asthma

Three studies reported the BDR using oscillometry.(Nair et al., 2011a, Park et al., 2019, Yaegashi et al., 2007) Yaegashi et al.(Yaegashi et al., 2007) retrospectively analysed data from asthmatic patients who underwent both spirometry and oscillometry. Patients with COPD or any other disorder of airflow obstruction that was not diagnosed as asthma were excluded as were patients with a smoking history of more than 10 pack years. Pirbuterol 0.8 mg was administered via pMDI, but spacer use was not reported. BDR tests were carried out 30 minutes after the administration

of the bronchodilator. The mean change (±SD) was reported in kPa/L/s to be (-0.16±0.16, -0.06±0.11, -0.06±0.08) in resistance at 5Hz (R5), R5-20 (the difference between R5 and R20) and resistance at 20Hz (R20), respectively. Statistical analysis was not performed to assess the relevance of the changes. Changes in other common oscillometry parameters such as reactance at 5Hz (X5) were not reported. The mean change in FEV_1 was 0.20±0.25L, meeting average ATS/ERS criteria for significant BDR.

Nair et al.(Nair et al., 2011a) conducted a study to compare the BDR in asthmatic and healthy controls using spirometry and oscillometry before and 15 minutes after using Salbutamol 400 mcg delivered via an Accuhaler (DPI). In the asthma group, the mean % change (95% CI) after administering salbutamol was -33.8 (-25.0 to -42.6), -20.1 (-12.4 to -27.8) and -73.0 (-103.8 to -249.7) in R5, R20 and X5, respectively. In the control group, the mean % change (95% CI) was -14.9 (-10.0 to -19.9), -15.7 (-10.4 to -21.0), and 40.09 (171.7 to -91.4) in R5, R20 and X5, respectively. A mean % change (95% CI) of 6.34% (7.6 to 5.0) in FEV_1 in the asthma group and 2.3% (3.0 to 1.6) in the healthy controls were found, thus not meeting ATS/ERS criteria for significant BDR. Baseline values and post-bronchodilator values were reported as % predicted. The change was reported as the percentage of change of from baseline in both oscillometry and spirometry.

In Park et al.(Park et al., 2019), authors also recruited 30 elderly patients with asthma. BDR was reported as the mean (±SEM) percentage of change in the absolute values for the following IOS parameters; resonant frequency (Fres), R5, R20, R5-20, X5 and area of reactance (AX). Results were as follows: −15.3% ± 2.6 in Fres, −12.7% ± 2.7 in R5, −6.4% ± 2.6 in R20, −10.3% ± 2.6 in R5-R20, −5.9% ± 7.3 in X5, and

−22.9% ± 7.3 in AX. In comparison, the % change in FEV_1 was reported as 9.2%±1.9.

In Figure 4.3, a bar chart of the percentage of change is provided.

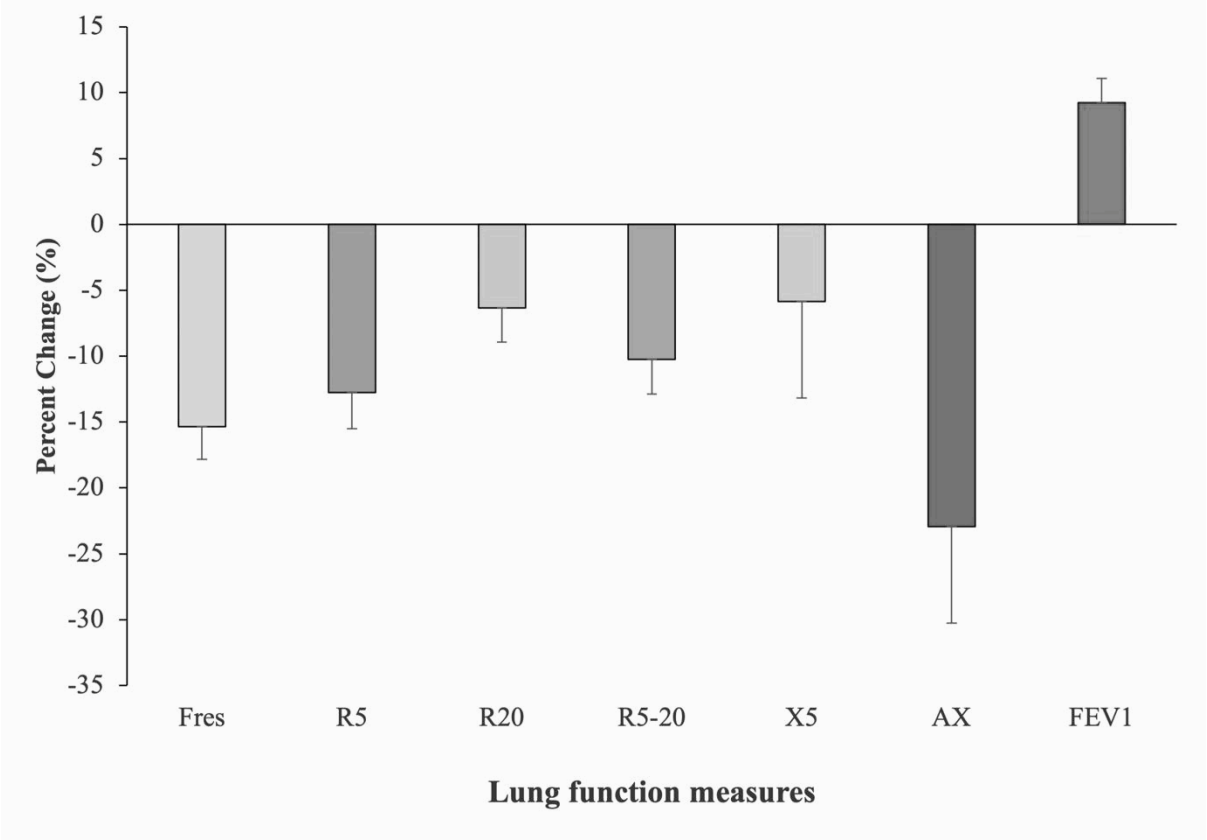


Figure 4.3. The percentage of change of IOS parameters and FEV_1 in Asthmatic patients following BDR.
Legend: Vertical axis is percentage of change in oscillometry parameters in comparison to FEV_1 in asthmatic patients. Data is adapted from Park et al.(Park et al., 2019)
Data presented in the figure are the mean % change (± standard error of mean (SEM))
Abbreviations: X5, reactance at 5 hertz; Fres, resonant frequency; R5, resistance at 5 hertz; R20, resistance at 20Hertz; R5-20, the difference between R5 and R20; AX, area of reactance; FEV_1, forced expiratory volume in 1 second

4.5.1.1 Oscillometry (R5, R5-20, X5, AX, Fres) for COPD

Two studies reported BDR using oscillometry in COPD patients.(Borrill et al., 2005, Park et al., 2019) Borrill et al.(Borrill et al., 2005) compared different lung function tests to determine the most reliable method for identifying BDR in COPD. In this study, IOS parameters R5, R20, X5 and Fres (abbreviated in the study to RF) were evaluated

following the administration of ascending doses of salbutamol. X5 and Fres showed statistically significant improvements after 20mcg, but only after 50mcg in R5. Although R20 showed changes at all doses, they were not statistically significant (see table 2). The changes of IOS parameters showed significant improvements across several doses, as shown in figure 4.4. As described previously, FEV_1 also showed statistically significant changes after 100mcg but only met the ATS/ERS criteria for significant of BDR after 400mcg and 800mcg. In this study, all IOS parameters showed higher variability compared to FEV_1, with Fres being the least variable.

As previously described, Park et al.(Park et al., 2019) conducted a prospective study to assess the use of IOS in demonstrating BDR and its role as an alternative to spirometry in 40 patients with COPD. The authors reported Fres, R5, R20, R5-20, X5 and AX. In this study, although statistical significance for the changes was not reported, IOS parameters showed notable mean % change. The mean % change (SEM) for X5, AX and Fres was -13.5 (3.2), -22.7 (4.5) and -9.6 (2.1), respectively. The mean % change (SEM) for R5, R20 and R5-20 was -9.3 (1.8), -6.8 (1.6) and -8.5 (1.6), respectively. In contrast, FEV_1 had a mean % change of 6.3 (1.0), although the ATS/ERS BDR significance level was not met (see figure 4.4).

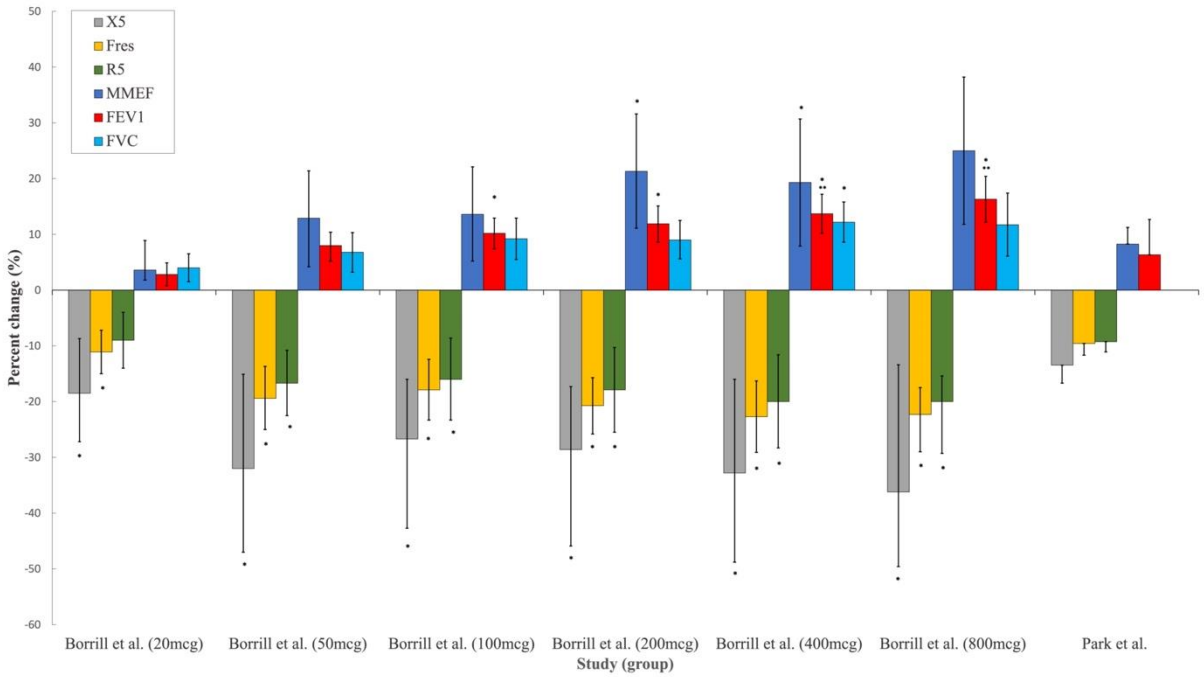


Figure 4.4. The percentage of change in spirometry indices (MMEF, FEV_1, and FVC) and in oscillometry indices (X5, Fres, and R5) in COPD patients.

Legend. Vertical axis is percentage of change in spirometry indices and oscillometry indices across different doses of salbutamol Borrill et al. Data presented in the figure are mean (95% CI) for Borrill et al. and mean and standard error for Park et al.

* = BDR is statistically significant.

** = BDR is clinically significant according to ATS/ERS criteria.

Abbreviations: MMEF, mean mid-maximal expiratory flow; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; mcg, microgram. X5, reactance at 5 hertz; Fres, resonant frequency; R5, resistance at 5 hertz; FEV_1,

4.6 DISCUSSION

To the best of our knowledge, this the first systematic review to consider evidence for tests of SAF to assess BDR in asthmatic and COPD patients. The studies included varied in design and patient demographics. In most of the studies, the diagnoses of asthma and COPD followed GINA and GOLD criteria, although the diagnostic criteria were not formally reported in other studies. There was heterogeneity of the small airways tests used, the devices, and the reported outcomes. Furthermore, in most of the studies, different bronchodilators, delivery systems, doses, interval times and measurements were used. Hence, it is challenging to draw any conclusion to

address whether tests of small airways could be used in the assessment of BDR. Moreover, the high study heterogeneity prohibited a meta-analysis.

In general, there is no clear consensus on how BDR tests should be conducted despite a number of published guidelines. Indeed, most of the studies included in this review had different methodologies for assessing BDR, which limits the certainty of evidence. As there are specific cut-off values for BDR significance, there should be a clear test procedure including aerosol device, time between tests, medication, and dosage. Moreover, the criteria of reporting the change are not clear. The ATS guidelines suggests reporting the absolute change and percentage of change but did not indicate where the percentage is derived i.e. % predicted or absolute values.(Graham et al., 2019) In the latest Association for Respiratory Technology & Physiology (ARTP), UK statement on pulmonary function testing, it was highlighted that there are six different methods for calculating the BDR change.(Sylvester et al., 2020) Nevertheless, it was proposed that the use of z-score or change of % predicted should be used as it may avoid age, height, and sex bias of the results.(Sylvester et al., 2020)

In six of the studies,(El-Khatib et al., 2014, Fakharian et al., 2008, Mariotta et al., 2005, Ohwada et al., 2011, Tavares e Castro et al., 2015, Yaegashi et al., 2007) means were reported despite the data being clearly skewed, weakening the evidence presented in this review. This variance is due to the inherent variability of SAF tests and to the effort-dependence in spirometry. In such cases, median and interquartile range should have been used.

Current asthma guidelines, such as the BTS and GINA include BDR of FEV_1 to diagnose asthma and differentiate it from other respiratory diseases such as COPD.

However, the criteria to identify BDR (>12% and >200 mL) in FEV_1 is not always observed in asthmatic patients (Janson et al., 2019b). In addition, this level of BDR has also been reported in patient with COPD (Janson et al., 2019b). Furthermore, the assessment of BDR using FEV_1 demonstrates high inter-patient and intra-patient variability in asthmatic and COPD patients, limiting its specificity or sensitivity in discriminating COPD from asthma (Kesten and Rebuck, 1994, Han et al., 2010). It has been proposed that the use of grading in assessing the BDR is more valuable than using a simple cutoff value as evidence shows that BDR relates to clinical outcomes such as exacerbation rates or quality of life (Ioachimescu et al., 2021, Hansen et al., 2019). FEV_1 is considered an assessment of larger airways function, although it can reflect major small airway dysfunction/loss. Evidence shows that small airways are affected in asthma (Dandurand et al., 2019) and dysfunction at this site increases with GINA-based severity (Fabbri et al., 2003, Postma et al., 2019).

The reported studies suggested differences in BDR between larger and small airways, depending on disease severity. In general, in mild to moderate disease, small airways showed greater BDR expressed as a change in L/s than overall airways (assessed by FEV_1 in L). In severe cases, a different pattern was seen with larger airways reflecting higher BDR, suggesting a fixed obstruction, loss of the small airways or a decrease in aerosol delivery to the small airways due to an increased obstruction in the large airways. These findings also align with the hypothesis that small airways are affected early (Jiang et al., 2019) in obstructive lung diseases and SAF tests should, therefore, be considered in their assessment.

In the studies of asthmatic patients, higher variance in BDR results were seen most in MMEF and FEF_{50} compared to FEV_1. Therefore, the variability seen in studies

using MMEF and FEF_{50} may impose a challenge to implement these measures in the assessment of BDR. Moreover, when assessing the BDR in MMEF, current guidelines suggest correction to the FVC (which influences the MMEF) (Graham et al., 2019), yet none of the included studies have reported this correction. The need to correct MMEF to FVC makes its use in the BDR assessment challenging.

As for FEV_1, obtaining MMEF and FEF_{50} requires a maximal inspiration followed by a forced maximal expiration, which is effort-dependent and the maneuver itself can result in changes in airway tone.(Suzuki et al., 1990, Froeb and Mead, 1968) Oscillometry can overcome this limitation, as this test is effort-independent. In asthmatic patients, oscillometry showed a decrease in all resistance parameters (R5, R20, R5-R20, relating to total, large and small airways resistance, respectively) after the administration of a bronchodilator. The greatest change seen was in the total resistance (R5) in the two studies that reported this technique in asthma, indicating the reversibility nature of the airways in asthmatic patients including the small airways. However, there are inconsistencies in how results are reported. For example, Nair et al,(Nair et al., 2011a) reported only the % of predicted values for oscillometry, leading to some values being >400% and limiting the ability to compare these results to other published literature which have used different parameters.

In COPD, IOS was used in two studies, demonstrating BDR and improvement in X5, R5, Fres, R5-20 and AX, with X5 and AX showing the most pronounced improvements compared to other IOS parameters. In the study by Borrill et al.(Borrill et al., 2005) the % change of R5, X5, and Fres was greater than FEV_1 across all doses given to patients but there was not data to support the clinical implications of the changes seen. In the study by Park et al.,(Park et al., 2019) all IOS parameters

(including R5-20) demonstrated greater % changes compared FEV_1, with the greatest seen in AX and X5. In this study, however, the changes of IOS parameters were lower compared to the findings in Borrill et al., which may be because of differences in aerosol delivery methods (pMDI vs Dosimeter) or differences in patient demography with this study including an older population. In oscillometry, higher oscillation frequencies (>15Hz) do not penetrate the small airways, which play a central role in the pathophysiology of COPD.(Bosken et al., 1990, Hogg et al., 1968) As resistance at higher frequency relates to the larger airways it was shown to be unrelated to the obstruction in COPD and explains why R20 did not show significant changes in these studies. The changes of X5, AX and Fres may be associated with the improvement of small airway patency, resulting in a reduction in hyperinflation and, hence, lung volume, consequently leading to an increase in lung compliance.

In summary, these studies suggest that oscillometry may detect significant BDR that is not detected by changes in FEV_1. However, in the study by Borrill et al.,(Borrill et al., 2005) IOS parameters had both a higher within test and within day variability than FEV_1 and, therefore, were less reproducible. In this study, only 24 COPD patients were included, and further larger studies are needed to determine the variabilities of these measurements. In general, oscillometry lacks knowledge of sensitivity as well as the reference ranges for multi-ethnic adults(Oostveen et al., 2013). Moreover, using different devices may affect oscillometry results.(Dandurand et al., 2019) Although new oscillometry devices can separate inspiratory and expiratory parameters (which may provide an evaluation of expiratory flow limitation), oscillometry is relatively expensive compared to spirometry and may require training. Therefore, these limitations may generally hinder the utilization of oscillometry in clinical practice. Although some

studies have suggested different BDR threshold for some oscillometry parameters,(Oostveen et al., 2013, Houghton et al., 2004, Houghton et al., 2005) the evidence of recognized BDR guidelines is still lacking. Thus, oscillometry is less attractive for BDR assessment compared to traditional spirometry measures (FEV_1 and FVC), which has been solely used and engrained into clinical practice.

Although the systematic protocol did not plan to assess the differences in BDR between asthma and COPD, Park et al.(Park et al., 2019) compared BDR by IOS for COPD and asthmatic patients with no statistical differences found between these groups. However, findings are limited as, firstly, due to the narrow demography of included patients (older than 70 years in both groups), which might impede discrimination between the two diseases.(Fabbri et al., 2003) Secondly, in the post-hoc analysis, they grouped asthma and ACOS together despite the clinical differences between the conditions,(Tommola et al., 2017) meaning it is not possible to draw conclusions on the comparison of BDR in asthma versus COPD.

4.6.1 Limitations and implication for research and clinical practice

This systematic review is limited by the small number of included studies, the differences in studies design, the use of different small airway tests and the different outcomes reported. Other differences also limit the evidence presented in this review, such as the use of different medications, doses, drug delivery devices and time interval to testing. Many factors have been reported that may alter the deposition of aerosolized drugs and there are differences in efficiencies among them.(Ari, 2014) Time interval between bronchodilator administration and testing has been reported to be an important aspect in assessing the lung function(Cavallazzi et al., 2020) and yet there is no consistency between the studies reported here. Collectively, these limitations

make comparison across the included studies impossible. Studies also did not report the demographics of participants in detail, with most not reporting ethnicity. We found that there is a statistically significant BDR demonstrated for both the small and larger airways in both asthmatic and COPD patients, but the implications are obscure. More research is needed to assess and quantify the response to extra-fine particle bronchodilators that are thought to have a greater role in the peripheral airways. However, there is a real need to define the sensitivity of the tests and, moreover, to understand what is a clinically important change for tests of SAF. This would include further assessment of whether/when agreed BDR in small airways might be important and associated with a demonstrable clinical or research benefit. Furthermore, asthma and COPD are both heterogeneous diseases in terms of pathology, clinical phenotype, and disease progression. Therefore, it is possible that small airway responsiveness in COPD may identify a subgroup of patients, namely those with patent though impaired small airways rather than those who have lost small airways. Such patients could be managed differently as they are likely to have increased therapeutic benefit using bronchodilators.

4.7 CONCLUSION

In asthma and COPD, there is evidence supporting the potential use of BDR measured using tests of SAF. However, the evidence to date is limited by the lack of consensus as to which bronchodilator should be used, at what dose, by which delivery mode, the time interval between drug administration, how to report BDR test results and the clinical impact of any change (minimal clinically important difference). Oscillometry is effort-independent and, hence, could be a method of choice but it

remains limited due to the lack of reference ranges for multi-ethnic adults, variability, and sensitivity to change as well as limited knowledge on the clinical impact with respect to a significant BDR. MMEF is highly variable but has shown some potential, especially in mild asthma but is unlikely to be clinically useful in assessing BDR without the recommended isovolumetric correction, which is a far more specialized technique. Oscillometry may also be useful, particularly for patients who are unable to perform spirometry, but the difference in hardware, the use of different frequencies (in the higher range) and the different units in which the parameters are reported are all major challenges in the development of standardized guidelines for assessing BDR. Moreover, SAF techniques that are not integral to basic spirometry require additional costs that are usually much higher than the cost of a spirometer. For these reasons, tests of SAF are currently less attractive for the assessment of BDR than the traditional spirometry parameters FEV_1 and FVC, which are deeply ingrained in general clinical practice. There is a need for robust evidence of a clear benefit to using SAF tests instead of or as an adjunct to the FEV_1 along with published guidelines that define a significant BDR before there is any chance of their adoption into routine practice.

4.8 SUMMARY OF THE CHAPTER

Measures the small airways exhibited higher BDR than conventional larger airways (i.e. FEV_1). This highlighted the importance for assessing the small airways in patients with asthma as well as targeting them for therapeutical purposes. Lack of standardisation of how BDR testing is conducted and how it is reported limited our understanding of how this current evidence. In chapter 5, the BDR for the small

(MMEF) and the large (FEV_1) airways was conducted and the predictors of a positive BDR for FEV_1 and MMEF was evaluated.

CHAPTER 5

5. SMALL AIRWAYS DYSFUNCTION AND THE BRONCHODILATOR RESPONSE OF THE SMALL AIRWAYS AND ITS ASSOCIATION WITH CONVENTIONAL BRONCHODILATOR RESPONSE IN ADULTS WITH ASTHMA: A REAL-WORLD RETROSPECTIVE ANALYSIS

5.1 INTRODUCTION

The previous systematic review of chapter 4 highlighted the presence of small airways response to bronchodilators in patients with asthma compared to conventional large airways. The Bronchodilator response (BDR) is acknowledged as the hallmark of asthma and has been previously recommended as the tool for confirming the diagnosis of asthma. However, it is uncertain how tests of small airways function are related to BDR. In this retrospective analysis of real-world data, the BDR in the small airways and conventional large airways were evaluated. Moreover, the BDR in those with small airways dysfunction and airflow obstruction at baseline were evaluated. This work has been partly published in abstract form at the 2021 American Association for Respiratory Care (AARC) Congress and published in Respiratory Care (RC) Journal (Almeshari et al., 2021a) (see appendix 8.5.1).

This chapter is being prepared for submission along with chapter 3 to a peer-reviewed journal.

The work was performed in collaboration and the authors' contributions are described below.

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Authors Contribution:

M.A.A. designed and planned the study, performed data analysis and visualisation and wrote the manuscript. E.S. designed and planned the study and revised the manuscript. N.Y.A. assisted in data analysis. J.A.S. and R.A.S. revised the manuscript.

5.2 ABSTRACT

Background: Asthma is a heterogeneous disease that is characterised by airflow obstruction. One hallmark of asthma is the bronchodilator response (BDR), which is usually measured using the forced expiratory volume in the first second (FEV_1). There is increasing interest in small airways dysfunction (SAD) in asthma, and the potential utility of measuring the small airways response to bronchodilators. This chapter aimed to assess the involvement of the small airways in the BDR.

Methods: A retrospective analysis of routinely collected health data obtained from adults with asthma or a clinical suspicion of asthma referred for routine spirometric assessment. Demographic data and pre-bronchodilator data assessed the prevalence and associated factors for SAD (categorised using Maximal Mid-Expiratory Flow (MMEF) z-scores). Pre and post-bronchodilator data were used to assess the BDR of both small airways and conventional spirometric indices in patients with and without SAD and airflow obstruction (AO).

Results: A total of 2328 records were screened, of which 329 unique patients with baseline and BDR records were included. Those with SAD at baseline had an OR of 4.50 (95% CI: 2.68-7.76) for having a positive BDR for FEV_1. All those with a positive BDR for FEV_1 had a positive BDR for MMEF. There was a weak negative correlation (R^2= 0.22, p <0.001) between the MMEF baseline z-score and FEV_1 BDR.

Conclusion: In asthma, SAD is associated with a positive BDR for FEV_1 and the BDR was seen not only in FEV_1 measurements, but also in MMEF. This further supports the involvement of the small airways in the disease process and questions whether

measurements of small airways function should be incorporated into routine clinical practice.

5.3 BACKGROUND

Asthma is a common, chronic, and heterogenous disease which is characterised by variable airflow limitation. The hallmark of asthma, as opposed to other chronic respiratory diseases, is the bronchodilator response (BDR). The BDR is considered the standard physiological and objective assessment for asthma and is also used to help in differentiating asthma from other respiratory-related diseases such as Chronic Obstructive Pulmonary Disease (COPD) (Chhabra, 2013). The term 'reversibility' was initially used when describing a response to bronchodilator therapies, however, in the 2019 spirometry standards update by the American Thoracic Society (ATS) and European Thoracic Society (ERS), the term 'responsiveness' was recommended, as 'reversibility' may imply fully reversing airways obstruction (Graham et al., 2019).

Spirometry is the most commonly used measure for assessing BDR. The Forced Vital Capacity (FVC) manoeuvre is usually used in a pre- and post-bronchodilator assessment with the forced expiratory volume in the first second (FEV_1) as the index and reported to assess airways responsiveness. No current guideline reports the utilisation of small airways indices such as Maximal Mid-Expiratory Flow (MMEF) for assessing BDR.

Short-acting beta2 agonists (SABA), such as salbutamol, are the most widely used bronchodilators for BDR testing and are commonly delivered using a jet nebulizer or pressurized metered dose inhalers (pMDI) with a spacer (Graham et al., 2019). Although several factors could impact the BDR testing such as type of device, dosage, or technique, there is no clear consensus on how BDR assessment should be carried

out. Indeed, the 2019 ATS/ERS pulmonary function testing guidelines suggested that this should be decided by the healthcare professional providing the care (Graham et al., 2019). The lack of standardisation in BDR testing was highlighted as a problem in the 2005 ATS/ERS task force, which stated that dose standardisation was needed to determine optimal response points (Miller et al., 2005b).

Several criteria have been suggested to define a significant BDR for FEV_1. However, a change for FEV_1 of at least 200 mL and >12% is frequently recommended due to the effort-dependent variability of the test especially following repeated measures (Tweeddale et al., 1987). This was also recommended by ATS/ERS pulmonary function guidelines published in 2005 (Pellegrino et al., 2005). The British Thoracic Society (BTS) defines a significant BDR for FEV_1 with a change of over 15% from the baseline and an increase of 200 mL in volume (British Thoracic Society, 1997).

Clinically, BDR is sometimes used to differentiate between asthma and COPD, however, studies have indicated that it may not be discriminatory (Chhabra, 2005, Janson et al., 2019b). A positive BDR can be found in patients with COPD (Albert et al., 2012, Tan et al., 2012). The BDR test has been highlighted to be important in the diagnosis and prognosis of asthma (Denlinger et al., 2016, Galant et al., 2011), however, some asthmatics patients may not have a positive BDR. In chapter 2, it was found that asthmatic patients with normal FEV_1 had lower MMEF values, indicating small airways dysfunction (SAD) as part of the disease paradigm (Almeshari et al., 2020b). This suggests that changes in FEV_1 may not be the only marker to capture a treatment response. Moreover, in children with asthma, low MMEF was associated with a significant BDR for FEV_1 (Lazova et al., 2022).

Inhaled extra-fine particle treatments have been developed specifically to target the small airways (Papi et al., 2018). Understanding the BDR for the small airways and how it is related to the overall lung function might be important for clinical trials and clinical practice.

5.3.1 Hypothesis and aims

We hypothesised that asthmatics with physiological evidence of SAD, as assessed by MMEF, would have an increased BDR regardless of the conventional AO as defined by FEV_1/FVC.

The study had three main aims:

- To investigate the BDR in patients with SAD compared to other those without.
- To determine the relationship between the baseline MMEF and the BDR for FEV_1.
- To assess the association of demographic features and spirometric baseline values for a positive BDR for FEV_1 and MMEF.

5.4 METHODS

5.4.1 Study design and setting:

The study and all study activities were approved by the Health Research Authority (HRA IRAS number 274729; REC Reference: 20/HRA/0203). The retrospective data were obtained from the lung function department in a tertiary hospital in the West Midlands of the UK.

5.4.2 Participants:

All routine lung function records of adults, tested between 1st January 2016 and 30th April 2021, with either a diagnosis or a clinical suspicion of asthma were considered for inclusion. The data was collected and compiled by the lung function department and anonymised prior to analysis.

5.4.2.1 Inclusion/exclusion criteria:

The following inclusion and exclusion criteria were applied:

5.4.2.1.1 Inclusion Criteria:

- Adults (aged 18 or over)
- A clinical diagnosis or clinical suspicion of asthma referred for lung function testing by a physician.
- Report of primary spirometry indices (FEV_1, FVC, MMEF) both pre and post bronchodilators.

5.4.2.1.2 Exclusion Criteria:

- The presence of other respiratory diagnoses including COPD, bronchiectasis and lung malignancy
- Any previous lung surgery likely to impact lung function parameters
- Entries with missing key parameters (FEV_1, FVC, MMEF) either pre or post bronchodilators.
- Paediatric patients (<18 years of age)

5.4.3 Outcomes:

The study had the following outcomes:

5.4.3.1 Primary outcomes:

- The BDR effect on large airways (FEV_1) and small airways (MMEF) in patients with SAD compared to those with conventional AO.

5.4.3.2 Secondary outcomes:

- Relationship of SAD to BDR in conventional large airways (i.e. FEV_1).

5.4.4 Lung function testing.

Participants were assessed using spirometry (MasterScreen Pro lung function system (Jaeger Ltd, Hochberg, Germany)), which was performed according to the Association for Respiratory Technology and Physiology/British Thoracic Society guidelines (Sylvester et al., 2020).

The categorisation was based on z-scores of the FEV_1/FVC (Quanjer et al., 2014a) for AO and MMEF for SAD. The z-score was calculated from the raw data provided using the Global Lung Initiative (GLI) 2012 formula. An FEV_1/FVC z-score of <-1.645 was taken to indicate the presence of AO, and the severity was classified by FEV_1 z-scores as follows: >-1.645: Mild, <-2: Moderate, <-2.5 Moderately severe, <-3: Severe, <-4: Very severe (Sylvester et al., 2020). The lower limit of normal (LLN) of MMEF was used to define SAD using a z-score of <-1.645.

A positive BDR was defined as a change of >12% and >200 mL in FEV_1 following American Thoracic Society/European Respiratory Society spirometry guidelines(Graham et al., 2019). A change of >30% predicted of the MMEF was considered a positive response for the small airways as previously recommended (Shim, 1989). The percentage of change will be calculated using the (% initial) equation

according to the Association for Respiratory Technology & Physiology (ARTP) statement (Sylvester et al., 2020). The used equation is as the following:

$$\%\ \text{Change} = \frac{(\text{Post Bronchodilator (absolute)} - \text{Pre Bronchodilator (absolute)})}{\text{Pre Bronchodilator}} \times 100$$

5.4.5 Statistical analysis:

Data analysis was performed using RStudio (based on R, from the R Core Team, version 4.2.0) software. Predicted values and z-scores were calculated using IBM SPSS (version 27) software. The normality of data was assessed using the Shapiro test, and then the normality of variance was assessed using Levene's test in normally distributed data. For normally distributed data, unpaired t-tests were used to compare two continuous variables and ANOVA was used to compare more than two. For non-normally distributed continuous variables unpaired Wilcoxon rank tests were used to compare two continuous variables and the Kruskal-Wallis test was used to compare more than two variables. P-values were adjusted using the Bonferroni method (Bland and Altman, 1995) for multiple comparisons. For categorical variables, Chi-square tests were used for both parametric and non-parametric analyses. Correlations were assessed using either Pearson's or Spearman's as appropriate. Backward stepwise logistic regression models were used for SAD and the probability of positive BDR in those with SAD and AO. Univariate logistic regression models were initially used to assess predictors individually and multivariate logistic models were then used to assess the significant predictors after adjusting the factors. Collinearity was assessed using the variance inflation factor (VIF) method. Variables with a VIF

value of >10 was removed from the multivariate regression model as previously recommended (Allison, 1999).

5.5 RESULTS

A total of 2328 lung function tests were performed during the study period for patients with a confirmed or suspected diagnosis of asthma. The records were screened as per the inclusion and exclusion criteria. The pre and post bronchodilator data was available for 329 patients. Patients were grouped based on baseline airways status. Figure 5.1 describes the number of records and reasons for exclusion in a flowchart.

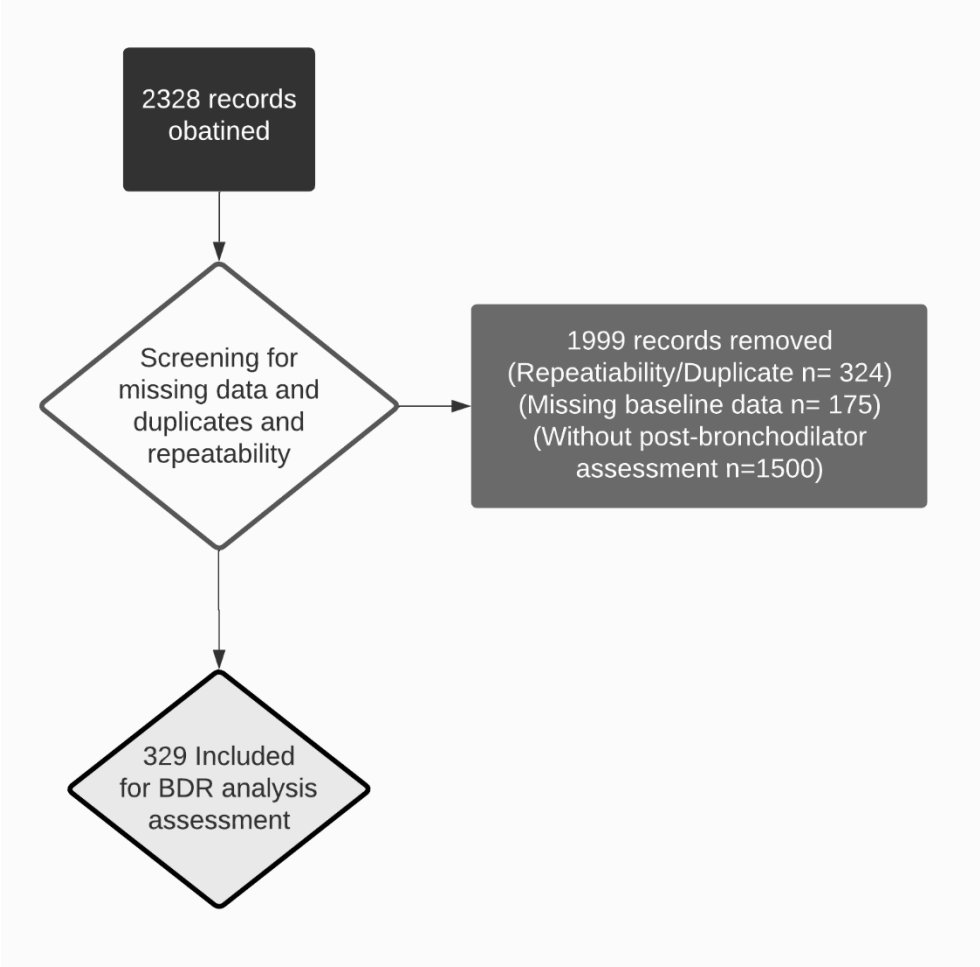


Figure 5.1. Flowchart of the screened records that shows the numbers that were assessed based on the inclusion/exclusion criteria.
Abbreviations: BDR: Bronchodilator Response.

5.5.1 Baseline characteristics:

The largest proportion of patients 201 (61.1%) had both SAD and AO (SAD+/AO+) at baseline. Two hundred and thirty-eight (72.3%) participants had evidence of SAD, of whom 37 (15.6%) had isolated SAD with no AO (SAD+/AO-) and 201 (84. 5%) had both SAD and AO (SAD+/AO+). Of the whole cohort, 236 (71.7%%) patients had AO, with 201 (85.2%) of these having both AO and SAD. The smallest group (35 patients; 10.6 %) was those with AO but no SAD (SAD-/AO+). There was

also a small group of patients (56 (17.0%)) who had no physiological evidence of SAD nor AO at baseline.

Overall, patients with SAD were younger than those without. The SAD+/AO- and SAD+/AO+ were significantly younger with a median age of 37.0 (IQR: 27.0-47.0) and 39.0 (IQR: 30.0-53.0) years respectively compared to SAD-/AO- (median of 52.5 IQR: 44.0-63.8). There were more males in the SAD-/AO+ group compared to the SAD+/AO+ and the SAD+/AO- groups. No differences were found in body mass index (BMI), smoking status or pack years between the groups.

At baseline, those with SAD had a significantly lower FEV_1 z-score than those without SAD, irrespective of AO status. The FVC z-score was significantly higher in the SAD-/AO+ group, compared to all other groups. The FEV_1/FVC z-score was the lowest in the SAD+/AO+ group (median: -2.49 IQR(-3.01 to -2.05)) followed by the SAD-/AO+ group (median: -1.92 IQR(-1.97 to -1.85)) and both were statistically lower than SAD-/AO- and SAD+/AO- groups.

5.5.2 BDR characteristics:

A positive BDR for FEV_1 was more common in patients with SAD. The greatest percentage of change for FEV_1 was observed in the SAD+/AO+ group (median change=11.00; IQR 6.03 to 15.40) and statistically greater than the SAD-/AO- group. The largest proportion of a positive BDR in FEV_1 was seen in the SAD+/AO- group (64.9%) followed by the SAD+/AO+ group (62.7%), both were statistically greater than SAD-/AO- and SAD-/AO+ groups.

A positive BDR for MMEF was also more common in patients with SAD. A total of 83.8% of patients in the SAD+/AO- group and 76.6% from the SAD+/AO+ group had

a positive BDR and both groups had a statically greater proportion compared to SAD-/AO- and SAD-/AO+ groups.

Apart from one patient, all patients with a positive BDR for FEV_1 displayed a positive BDR for MMEF, however, 61 patients (18.5%) displayed a positive BDR for MMEF but not FEV_1.

In figure 5.2, the percentage of change for FEV_1, FEV_1/FVC, and MMEF are reported between the groups. Patient demographics, baseline lung function and BDR change are reported in table 3.1.

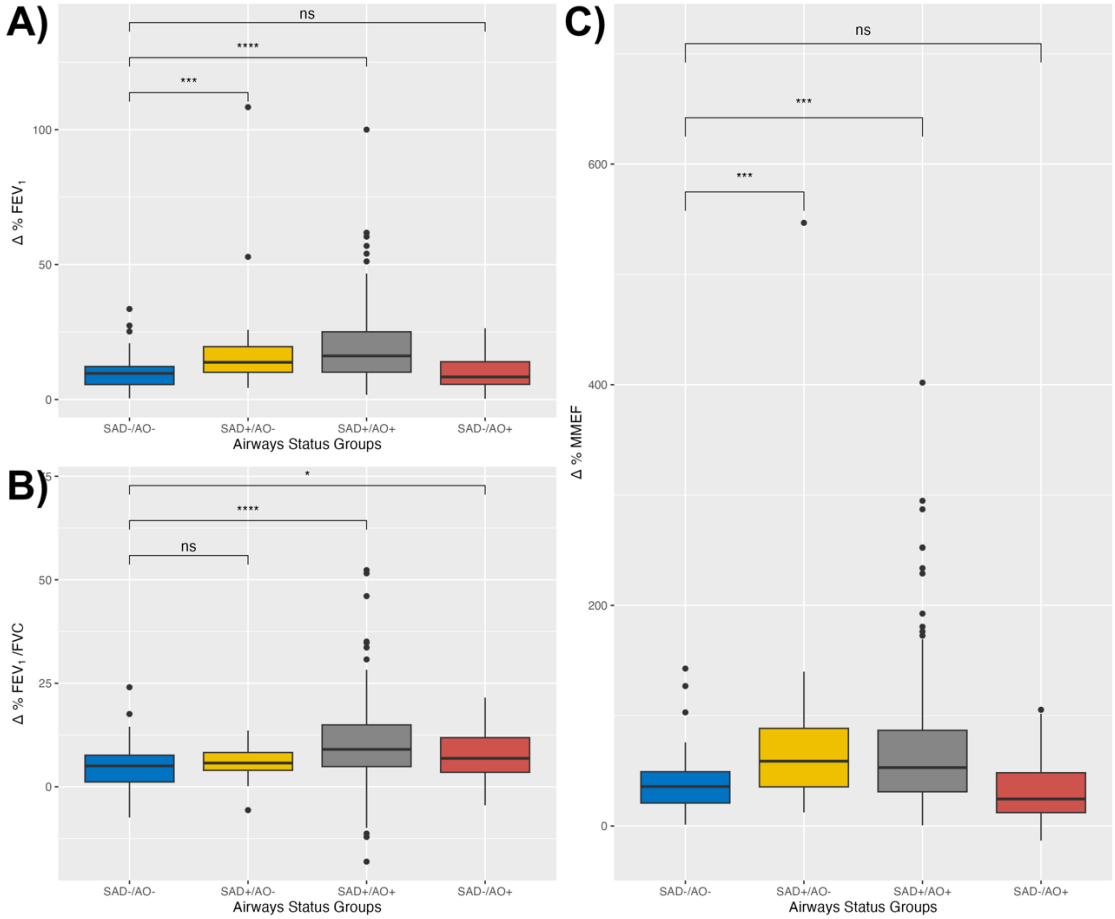


Figure 5.2. The percentage of change for FEV_1 (A), FEV_1/FVC (B), and MMEF (C). The figures show that those with SAD had a higher bronchodilator response.

Abbreviation: FEV_1: forced exhaled volume in the 1st second, FVC: Forced vital capacity, MMEF: Mid-maximal expiratory flow, SAD: Small airways dysfunction, AO: Airflow obstruction.

("****"= p < .0001, "***"= p < .001, "**"= p < .01, "*"= p < .05, ns.= Not significant)

Table 5.1. Demographics and baseline values based on physiological characteristics.

	Overall (N=329)	SAD-/AO- **(N=56)**	SAD+/AO- **(N=37)**	SAD+/AO+ **(N=201)**	SAD-/AO+ **(N=35)**	**P-value**
Age	43.0 (31.0 to 57.0)	52.5 (44.0 to 63.8)	37.0 (27.0 to 47.0)*	39.0 (30.0 to 53.0)*	45.0 (30.5 to 70.0)	**<0.001**
Sex						
Female	177 (53.8%)	31 (55.4%)	24 (64.9%)	111 (55.2%)	11 (31.4%)†,‡	**0.028**
BMI	27.2 (23.9 to 31.6)	28.3 (25.6 to 33.2)	28.4 (24.1 to 34.7)	26.8 (23.5 to 31.2)	26.4 (24.6 to 29.5)	0.172
Smoking Status						
Current Smoker	74 (22.5%)	10 (17.9%)	10 (27.0%)	47 (23.4%)	7 (20.0%)	0.266
Never Smoker	170 (51.7%)	25 (44.6%)	20 (54.1%)	109 (54.2%)	16 (45.7%)	
Previous Smoker	85 (25.8%)	21 (37.5%)	7 (18.9%)	45 (22.4%)	12 (34.3%)	
Pack Years	8.00 (3.00 to 20.0)	10.0 (3.00 to 23.0)	6.00 (3.00 to 11.0)	9.50 (4.00 to 20.0)	7.00 (3.25 to 18.0)	0.687
FEV_1						
% Predicted	73.6 (60.4 to 84.0)	81.7 (74.7 to 90.2)	78.2 (62.8 to 81.3)*	65.3 (56.0 to 77.8)*	94.1 (87.1 to 99.1)†,‡	**<0.001**
Z-score	-1.93 (-2.75 to -1.22)	-1.37 (-1.82 to -0.750)	-1.76 (-2.51 to -1.51)*	-2.51 (-3.09 to -1.77)*	-0.48 (-0.88 to -0.04)†,‡	**<0.001**
FVC						
% Predicted	89.4 (76.4-102)	88.5 (78.3-101)	87.4 (70.2-91.2)	86.8 (75.0-99.2)	113 (104-121)*,†,‡	**<0.001**
Z-score	-0.82 (-1.77 tot 0.16)	-0.82 (-1.54 tot 0.003)	-1.03 (-2.11 to -0.73)	-1.05 (-1.89 to -0.13)	0.950 (0.320-1.51)*,†,‡	**<0.001**

Table 5.1. Demographics and baseline values based on physiological characteristics.

	Overall (N=329)	SAD-/AO- **(N=56)**	SAD+/AO- **(N=37)**	SAD+/AO+ **(N=201)**	SAD-/AO+ **(N=35)**	**P-value**
FEV_1/FVC Ratio	66.4 (60.6 to 72.1)	75.3 (69.5 to 79.7)	75.0 (71.2 to 76.2)	63.4 (57.9 to 68.0)*,†	66.5 (61.0 to 70.1)*,†	**<0.001**
FEV_1/FVC Z-score	-1.99 (-2.63 to -1.60)	-0.89 (-1.40 to -0.20)	-1.47 (-1.57 to -1.25)	-2.49 (-3.01 to -2.05)	-1.92 (-1.97 to -1.85)	
MMEF						
% Predicted	46.4 (33.9 to 58.4)	69.3 (57.1 to 76.5)	55.30 (46.7 to 58.1)*	37.6 (29.1 to 46.7)*,†	63.2 (53.1 to 67.3)‡	**<0.001**
Z-score	-2.13 (-2.71 to -1.60)	-1.18 (-1.41 to -0.75)	-1.92 (-2.09 to -1.74)	-2.55 (-3.05 to -2.18)	-1.39 (-1.55 to -1.26)	
∆ FEV_1 (% change)	13.3 (7.99 to 20.7)	9.68 (5.55 to 12.2)	13.8 (10.1 to 19.6)*	16.2 (10.1 to 25.1)*	8.37 (5.62 to 14.0)†,‡	**<0.001**
∆ FEV_1/FVC Ratio	7.60 (3.43 to 12.7)	5.04 (1.16 to 7.63)	5.74 (3.99 to 8.28)	9.04 (4.88 to 14.9)*,†	6.87 (3.50 to 11.9)	**<0.001**
∆ MMEF (% change)	47.4 (26.2 to 75.8)	35.8 (20.8 to 49.2)	58.8 (35.5 to 88.5)*	52.9 (31.0 to 86.7)*	24.5 (12.1 to 48.3)†,‡	**<0.001**
+ FEV_1 BDR	175 (53.2%)	15 (26.8%)	24 (64.9%)*	126 (62.7%)*	10 (28.6%)†,‡	**<0.001**
+ MMEF BDR	235 (71.4%)	34 (60.7%)	31 (83.8%)*	154 (76.6%)*	16 (45.7%)†,‡	**<0.001**

Legend: Groups were based on the physiological characteristics and labelled accordingly. The + FEV_1 BDR is a change of >12% and 0.2L. The + MMEF BDR is a change of >30%.
Abbreviation: SAD: small airways dysfunction, AO: airflow obstruction, BMI: Body mass index, FEV_1: forced exhaled volume in the 1st second, FVC: Forced vital capacity, MMEF: Maximal mid-expiratory flow.
Values are in Median (Q1 to Q3), or n (%).

Kruskal Wallis test was used to assess the statistical difference between the continuous groups. Pairwise statistical analysis was assessed using the Wilcoxon rank test for continuous variables. The Chi-square test assessed the statistical difference between the categorical and pairwise groups.
* Statistically different from SAD-/AO- group; †, Statistically different from SAD+/AO- group; ‡ Statistically different from SAD+/AO+ group.

Most patients (243; 73.9%) were receiving Short-Acting Beta-2 Agonist (SABA). 145 (44.1%) were receiving Inhaled corticosteroids/Long-Acting Beta-2 Agonist combination inhalers (ICS/LABA), and ICS inhalers alone (79; 24.0%). There were no differences in medication use between the physiologically defined groups except in ICS/LABA and diabetes mellitus medications. Those in the SAD+/AO+ group reported higher use of ICS/LABA compared to other groups. Medications use (as reported by patients) are provided in table 5.2.

Table 5.2. Medication use as reported by patients and stratified by physiological characteristics.

	Overall **(N=329)**	SAD-/AO- **(N=56)**	SAD+/AO- **(N=37)**	SAD+/AO+ **(N=201)**	SAD-/AO+ **(N=35)**	**P-value**
SABA	243 (73.9%)	37 (66.1%)	28 (75.7%)	156 (77.6%)	22 (62.9%)	0.140
ICS	79 (24.0%)	14 (25.0%)	12 (32.4%)	47 (23.4%)	6 (17.1%)	0.491
LABA	7 (2.1%)	0 (0.0%)	1 (2.7%)	5 (2.5%)	1 (2.9%)	0.684
LAMA	43 (13.1%)	7 (12.5%)	2 (5.4%)	31 (15.4%)	3 (8.6%)	0.317
SAMA	4 (1.2%)	0 (0%)	1 (2.7%)	3 (1.5%)	0 (0.0%)	0.587
ICS/LABA	145 (44.1%)	22 (39.3%)	13 (35.1%)	101 (50.2%)	9 (25.7%)	**0.022**
Montelukast	48 (14.6%)	6 (10.7%)	6 (16.2%)	33 (16.4%)	3 (8.6%)	0.511
Antihistamine	29 (8.8%)	1 (1.8%)	3 (8.1%)	22 (10.9%)	3 (8.6%)	0.203
HTN	36 (10.9%)	7 (12.5%)	4 (10.8%)	20 (10.0%)	5 (14.3%)	0.863
DM	7 (2.1%)	4 (7.1%)	0 (0.0%)	2 (1.0%)	1 (2.9%)	**0.031**
Oral CS	8 (2.4%)	0 (0.0%)	1 (2.7%)	7 (3.5%)	0 (0%)	0.360

Legend: Groups were based on the physiological characteristics and labelled accordingly.
Abbreviation: SABA: short-acting beta-agonist, ICS: Inhaled corticosteroids, LABA: Long-acting beta-agonist, LAMA: Long-acting muscarinic antagonists, SAMA: Short-acting muscarinic antagonists, CS: Corticosteroid, HTN: Hypertension medications, DM: Diabetes mellitus medications.
Values are in n (%).

There was a weak negative correlation between baseline MMEF z-scores and a positive BDR for FEV_1 as measured in the percentage of change (R^2 = 0.22, p <0.001), as seen in figure 5.3. The SAD-/AO- group (n=15, 26.8%) and SAD-/AO+ group (n=10, 28.6%) contained fewer people with a BDR for FEV_1 compared to the SAD+/AO- group (n=24, 64.9%) and SAD+/AO+ group (n=126, 62.7%).

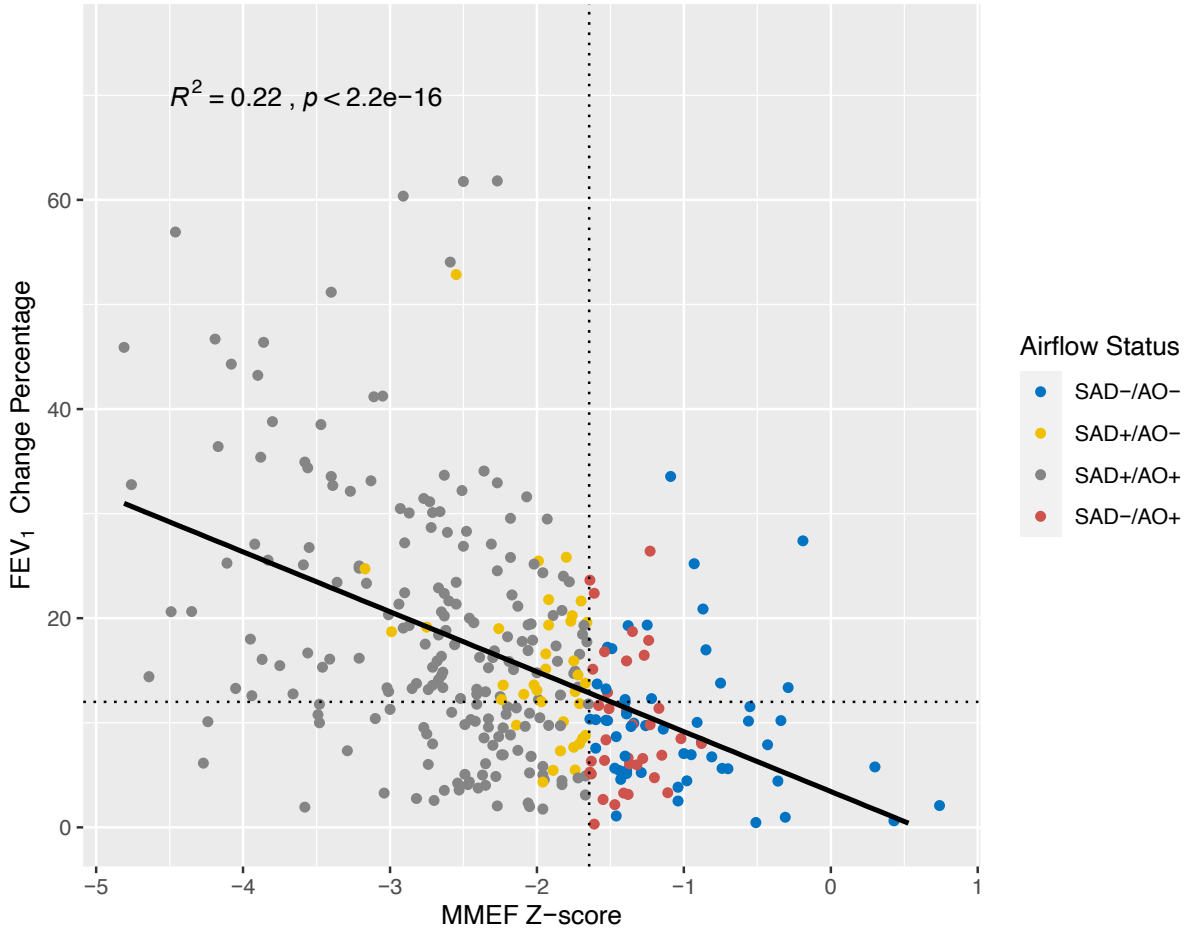


Figure 5.3. scatter plot of the FEV_1 BDR relationship to the MMEF z-score at baseline.
The colours represent the study groups. The black line represents the linear regression line (y= 3.42-5.73 X) shaded line is 95% CI of the regression line.

There was a strong correlation between the MMEF z-score and FEV_1 and FEV_1/FVC z-score (r=0.80; p<0.001 and r=0.78; p<0.001, respectively). There was also a weak positive correlation for MMEF z-score with age (r=0.25; p<0.001). There

was also a weak positive correlation between FEV_1/FVC with BMI r=0.20; p<0.001. Detailed correlations are provided in table 5.3.

Table 5.3. Correlation coefficient matrix for the baseline value and continuous demographics.

Characteristic	Age	BMI	MMEF z-score	FEV_1 z-score
Age				
BMI	0.06			
MMEF z-score	**0.25***	0.07		
FEV_1 z-score	-0.08	-0.05	**0.80***	
FEV_1/FVC z-score	0.10	**0.20***	**0.76***	**0.48***

Abbreviation: BMI: Body mass index, FEV_1: forced exhaled volume in the 1st second, FVC: Forced vital capacity, MMEF: Mid-maximal expiratory flow. Values are Spearman's correlation coefficient (r). * Statistically significant.

There was a strong correlation between the % of change in FEV_1 and MMEF (R^2 = 0.86, p <0.001), as seen in figure 5.4.

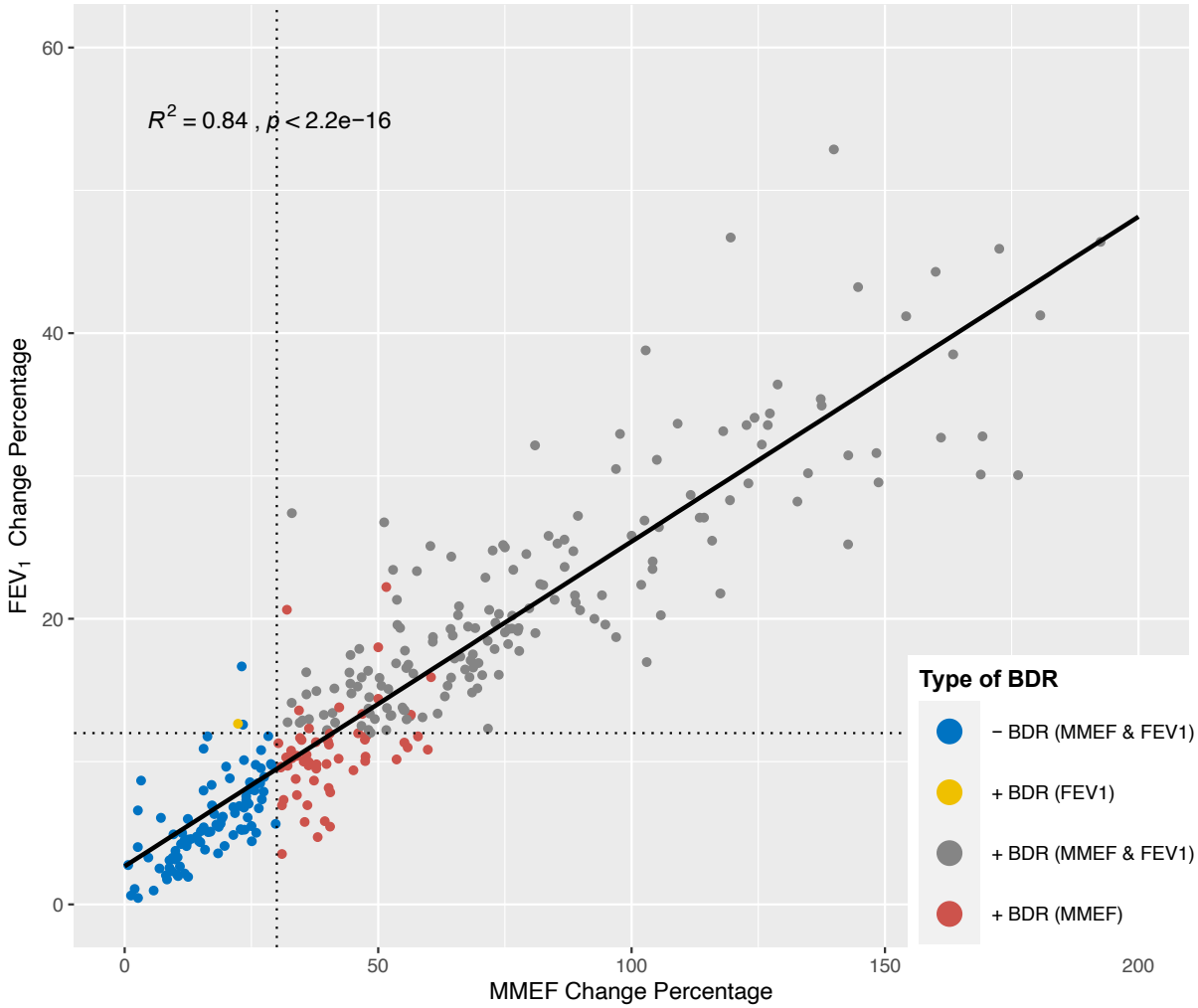


Figure 5.4. scatter plot of the FEV_1 BDR relationship to the MMEF BDR. The colours represent the type of BDR. The black line represents the linear regression line (y= 2.67+0.23 X) shaded line is 95% CI of the regression line.

5.5.3 The relation between BDR and severity

Overall, MMEF had higher percentage of change compared to the FEV_1 and a higher proportion of patients had a positive BDR for MMEF compared to FEV_1.

For FEV_1, the greatest change was found in the severe group (median: 26.1%; IQR(15.8 to 33.6)) and the highest proportion of patients with a BDR was also found in that group (81.8%). The lowest change was found in patient without AO (the AO- group).

For MMEF, the greatest percentage of change was found in the very severe AO group (median: 78.6%; IQR (32.6 to 162)). The severe AO group had a high percentage of change for MMEF (median: 78.0%; IQR(52.5 to 135)) and had the highest proportion of a positive BDR (90.9%). The lowest percentage of change for MMEF was found in the mild AO group. The percentage of change for FEV_1 and MMEF along with the proportions of positive BDR is reported in table 5.4.

Table 5.4. The change of FEV_1 and MMEF and the proportion of positive BDR for FEV_1 and MMEF stratified by physiological severities of airflow obstruction (AO).

	Overall (N=329)	AO- (N=93)	Mild (N=96)	Moderate (N=30)	Moderately severe (N=46)	Severe (N=44)	Very severe (N=20)	P-value
∆ FEV_1 (% change)	13.3 (7.99 to 20.7)	10.6 (6.97 to 16.4)	10.9 (6.19 to 16.4)	17.5 (7.59 to 21.2)	15.7 (9.95 to 22.1)	26.1 (15.8 to 33.6)*,†,‡	22.9 (13.1 to 43.5)*,†	<0.001
∆ MMEF (% change)	47.4 (26.2 to 75.8)	42.2 (26.0 to 65.7)	35.8 (19.1 to 55.4)	56.7 (24.9 to 76.8)	51.1 (30.4 to 78.6)	78.0 (52.5 to 135)*,†,‡	78.6 (32.6 to 162)*,†	<0.001
+ FEV_1 BDR	175 (53.2%)	39 (42.0%)	41 (42.7%)	20 (66.7%)	28 (60.9%)	36 (81.8%)	11 (55.0%)	<0.001
+ MMEF BDR	235 (71.4%)	65 (69.9%)	58 (60.4%)	21 (70.0%)	35 (76.1%)	40 (90.9%)	16 (80.0%)	0.008

Legend: Groups were based on the physiological severity and labelled accordingly.
Abbreviation: AO: airflow obstruction, FEV_1: forced exhaled volume in the 1st second MMEF: Maximal mid-expiratory flow.
Values are in Median (Q1 to Q3), or n (%).
Kruskal Wallis test was used to assess the statistical difference between the continuous groups. Pairwise statistical analysis was assessed using the Wilcoxon rank test for continuous variables. The Chi-square test assessed the statistical difference between the categorical and pairwise groups.
* Statistically different from normal group; †, Statistically different from mild group; ‡ Statistically different from moderately severe group.

5.5.4 Predictors of BDR:

5.5.4.1 Predictors of BDR for FEV_1:

A prediction regression model was used to identify any predictors of the BDR for FEV_1. Demographics (age, sex, BMI, smoking status, pack years, SAD at baseline, and AO at baseline) and baseline lung function parameters (FEV_1/FVC and MMEF) were included in the univariate analysis. From this univariate model, predictors of a positive BDR for FEV_1 included SAD at baseline with an OR of 4.50 (95% CI: 2.68 - 7.76); age with an OR of 0.97 (95% CI: 0.96-0.98); baseline FEV_1/FVC z-score with an OR of 0.63 (95% CI: 0.49 - 0.80); baseline MMEF z-score with an OR of 0.47 (95% CI: 0.35 - 0.61). No other factors were found to be significant predictors.

Only factors which were predictive of BDR for FEV_1 were considered for inclusion in the multivariate analysis. The final factors included in the multivariate analysis were; age, SAD at baseline, baseline FEV_1/FVC, and baseline MMEF). In the multivariate analysis model, the presence of SAD remained a predictor of BDR for FEV_1 with an OR of 2.35 (95% CI: 1.13 - 4.94) and the older the patients were, the less likely they were to have a positive BDR for FEV_1 response with an OR of 0.98 (95% CI: 0.97-0.99). In table 5.5, the univariate and multivariate regression analyses are reported.

Table 5.5. The univariate and multivariate logistic regression of a positive BDR for FEV_1.

Characteristic/variable	Univariate			Multivariate		
	OR	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
Age	0.97	0.96-0.98	**<0.001**	0.98	0.97-0.99	**0.002**
Sex						
Female (Ref)	–	–				
Male	1.11	0.72-1.72	0.99			
BMI	1.01	1.00-1.08	0.33			
Smoking Status						
Never Smoker (Ref)	–	–				
Previous Smoker	0.65	0.39-1.10	0.99			
Current Smoker	1.12	0.65-1.96	0.99			
Pack Years	0.98	0.96-1.00	0.81			
SAD at baseline						
SAD- (Ref)	–	–		–	–	
SAD+	4.50	2.68-7.76	**<0.001**	2.35	1.13-4.94	**0.02**
AO at baseline						
AO- (Ref)	–	–				
AO+	1.88	1.16-3.08	0.13			
Baseline FEV_1/FVC*	0.63	0.49-0.80	**0.003**	1.11	0.73-1.69	0.60
Baseline MMEF*	0.47	0.35-0.61	**<0.001**	0.64	0.36-1.08	0.10

Abbreviation: OR: Odds ratio, BMI: Body mass index, FEV_1: forced exhaled volume in the 1st second, FVC: Forced vital capacity, MMEF: Mid-maximal expiratory flow.
* All values are in z-score. All p-values are corrected using Bonferroni method.

5.5.4.2 Predictors of BDR for MMEF:

A prediction regression model was used to identify any predictors of the BDR for MMEF. Demographics (age, sex, BMI, smoking status, pack years, SAD at baseline, and AO at baseline) and baseline lung function parameters (FEV_1 and FEV_1/FVC) were included in the univariate analysis. From this univariate model, predictors of a positive BDR for MMEF included SAD at baseline with an OR of 2.86 (95% CI: 1.71-4.79), whereas the higher the baseline FEV_1 z-score (OR of 0.65 (95% CI: 0.52-0.80)). No other factors were found to be predictors.

In the multivariate analysis model combining the significant factors (SAD at baseline and baseline FEV_1), the presence of SAD remained a predictor of positive BDR for MMEF with an OR of 1.90 (95% CI: 1.01-3.57), as did a higher FEV_1 value

with an OR of 0.75 (95% CI: 0.58-0.97). In table 5.6, the univariate and multivariate regression analyses are reported.

Table 5.6. The univariate and multivariate logistic regression of a positive BDR for MMEF.

Characteristic/variable	Univariate			Multivariate		
	OR	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
Age	0.98	0.97-1.00	0.25			
Sex						
Female (Ref)	–	–				
Male	0.72	0.44-1.16	0.99			
BMI	1.03	0.99-1.16	0.99			
Smoking Status						
Never Smoker (Ref)	–	–				
Previous Smoker	1.03	0.58-1.84	0.99			
Current Smoker	1.33	0.72, 2.54	0.99			
Pack Years	0.99	0.98-1.01	0.81			
SAD at baseline						
SAD- (Ref)	–	–		–	–	
SAD+	2.86	1.71-4.79	**<0.001**	1.90	1.01-3.57	**0.04**
AO at baseline						
AO- (Ref)	–	–				
AO+	1.11	0.65-1.87	0.99			
Baseline FEV_1*	0.65	0.52-0.80	**0.001**	0.75	0.58-0.97	**0.03**
Baseline FEV_1/FVC*	0.75	0.59-0.96	0.28			

Abbreviation: OR: Odds ratio, BMI: Body mass index, FEV_1: forced exhaled volume in the 1st second, FVC: Forced vital capacity, MMEF: Mid-maximal expiratory flow.
* All values are in z-score. All p-values are corrected using Bonferroni method.

5.5.4.3 Predictors of BDR for MMEF alone:

A prediction regression model was used to identify any predictors of the BDR for MMEF with the absence of BDR for FEV_1. Demographics (age, sex, BMI, smoking status, pack years, SAD at baseline, and AO at baseline) and baseline lung function parameters (FEV_1 and FEV_1/FVC) were included in the univariate analysis. From this univariate model, predictors of a positive BDR for MMEF alone included age (OR: 1.03 (95% CI: 1.01-1.04)), male sex were less likely to have BDR for MMEF alone (OR: 0.55 (95% CI: 0.30-0.97)), SAD at baseline were less likely to have a BDR for MMEF

alone (OR: 0.47 (95% CI: 0.26-0.85)), AO at baseline were less likely to have a BDR for MMEF alone (OR: 0.45 (95% CI: 0.25-0.80)), and the higher the FEV1/FVC the less likely a BDR for MMEF alone would be found (OR: 1.37 (95% CI: 1.03-1.81)). No other factors were found to be predictors.

In the multivariate analysis model combining the significant factors (age, sex, SAD at baseline, AO at baseline, and baseline FEV_1/FVC), the presence of SAD remained a predictor of positive BDR for MMEF with an OR of 1.90 (95% CI: 1.01-3.57), as did a higher FEV_1 value with an OR of 0.75 (95% CI: 0.58-0.97). In table 5.7, the univariate and multivariate regression analyses are reported.

Table 5.7. The univariate and multivariate logistic regression of a positive BDR for MMEF alone.

Characteristic/variable	Univariate			Multivariate		
	OR	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
Age	1.03	1.01-1.04	**<0.001**	1.02	1.01-1.04	**0.008**
Sex						
Female (Ref)	–	–		–	–	
Male	0.55	0.30-0.97	**0.04**	0.57	0.31-1.04	0.07
BMI	0.97	0.93-1.02	0.26			
Smoking Status						
Never Smoker (Ref)	–	–				
Previous Smoker	0.85	0.41-1.80	0.66			
Current Smoker	1.64	0.77, 3.62	0.21			
Pack Years	1.01	0.99-1.02	0.25			
SAD at baseline						
SAD- (Ref)	–	–		–	–	
SAD+	0.47	0.26-0.85	**0.01**	0.67	0.31-1.46	0.3
AO at baseline						
AO- (Ref)	–	–				
AO+	0.45	0.25-0.80	**0.007**	0.57	0.24-1.36	0.2
Baseline FEV1*	1.17	0.93-1.48	0.19			
Baseline FEV1/FVC*	1.37	1.03-1.81	**0.029**	0.97	0.63-1.52	0.99

Abbreviation: OR: Odds ratio, BMI: Body mass index, FEV_1: forced exhaled volume in the 1st second, FVC: Forced vital capacity, MMEF: Mid-maximal expiratory flow.
* All values are in z-score. All p-values are corrected using Bonferroni method.

5.6 DISCUSSION

In this retrospective data analysis of 329 patients with a diagnosis or a clinical suspicion of asthma, three main findings were observed:

Firstly, BDR for FEV_1 and MMEF was common (53.2% and 71.4%, respectively). This was expected for FEV_1 and in keeping with an asthma cohort. A higher proportion of patients with a positive BDR for MMEF highlights how common a small airways BDR is and the response seen in the MMEF to therapies. This question the importance of targeting the BDR for MMEF, especially since therapies are available which can reach the small airways. However, further research is needed to evaluate the effectiveness of therapies such as ultra-fine aerosol medications to the small airways and in asthmatic patients with SAD.

Secondly, apart from one patient, a positive BDR for MMEF was found in all patients with a positive BDR for FEV_1, however some patients had a positive BDR for MMEF alone (n=61, 18.5%). This indicates that while BDR in FEV_1 is likely to identify patients with a BDR in MMEF, BDR in FEV_1 alone cannot be used as the sole test to identify BDR in the small airways, and tests of small airways function are needed to ensure all those with a BDR are identified. Further studies are needed to identify if treating BDR in MMEF lead to improvements in patient reported outcomes.

Lastly, patients with SAD at baseline were more likely to have a positive BDR for FEV_1 and MMEF. This association was also confirmed when regression models were utilised. It is known that patients with SAD and those with BDR in FEV_1 are more likely to be symptomatic (Janson et al., 2019b). It is unclear if those with BDR for MMEF are also symptomatic. The large improvement in MMEF following bronchodilator

challenge also suggests patients with SAD are responsive to therapies. Again, it is unclear whether targeting SAD with therapies, and using BDR in MMEF as a marker of response will lead to clinical improvements, but if this were the case, it might imply a possible phenotype of asthma where an increased BDR is expected.

As stated, these findings might be of clinical relevance. In asthma, significant BDR in FEV_1 is associated with wheeze, atopy, poor symptom control, and inversely correlates to Asthma Control Test (ACT) scores (Janson et al., 2019b, Heffler et al., 2016). There are treatments which can target the small airways and there is increasing evidence that biological therapies impact positively on small airways inflammation (Zinellu et al., 2019). Measuring SAD at baseline and following bronchodilation should provide a means to objectively track small airways responses to therapies. Assessing the function of small airways provides an opportunity to identify these individuals and evaluate targeting SAD specifically as a therapeutic strategy, which should be carried out in a comprehensive prospective study.

Overall, MMEF had a higher percent of BDR than FEV_1, implicating higher sensitivity to bronchodilators. This may also be interpreted to confirm that the small airways are the main driver of airflow within the lungs. This was also reported in a previously published systemic review (Almeshari et al., 2021b). In this report, physiological severities appear to be linked to BDR. Those in the severe and very severe groups had greater percentage of change for FEV_1 compared to those in normal, mild, or moderately severe groups. Similar results were found for the MMEF. This could be attributed to the degree of airflow impairment and the increased gap for improvement. However, this is inconclusive and requires further study. Other studies have reported that in severe cases of asthma, the percentage of change in FEV_1 was

higher than MMEF (Lipworth and Clark, 1997, El-Khatib et al., 2014). In the first study by Lipworth and Clark, severity criteria was not defined or reported, however El-Khatib et al. defined the severe group as those with a % predicted FEV_1 of < 50%. This contrasts with the current study where severity was based on FEV_1 z scores. In this chapter, the FEV_1 z-score was strongly correlated with MMEF z-score (r=0.80). This may explain the reason that in the severe groups greater MMEF change was found. Nevertheless, it is unclear why in severe cases the BDR for MMEF can be lower than FEV_1, however in severe cases, a fixed AO is expected (Lee et al., 2007). This should be further evaluated by utilising different aerosol delivery devices to assess whether this phenomenon is due to significance of the bronchoconstriction in the larger airways that is preventing the bronchodilators from reaching the small airways or due to the disease progression in which the effect of bronchodilators is limited in the small airways.

In the current study, patients that reported more use of ICS/LABA combination were those with SAD and AO. Since asthma is treated on the basis of controlling symptoms, it is likely that people with SAD and AO experience higher symptoms and therefore have an increased use of medicines. In keeping with this, It was previously reported that those with lower MMEF had increased symptoms and higher blood and sputum eosinophilic count (Riley et al., 2016). The same group had the lowest baseline MMEF and the greatest BDR for FEV_1. This highlights the importance of assessing MMEF at baseline, as this might enable the identification of a treatable trait, BDR in MMEF which is associated with clinical symptoms and medication use.

Despite the previous report of the association of SAD with clinical features such as frequent exacerbation (Kraft et al., 2022) and persistent symptoms (Riley et al.,

2016), the association of BDR to symptoms was not investigated in this study, due to limitations of the data recorded in routine practice. In chapter 3, smoking was associated with prevalence of SAD, however, there was no association between smoking behaviour and BDR in this smaller group. This might reflect a lack of power to detect a relationship. Furthermore, It was previously reported that there are association between low MMEF values and airways hyperresponsiveness (Kim et al., 2021). This finding supports the analysis of the current study, and that the small airways are likely to be the main driver for physiological airflow within the lungs.

The strong correlation between the commonly reported spirometry indices (FEV_1 and FEV_1/FVC) to MMEF presented in this study reflects the importance of assessing BDR for MMEF. There was a negative correlation between baseline MMEF and percentage of change for FEV_1 but the correlation co-efficient was weak (r^2=0.22), albeit statically significant. Understanding this relationship is essential as it was previous suggested that BDR for FEV_1 is a phenotype feature for asthma, not merely a discriminating feature (Janson et al., 2019b). As shown in this and in the previous chapter, MMEF generally has greater % of BDR compared to FEV_1, which highlights the physiological features of small airways function. Although MMEF was reported to have higher percentage of variance compared to FEV_1, it was not statically significant (Xu et al., 2022). Higher variance for MMEF is expected due to the FVC manoeuvre which records the mean flow in the middle of the manoeuvre (usually between the 2nd and 4th second), whereas the FEV_1 records the amount of volume after forcefully exhalation. These findings support the importance of reporting baseline and BDR value for MMEF in routine clinical practice for asthma. However, studies are needed to develop clinical standards of testing.

Reporting the BDR is sometimes not well documented. Moreover, there are several ways for reporting the BDR. Indeed, in the ARTP statement for lung function there were six equation for reporting BDR (Sylvester et al., 2020). These methods are also dependent on how values are reported (i.e. % predicted, absolute, or z-score). Furthermore, the BDR testing technique is not standardised. It was stated in the ERS/ATS pulmonary function guidelines that "The choice of bronchodilator, dose, and mode of delivery is a clinical decision depending on what the referring clinician wishes to learn from the test" (Graham et al., 2019). Although this recommendation was for FEV_1 and FVC, it highlights a current gap in guidelines which should be addressed with evidence. Despite increased evidence for the small airways involvement in chronic lung diseases (Kwon et al., 2020, Usmani et al., 2016a, Alobaidi et al., 2022, Almeshari et al., 2022a), assessing it and its response to bronchodilator remains unstandardised.

The strengths of this chapter were the utilisation of routinely collected data of real-world patients to be assessed within a specialised department of a tertiary hospital. Moreover, this chapter showed clear and strong evidence for the association of SAD at baseline and the BDR for FEV_1.

There were limitations for this chapter as well. The pragmatic use of routinely collected data was associated with some missing data fields. The study lacked patient reported outcomes such as the ACT or asthma quality of life questionnaire (AQLQ). Data restrictions also prevented us from calculating severity using GINA criteria. The MMEF BDR was not corrected for iso-volume, as previously recommended (Cockcroft and Berscheid, 1980), also due to data limitations. Moreover, the medications data was limited to patient self-report and not by reviewing prescriptions. Nevertheless, the study provides evidence to support the measurement of SAD and BDR in small airways,

especially in future studies with interventions targeting those with symptoms and SAD or for BDR in the small airways as measured by MMEF, even in the absence of a positive BDR for FEV_1 or lack of AO.

5.7 CONCLUSION

In asthma, SAD at baseline is associated with a positive BDR in both FEV_1 and MMEF. This highlights the involvement of the small airway in the disease process and its effects on the overall physiological airways function. Moreover, the higher percentage of change in the small airways emphasises the importance of assessing the small airways in routine clinical settings. However, more research is needed particularly in the association of small airways function, clinical symptoms, and patient reported outcomes.

5.8 SUMMARY OF THE CHAPTER

This chapter highlights the importance of evaluating small airways function in patients with asthma. It appears that patients with SAD are more likely to have a positive BDR for both FEV_1 and MMEF. This has two main clinical implication, firstly, therapeutics that target the small airways could be more beneficial in this group as the small airways seems to be the driver for physiological response. Secondly, the BDR for the small airways should be included in routine reporting due to its relevance to disease status and response to treatment.

CHAPTER 6

6. GENERAL DISCUSSION

In the presented thesis, the aim was to assess the relevance of evaluating small airways function in patients with asthma and to start to explore whether these tests have any utility in diagnosing asthma, assessing disease activity or severity or identifying potential subgroups of asthma and their response to treatment.

In the first results chapter, a systematic review was conducted to assess the current published knowledge of the diagnostic value of physiological small airways function tests in asthma. Spirometry and oscillometry indices were evaluated. Although currently published data did not support tests of small airways function to diagnose asthma (mainly due to the small number of studies, their heterogeneity and poor quality), a pattern of small airways impairment was found in many patients included in all studies. To follow this, a retrospective analysis of real-world data was conducted in chapter 3. This chapter sought to assess whether tests of SAD could be used as a biomarker for asthma. In that chapter, the prevalence of small airways dysfunction (SAD) was evaluated in 1829 patients with asthma. In that cohort, SAD was prevalent and a strong correlation was found between traditionally reported spirometric indices (Forced expiratory volume in the first second (FEV_1), the forced vital capacity (FVC) and FEV_1/FVC) and the maximal mid-expiratory flow (MMEF). Moreover, looking at baseline MMEF results, an association was found between smoking and SAD as measured by z-scores.

As BDR is the hallmark of asthma and clinically used to confirm its diagnosis, in chapter 4, a systematic review was conducted, assessing the small airways bronchodilator repones (BDR) in asthma. The systematic review aimed to understand the current evidence for measuring the BDR for small airways function (assessing both MMEF and oscillometry indices) compared to FEV_1, which is the most commonly used index for BDR. Generally, although studies were small, heterogeneous and often of modest quality, the small airways appeared to exhibit a greater BDR to treatment compared to the BDR seen in FEV_1. This was further explored with a real-world data study. In chapter 5 a retrospective analysis for BDR in asthma and how SAD is related to BDR was carried out utilising spirometry. In keeping with the results reported in the systematic review of chapter 4, MMEF had a greater response to bronchodilators compared to FEV_1. It was also found that patients with evidence of SAD at baseline frequently had a positive BDR for both FEV_1 and MMEF. This relationship was maintained in a multivariate analysis.

In summary, the main findings of this thesis are:

- SAD is common in asthma.
- Testing and reporting small airways function is not well documented.
- Currently, tests of small airways function cannot be used independently with confidence to diagnose asthma.
- SAD appears associated with physiological severity (measured by FEV_1), suggesting this might form a biomarker of disease.
- In general, MMEF was more impaired (in % predicted and Z scores) than FEV_1.
- SAD was associated with BDR.

- In BDR assessment, MMEF had greater percentage of change than FEV_1.
- All patients with a positive BDR for FEV_1 had a positive BDR for MMEF, but some (18.2%) had a positive BDR for MMEF with no positive BDR for FEV_1.

6.1 THE USE OF SMALL AIRWAYS IN THE DIAGNOSIS OF ASTHMA

Asthma is a heterogenous disease which can vary in its symptoms and severity over time, ranging from no to debilitating symptoms. Airways physiology is characteristically variable in asthma and the Global Initiative for Asthma (GINA) report is defining asthma as a disease with variable airflow limitation (Global Initiative for Asthma (GINA), 2022). This heterogeneity makes diagnosing asthma a challenge for clinical practice, as patients may not be symptomatic at the time of clinical assessment and while a history of symptoms is considered one of the main criteria for making an asthma diagnosis, objective assessments are needed to confirm the diagnosis. In current guidelines such as the National Institute for Health and Care Excellence (NICE), an asthma diagnosis can be confirmed with a positive BDR for FEV_1. When reviewing current asthma guidelines from several countries (as described in the introduction chapter), none included the assessment of small airways function, however, data from this thesis, including the systematic review and real world data study, suggest that SAD may be important in asthma.

As described throughout this thesis, there is increasing evidence of SAD in asthma (Usmani et al., 2016a, Postma et al., 2019). However, despite this, few studies have adequately tested the use of small airways function to diagnose asthma either in place of, or as an adjunct to larger airways function (including FEV_1 and FVC). During

the systematic review, all studies identified a signal of SAD in asthma, with consistent reporting of a high prevalence of SAD and a lower MMEF than FEV_1. This was also described in other obstructive disease processes (Stockley et al., 2017, Kwon et al., 2020). However, studies reported to date have been heterogeneous, lacked consistent methodology for small airways function assessments and showed signs of bias. Although large number of abstracts were evaluated in the systematic review (n=7072), only ten studies met the inclusion/exclusion criteria. Moreover, due to the heterogeneity of the studies methodologies, samples, recruitment criteria, and impairment definition, the utility of small airways function in asthma diagnosis was inconclusive.

To assess this further, a real world data study was conducted using retrospective lung function data from patients suspected of having asthma or with a clinical diagnosis of asthma. SAD prevalence was high in general, and especially prevalent in in those with AO (69.3%) where there was a strong correlation with MMEF and FEV_1 and FEV_1/FVC. These results suggest SAD may be measurable in asthma, but does not support its use as a diagnostic test independently.

In the presented thesis, not enough evidence was found to support the utility of small airways function tests, such as MMEF, to diagnose asthma independently. In the systematic review, studies used different cut-off points that may not be applicable to a larger population. In the retrospective analysis, there was a lack of control participants that made it impossible to conduct a diagnostic analysis. However, SAD was prevalent in asthma and SAD was a predictor of BDR, which supports previous reports that SAD is a phenotype of asthma (Cottini et al., 2021, Lipworth et al., 2014, van der Wiel et al., 2013). Supporting this hypothesis, some studies of small airways functions have

concluded that physiological small airways functions may be used in addition, but not as a surrogate, to conventional spirometry for asthma diagnosis due to the limited data on how these test should be interpreted for asthma diagnosis (Saadeh et al., 2014, Shirai and Kurosawa, 2016). However, further studies were suggested to support the inclusion of physiological small airways function in asthma diagnosis and distinguishing it from chronic obstructive pulmonary disease (COPD) (Mori et al., 2011, Li et al., 2015).

Before MMEF can be included in the diagnosis of asthma, its diagnostic test accuracy should be evaluated in a well distrusted cohort of patients with confirmed asthma and healthy controls. The diagnostic value of the MMEF should then be validated on a different cohort.

Although the use of MMEF in clinical practice has been considered as inappropriate (Quanjer et al., 2014b) due to the high variability and not meeting the AO criteria, a recent study, evaluated multiple spirometry indices, including FEV_1 and MMEF (Xu et al., 2022). In the forementioned study, MMEF had higher variability than FEV_1, however it was not statically significant. A major barrier for adopting MMEF in clinical practice is the lack of standardisation and the reliance on % predicted values. This is discussed further below.

6.2 SAD AS A BIOMARKER OF ASTHMA

In chapters 2, SAD was highlighted as a feature of asthma and it was subsequently evaluated in cross-sectional real-world data study (chapter 3), but there was insufficient data to support tests of small airways function being used to diagnose asthma. However, even if tests of small airways do not yet meet the criteria needed to

diagnose asthma, they may provide important information about asthma in a proportion of patients. In essence, SAD could be a biomarker of asthma, identifying a subgroup, or a phenotype of asthma. Indeed, SAD is associated with poor asthma control, persistent symptoms, and patients with SAD were more likely to visit the emergency room (Cottini et al., 2021, Lipworth et al., 2014, van der Wiel et al., 2013, Riley et al., 2016). This is clinically important as SAD was previously reported to be highly prevalent in asthma (Postma et al., 2019, Usmani et al., 2016a).

In chapter 3, the prevalence and predictors of SAD were evaluated in patients with asthma. SAD was defined using the lower 5th percentile (z-score <-1.645) of the MMEF. In patients with AO, SAD prevalence was high (85.3%). SAD was also present in patients without AO. This indicated the possibility of SAD to be an early marker of airflow limitation. However, longitudinal studies are needed to evaluate the decline of small airways function and its relation to AO.

It was also found that some patients had AO in the absence of SAD (3.2%), in contrast to findings in patient with COPD (Alobaidi et al., 2022), where all patients with AO had small airways impairment. However, in the patients reported in chapter 3, the FEV_1 and FVC were within the normal range, but the FVC was higher, which had driven the FEV_1/FVC ratio to be below the lower limit of normal (LLN). This could be seen as a false positive AO, however, further assessment using methods such as body plethysmography is needed to rule out hyperinflation. Despite this, MMEF had a stepwise decrease in MMEF with AO severity as assessed by FEV_1 z-score. This highlighted the reliability and relevance of MMEF in assessing patients with asthma as it correlated with physiologically defined severities.

The risk factors assessed in chapter 3 found that current smokers were at an increased risk for developing SAD (Odds ratio (OR): 2.33; 95% CI: 1.75-3.10). Similar results were reported in asthmatics assessed via oscillometry (Cottini et al., 2021). Smoking asthmatics were found to be at an increased risk for developing SAD (OR: 3.06; 95% CI: 1.60-6.05). Other spirometric indices (FEV_1 and FEV_1/FVC) were also associated with SAD. Higher FEV_1 and FEV_1/FVC were associated with lower likelihood of SAD. This mirrors the importance of SAD on the overall lung function and spirometric indices, which is known to be associated with clinical symptoms and disease severities.

The body of evidence described in chapters 2 and 3 supports the utility and feasibility of assessing small airways function in asthma. It also supports the evidence of the prevalence of SAD in asthma, which, as described in chapter 3, could be addressed with specific treatments which reach the small airways (Carr et al., 2017). In asthma, SAD has been described as a phenotype where patients were more likely to be cigarette smokers, older, have asthma related night-time awakenings, and be overweight (Cottini et al., 2021). SAD in asthma could be treated using therapies shown to reach the small airways, although clinical studies would be needed to determine efficacy. However, as previously stated, to enable this, standardisation of assessments is needed to guide clinical trials and clinical reporting.

6.3 BDR FOR THE SMALL AIRWAYS AS A BIOMARKER OR AS A DIAGNOSIS TOOL OF ASTHMA.

The BDR is usually used to assess the variability of airflow limitation. An association was found between patients with BDR for FEV_1 and clinical symptoms (Tan

et al., 2013, Janson et al., 2019b). The hallmark of asthma is the variability of airflow limitation, which can be assessed with BDR testing. Therefore, the BDR (usually of FEV_1) is considered a tool to assist with diagnosing asthma and for differentiating it from other diseases such as COPD.

In chapter 4, the BDR for MMEF was found to be greater than FEV_1. This highlighted the responsiveness of the small airways to bronchodilator treatments. In chapter 5, similar results were found. Moreover, an association between SAD at baseline and a positive BDR for MMEF and FEV_1 was reported.

In chapter 4, the aim was to systematically review the evidence of BDR of the small airways compared to FEV_1. Eleven studies were found utilising two devices (spirometry and oscillometry) to assess the BDR. There was heterogeneity between the studies in term of design, units of measure, dosage, aerosol delivery devices, and interval time between the pre- and post-tests. These are all factors that may affect the outcomes of the test. However, there was a pattern where MMEF had a greater BDR than FEV_1 in all but two studies, where severe asthmatics were included (El-Khatib et al., 2014, Lipworth and Clark, 1997). The heterogeneity found between the studies made it difficult to draw a definitive conclusion, highlighting again the significant impact of the lack of consensus for BDR testing in general and specifically for the BDR testing for the small airways.

Chapter 5 aimed to evaluate the BDR for MMEF compared to FEV_1 by utilising real-world data from the electronic health records of patients. The data were obtained from a specialised unit in a tertiary hospital with lung function tests performed by highly trained respiratory physiologists in accordance with national guidelines.

Similar to the results found in chapter 4, MMEF had greater BDR than FEV_1, however, a greater BDR for MMEF was found in asthma patients with severe AO compared to FEV_1. It is unclear why patients with severe AO in our study had a greater BDR for MMEF compared to FEV_1 and needs further exploration. An important association was also found between SAD at baseline and BDR. Patients with SAD had a greater BDR for both MMEF and FEV_1. BDR is known to be associated with clinical symptoms (Janson et al., 2019b) and this finding links SAD with BDR, providing another reason for assessing SAD.

Evidence presented in this thesis does not support the use of BDR for MMEF as a primary diagnostic tool for asthma. Not all patients with asthma exhibited a positive BDR neither for FEV_1 nor MMEF. However, most patients (71.4% for MMEF and 53.2% for FEV_1) had a positive BDR, and this proportion is increased in those with SAD at baseline (77.7% for MMEF and 63.0% for FEV_1), which suggests that SAD at baseline is biomarker for asthma and BDR.

6.4 THE LACK OF STANDARDS FOR MEASURING SAD AND BDR

The diversity of reporting methodologies reported in chapter 2 highlighted the lack of consensus for the assessment of small airways function. This was further complicated by the lack of robust reference ranges for oscillometry, and the units reported for spirometry. The lack of consensus on accepted methods and standardisation was also reported in a recent review (Cottini et al., 2022). In a recently published systematic review, it was also noted that studies have used various methodologies and units in identifying SAD using MMEF (Knox-Brown et al., 2022).

For MMEF, the lower limit of normal of % predicted has been reported to be below 40% (Hansen et al., 2006, Quanjer et al., 2014b). This highlighted the importance of adapting z-scores, also known as standardised residuals, for clinical and research purposes. Indeed, in the most recent ARTP statement for lung function assessments recommended that reporting and defining impairments to be based on z-scores as it avoids age and sex biases (Sylvester et al., 2020).

Similarly, there were no universally accepted methodology or criteria for BDR testing. Several factors affect the BDR such as bronchodilator dosage, time between the pre- and post-test, or the delivery devices. The ATS/ERS spirometry standardisation guidelines have not indicated a specific cut-off point of a positive BDR for FEV_1 and stated that "The choice of bronchodilator, dose, and mode of delivery is a clinical decision depending on what the referring clinician wishes to learn from the test" (Graham et al., 2019). In NICE guidelines, the optimal cut-off point of a positive BDR for FEV_1 was indicated to be a >12% change and an increase of volume of >200mL (National Institute for Health Care Excellence, 2017), which was also reported in the 2005 ATS/ERS spirometry guidelines (Miller et al., 2005b). Similar cut-off was reported in GINA, however, a change of >15% and an increase in volume of >400 mL was reported to have a greater confidence of BDR positivity (Global Initiative for Asthma (GINA), 2022). However, it was reported that a change of >8% would be a minimal clinically important difference (MCID) (Ward et al., 2015).

In the GINA report, a salbutamol was recommended as the drug of choice with a dosage between 200-400 mcg or equivalent. This highlights the lack of evidence on how BDR is conducted as dosage would make a great impact on BDR. Indeed, it was previously reported, albeit in COPD patients, that those that received a salbutamol

dosage of 200 mcg had a mean change 11.9% (95%CI 8.6 to 15.1) for FEV_1, whereas those that had a 400 mcg dosage had a mean change of 13.7% (95%CI: 10.2 to 17.2) for FEV_1 (Borrill et al., 2005). This highlights the importance of implementing evidence based standardisation that should help in delivering the best practice. Implementing cut-off points should be specific on multiple factors that affects the bronchodilator delivery and response.

The lack of BDR standardisation is also extended for MMEF. Few studies was found to utilise a predefined cut-off point for MMEF, which was based on the a study published in 1989 by Shim (Shim, 1989). This highlights the need to update this positive BDR criteria for MMEF and the standardisations of it as well.

6.5 STRENGTHS AND LIMITATION

6.5.1 Strengths

In this thesis, strengths were centred around the design of the thesis. Two systematic reviews were designed, prospectively registered, conducted and reported using standardised methodologies (chapters 2 and 4). The systematic reviews guided the following two retrospective analysis of real-world data (chapter 3 and 5). This made the approach of analysing the data more systematic and well informed from the previous evidence and helped in identifying the gaps in the literature that needed exploring. The retrospective studies (chapters 3 and 5) included a large number of patients being evaluated for asthma. The records were consecutively collected and was conducted in a specialised lung function unit at a tertiary hospital by highly trained respiratory physiologists. Defining and stratifying SAD and AO were based on z-scores. The z-score cut-off point statically represent the lower 5^{th} percentile. This LLN

was recommended in the ARTP statement as it avoids age and sex biases (Sylvester et al., 2020).

6.5.2 Limitations

In this thesis, several limitations were identified which may have helped in better understanding the role of SAD in asthma.

The MMEF is an index that is produced from an effort-dependent manoeuvre (FVC manoeuvre). This meant that patients may not always produce the same results due to fluctuating efforts. Several guidelines were set for acceptability and repeatability of spirometry, however they are only for FEV_1 and FVC. This limits the interpretation of the MMEF as there are no acceptability or repeatability criteria for it.

Due to the quantitative nature of the data, the MMEF was not corrected (iso-volume) with the FVC. To correct the MMEF with the FVC, the pre- and post- volume over time spirograms are needed to be evaluated and the post-BD MMEF time adjusted to the pre-BD MMEF timing. It was previously recommended to correct the MMEF with the FVC for BDR testing to increase the MMEF's sensitivity (Cockcroft and Berscheid, 1980). The MMEF is the average flow of the middle (25%-75%) of the FVC. The correction was recommended as the MMEF is a flow over time measure (L/s). Pre-bronchodilator, patients may take longer time to empty the lung to RV, which reflects the length and time of the MMEF measure. The correction was suggested to help in identifying changes which may not be found without correction. This was recommended because post-bronchodilator a different volume was measured which will affect the MMEF and may not detect the change. Despite not correcting for FVC, positive BDR for MMEF was found in this thesis in 71.4% of patients.

There were also some limitations from the dataset which prevented further analysis. These included the lack patients reported outcome such as the asthma control test (ACT). This could help understand the association of such patients reported outcomes with SAD and BDR. Furthermore, there were not enough data to stratify patients based on GINA severity stages. However, physiological severity was assessed and reported.

There is a lack of standardisation of how MMEF should assessed for acceptability and repeatability. Moreover, there are no standardisation of how BDR is conducted. The procedure could be affected by multiple factors such as bronchodilator dosage or aerosol delivery device. This led to variability in reporting methods as indicated in chapter 4. In this thesis, a pragmatic approach was used to define the BDR for FEV_1, which was used in the 2005 ATS/ERS guidelines (Miller et al., 2005b) and used as an example in supplementary materials of the 2019 update (Graham et al., 2019) and in NICE's guideline for positive BDR response (National Institute for Health Care Excellence (NICE), 2017). Similar approach was utilised with the BDR for MMEF. A previous study reported a 30% change of MMEF would be clinically positive response and therefore was used in the current thesis (Shim, 1989).

6.6 SUGGESTIONS FOR FUTURE WORK

6.6.1 MMEF as a diagnostic measure for asthma

As reported in this thesis, MMEF is a marker for small airways function. With the availability of robust reference ranges and access to spirometry it is feasible to assess the utility of MMEF in diagnosing asthma. This will require a cohort of patients with confirmed asthma and control subjects. Formal diagnostic test accuracy should

be conducted by utilising z-score of participants. Tests should be conducted to assess whether MMEF is able to discriminate between those with a confirmed asthma and healthy subjects. Asthma should be confirmed by a clinical diagnosis from a specialist physician, a positive BDR for FEV_1, and fractional exhaled nitric oxide (FeNO) of > 40 parts per billion (ppb). The derived cut-off points should be derived using a receiver operating characteristics (ROC) curve. Methods such as Youden index can be used to find the optimal cut-off point (Youden, 1950). These derived measures should also be validated in another cohort of patients and healthy subjects.

6.6.2 Standardisations of MMEF reporting

As described in this thesis, the MMEF is an index that reflects the small airways which are relevant to patients with asthma. The MMEF can be measured by the same manoeuvre used to produce FEV_1 and FEV_1/FVC with no extra tests required and therefore at no extra cost. Moreover, the global lung initiative (GLI) has produced the reference range for MMEF . However, unlike FEV_1 or FEV_1/FVC, the MMEF is more variable, therefore reporting it using the % predicted may not be appropriate. Further research is needed to assess the acceptability and repeatability criteria for MMEF and to assess what physical characteristics of patients may affect the test.

6.6.3 Standardisation of BDR testing

Assessing the BDR is common procedure for patients with asthma. Reviewing the relevant guidelines such as American Thoracic Society (ATS) and the European Thoracic Society (ERS), there are no specific standardisation for how BDR should be conducted. For BDR, several factors may affect the test, including the dose of the

bronchodilator, the aerosol deliver device, or the length of time between the tests. These factors are not mentioned in the relevant guidelines. However, there are clear guidance on drugs withholding times that may affect the test. This area needs addressing as BDR has been associated with clinical symptoms. Clinical trials should be carried out using commonly found aerosol devices such as small volume nebuliser (SVN) and pressurised metered dose inhalers (pMDI). Salbutamol is commonly used as the bronchodilators; however different doses has been reported. Similar findings were observed for withholding times. Standardisation should also be extended to the reporting of BDR. The ARTP statement listed six different methods for reporting the change of BDR tests, however, in chapter 4, only two of the included studies reported how change was calculated. This highlights the need for a standardisation of baseline values and change to guide future research work which will impact clinical practice and patients outcome.

6.6.4 Characteristics and specialised treatments of those with BDR for MMEF alone

In chapter 5, it was highlighted that all patient with BDR for FEV_1 had a BRD for MMEF as well. However, some patients had BDR for MMEF alone. This indicated that some patients may exhibit physiological response in the small airways that may not be reflected in the larger airways. This is important as these patients may benefit from specialised aerosolised treatment that target the small airways such as extra-fine inhalers. These treatments may have higher deposition in the small airways and improve patients' outcomes. It would be helpful to conduct trials to assess the response

of the small airways to extra-fine particles in those with SAD, focusing on patient centred outcomes.

6.6.5 Those with AO without SAD

In chapters 3 and 5, some patients were presented with AO in the absence of SAD. This group of patients had a lower likelihood of BDR for both MMEF and FEV_1 opposed to those with SAD. However, low MMEF (but not SAD) was observed. This group of patients was small; however, it requires further research to understand the type of abnormality, in terms of symptoms and patients reported outcomes. It seems that this group of patients has unique characteristics that should be explored.

6.7 CONCLUSION

The presented thesis underlined that in adults with asthma, small airways function is relevant for the assessment of disease and perhaps diagnosis. With the evidence of a high prevalence of SAD in asthma, small airways function could be utilised for clinical and research purposes. It also appears that SAD is an early marker for disease progression as it may occur in the absence of physiologically defined AO. The impairment of small airways as measured by MMEF z-score was greater than the larger airways as measured by FEV_1. This highlights the potential importance of assessing the small airways to guide treatment choices and measure treatment-associated outcomes. SAD was associated with a positive BDR for both FEV_1 and MMEF. This highlights the importance of assessing SAD as predictor for BDR which is known to be associated with clinical symptoms. All patients with a positive BDR for FEV_1 had a positive BDR for MMEF, whereas some had a positive BDR for MMEF

alone. This highlights the potential importance of targeting the small airways using aerosolised treatments, and the need for further study of clinical outcomes associated with the treatment of BDR in MMEF.

Sadly, further research is impeded by the diversity of how SAD is measured and reported, with no consensus found. Furthermore, quantifying and reporting BDR for FEV_1, let alone MMEF is not adequately standardised. This mirrored the discrepancy of how BDR is quantified in terms of units, dose of the bronchodilator, aerosol delivery device, and length of time between the pre- and post-tests, which may impact the results of the BDR assessment. Standardisation would enhance the impact of research into SAD and BDR, and would enable decisions to be made as to the inclusion of tests of SAD into clinical practice.

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8. LIST OF APPENDICES

8.1.1 Part of chapter 1 publication

Check for updates

Review Article

Chronic Respiratory Disease

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The diagnosis of asthma. Can physiological tests of small airways function help?

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Abstract
Asthma is a common, chronic, and heterogeneous disease with a global impact and substantial economic costs. It is also associated with significant mortality and morbidity and the burden of undiagnosed asthma is significant. Asthma can be difficult to diagnose as there is no gold standard test and, while spirometry is central in diagnosing asthma, it may not be sufficient to confirm or exclude the diagnosis. The most commonly reported spirometric measures (forced expiratory volume in one second (FEV_1) and forced vital capacity assess function in the larger airways. However, small airway dysfunction is highly prevalent in asthma and some studies suggest small airway involvement is one of the earliest disease manifestations. Moreover, there are new inhaled therapies with ultrafine particles that are specifically designed to target the small airways. Potentially, tests of small airways may more accurately diagnose early or mild asthma and assess the response to treatment than spirometry. Furthermore, some assessment techniques do not rely on forced ventilatory manoeuvres and may, therefore, be easier for certain groups to perform. This review discusses the current evidence of small airways tests in asthma and future research that may be needed to further assess their utility.

Keywords
Asthma, small airways function, diagnosis, spirometry, oscillometry

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Background

Asthma is a highly heterogeneous, chronic respiratory disease with variations in inflammatory processes, clinical course, severity and response to treatment. Inflammation of the airways leads to both clinical symptoms such as chest tightness, wheezing, coughing (classically worse at night or early morning[1]) and variable expiratory airflow limitation that changes with time and intensity, becoming fixed in a proportion of cases.

Symptomatology, exacerbations, airways inflammation and airway remodelling can be reduced with an appropriate diagnosis and treatment plan. However, there is still a significant burden of undiagnosed, hence untreated asthma in both children and adults.[2] Case-finding studies suggest under-diagnosis is common, with one large study describing undiagnosed asthma in 50% of all cases.[3] Confirming the diagnosis is also associated with diagnostic delay, with one study describing a median delay between meeting symptom-based criteria and a physician diagnosis of 1.7 years.[4] Undiagnosed asthma and diagnostic delay are critical, as both are linked to poor clinical outcomes.[5,6]

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Misdiagnosis is also common, with studies describing approximately 30% of patients who are diagnosed with asthma having no objective evidence of asthma when tested more thoroughly.[7,8] Over-diagnosis is also problematic, as potentially alternative diagnoses may be missed and patients might take long term therapy which is not required.

Some of this diagnostic uncertainty reflects the fact that there is no gold standard test to diagnose asthma. A diagnosis is based on suggestive symptoms and a detailed medical history and examination, as well as objective measures, most commonly spirometry with reversibility and serial peak flows.[9] However, symptoms can be variable and intermittent as well as being common across a variety of respiratory and non-respiratory medical conditions.

Although spirometry is used to objectively assess asthma, the sensitivity of spirometry to diagnose asthma has been quoted to be as low as 29% against a reference standard of bronchial provocation test.[10] Normal spirometry does not exclude asthma, as airflow obstruction can be transient, manifesting only at certain times of the day or in response to allergy triggers.[11] Abnormal results do not diagnose asthma, as airflow obstruction may be observed in patients with other diseases such as Chronic Obstructive Pulmonary Disease (COPD).[10,12]

Performing spirometry can be challenging as measurements require significant patient effort and an ability to follow the instructions of healthcare specialists.[10,13] Exhaling forcefully through a mouthpiece is not a natural breathing manoeuvre, which can make it challenging to obtain accurate results.[14] Results are interpreted in comparison with predicted values based on height, age, sex and race. However, the 'normal' reference ranges are wide and differentiating between health and disease is not always straightforward. Furthermore, the observable differences in lung size across ethnic groups are not all represented sufficiently in reference populations,[15] just as the extremes of age are under-represented.

Traditionally reported spirometric parameters such as the forced expiratory volume in one second (FEV_1), the forced vital capacity (FVC) and FEV_1/FVC may not reflect dysfunction in the small airways.[16] Indeed, asthma was classically considered a disease of the large airways but there has been an increasing awareness that the small airways (defined as bronchial passages less than 2 mm in diameter) are also affected. Autopsy specimens from fatal cases of asthma have demonstrated inflammation in both the small and large airways with no definitive differences in the composition of inflammation at either site.[17] Small airways dysfunction (SAD) has been described in children with mild or intermittent asthma symptoms with a normal FEV_1, suggesting small airways involvement is an early manifestation of the disease.[18] In a study of transbronchial biopsies, the inflammatory cell infiltrate in the small airways was greater than that in the medium and large airways in patients with poorly controlled asthma symptoms.[19] Furthermore, there are now inhaled treatments with extra-fine particles that can target the small airways, leading to increased symptomatic benefit and improved clinical outcomes for asthma patients.[20] All of these studies suggest the small airways might be important in asthma and an important therapeutic target. In theory, physiological assessment of small airways function could also provide the means to diagnose asthma with greater certainty and monitor response to treatment.

In this review, the pathological basis for small airways involvement in asthma will be discussed alongside the current tools available to assess small airways function. We will consider the current evidence to support whether tests of small airways could diagnose asthma or the response to treatments, which can now target small airway function.

The small airways and the evidence for their involvement in asthma

Studies suggest that lungs with a volume of 5 L contain approximately 30,000 small airways and that most small airways are 0.51 mm–1.0 mm in diameter.[21] These airways account for more than 98% of the cross-sectional area of the lung, terminate within the alveolar sacs, contain no cartilage to support their structure and are, therefore, more prone to collapsing.[22] However, the large cross-sectional surface area of the small airways also means that they only account for 10% of the total airway resistance.[23] This led to the small airways being described as the 'quiet zone' as extensive small airways disease can be present with little abnormality in conventional pulmonary function tests, which are insensitive to small airways function.[24]

There is increasing evidence that small airways involvement is present in asthma and that it is associated with both worse symptoms and poorer clinical outcomes.[22,25] Pathological post-mortem studies have demonstrated inflammation and airway remodelling in the small airways of asthmatic patients, especially those of an eosinophilic phenotype, which traditionally can often be reduced with appropriate treatment.[26,27] Biopsy studies in asthma have also confirmed the presence of small airways inflammation and alveolar eosinophils, the burden of which correlated with lung function decline.[28] An increase in airway smooth muscle mass, mucus plugging and goblet cell hyperplasia have all been described in the large and small airways in asthma[29] but there appear to be differences in the distribution of inflammation. Post-mortem studies in fatal asthma suggest that inflammation is mainly contained within the inner wall of the large airways. In contrast, inflammation tends to occur in the outer airway wall of the small airways,[27] extending to the perivascular

region of the pulmonary arteries and the peribronchiolar alveoli.[30]

Children with asthma have been shown to have greater disease involvement in the peripheral as opposed to the central airways,[31] and SAD has been described in children with mild or intermittent asthma symptoms, often in the absence of an abnormal FEV_1[18]. This might lead to the assumption that SAD is an early feature of asthma. However, SAD is not universal in asthma, and it appears to affect only a subset of patients. In the previously discussed study of small airways function in children, only one third had abnormalities in tests of small airways function.[18] A systematic review conducted in 2016 suggested that SAD could be measured in approximately 50–60% of patients with asthma and that SAD could occur in asthma patients without any evidence of larger airway obstruction.[22] A multinational study called AssessmenT of smalL Airways involvemeNT In aSthma (ATLANTIS) in 2019 assessed the presence of SAD in 773 adults with asthma using multiple tests of small airway function.[32] In this group, SAD was also common but, crucially, different SAD techniques and devices altered the detected prevalence of SAD, suggesting that different tests identified different groups of patients. This highlights the critical nature of test selection when comparing studies (discussed in more detail later).

Small airways dysfunction as a phenotype of asthma

A phenotype can be defined as any observable clinical characteristic or trait of a disease that stratifies its presentation, outcomes or response to treatment, without any implication of a mechanism.[33] Asthma is now stratified into clinical phenotypes, with the aim of providing treatment pathways based on the likelihood of response.[34] Cluster analyses have identified asthma phenotypes using several different features, including the age of symptom onset, the presence of atopy, the severity of airways obstruction, the presence of co-morbidities such as obesity and the requirement and response to medication.[35] One notable analysis of 439 patients described several asthma phenotypes: early-onset atopic asthma, obesity-associated asthma, non-eosinophilic asthma, benign asthma, early symptom predominant asthma and inflammation predominant asthma, with treatment recommendations for each phenotype.[36] Several trials have been proposed to classify phenotypes of asthma by observing the response to triggers or clinical characteristics.[37]

Given the SAD is only present in a proportion of asthma patients, it is possible that this too could be considered a phenotype. Studies comparing asthma patients with and without small airways disease (measured using physiological tests) have described clinical differences between the groups. These include a reduced FEV_1 in combination with a history of smoking, raised blood eosinophils and poorly controlled asthma.[38] Bronchial hyper-responsiveness (BHR) has also been shown to be a feature of those with SAD. In one study of 94 patients with asthma, those with small airways obstruction had more severe BHR as well as lower FEV_1, FVC and FEV_1/FVC values and higher levels of reversibility.[39] In the same study, patients with small airways obstruction using inhaled corticosteroids (ICS) had a significantly higher daily dose of ICS than patients without small airways obstruction (800 vs 500 μg per day beclomethasone dipropionate equivalent).

There are also specific therapies that may be more beneficial to those with SAD, particularly inhalers with extra and ultrafine particles that are more likely to reach the small airways. Inhaler devices that have been routinely used in clinical practice may not effectively deliver ICS into small airways. Conventional aerosol-generating devices such as small-volume nebulizers (SVN) or pressurised metered-dose inhalers (pMDI) generate fine, aerosolized particles with a mass mean aerodynamic diameter (MMAD) of 2–5 μm. Although other factors contribute to drug deposition in the lungs (including inhaler technique and flow rates), particles of this size may not efficiently reach small airways compared to extra-fine inhalers (1–2 μm).[40,41]

Particle size is a major determinant in the deposition and distribution of inhaled drug within the lungs. In a study of 12 asthmatic subjects, the lung distribution of inhaled technetium-99m-labelled monodisperse albuterol aerosols was assessed by planar gamma-scintigraphy. Here, smaller particles achieved greater total lung deposition but bronchodilation (assessed by FEV_1 and MMEF) was greatest with the larger particle size.[42] Ciclesonide is an extra-fine particle ICS (with a mass median aerodynamic diameter (MMAD) of 1.0 μm) that shows both high overall lung deposition and peripheral lung distribution in healthy volunteers and patients with asthma.[43,44] Moreover, ciclesonide has been associated with improved asthma outcomes in patients, including a reduction in exacerbation frequency, better asthma control and improved tests of small airways function.[20,45] This highlights the need of more research with an emphasis on small airways response in asthmatic subjects.

There has been a move to develop extra-fine particles (defined as particles less than 2 μm in MMAD) for inhalation to address this limitation. These particles have shown higher deposition rates in the lung periphery and a better response to treatment, especially when patients have evidence of SAD.[46] Currently, the EU Clinical Trials Registry 16[47] and the USA Clinical Trials Registry collectively report 151 studies on treating small airways in asthma,[48] highlighting the interest in this area.

Endotypes are defined as subtypes of a disease or condition which share pathophysiological feature at the molecular and/or cellular level.[49] A number of asthma

Table 1. Summary of objective tests used in diagnosing asthma by various organization.

Objective test	Recommended by which organization	Recognized limitations of test
Spirometry	NICE[92]	FEV_1 limitation may not be a marker for asthma as it is found in other obstruction diseases.[93] The test is effort-dependent
Reversibility	GINA[94], BTS/SIGN,[95] SINA,[93] NICE, ATS/ERS (severe)	Not only asthmatic patients have reversibility.[96] Effort-dependent
Peak flow monitoring	GINA, BTS/SIGN, SINA, NICE	Effort-dependent. Different PEF metres may have different results
Bronchial challenge	GINA, BTS/SIGN, SINA	Not as widely available, can be time consuming
DL_{CO}	Not recommended, only in severe asthma (ATS/ERS), and not all cases	
Biomarkers of inflammation in sputum (eosinophilic and neutrophilic)	BTS/SIGN, SINA	Not all patients produce sputum No "normal" ranges for cytokines. May be present with other diseases.[94] Needs technical expertise and time consuming[97]

NICE: national institute of clinical excellence UK; FEV1: forced expiratory volume in the first second; GINA: global initiative for asthma; BTS/SIGN: british thoracic society/scottish intercollegiate guidelines network; SINA: Saudi initiative for asthma; ATS/ERS: American thoracic society/European respiratory society; DL_{CO}: diffusing capacity for carbon monoxide.

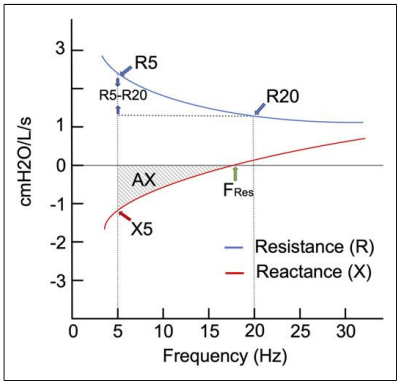


Figure 1. Illustration of oscillometry technique indices locations in resistance and reactance curves. Legend: The red line is the reactance line, and oscillation at 5 Hz is (X5). When reactance pressure reaches 0, this is the point of resonant frequency (Fres). The area under the curve between X5 and Fres is the area of reactance (AX). The blue line is the resistance line, and resistance at 5 Hz is the total lung resistance (R5). Resistance at 20 Hz is the large airways resistance (R20). The difference in resistance between R5 and R20 is considered as the small airways resistance (R5-R20).

endotypes have been proposed but currently it is unclear if SAD is associated with a separate endotype, or if SAD is present across several endotypes.[50] The limited studies to date have not found a 'small airways specific' inflammatory endotype but, in common with the larger airways, have described higher numbers of activated eosinophils in the small airways of patients with asthma.[51] In addition, alveolar inflammation has been specifically implicated in nocturnal symptoms, perhaps reflecting a symptom-based phenotype.[52]

In summary, current evidence suggests that small airways involvement could be a phenotype of asthma, which may be associated with clinical traits and a treatment response. Evidence to support SAD reflecting a specific endotype is currently lacking, but SAD has been associated with a predominance of eosinophilic inflammation.

The diagnostic challenge of asthma; can tests of small airways help?

The lack of a gold standard test makes diagnosing asthma challenging in some circumstances and, although most guidelines include similar steps to confirm a diagnosis, there are some differences. In Table 1, the current objective tests used by various guidelines are listed alongside their limitations. Of note, current guidelines do not include tests of small airways function in the diagnostic process. This may represent a missed opportunity given that patients with SAD and asthma tend to have poorer symptom control and that there are now treatments available to target this dysfunction. Studies have emphasised that the uptake and implementation of asthma guidelines remain suboptimal globally,[53–55] with some suggestion that the lack of objective measures to diagnose asthma (rather than support a diagnosis) are hindering patient care. Therefore, improving diagnostic criteria could improve patient outcomes. Perhaps tests of small airways could offer an opportunity to improve the diagnosis of asthma and identify patients who may benefit most from specific

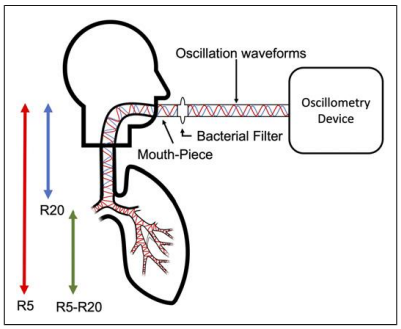


Figure 2. A diagrammatic representation of oscillometry. Legend: Higher frequencies travel shorter than lower frequencies. Resistance at 20 Hz (R20) (blue wave) is considered as a measure of larger airways, and resistance at 5 Hz (R5) (red wave), where waveforms travel further and considered as a measure of the total airways, therefore R5-R20 is considered as a measurement of smaller airways.

therapies, such as ultrafine inhaled medicines. There are several methodologies that can assess small airways function. Unfortunately, there is currently no agreed gold standard and specific small airways tests are often selected over others with no clear rationale. The most commonly used tests of small airways function are discussed below.

Physiological techniques to assess small airways function

Spirometry. Spirometry can provide information about small airways function, including measures of the forced expiratory flow when 50% (FEF_{50}) and 75% (FEF_{75}) of FVC has been expired as well as the average flow over 25–75% range (FEF_{25-75}). The FEF_{25-75} is also referred to as the maximal mid-expiratory flow (MMEF). This measurement has been used to assess small airways limitation in certain patient groups.[56] However, the FVC can affect test results and it is recommended that MMEF is corrected for FVC, particularly in bronchodilator response testing.[57,58] As MMEF is a highly variable measure, current spirometry guidelines only utilise FEV_1 and FVC as the clinically important measurements.[59] In 2014, a large, retrospective study suggested there was little value in reporting MMEF where FEV_1 and FVC was available,[60] which questioned the use of this test in clinical care. However, the participants included in this study were extremely heterogeneous, and not representative of a specific disease population, thereby limiting the results of the analysis. Studies in highly selected populations show that MMEF can be a useful physiological marker of small airways function that relates to different aspects of disease and its progression.[56,61]

MMEF in asthma

The MMEF has been used to help exclude cough variant asthma from chronic cough of other causes[62] and has been found to be abnormal in patients with mild asthma and bronchodilator reversibility.[39] Compared to the FEV_1, the percentage predicted of MMEF has consistently been lower in multiple groups with asthma, despite a normal or near-normal percentage predicted FEV_1[63]. Nevertheless, high variability and poor reproducibly are the major drawbacks of using MMEF in diagnosis.

Oscillometry

To overcome the limitations of maximal forced breathing manoeuvres, other tests that do not rely on such effort-dependent manoeuvres should be considered. These include forced oscillation techniques (FOT) and impulse oscillometry (IOS). The FOT was first developed in the 1950s and uses sinusoidal pressure oscillations.[64,65] The IOS uses the same concept but uses square wave pressure oscillation ('pulses') of multiple frequencies of oscillation at the same time. Both FOT and IOS are easy to perform, but result in complex measurements, describing lung impedance (Zrs; defined as the spectral relationship between volume and pressure) from which lung reactance (Xrs; defined as the amount of airway recoil against the oscillating pressure wave) and resistance (Rrs; defined as the amount of energy required for the oscillating pressure wave to move through the airways) are derived.[66]

All oscillometry devices generate oscillating sound waves between 3 and 35 Hz, with higher frequencies travelling shorter distances (measuring larger airways) and lower frequencies travelling further (measuring 'total' airway function). The use of multiple frequencies enables the assessment of most of the airway tree[65,67] and although oscillometry is primarily used to assess SAD, it can also be used to assess the large airways.[68] Higher resistance within the airways (for example, in the presence of bronchoconstriction) will cause Rrs to increase. In contrast, in emphysema, where there is an increase in compliance, Xrs will decrease, becoming more negative.[69] In Figure 1 is a graphical representation of the resistance and reactance curves, with all indices highlighted.

The main indices reported in oscillometry are the total airway resistance measured at 5 Hz (R5), large airways resistance, measured at 20 Hz (R20) and small airways resistance (R5-R20), which is simply the difference between R5 and R20, reactance at 5 Hz (X5) and AX, which is the area under the Xrs curve. Figure 2 is an illustration of how waveforms travel and how resistance is assessed.

For patients, oscillation techniques are simple and non-invasive. It involves the patient making a seal around the mouthpiece of the device, holding their cheeks and

breathing normally and quietly. When switched on, the device sends oscillatory pressure waves through the mouth into the airways. The test is short, with measurements recorded in under 20 s. The use of tidal breathing makes this measurement particularly useful in patients who have difficulty understanding or performing forced manoeuvres. However, the use of oscillation techniques has been limited by a number of factors. First, there is a need for large population-based studies to produce predicted values for a broader group of patients globally.[70] Second, different oscillometry devices have been shown to produce different values, limiting the ability to compare results across studies and to form large oscillometry databases that can be used in calculating reference values.[71] Despite this, there is some evidence that oscillometry can identify different asthma phenotypes,[72] which makes the test worthy of further investigation and development.

Oscillometry in asthma

Previous diagnostic test accuracy (DTA) studies have described that R5 had a sensitivity of 69–72% and specificity of 61–86% in diagnosing asthma when a positive bronchodilator response in FEV_1 was used as a reference standard,[73,74] comparing favourably to FEV_1. A systematic review and meta-analysis reviewing the DTA of bronchodilation response (BDR) using FEV_1 found a sensitivity of 38.9% (95%CI: 18.3–65.6) and specificity of 94.6 (95%CI: 85.7–99.7)[75]. Also, these tests might be able to differentiate whether respiratory symptoms relate to active asthma or another disease process. One study suggested small airways evaluated by IOS indices, R5-R20 and X5 and AX correlated more strongly with clinical symptoms (assessed by the asthma control test (ACT) score) than spirometry.[76]

Multiple breath washout

Ventilation heterogeneity is defined as the non-uniform distribution of inspired gas within the lung, which can be caused by luminal inflammation, mucus, variable thickening of the airway walls, smooth muscle hyperplasia/hypertrophy, and mucous cell metaplasia. The multiple breath washout (MBW) was first introduced in the 1950s to calculate ventilation heterogeneity using the lung clearance index (LCI). The test can be conducted using two techniques; intrinsic and extrinsic methods. In the intrinsic method, with air within the lungs and airways is 'washout out' as the patient breathes 100% oxygen and the measured volume of nitrogen is used to calculate the functional residual capacity (FRC).[77] . With the extrinsic technique, a tracer gas such is sulphur hexafluoride (SF6) is initially washed in and then washed out of the airways, which may be useful in overcoming the effects of high concentration of oxygen on breathing pattern in some populations.[78] The MBW test has also been considered in the assessment of small airway function. Although MBW is a simple, submaximal and non-invasive assessment, it is time consuming[79] and interpretation of the results can sometimes be difficult.[57] S_{acin} and S_{cond} are used as the two main indices to determine ventilation heterogeneity. The S_{acin} is the ventilation heterogeneity peripheral to the acinar entrance, while S_{cond} is the ventilation heterogeneity at the conductive lung zone.[80] Figure 3 provides a representation of how MBW is conducted.

MBW in asthma

There are a number of studies of MBW in asthma, of which only a few discuss or reference SAD. In patients with asthma, an abnormally high S_{acin} has been associated with an increased likelihood of responsiveness to inhaled corticosteroids and was considered suggestive of SAD.[81] S_{cond} is a predictor of airway hyper-responsiveness in adults with asthma.[82]

Despite the potential of MBW test in assessing small airways function and the advantages of a test which allows tidal breathing, the software for calculating $S_{acin\ and}$ S_{cond} is not widely available and limited to specialist centres. MBW also lacks robust, universally accepted reference ranges.[77] Table 2 provides a summary of small airways function tests.

Lung volumes

Using body plethysmography or gas dilution techniques, specific lung volumes and capacities can be obtained including residual volume (RV), FRC and total lung capacity (TLC). An increased RV may be linked to small airways obstruction due to air trapping caused by narrowing of the airways. The RV/TLC ratios have been used to assess the presence SAD.[22,32] Moreover, RV/TLC is considered a more specific index of air trapping in asthma.[57] Similar to spirometry, lung volume parameters have robust reference ranges for most populations.[83–85] The disadvantage of lung volumes is mainly around their specificity to small airways obstruction,[57] as elevated values can be due to other disease processes causing hyperinflation (such as emphysema).

Lung volumes in asthma

In one study of 321 physician-diagnosed subjects with asthma, 52% and 57% had an abnormal residual volume and abnormal RV/TLC ratio, respectively. There was a negative correlation between RV and $FEF_{25–75}$. The authors described a significant proportion of asthmatic patients having an elevated residual volume and an abnormal RV/TLC ratio in the presence of normal FEV_1/FVC ratio and absence of significant BDR.[86] A second study also found a high prevalence of RV dysfunction in asthma patients with a normal FEV_1/FVC ratio but with symptoms,[87] highlighting the potential for this test to identify patients with active lung disease.

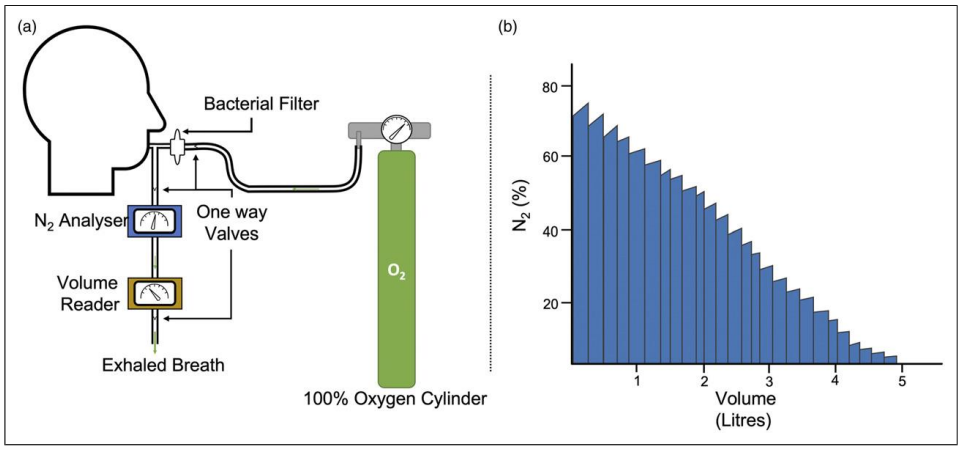


Figure 3. A diagrammatic representation of how intrinsic multiple breath washout is conducted. Legend: In (A) subjects breathe 100% of oxygen to washout nitrogen within the lungs and the amount of exhaled air is calculated. In (B) the amount of nitrogen exhaled nitrogen is analysed and volume is quantified. Lung clearance index is calculated by dividing the cumulative exhaled volume by the functional residual capacity.

Table 2. Summary of advantages and disadvantages of small airways function tests.

Small airways function test	Advantages	Disadvantages/Limitation	Reference range
FOT/IOS	Easy to perform	There are differences among different devices Difficult to interpret due to lack of training Lack of agreed reference ranges	Limited to some populations
MBW	Easy to perform	Relatively time consuming Difficult to interpret	Available
FEF_{25-75} (MMEF) FEF_{50}	Highly available Easy to interpret Widely implemented	Patient dependent Highly variable	Available
FeNO	Widely implemented Easy to interpret Easy to perform	Not sensitive to all phenotypes Not conclusive for small airways Not sensitive with patients on ICS**	Available

FOT/IOS: forced oscillation technique/impulse oscillometry; MBW: multiple breath washout technique; FEF_{25-75}: the mean forced expiratory flow between the 25% and 75% of the forced vital capacity; MMEF: the mean mid-maximal expiratory flow; FEF_{50}: The forced expiratory flow in the middle of the forced vital capacity; FeNO: fractional exhaled nitric-oxide; ICS: inhaled corticosteroids.

The use of small airways in the clinical diagnosis of asthma

The evidence presented suggest that tests of small airways function can be altered in some patients with asthma, but to be adopted into clinical practice, these differences have to have clinical significance in terms of diagnosis, pathology, progression or treatment response.

Head-to-head studies have reported that some patients with symptoms of or inflammation consistent with asthma, have altered small airways test results, even without objective evidence of airflow obstruction (add reference). Since asthma remains a clinical diagnosis, and a patient can have asthma without measurable airflow obstruction at the time of testing, the combination of symptoms and SAD could be sufficient to diagnose asthma, and may help identify specific groups of patients to inform treatment approaches. Studies to date have not shown major differences in the inflammatory endotype of patients with SAD and those without, but SAD is commonly associated with eosinophilic inflammation (add reference), which points towards a specific group of therapies. Ultrafine aerosol particles can reach the small airways, and therefore it would make sense to target these therapies with people with

measurable SAD and use SAD to track the response to therapy.

Next to consider is which tests to deploy. There are no gold standard recommended tests of SAD. Of the tests of small airways discussed above, only MMEF has well validated predicted ranges, although these are wide. With other tests, there would be uncertainty as to what represented an abnormal result. MMEF is routinely captured during normal spirometry, and therefore has no extra equipment or resource costs, and does not lengthen the time to perform tests. A disadvantage of MMEF is the forced nature of the manoeuvre. IOS, FOT and MBW use tidal breathing, but MBW is a lengthy test and requires specialised equipment. IOS and FOT also require specific devices, but the test is quick to perform and can be used by the bedside. MBW, IOS and FOT can be difficult to interpret, and with IOS and FOT, the exact device used alters results, meaning results are not comparable across centres.

The ongoing COVID pandemic has significantly impacted the provision of pulmonary function tests, leading to delays in the assessment of pulmonary diseases. Infection control measures in lung function laboratories aim to prevent the transmission of diseases between healthcare providers and patients or participants.[88] The evidence for the transmission of infections is limited[89] but pulmonary function testing is considered an aerosol-generating procedure. During the COVID-19 pandemic many laboratories reduced or stopped providing these tests. There is some evidence that FVC manoeuvres produce more and larger droplet particles than tidal breathing[90,91] and so it might be the case that submaximal assessments such as oscillometry or MBW, may be safer in terms of aerosol generation. However, this would need to be specifically tested.

In summary, these tests appear to be telling us something about certain groups of people with asthma, and the expansion of ultrafine inhaled therapies and strategies to target eosinophilic asthma may provide a clinical rationale to assess small airways. However, there are still barriers to deploying these tests in the clinic.

Knowledge gaps that limit the utility of small airways testing in asthma

Although studies have aimed to stratify asthma by small airways function, comparing study results is complex. The lack of a gold standard to assess SAD has resulted in studies varying in testing protocols, equipment used, and accepted cut-offs for identifying diseased and non-diseased states. Even within a specific methodology (such as oscillometry), different devices capture different measurements, which has prevented the development of common reference ranges.[71] These constraints have considerably limited our ability to draw firm conclusions from data published to date, despite promising results from smaller studies.

More research is urgently needed. First, to understand the importance of inflammation within the small airways in asthma and to identify if this requires specific treatment. Second, to clarify which tests of small airways function are most useful in identifying pathological change in asthma. This includes assessing when each test becomes abnormal and to decipher if certain tests are identifying different cohorts or subsets of patients. This will evaluate their diagnostic accuracy to determine if they might be of use in all cases of asthma (which current evidence suggests is unlikely) or a subset of patients (a phenotype). Third, to assess the variability of repeat testing and the accuracy of SAD tests in identifying disease severity and treatment response. Lastly, to determine if there is a relationship between measured SAD and inflammatory signals. If so, this could be used to stratify treatment decisions by inflammatory pathway and degree, potentially improving patient outcomes. However, this approach requires a consensus on the methods for assessing small airways to interpret insights from different studies.

Conclusion

Asthma is a common and increasingly prevalent condition associated with poor patient outcomes, including mortality and morbidity. There is an ongoing need to adequately diagnose, manage and control asthma more effectively. Asthma is heterogeneous, comprising several clinical phenotypes and cellular endotypes with different responses to treatment. We need specific tools to identify the subsets of patients most likely to benefit from specific and stratified therapeutic approaches and to monitor treatment response.

Studies over time have highlighted the involvement of the small airways in asthma pathology and recent advances in treatments that now reach the small airways offer a new therapeutic paradigm for asthma. Multiple physiological tests of small airways exist, which could be used to identify SAD and measure the response to treatment. However, currently there is no universally accepted approach to choosing a specific test for a specific population or clinical question and there still needs to be significant expansion of reference ranges to aid interpretation. Further research is needed but this is still an area of great promise that could potentially improve patient care and outcomes.

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8.2.1 Published Abstract In The European Respiratory Journal (ERJ)

Abstract

Introduction: Asthma is a common, heterogeneous disease that is characterized by chronic airway inflammation and variable expiratory airflow limitation. Current guidelines use spirometric measures for asthma assessment. This systematic review aimed to assess the use of tests of small airways function to diagnose asthma.

Methods: Standard systematic review methodology was used and a range of electronic databases was searched (Embase, MEDLINE, CINAHL, CENTRAL, Web of Science, DARE). Studies that used physiological small airways function tests to diagnose asthma in adults with no restrictions on language or date were included. The risk of bias and quality assessment tools used were AHRQ tool for cross-sectional studies and QUADAS-2 for diagnostic test accuracy (DTA) studies.

Results: 7072 studies were identified and 10 studies met the review criteria. 7 included oscillation techniques and 5 included maximal mid-expiratory flow (MMEF). Studies were small and of variable quality. In oscillation, total resistance (R5) was higher in asthmatic compared to control and reactance was lower. Predicted percentage of MMEF in asthmatic was lower than controls in all studies and lower than predicted FEV1. R5 showed 69-72% sensitivity and 61-86% specificity.

Conclusion: Small airways tests were found to be different in patients with asthma, showing more limitation in resistance, reactance and lower predicted values in MMEF. Further studies are needed to assess the effectiveness of these tests on a larger scale using different indices reported from the tests such as the difference between inhalation and exhalation in oscillation techniques and how demographics and comorbidities alter results.

Respiratory physiology

BMJ Open Respiratory Research

Physiological tests of small airways function in diagnosing asthma: a systematic review

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ABSTRACT

Background Asthma is a common, heterogeneous disease that is characterised by chronic airway inflammation and variable expiratory airflow limitation. Current guidelines use spirometric measures for asthma assessment. This systematic review aimed to assess whether the most commonly reported tests of small airways function could contribute to the diagnosis of asthma.

Methods Standard systematic review methodology was used, and a range of electronic databases was searched (Embase, MEDLINE, CINAHL, CENTRAL, Web of Science, DARE). Studies that included physiological tests of small airways function to diagnose asthma in adults were included, with no restrictions on language or date. The risk of bias and quality assessment tools used were Agency for Healthcare Research and Quality tool for cross-sectional studies and Quality Assessment of Diagnostic Accuracy Studies 2 for diagnostic test accuracy (DTA) studies.

Results 7072 studies were identified and 10 studies met review criteria. 7 included oscillation techniques and 5 included maximal mid-expiratory flow (MMEF). Studies were small and of variable quality. In oscillometry, total resistance (R5) and reactance at 5 Hz (X5) was altered in asthma compared with healthy controls. The percentage predicted of MMEF was lower in patients with asthma compared with controls in all studies and lower than the % predicted forced expiratory volume in 1 s. In DTA of oscillometry, R5 showed a sensitivity between 69% and 72% and specificity between 61% and 86%.

Conclusion There were differences in the results of physiological tests of small airway function in patients with asthma compared with controls. However, studies are small and heterogeneous. Further studies are needed to assess the effectiveness of these tests on a larger scale, including studies to determine which test methodology is the most useful in asthma.

Key messages

- Is there evidence to support the use of physiological tests of small airways function in the diagnosis of asthma?
- There is evidence of small airways dysfunction in asthma, which some physiological tests can identify. However, studies are small and heterogeneous and more studies are needed to understand the clinical utility of these tests.
- This systematic review provides a summary of the current evidence around physiological tests of small airways and asthma. It includes recommendations for the future work required to before the adoption of physiological small airways tests in the diagnosis of asthma.

BACKGROUND

Asthma is a common but heterogeneous disease characterised by chronic airway inflammation and clinically defined by the presence of respiratory symptoms that vary over time and in intensity. Physiologically, asthma is characterised by variable expiratory airflow limitation which may become persistent over time.[1] Symptoms and airflow limitation can be extremely variable, including the age of onset, triggers for symptoms, the decline in lung function and therapeutic response.

It is estimated that 339 million people are affected by asthma globally[1] but diagnosing asthma is often challenging as there is no gold standard test. This has led to a high burden of undiagnosed disease, especially in children and older adults.[2 3] According to current guidelines,[1 4] a diagnosis of asthma should be objectively supported with an assessment of forced expiratory volume in 1 s (FEV_1) reversibility. However, some patients with asthma have no evidence of reversibility or airflow obstruction[5 6] and airflow obstruction and reversibility are seen in patients with alternative diagnoses such as chronic obstructive pulmonary disease (COPD).[7 8] Furthermore, the forced manoeuvres required for spirometry requires effort and coordination, which can be difficult for some individuals.[9]

In the past, asthma was thought to only affect larger airways[10] but current evidence suggests that small airways (defined as airways of ≤2 mm in diameter) are affected as well. The small airways may form a site of active disease, even in the absence of airflow

obstruction.[11] If the small airways are the first to be affected in asthma, identifying small airways dysfunction (SAD) may help identify asthma earlier, enabling treatment. However, there are a large number of tests that report small airways function. Some of these are being used as secondary outcomes in experimental studies of asthma, to determine asthma phenotype and assess the response to new therapies.[12] The evidence to support the use of any physiological test of small airways function in the diagnosis of asthma is unclear.

This systematic review aimed to assess the evidence to support the use of commonly reported physiological tests of small airways function to diagnose asthma in adults, and assess if the selected tests should be included in future clinical studies of the disease.

METHODS

The protocol was prospectively registered in the international registry of systematic reviews (PROSPERO) with registration number CRD42019133239. The review was prepared in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[13] and the PRISMA checklist is provided in online supplemental material file S1. Meta-analysis was considered where homogenous results were provided, otherwise data were pooled for graphical presentational purposes.

Through both scoping searches and discussion with experts, the following test were selected to be included in the search, forced oscillation technique (FOT), impulse oscillometry (IOS) and maximal mid-expiratory flow (MMEF) also known as forced expiratory flow between 25% and 75% of forced vital capacity (FVC) ($FEF_{25\%-75\%}$), and multiple breath washout test (MBW). These tests were selected as they represented some of the most commonly reported physiological tests of small airways function in obstructive lung disease in adults. Online supplemental figure S2 shows the Population, Intervention, Comparison and Outcome (PICO) chart with the studies selection criteria.

Eligibility criteria

Studies were considered for inclusion if they used one of the proposed physiological small airways function tests (FOT/IOS, MBW, MMEF) in diagnosing asthma in adults aged >18 years old. Patients with either a physician diagnosis or a suspected diagnosis of asthma were considered for inclusion. FEV_1 was used as the comparator as it is the current standard in physiological airway assessment. Studies were excluded if they included only children (<18 years), patients with respiratory infections within 2 months of the assessment, did not assess FEV_1, included patients with asthma-COPD overlap, were laboratory-based studies, animal-based studies or case series of less than 10 participants. There were no language or publication date restrictions.

Search queries were carried out in May 2019 (and the detailed search strategy is found in online supplemental material file S3) on the following electronic databases: Embase, MEDLINE, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science (Abstracts and Proceedings) up to 5 years and DARE database for grey literature. Clinicaltrials.gov and EudraCT were also searched for active trials or published data. Hand searching of references listed in the selected articles was included. Search terms contained subject heading and terms for the selected test (IOS/FOT, MBW and MMEF) combined with terms of asthma and small airways function.

Study selection

Search results were imported into EndNote 9.1 (Clarivate Analytics) where duplicates were removed and data was uploaded to Rayyan[14] (a webapp tool used for screening titles and abstracts). Abstracts were screened blindly and independently by the authors MA and NYA using the predefined inclusion and exclusion criteria. Disagreements were resolved by discussion, otherwise by the third reviewer, whose initials were RGE. Full-text articles were acquired and imported into EndNote 9.1 by author MA and similar abstract screening methodology was used in screening full texts for eligibility.

Data extraction

Data were extracted by author MA and checked by author NYA for consistency and accuracy using a custom, piloted data extraction form. Diagnostic criteria used to identify asthma, tests used to aid the diagnosis such as airway reversibility, asthma severity, phenotype, medications, the device used and comorbidities were extracted to aid narrative review and provide clinical context. Studies were categorised based on the small airways test used. In diagnostic test accuracy (DTA) studies, sensitivity and specificity values were extracted and a 2×2 contingency table was calculated.

Quality and risk of bias assessment

Quality and risk of bias were assessed using validated tools based on study design. Cross-sectional studies were assessed using the Agency for Healthcare Research and Quality (AHRQ) checklist tool.[15] The Quality Assessment of Diagnostic Accuracy Studies 2[16] (QUADAS-2) was used in DTA. The QUADAS-2 tool assesses the risk of bias of studies over four domains: flow and timing, reference standard, index test and patient selection. The tool also assesses for applicability concerns under three domains: reference standard, index test and patient selection.

Descriptions of the tests of small airways function included in the reported studies

Here, only tests included in the analysed studies are described.

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Table 1 The characteristics of included studies without a diagnostic test accuracy analysis

ID	Sample size	Age	BMI	SA device	SA function	FEV_1	Diagnosis criteria
Mendonça *et al*[23] USA Cross-sectional	Asthma 35 Control 34	21 (3) 22 (2)	66 kg (12)*	NR	**Asthma**: MMEF% 69 (20) R8 cmH_2O 2.91 (0.99) **Control**: MMEF 93% (20) R8 cmH_2O 2.21 (0.48)	88 (11) 95 (10)	Previous diagnosis of asthma
Mori *et al*[24] Japan Cross-sectional	Asthma 49 Control 13	53 (15) 42 (16)	23.9 (6.3) 21.2 (3.3)	FOT-MostGraph-01	**Asthma**: MMEF% 49.9 (27.7) X5 cmH_2O −0.96 (1.03) R5–R20 cmH_2O 0.86 (0.62) R5 cmH_2O 4.2 (1.43) **Control**: MMEF 88.9 (22.1) X5 cmH_2O −0.05 (0.27) R5–R20 cmH_2O 0.32 (0.44) R5 cmH_2O 3.29 (1.17)	80.5 (20.2) 105.4 (17.8)	GINA 2009
Mousa and Kamal[25] Egypt Cross-sectional	Asthma 25 Control 20	45 (13) 34 (13)	29.27 (6.03) 26.6 (4.97)	IOS-Masterscreen	**Asthma**: R5% 245.24 (109.18) X5 (Unit NR) −2.87 (1.84) **Control**: R5% 109.25 (19.40) X5 (Unit NR) −0.28 (0.10)	59.68 (23.73) 89.75 (8.70	GINA 2017
Koruga *et al*[22] Serbia Cross-sectional	Asthma 31	23 (5)	NR	IOS-Masterscreen	**Asthma**: X5 kPa −0.09 (0.05) AX kPa 0.23 (0.16) R5 kPa 0.34 (0.09)	4.47 L (0.64)	Previous diagnosis of asthma
Nair *et al*[26] UK Cross-sectional	Asthma 82 Control 61	49 (17) 28 (10)	NR	IOS-Masterscreen	**Asthma**: X5% 441.72 (137.86) R5% 162.22 (7.5) **Control**: X5% −229.8 (125.75) R5% 111.01 (3.96)	83.99 (2.23) 99.25 (1.72)	Previous diagnosis of asthma
Gulden *et al*[30] Turkey Cross-sectional	Asthma 443	37 (15)	NR	Vmax 229	MMEF L/s 3.17 (5.8)	2.99 (0.9)	GINA 2006
Son *et al*†[31] Korea Cross-sectional	Asthma 125	43 (1)	NR	NR	1. MMEF% 97.67 (3.48) 2. MMEF% 95.08 (5.74) 3. MMEF% 70.16 (4.64)	1. 107.84 (1.79) 2. 105.2 (3.43) 3. 96.16 (2.71)	Clinical suspicion of asthma

Values reported in mean (SD).
*Weight in kg.
†Values reported in mean (SEM).
BMI, body mass index; FEV_1, forced expiratory volume in 1 s; FOT, forced oscillation technique; GINA, Global Initiative for Asthma; ID, study identification (authors) country, research type; IOS, impulse oscillometry; NR, not reported; SA, small airways.

differed among studies. Four studies used Global Initiative for Asthma guidelines,[24 25 28 30] one American Thoracic Society guidelines[27] and one the global strategy: Joint Report of the National Institute for Heart, Lungs and Blood and WHO.[29] Three studies recruited patients based on a previous diagnosis of asthma, without reporting the diagnosis criteria used.[22 23 26] One study reported that patients with symptoms of asthma were included without any formal diagnosis.[31] All included studies were based in different countries (the USA, UK, Japan, Korea, Turkey, Egypt, Russia, Serbia, Iran and China) from four different continents (North America, Europe, Asia and Africa) making the ethnicity of participants heterogeneous. Body mass index (BMI) was only reported in three of the included studies.[23–25] Meta-analysis of the data were inappropriate due to the variety and scope of methodological design. Where appropriate, data were displayed graphically to aid the representation of results. No MMEF studies explicitly corrected for FVC, which can potentially affect interpretation.

Risk of bias

Two risk of bias and quality assessment tools were used in this systematic review, based on the design of the included studies. Seven studies were assessed using the AHRQ tool for cross-sectional studies[15] (see figure 2A). This highlighted potential methodological issues around subject selection and quality assurance concerns, which may have impacted on the reliability of results and the

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Oscillometry

Oscillometry can be assessed using either the FOT or IOS. Oscillometry transmits oscillating sound signals of various frequencies along the bronchial tree, providing a measure of the total airway resistance (resistance at 5 Hz (R5)) and the proximal airway resistance (resistance at 20 Hz (R20)), which allows for the derivation of small airways resistance (R5–R20). Reactance at 5 Hz (X5) relates to physical properties of the lung parenchyma and its ability to expand and facilitate alveolar filling. Resonant frequency (Fres) is the point at which reactance is zero (when forces of inertia and capacitance are equal). The area of reactance (AX) is the sum of area under the reactance curve between X5 and Fres.[17 18] Limitations with this technique include the lack of universal normal ranges for all populations and variance of results between different devices, which can impede interpretation.[19]

Maximum mid-expiratory flow

The MMEF is the mean forced expiratory flow between 25% and 75% of the FVC ($FEF_{25\%–75\%}$) and is taken from the spirometric blow with the largest sum of FEV1 and FVC. The MMEF is highly dependent on the validity of the FVC measurement and the level of expiratory effort.[20 21] MMEF is commonly reported in studies of small airways as it is readily accessible from spirometry reports.

Patient and public involvement

Due to the nature of the study design, patients and public were not involved in this systematic review.

RESULTS

Study selection

Initial searches identified 7072 abstracts. After the removal of duplicates, 5764 abstracts were screened of which 469 abstracts included for full text screening. Ten articles ultimately met the inclusion criteria (figure 1 shows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram). Articles excluded in the full-text screening phase are described in online supplemental material file S4 with reasons given. All included studies were cross-sectional in design and 3/ 10 of the included studies were DTA studies.

Study characteristics

Seven of the included articles reported oscillometry (IOS/ FOT)[22–28] and five reported MMEF.[23 29–31] None of the included studies reported MBW use in diagnosing asthma. Seven studies were not designed as DTA studies and are presented in table 1. Three studies were designed as DTA studies and these are presented in table 2. The diagnostic criteria used to confirm a diagnosis of asthma

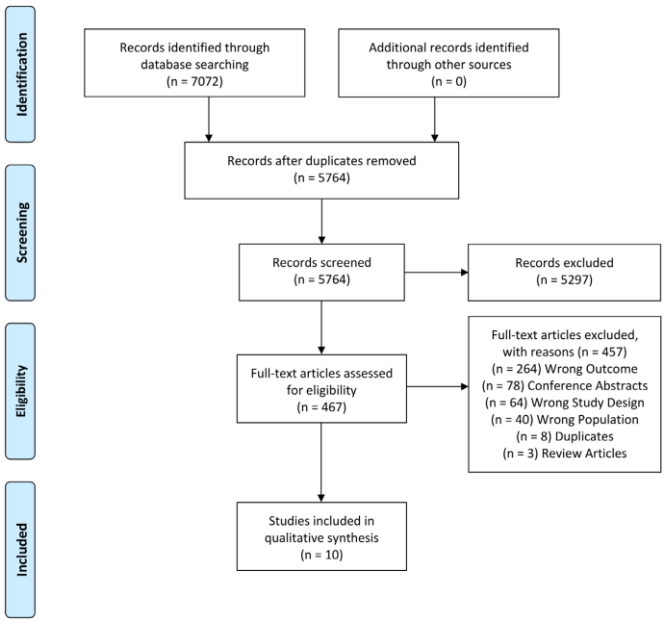


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta- Analyses flow chart of included studies.

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Table 2 The characteristics of included studies with a diagnostic test accuracy analysis

ID	Sample size	Age	SA device	FEV_1	SA test	Cut-off	TP	FN	FP	TN	Sen. %	Spc. %	Diagnosis criteria
Li *et al*[27]	Asthma 561	50.5 (18.8)*	MasterLab-IOS	NR	R5	NR	404	157	80	125	72	61	ATS guidelines
China	Control 205				X35		297	264	49	156	53	76	
Cross-sectional													
Nikkhah *et al*[28]	Asthma 87	41.4 (15.5)	MasterScreen-IOS	2.2 (0.6) L	R5	>0.51	60	27	12	75	69	86	GINA 2008
Iran	Control 87	37.6 (17.8)		3.2 (0.9) L	X5	≤−0.2	36	51	8	79	41	91	
Cross-sectional													
Iartsev[29]	1. Asthma 209	1. 47.4 (0.8)	Jaeger Master	1. 101 (0.9)	MMEF all	90%	138	71	19	197	66	91	Global strategy: Joint
Russia	2. Asthma 75	2. 47.4 (0.9)	Screen	2. 70 (0.73)	groups	70%	74	1	0	216	99	100	Report of the NHLBI
Cross-sectional	3. Asthma 81	3. (1.6)		3. 53.1 (1.6)		50%	80	1	0	216	99	100	and WHO 1993
	Control 216	43.8 (0.8)		102.6 (1.4)									

*For both groups.
.ATS, American Thoracic Society; FEV_1, forced expiratory volume in 1 s; FN, false negative; FP, false positive; GINA, Global Initiative for Asthma; ID, study identification (authors) country, research type; NHLBI, National Heart, Lung, and Blood Institute; NR, not reported; SA, small airways; Sen, sensitivity; Spc, specificity; TN, true negative; TP, true positive.

reporting of study follow-up. There was an overall low risk of bias around patient recruitment (including the source of subjects), the inclusion/exclusion criteria and time periods when patients were identified. Response rates and completeness of results were all reported. A summary of all included studies using both tools is available in online supplemental material file S5.

Three studies were assessed using QUADAS-2 tool for DTA studies (see figure 2B). One study had a high risk of bias and applicability concern in the patient selection phase. Two studies had a high risk of bias in the index test.

Results of individual studies

Oscillometry

Seven studies used oscillometry. One study used FOT,[24] five studies used IOS[22 25–28] and one study did not reported which type of oscillometry was used.[23] Five studies reported R5,[22–26] which represent the total lung resistance. Only one study reported R5–R20.[24] The values of the test were reported in different units with Mori *et al*[24] and Mendonça *et al*[23] reporting results in $cmH_2O/L/s$, Nair *et al*[26] and Mousa and Kamal the % predicted values and Koruga *et al*[22] and Nikkhah *et al*[28] in kPa/L/s.

Mori *et al*[24] reported R5, R5–R20, X5 and MMEF in 49 asthmatic patients,13 controls and 51 COPD patients. They described differences in MMEF, R5-R20 and X5 when comparing asthma to control subjects but not R5. In addition, they reported that the coloured three-dimensional model provided by the FOT device could differentiate between asthma, COPD and healthy subjects, with a higher resistance and lower reactance observed in asthma. Asthma severity was not reported and 24 of the asthmatic subjects were ex-smokers.

Mendonça *et al*[23] studied 35 asthmatic and 34 non-asthmatic participants but used a different technique and frequency than the commonly reported value. Oscillometry values were reported in $cmH_2O/L/s$. The whole breath resistance at 8 Hz (R8) and the minimum resistance at maximum inhalation R_{min} were both different when comparing the asthmatic (R8=2.91±0.99) and non-asthmatic group (R8=2.21±0.48). In the asthmatic patients, both the MMEF % predicted value was lower (69%±20) than healthy controls (93%±20) and a higher R_{min} was observed. They also conducted a methacholine challenge test (MCT) in all participants and found that (31/35) asthmatic subject and (8/34) non-asthmatic group had a positive result. A subgroup analysis was reported including asthmatics with positive MCT (31/35) and non-asthmatic with a negative MCT (26/34) and similar results were reported to the overall analysis with a higher R_{min} in positive MCT (1.41±0.42) compared with (1.02±0.24) in negative MCT. Moreover, MMEF was lower in the MCT positive group (68%±18) compared with (99%±18) in negative MCT group. The mean FEV_1 was 88%±11 predicted in the asthmatic group and 95%±10 predicted in the non-asthmatic group, both

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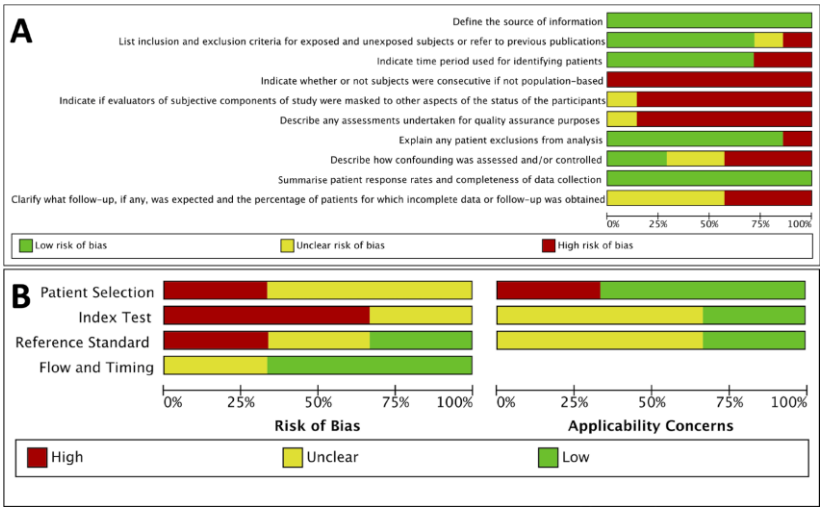


Figure 2 (A) Graph of Agency for Healthcare Research and Quality tool for quality/risk of bias of cross-sectional studies. (B) Graph of Quality Assessment of Diagnostic Accuracy Studies 2 tool for diagnostic test accuracy studies.

within the normal range. The authors examined the ability of MMEF, R_{min} and FEV_1 to predict airway hyperresponsiveness to methacholine by producing a receiver operating characteristic (ROC) curve which showed that MMEF had the highest area under the curve (AUC) of 0.87, while R_{min} and FEV_1 had AUC of 0.85 and 0.78, respectively. R8 was not reported in the ROC curve.

Mousa and Kamal[25] recruited 25 asthmatic patients and 20 healthy controls (with differences in the mean ages of the groups: asthmatic=45 years and the controls=34 years). Mean BMI did not differ between groups. The severity of the asthmatic group was not reported. IOS was used to assess asthma, with X5 and R5 being reported. R5 was reported in % predicted, but the X5 was reported in absolute values, but did not indicate the unit used. X5 and R5 were different between the two groups (asthma: mean X5 −2.87±1.84 and R5% 245.24±109.18. Healthy controls mean X5 −0.28±0.10 and R5% 109.25±19.40). FEV_1 was lower in the asthmatic group with a mean of 59.68%±23.73 predicted compared with the healthy controls mean of 89.75%±8.70 predicted.

Koruga *et al*[22] included 31 male military recruits in Serbia with a previous diagnosis of asthma. Histamine was used to assess bronchial hyperreactivity, recording the dose that decreased FEV_1 by 20% predicted value (PD20). X5, R5 and Ax was reported at baseline and after PD20. They found that the overall change in FEV_1 after PD20 was 25.66%, while the R5 and X5 had a change of 66.64±62.91 and 132.18±148.13, respectively. No controls were included in the study.

Similar to Koruga *et al*[22] and Mousa and Kamal,[25] Nair *et al*[26] used a Masterscreen-IOS device, but reported X5 and R5 as % predicted values. Nair *et al* included 82 patients with previous diagnosis of asthma and 61 healthy subjects. The asthma group was older (mean age 49 years vs mean age 28 years in the control group). Weight was not reported in either group. Nineteen per cent of the asthma patients were current or previous smokers, but the controls were all never smokers. All inhaled drugs such as short acting beta-agonists and long acting beta-agonists were withheld before reversibility testing except inhaled corticosteroids. Asthma severity and comorbidities were not reported. Airways reversibility was assessed using 400 µg of salbutamol via a metered dose inhaler and spacer and reported a mean change of 6.34% of FEV_1 in the asthma group and 2.25% in the healthy controls. The mean percentage of change after administering salbutamol was −33.78±4.43 and −72.93±88.73 in R5 and X5, respectively in the asthma group. In the control group, the mean change was −14.91±2.48 in R5 and 40.09±65.64 in X5.

Maximal mid-expiratory flow

Guldent Pasaoglu *et al*[30] recruited 433 asthmatic patients (mean age 37 years) and 152 patients with COPD (mean age 54 years), aiming to assess differences in clinical and spirometric features of asthma and COPD. 29% of the asthma group and 64% of the COPD group were current smokers. Reversibility was assessed in both groups using 200 µg of salbutamol and defined by an increase of more than 12% and 200 mL of the FEV_1 value. 62.1% of the asthma group met criteria for reversibility compared with 39.5% in the COPD group. MMEF was the only parameter that was below the normal range in non-smoking asthmatic patients with normal auscultation, suggesting that MMEF was a physiological marker of asthma in

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non-smoking asymptomatic patients. Although bronchodilator responses were measured, these were not reported.

Son *et al*[31] conducted a retrospective study of 125 patients with a clinical suspicion of asthma who had undergone an MCT. Patients were stratified into three groups based on their FEV_1 and MMEF response to MCT. The positive response to MCT was considered if there was a decline of 20% in FEV_1 and for MMEF, as well. Group 1 included patients with negative MCT tests for both parameters. Group 2 included patients with a negative FEV_1 and a positive MMEF. Group 3 included patients with positive test to both parameters. The mean ages of the included subjects were 45 years in group 1, 39 years in group 2 and 43 years in group 3. Eight subjects had a previous diagnosis of asthma, three in group 1 and five in group 3. Allergic rhinitis was reported in 34 subjects, 16 of them were positive to MCT in both spirometric indices, therefore included in group 3. Mean baseline MMEF in groups 1 and 2 was 97.67%±3.48 predicted and 95.08%±5.74 predicted, respectively. In group 3, mean MMEF was 70.16%±4.64 predicted. The authors suggested that MMEF may be a more sensitive marker of asthma than FEV_1 in patients with otherwise normal spirometry results.

DTA studies

Impulse oscillometry

Li *et al*[27] and Nikkhah *et al*[28] assessed the DTA of IOS for asthma. The majority of participants in Nikkhah *et al* study were women, while Li *et al*[27] had a majority of male participants. Neither study reported participants' weight or BMI. Nikkhah *et al* cut-offs were not pre-specified, but were proposed after plotting an ROC curve. Li *et al* did not report a cut-off value. They both studied resistance at 5 Hz, but reactance was studied at different frequencies with Li *et al* at 35 Hz and Nikkhah *et al* at 5 Hz. The sensitivity of R5 was reported as 72% by Li *et al* and 69% by Nikkhah *et al* while specificity reported by Li *et al* at 61% and Nikkhah *et al* at 86%. Reactance had lower sensitivity in both studies. Both studies did not report the asthma severity of the participants or clinical comorbidities and Li *et al* did not report the FEV_1 results, although they performed bronchodilator response tests on all participants. Figure 3A shows the pooled data of R5 of the two studies.

Maximal mid-expiratory flow

There was only one DTA study which used MMEF in asthma compared with controls (Yartsev).[29] The asthma group was older than the control group. Both the asthma and control groups had a majority of female participants. Asthma severity and comorbidities of participants were not reported. The author stratified asthma patients into three groups based on the baseline FEV_1. Group 1 included participants with FEV_1 of >80% predicted value, group 2 with FEV_1 60%–80% predicted and group 3 with FEV_1 25%–60% predicted. In MMEF tests, the cut-off used was 90% predicted in group 1, 70% predicted in group 2 and 50% predicted in group 3. The DTA of MMEF in group 1 was a sensitivity of 66% and specificity of 91%. Identical results were found in groups 2 and 3 with a sensitivity of 99% and specificity of 100%. The accuracy of MMEF was assessed on all groups with a cut-off value of 70% showed a sensitivity of 88% and specificity 97%. Using FEV_1, cut-off was set at 120% predicted in group 1, 90% predicted in group 2, 70% predicted in group 3. The DTA of FEV_1 in group 1 was a sensitivity of 77% and specificity of 65%. In groups 2 and 3, identical sensitivity of 100% and specificity of 100% was reported. All groups were assessed for accuracy using FEV_1, with a 70% predicted cut-off, showing a sensitivity of 92% and specificity of 88%. DTA data were pooled into the forest plot shown in figure 3B.

Synthesis of results

Small airways function in asthma were found to be different when compared with healthy controls. The % predicted MMEF value appeared consistently lower than the % predicted FEV_1, as shown in figure 4. In oscillometry, R5 was also found to be consistently higher in asthmatic when compared with healthy controls as shown in figure 5. These results highlight the presence of small airways limitation in asthmatic patients with

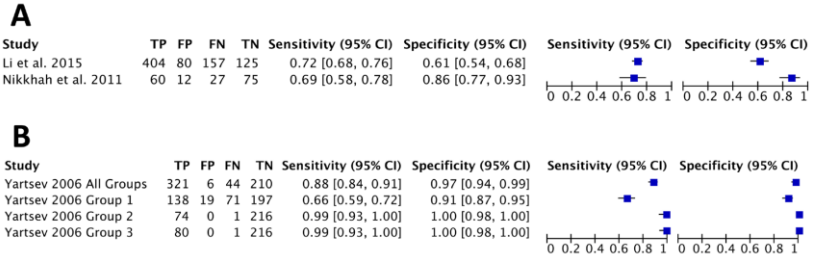


Figure 3 (A) Diagnostic test accuracy (DTA) forest plot of R5. (B) DTA forest plot of maximal mid-expiratory flow. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

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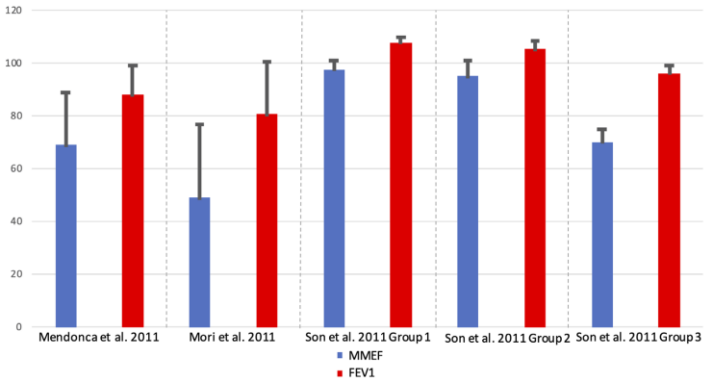


Figure 4 Comparison of % predicted of MMEF to FEV_1 in asthmatic patients. FEV_1, forced expiratory volume in 1 s; MMEF, maximal mid-expiratory flow.

heterogeneous characteristics including age, ethnicity and weight.

Risk of bias across studies

There were some concerns of bias in regard to reporting outcomes. Kamal and Mousa[25] reported R5 as the % predicted value while X5 was reported without a unit of measurement. Iartsev[29] did not report how the cut-offs were determined or how subjects were recruited.

DISCUSSION

To the authors' knowledge, this is the first systematic review to assess the use of physiological tests of small airways function in the diagnosis of asthma. Previous work has suggested that SAD is associated with asthma and that the prevalence of SAD increases with the severity of asthma.[32 33] This review suggests that most published studies of small airways function tests in asthma are heterogeneous, of varying methodological quality and have primarily identified SAD rather than using measures of small airways to diagnose asthma. No studies reported the severity of asthma in the participants and participants groups were often poorly matched or characterised in terms of other comorbidities and weight.

This review focuses on MMEF and oscillometry and does not explore all potential measures to assess small airways function. MMEF and oscillometry were chosen as these represented the most commonly cited small airways measures. The clinical utility of oscillometry techniques has been described in asthma and other lung conditions such as interstitial lung diseases and COPD.[19] Oscillometry has been suggested as a useful tool in diagnosing asthma in children.[34] However, there remains a lack of universal reference ranges, especially in adults. Height[23] and sex[35] appear to alter values. Oostveen *et al*[35]

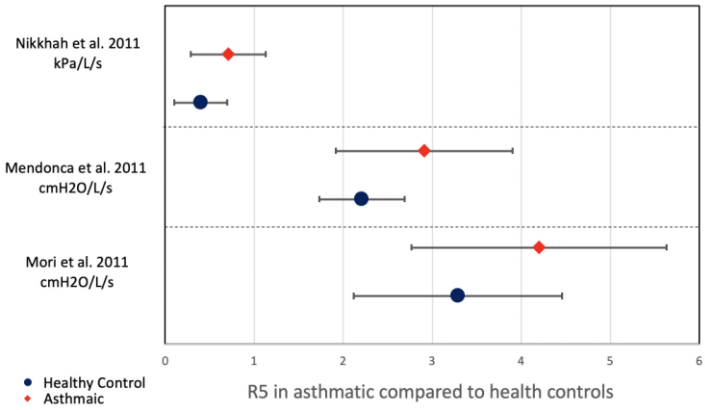


Figure 5 Comparison of R5 between asthmatic patients to healthy contr ols.

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conducted a multicentre study on healthy subjects in an effort to produce reference ranges for oscillometry in adults, but only one ethnicity was studied. Another study was also conducted in Japan to establish reference ranges for Japanese adults.[36] Understanding and interpreting oscillometry remains challenging. In this review, it was unclear if oscillometry studies provided the most robust measure of small airways function. The R5–R20 (often referred to as resistance of the small airways) was only reported by Mori *et al*.[24] Airways reversibility, a hallmark of asthma, was only assessed using oscillometry by Nair *et al*[26] and, here, the mean percentage change in the FEV_1 in the asthma group was 6.34%, which is less than the standard reversibility change of 12%.

The MMEF is an effort-dependent test and guidelines for reproducibility of the manoeuvre is based on FVC and FEV_1.[37] In all the included articles that studies MMEF, the % predicted of MMEF was found to be lower in asthmatic groups compared with control groups. Moreover, the % predicted value of MMEF was lower than the % predicted FEV_1 in the asthmatic group, suggesting that small airways limitation might be an early marker of airways obstruction. The potential utility of MMEF in early disease was described in one study of patients with alpha-1 antitrypsin deficiency, where an MMEF less than 80% predicted, with a normal FEV_1/FVC ratio, was associated with increased respiratory symptoms and a faster decline in FEV_1 compared with those with an MMEF of 80% or greater and normal spirometry, suggesting a role for MMEF in early disease monitoring.[38]

There are significant limitations to the evidence base described in this review including study heterogeneity, poor patient characterisation and differences in reported values. Not all tests of small airways function have been assessed in asthma (eg, MBW). There are no universally accepted predicted values for oscillometry, especially in adults, making the interpretation of the results more difficult. Oscillation techniques produce many parameters in both inspiratory and expiratory phases and the differences in reported values limits comparisons between studies. MMEF was not corrected for FVC in any study, and this is a limitation as MMEF is a timed/flow measurement and FVC exhalation curve changes may affect the results.[39] Nevertheless, most studies provide at least some signal of SAD in asthma suggesting these indices could be helpful in diagnosing and monitoring asthma. To take this field forward, further research is needed. This should include standardising the assessment of small airways tests (although different tests may have greater or lesser utility in different diseases) and forming normal reference ranges to aid interpretation. Studies in asthma need to predefine how asthma was diagnosed, and report clearly which small airways tests have been measured, by what device, what units are reported and what would be considered an abnormal result or clinically meaningful change in a specified value.

CONCLUSION

Physiological tests of small airways function are feasible in diagnosing asthma and have been shown to be altered in asthma when compared with healthy adults. However, a lack of robust reference ranges and the heterogeneity of approach complicate their use.

Further studies are needed to assess small airways function in asthma, especially in early disease. Larger studies are needed to assess the impact of demographic characteristics and comorbidities such as obesity or allergic rhinitis. This systematic review of current literature suggests these tests may have promise as part of the future diagnostic criteria of asthma, but more work is needed before they can be embedded into clinical care.

Correction notice The license type of the paper has changed from CC BY-NC to CC BY.

Contributors MA and ES conceived, planned and analysed the data, and made a major contribution in writing the manuscript. MA, NYA and RGE performed abstract screening, full-text screening and quality assessment. MA and RGE planned and performed searching strategy and data synthesis. RGE and JS contributed to data analysis and writing the manuscript. All authors have read and approved the manuscript.

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Patient consent for publication Not required.

Data availability statement All data relevant to the study are included in the manuscript or uploaded as supplementary information. All the included data has been obtained from the included peer-reviewed articles.

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8.2.3 Protocol Registry In PROSPERO

The use of physiological tests of small airways to diagnose asthma

Citation

Mohammed Almeshari, Nowaf Alobaidi, Ross Edgar, James Stockley, Elizabeth Sapey. The use of physiological tests of small airways to diagnose asthma. PROSPERO 2019 CRD42019133239 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019133239

Review question

What physiological tests of small airways function have been used to diagnose asthma?

Searches

The following electronic databases will be searches from inception up to April 2019:

EMBASE

MEDLINE

CINAHL

Cochrane Central Register of Controlled Trials (CENTRAL)

Web of Science (Abstracts & Proceedings) up to 5 years

Grey literature

Hand searching of references of the selected articles

Types of study to be included

Randomized Clinical trials

Non-randomized clinical trials

Diagnostic Test Accuracy studies

Case series with >10 participants

Condition or domain being studied

Asthma diagnosis via small airway physiological tests.

Participants/population

Adults (>18 years) with clinical suspicion of asthma.

Intervention(s), exposure(s)

Non-invasive, physiological small airway tests.

Comparator(s)/control

We will use the current standard diagnostic method of physiological assessment, which is spirometry reversibility.

Context

Studies in clinical settings where physiological tests of small airways are carried out by medically trained professional on adults (>18 years) with clinical suspension of asthma and the result compared with spirometry reversibility. Participants should not be suffering from other respiratory conditions that may effect the result of the spirometry.

Main outcome(s)

Physiological small airway tests used in diagnosing asthma.

Measures of effect

What small airway tests were used.

Additional outcome(s)

The effectiveness of physiological small airway tests in diagnosing asthma.

Measures of effect

Outcomes taken at post-intervention will be included.

Data extraction (selection and coding)

Two reviewers will independently screen title and abstract for inclusion against the inclusion and exclusion criteria listed above. Disagreement will be resolved through discussion and the third reviewer will resolve when necessary .

Full-text will be screened using the same independent process of two reviewers and a third where disagreement persists after discussion. There will be documented reasons for exclusion that will be reported. This process will be reported using PRISMA flow diagram.

Data extraction will be undertaken using an electronic data capture form. This will include but not be limited to will be on study design, patient characteristics, interventions, comparators, and outcomes. Data extraction will be done by one reviewer and checked for accuracy by a second reviewer with disagreement being checked by a third member of the team. Study's author will be contacted directly if data are ambiguous or missing.

Risk of bias (quality) assessment

All the final selected studies will be assessed for risk of bias using a pre-specified tool depending on the study design.

The reviewers will independently check each selected article to minimize bias.

Disagreement will be resolved using a third review. Information from the risk of bias assessments will be utilized when

synthesising the data to explain differences in study results and to comment upon the reliability of conclusion that arise

from the analysis

Tools to be used:

RCT: Cochrane RoB 2.0

NRCT: ROBINS-I

DTA: QUADAS 2

Case Series: JBI Critical Appraisal Checklist for Case Series

Strategy for data synthesis

A narrative synthesis will be carried out from the included studies and will be structured upon the tests being used.

Where appropriate standard meta-analytic methods will be used. Methodological heterogeneity will be assessed and reported. If any meta-analyses contain 10 or more studies, the likelihood of publication bias will be investigated through the construction of funnel plots and appropriate tests for small study effects (such as the Peters Test).

Analysis of subgroups or subsets

Where necessary data are available, subgroup analysis will be used to assess the effectiveness of small airways tests.

Contact details for further information

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Organisational affiliation of the review

University of Birmingham

https://www.birmingham.ac.uk

Review team members and their organisational affiliations [1 change]

Mr Mohammed Almeshari. University of Birmingham

Mr Nowaf Alobaidi. University of Birmingham

Mr Ross Edgar. University of Birmingham

Dr James Stockley. University of Birmingham

Dr Elizabeth Sapey. University of Birmingham

Type and method of review

Diagnostic, Narrative synthesis, Systematic review

Anticipated or actual start date

25 April 2019

Anticipated completion date

27 September 2019

Funding sources/sponsors

King Saud University

University of Birmingham

Conflicts of interest

Language

English

Country

England

Stage of review [2 changes]

Review Completed published

Details of final report/publication(s) or preprints if available [1 change]

https://bmjopenrespres.bmj.com/content/7/1/e000770

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Asthma; Diagnostic Tests, Routine; Humans; Lung

Date of registration in PROSPERO

07 May 2019

Date of first submission

23 April 2019

Stage of review at time of this submission [2 changes]

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Revision note

Progress update and addition of reviewer

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

07 May 2019

12 February 2020

14 February 2021

8.2.4: PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6

Search	**8**	**Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.**	**S.3**
Study selection	**9**	**State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).**	**6**
Data collection process	**10**	**Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.**	**6**
Data items	**11**	**List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.**	**6**
Risk of bias in individual studies	**12**	**Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.**	**7**
Summary measures	**13**	**State the principal summary measures (e.g., risk ratio, difference in means).**	**n/a**
Synthesis of results	**14**	**Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.**	**n/a**
Risk of bias across studies	**15**	**Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).**	**7**
Additional analyses	**16**	**Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.**	**N/A**
RESULTS			
Study selection	**17**	**Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.**	**8**
Study characteristics	**18**	**For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.**	**8**

Risk of bias within studies	**19**	**Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).**	**9**
Results of individual studies	**20**	**For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.**	**9**
Synthesis of results	**21**	**Present results of each meta-analysis done, including confidence intervals and measures of consistency.**	**14**
Risk of bias across studies	**22**	**Present results of any assessment of risk of bias across studies (see Item 15).**	**14**
Additional analysis	**23**	**Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).**	**N/A**
DISCUSSION			
Summary of evidence	**24**	**Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).**	**15**
Limitations	**25**	**Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).**	**15**
Conclusions	**26**	**Provide a general interpretation of the results in the context of other evidence, and implications for future research.**	**17**
FUNDING			
Funding	**27**	**Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.**	**1**

8.2.5: PICO chart with details of study selection criteria.

Population

- Adults >18 years old with asthma or clinical suspicion of asthma

Intervention

- Physiological tests small airways function

Comparator

- FEV_1

Outcome

- Diagnosis of asthma

8.2.6: Search strategy and number of results from databases:

Medline:
1. exp Asthma/
2. exp Bronchial Spasm/
3. exp Bronchial Hyperreactivity/ or exp Respiratory Hypersensitivity/
4. exp Airway Resistance/ or exp Bronchoconstriction/
5. airway reactivity.ab,ti.
6. exp Respiratory Function Tests/
7. small airway*.ab,ti.
8. distal airway*.ti,ab.
9. MMEF.mp.
10. fef25*.mp.
11. FOT.mp.
12. Forced Oscillatory.mp.
13. Impulse Oscillatory.mp. or exp Oscillometry/
14. Impulse Oscillatory.mp.
15. Impulse Oscillimatry.mp.
16. Impulse Oscillation.mp.
17. (IOS and airway*).mp.
18. exp Nitric Oxide/ and asthma.mp.
19. Fractional expired nitric oxide.ti,ab.
20. Fractional exhaled nitric oxide.ti,ab.
21. FeNO.ti,ab.
22. (FeNO and asthma).ti,ab.
23. multiple breath washout.mp.
24. MBW.ti,ab.
25. MBW.ti,ab. and airway*.mp.
26. exp Spirometry/
27. (Reversibility and asthma).ti,ab.
28. exp Respiratory Function Tests/
29. exp Peak Expiratory Flow Rate/
30. exp Asthma/
31. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
32. 26 or 27 or 28 or 29
33. adult*.mp.
34. 1 or 2 or 3 or 4 or 5
35. 30 and 31 and 32 and 33 and 34
36. Diagnos*.ti,ab.
37. 35 and 36

Results: 1856

EMBASE:
1. exp asthma/
2. exp bronchospasm/
3. exp bronchus hyperreactivity/
4. Respiratory Hypersensitivity.mp.
5. exp airway resistance/
6. exp bronchoconstriction/
7. airway reactivity.ab,ti.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp lung function test/
10. small airway*.ab,ti.
11. distal airway*.ti,ab.
12. MMEF.mp.
13. fef25*.mp.
14. FOT.mp.
15. Forced Oscillatory.mp.
16. Impulse Oscillatory.mp. or exp Oscillometry/
17. Impulse Oscillatory.mp.
18. Impulse Oscillimetry.mp.
19. Impulse Oscillation.mp.
20. (IOS and airway*).mp.
21. exp Nitric Oxide/ and asthma.mp.
22. Fractional expired nitric oxide.ti,ab.
23. Fractional exhaled nitric oxide.ti,ab.
24. (FeNO and asthma).ti,ab.
25. multiple breath washout.ti,ab.
26. MBW.ti,ab. and airway*.mp.
27. exp spirometry/
28. (Reversibility and asthma).ti,ab.
29. exp lung function test/
30. exp peak expiratory flow/
31. exp asthma/
32. adult*.mp.
33. diagnos*.ti,ab.
34. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
35. 27 or 28 or 29 or 30
36. 8 and 31 and 32 and 33 and 34 and 35

Results: 2553

Web Of Science:

TS=(Asthma OR bronchospasm OR bronchus hyperreactivity OR Respiratory Hypersensitivity OR airway resistance OR bronchoconstriction OR airway reactivity)
AND
TS=(lung function test OR small airway* OR distal airway* OR Pulmonary function OR PFT OR MMEF OR fef25* OR FOT OR Forced Oscillatory OR Impulse Oscillatory OR Oscillometry OR Impulse Oscillimetry OR Impulse Oscillation OR IOS OR Nitric Oxide ORFractional expired nitric oxide OR Fractional exhaled nitric oxide OR FeNO OR multiple breath washout OR MBW)
AND
TS=(Spirometry OR Reversibility OR lung function test* OR peak expiratory flow OR PEF*)
AND
TS=(Adult*)
AND
TS=(Diagnos*)

Up to 5 years = 975

CENTRAL (Cochrane)

#1 Asthma OR bronchospasm OR bronchus hyperreactivity OR Respiratory Hypersensitivity OR airway resistance OR bronchoconstriction OR airway reactivity
#2 lung function test OR small airway* OR distal airway* OR Pulmonary function OR PFT OR MMEF OR fef25* OR FOT OR Forced Oscillatory OR Impulse Oscillatory OR Oscillometry OR Impulse Oscillimetry OR Impulse Oscillation OR IOS OR Nitric Oxide ORFractional expired nitric oxide OR Fractional exhaled nitric oxide OR FeNO OR multiple breath washout OR MBW
#3 Spirometry OR Reversibility OR lung function test* OR peak expiratory flow OR PEF*
#4 adult*
#5 diagnos*
#6 #1 AND #2 AND #3 AND #4 AND #5

Results: 813

CINAHL:
S1 (MH "Asthma+")
S2 (MM "Bronchial Spasm")
S3 TI bronchospasm OR AB bronchospasm
S4 "bronchus hyperreactivity"
S5 "bronchus hyperreactivity"
S6 TI bronchus hyperreactivity OR AB bronchus hyperreactivity

S7 TI bronchus hyperreactivity OR AB bronchus hyperreactivity
S8 (MH "Respiratory Hypersensitivity+")
S9 (MM "Airway Resistance")
S10 TI airway resistance OR AB airway resistance
S11 (MM "Bronchoconstriction")
S12 "airway reactivity"
S13 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12
S14 (MH "Respiratory Function Tests+")
S15 TI small airway* OR AB small airway*
S16 TI distal airway* OR AB distal airway*
S17 TI MMEF OR AB MMEF
S18 TI fef25* OR AB fef25*
S19 TI FOT OR AB FOT
S20 TI MMEF OR AB MMEF AND airway*
S21 TI Forced Oscillatory OR AB Forced Oscillatory
S22 TI Impulse Oscillimetry OR AB Impulse Oscillimetry
S23 TI Impulse Oscillimetry OR AB Impulse Oscillimetry
S24 TI Impulse Oscillation OR AB Impulse Oscillation
S25 TI (IOS and airway*) OR AB (IOS and airway*)
S26 AB (Nitric Oxide AND asthma) OR TI ((Nitric Oxide AND asthma)
S27 AB (feno AND asthma) OR TI (feno AND asthma)
S28 TI multiple breath washout OR AB multiple breath washout
S29 "MBW"
S30 S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29
S31 (MM "Spirometry") OR (MM "Airway Resistance") OR (MH "Respiratory Airflow+") OR (MH "Forced Expiratory Flow Rates+") OR (MM "Peak Expiratory Flow Rate")
S32 "diagnos*"
S33 S1 AND S13 AND S30 AND S31 AND S32
S34 (MH "Asthma+")
S35 (MM "Bronchial Spasm")
S36 TI bronchospasm OR AB bronchospasm
S37 "bronchus hyperreactivity"
S38 "bronchus hyperreactivity"
S39 TI bronchus hyperreactivity OR AB bronchus hyperreactivity
S40 TI bronchus hyperreactivity OR AB bronchus hyperreactivity
S41 (MH "Respiratory Hypersensitivity+")
S42 (MM "Airway Resistance")
S43 TI airway resistance OR AB airway resistance
S44 (MM "Bronchoconstriction")
S45 "airway reactivity"
S46 S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45

S47 (MH "Respiratory Function Tests+")
S48 TI small airway* OR AB small airway*
S49 TI distal airway* OR AB distal airway*
S50 TI MMEF OR AB MMEF
S51 TI fef25* OR AB fef25*
S52 TI FOT OR AB FOT
S53 TI MMEF OR AB MMEF AND airway*
S54 TI Forced Oscillatory OR AB Forced Oscillatory
S55 TI Impulse Oscillimetry OR AB Impulse Oscillimetry
S56 TI Impulse Oscillimetry OR AB Impulse Oscillimetry
S57 TI Impulse Oscillation OR AB Impulse Oscillation
S58 TI (IOS and airway*) OR AB (IOS and airway*)
S59 AB (Nitric Oxide AND asthma) OR TI ((Nitric Oxide AND asthma)
S60 AB (feno AND asthma) OR TI (feno AND asthma)
S61 TI multiple breath washout OR AB multiple breath washout
S62 "MBW"
S63 S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62

Results: 875

Total Before duplicates removal = 7072

8.2.6: List of excluded articles and reasons:

Reason of Exclusion	Citations Numbers
A. Wrong Outcome	1-264
B. Wrong Population	265-304
C. Wrong Study Design	305-368
D. Abstracts Only	369-446
E. Review articles	447-449
F. Duplicates	450-457

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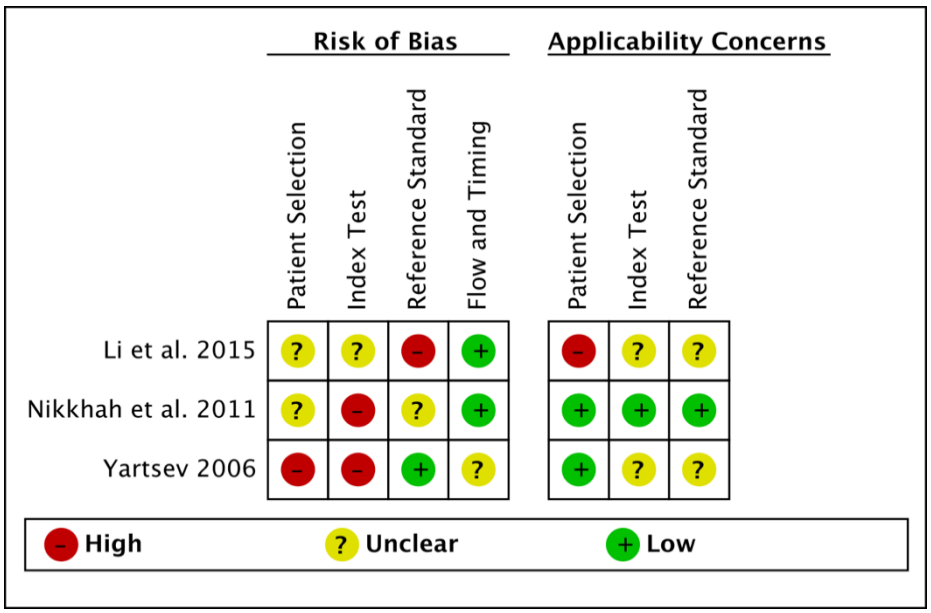
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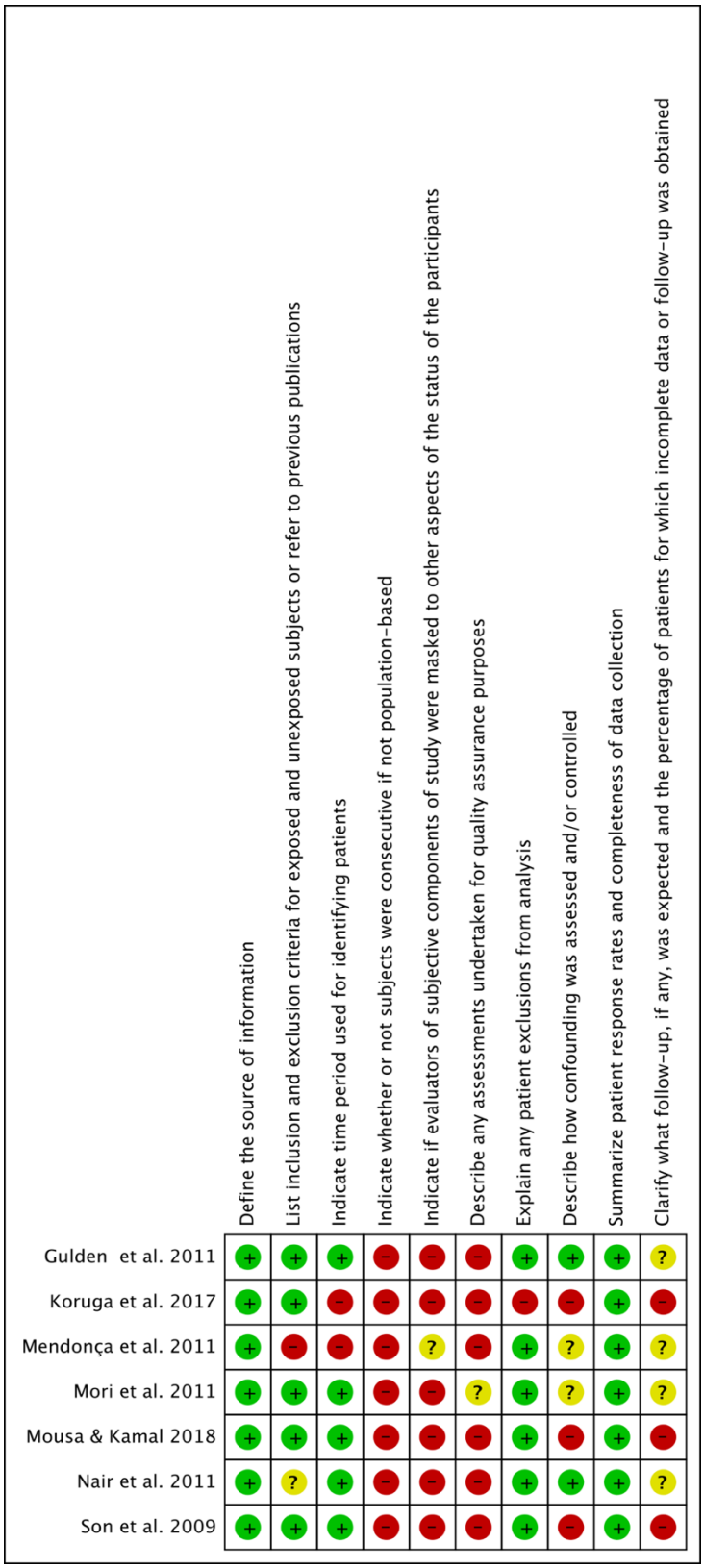
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8.2.8: Summary for risk of bias:



QUADAS-2 Summary



AHRQ Summary

8.3.1 Published Abstract in CHEST Journal

CHEST Congress 2022 | Bologna ITALY | 27-29 June

Allergy and Airway

TYPE: Abstract

TOPIC: Allergy and Airway

THE RELEVANCE OF SMALL AIRWAYS FUNCTION IN ASSESSING SMOKING IN PATIENTS WITH ASTHMA WITHOUT AIRWAYS OBSTRUCTION: A RETROSPECTIVE ANALYSIS

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PURPOSE: Well controlled asthmatic patients may not have evidence of airflow obstruction as measured by FEV_1/FVC. Cigarette smoking is known to increase the incidence and severity of airflow obstruction. The aim of this study is to evaluate the physiological features of ever smoking asthmatic patients compared to never smokers.

METHODS: Spirometry records of adult patients with a clinical diagnosis of asthma were retrospectively obtained from the pulmonary function unit of a tertiary hospital in the West Midlands, United Kingdom. The 2012 Global Lung Initiative equations were used to produce % predicted values and z-scores. Only patients without airflow obstruction as measured by FEV_1/FVC z-score were included in the analysis.

RESULTS: A total of 1434 records of asthmatic patients without prebronchodilator airflow obstruction were included in the analysis, of which 489 (34.1%) were ever smokers. Never smokers had higher % predicted MMEF (91.9±27.8 VS 84.6±26.2), MMEF/FVC (100±29.4 VS 91.4±26.5), FEV_3/FVC (95.9±3.40 VS 94.6±3.53), and FEV_1/FVC (80.9±6.45 VS 78.2±5.89) compared to ever smokers ($P<0.001$), There were no differences in % predicted FEV_1 (91.9±15.4 VS 90.4±15.6) or % predicted FVC (92.5±15.1 VS 93.1±15.6), see figure 1.

CONCLUSIONS: In asthmatic patients, physiological small airways indices may be more sensitive to detecting early impairment due to smoking than larger airways indices.

CLINICAL IMPLICATIONS: Smoking asthmatic patients may have increased incidence rates of small airways dysfunction and should be assessed and managed accordingly.

DISCLOSURE: Nothing to declare.

KEYWORD: Asthma

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ALLERGY AND AIRWAY

8.3.2 Published Abstract CHEST Journal

CHEST Congress 2022 | Bologna ITALY | 27-29 June

Allergy and Airway

TYPE: Abstract

TOPIC: Allergy and Airway

THE PREVALENCE OF SMALL AIRWAYS DYSFUNCTION IN ASTHMATICS WITH AIRFLOW OBSTRUCTION

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PURPOSE: To evaluate the prevalence and characteristics of small airways dysfunction (SAD) in adult asthmatic patients with persistent airflow obstruction as measured by FEV_1/FVC.

METHODS: Spirometry records of adult patients diagnosed with asthma were retrospectively obtained from the pulmonary function unit of a tertiary hospital in the West Midlands, United Kingdom. The 2012 Global Lung Initiative equations were used to produce % predicted values and z-scores. Airflow obstruction was defined as a z-score of <-1.645 in FEV_1/FVC. The SAD was defined as a z-score of <-1.645 in MMEF. The z-score for FEV_1 was used to categorize the severity of the obstruction as per the ARTP guidelines. Demographics were also obtained to assess the characteristics of patients with and without SAD.

RESULTS: A total of 395 records were obtained, of which 337 (85.3%) had evidence of SAD as measured by MMEF. Although most patients with mild airflow obstruction had evidence of SAD (63.1%), it was the only severity group with a prevalence of less than 100%. SAD was more prevalent in females (89.53%) than males (81.37%) ($p= 0.032$). No statistical differences were found between smoking history, age, weight, height, or ethnicity when compared to those with and without SAD.

CONCLUSIONS: As measured by MMEF, the prevalence of SAD is high in asthmatic patients with physiological airflow obstruction and is more common in females.

CLINICAL IMPLICATIONS: In asthmatic patients with airflow obstruction, therapies that also target small airways should be considered in the treatment plan.

DISCLOSURE: Nothing to declare.

KEYWORD: Asthma

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ALLERGY AND AIRWAY

8.4.1 Published Abstract in Thorax Journal

Data extraction was performed by all authors manually and transcribed to an excel spreadsheet. A brief risk of bias assessment was conducted at the same time using the COSMIN taxonomy: Measurement Properties of Outcome Measurement Instruments.[1]

Results 16 articles (249 screened) were included (table 1). N=2271 patients. Most studies (10/16) were moderate risk of bias. Overall there was weak-strong correlations for the included tests with a gold standard r=0.38- 0.85. There were few reported issues with feasibility or safety of the tests. However all tests were supervised in a clinical setting. The test that correlated highest with gold standard was the 4MGS with the ISWT (r=0.78) and with the 6MWT (r=0.85).

Discussion The 4MGS correlates highest with gold standard measures of exercise tolerance. However it may be difficult to standardise in a remote assessment or prescribe exercise from. Clinicians should strive for face-to-face standardised exercise tests where possible to be able to guide exercise prescription.

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P77 PSYCHOLOGICAL FACTORS INFLUENCING PATIENT ACTIVATION IN HEALTH-COACHING PROGRAMMES IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE. A SYSTEMATIC REVIEW AND NARRATIVE SYNTHESIS

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10.1136/thorax-2020-BTSabstracts.222

Introduction Chronic obstructive pulmonary disease (COPD) requires effective strategies to support the humanistic and economic challenges involved in managing the complex symptom burden experienced by people living with COPD. Health coaching aims to achieve collaboration between patients and healthcare professionals to enhance patient activation with health-promoting behaviours. This review aimed to identify psychological factors that positively influence the implementation of health-coaching programmes in COPD thus providing insight into how health-coaching can enhance patient activation and improve outcomes in COPD care.

Methods A comprehensive systematic search of the literature was performed using multiple electronic databases: AMED, CINAHL, EMBASE, EMCARE, Medline, PsychINFO and PubMed from 2009–2019. Studies of any research design reporting qualitative or quantitative data investigating the influence of patient psychological factors in health-coaching in COPD were included. Study quality was assessed using the Critical Appraisal Skills Programme and AXIS critical appraisal tools. An integrative thematic analysis approach was used to synthesise data from eligible studies and summarise findings.

Results A total of 682 abstracts were screened and 48 full-text articles reviewed. Fourteen studies including seven qualitative and seven cross-sectional studies met the criteria for inclusion. The heterogeneity of the results made pooling and meta-analysis difficult although several valuable themes emerged from the integrative analysis. The qualitative datasets included a total of 244 patients and demonstrated two crucial themes in patients being activated with health-coaching programmes: the desire to maintain independence in activities of daily living and the need to have ownership of their disease. The cross-sectional studies included 2674 participants and highlighted fundamental characteristics associated with low activation for health-coaching: increased levels of anxiety and depression and a negative illness perception.

Conclusions This systematic review triangulated rich in-depth perspectives along with associations between psychological factors and patient activation during health-coaching in COPD. The holistic understanding of these identified factors provides an opportunity to optimise the efficacy of health-coaching in clinical practice, particularly given the intricacies of human nature and the complexity of health-coaching interventions.

P78 SMALL AIRWAYS RESPONSE TO BRONCHODILATOR IN ASTHMA AND COPD: A SYSTEMATIC REVIEW

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10.1136/thorax-2020-BTSabstracts.223

Introduction and Objectives The airways response to bronchodilators (BDR) has been used as a test to diagnose asthma and to differentiate it from other obstructive pulmonary diseases. The main outcome in assessing BDR is FEV_1, mainly a large airway measure. Measures of small airways are not included in everyday practice for BDR testing, although evidence suggests small airways dysfunction is found in asthma and COPD patients. This systematic review assessed the current evidence on small airways response to short-acting inhaled bronchodilators in asthma and COPD.

Methods The protocol was registered in PROSPERO (CRD42020164140). Electronic medical databases (EMBASE and Medline) were searched using related keywords. Abstracts and full texts were screened independently by two reviewers. Studies that reported the change of physiological small airways function (spirometric, oscillometry, multiple breath washout) and FEV_1 were included. The revised Cochrane risk of bias tool for RCT and the NIH quality assessment tool for cohort and cross-sectional studies were used to evaluate the studies.

Results Of 934 articles identified from the databases search, 13 met the inclusion criteria, with asthma (n=10) and COPD (n=3) patient studies. A total of 1110 participants were included; 911 were asthmatic, 90 COPD and, 109 were controls. Heterogeneity between studies was noted in the (1) diagnostic criteria for asthma or COPD, (2) agreed criteria for demonstrating BDR using standard spirometry, (3) methods used to deliver aerosolised medications and, (4) included measures of small airways function. Using spirometry, MMEF showed higher percentage of change (5.3–47%) in asthma and (3.6–25%) COPD, than FEV_1 which was (3.9–32%) in asthma and (2.8–16.3%) COPD [**Abstract P78 figure 1**]. The contrary was noted in severe asthma patients. Using oscillometry, BDR was observed with total resistance change of (R5) in asthma patients (-0.16 kPa/L/s) and between (-9.0— -22.4 kPa/L/s) in COPD patients.

Conclusions Small airways function appears to change following BDR, but currently studies are too heterogeneous to recommend their inclusion in clinical practice. More research is needed to form a consensus on how to assess BDR in general and in small airways in specific, and whether this adds utility to the diagnosis and management of airway disease patients.

8.4.2 Published Article In The International Journal of COPD

International Journal of Chronic Obstructive Pulmonary Disease Dovepress
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ORIGINAL RESEARCH

Small Airways Response to Bronchodilators in Adults with Asthma or COPD: A Systematic Review

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Background: Bronchodilator responsiveness (BDR) is commonly used in the diagnosis of lung disease. Although small airways dysfunction is a feature of asthma and COPD, physiological tests of small airways are not included in guidelines for BDR testing. This systematic review assessed the current evidence of BDR using small airways function in asthma and COPD.

Methods: The systematic review used standard methodology with the protocol prospectively registered on PROSPERO (CRD42020164140). Electronic medical databases (EMBASE and Medline) were searched using related keywords. Abstracts and full texts were screened independently by two reviewers. Studies that reported the change of physiological small airways function and FEV_1 were included in the review. The revised Cochrane risk of bias tool for RCT and NIH quality assessment tool for cohort and cross-sectional studies were used to evaluate the studies.

Results: A total of 934 articles were identified, with 12 meeting the inclusion criteria. Ten studies included asthma patients, 1 study included COPD patients and 1 study included both asthma and COPD. A total of 1104 participants were included, of whom 941 were asthmatic, 64 had COPD and 109 were healthy controls. Studies were heterogeneous in design including the device, dose and time intervals for BDR assessment. A small airway BDR was seen for most tests in asthma and COPD, including oscillometry (R5-20, reactance (X5), area of reactance (AX) and resonant frequency (Fres)) and Maximal Mid Expiratory Flow.

Conclusion: There is a measurable BDR in the small airways. However, with no consensus on how to assess BDR, studies were heterogeneous. Further research is needed to inform how BDR should be assessed, its clinical impact and place in routine clinical practice.

Keywords: asthma, COPD, bronchodilator, reversibility, small airways function

Introduction

Testing for bronchodilator responsiveness is currently included in the diagnosis of asthma and can help in differentiating asthma from other respiratory-related diseases such as chronic obstructive pulmonary disease (COPD).[1] The term "reversibility" is often used but, in the 2019 spirometry standards update by the American Thoracic Society (ATS) and European Thoracic Society (ERS), the term 'responsiveness' was recommended, as "reversibility" may imply fully reversing airways obstruction.[2] The effort-dependent forced vital capacity (FVC) maneuver is usually used in a pre- and post-bronchodilator assessment with the forced expiratory volume in the first second (FEV_1) as the index usually reported to assess airways responsiveness.

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Evidence suggests that small airways dysfunction is prevalent in both asthma and COPD.[3,4] Spirometry is the current gold standard to diagnose airways obstruction and maximal mid-expiratory flow (MMEF), also known as forced expiratory flow between 25% and 75% of FVC (FEF_{25-75}), and occasionally called MEF and FEF_{50}, is the index parameter most commonly used to evaluate small airways function by spirometry.[2,5,6] However, administering bronchodilators can change both the FEV_1 and the FVC directly so, as FVC influences MMEF, a volume adjustment is needed to accurately evaluate any response when using MMEF.[2]

Short-acting beta2 agonists (SABA), such as salbutamol, are the most widely used bronchodilators for bronchodilator response (BDR) testing and are commonly delivered using a jet nebulizer or pressurized metered dose inhalers (pMDI) with a spacer.[2] However, there are many factors which can impact on the results of BDR testing and, currently, there is no consensus regarding the dose, technique or device used. The latest ATS/ERS guidelines released in 2019 suggest that this should be decided by the healthcare professional providing care.[2] In a previous guideline of the ATS/ERS task force, it was highlighted that dose standardization was needed to determine reversibility/response cut-off values.[7]

The effectiveness of aerosolized medication and the BDR is dependent on the deposition in the lungs which, in turn, is dependent on multiple factors, including the concentration of the drug, technique of delivery and the size of particles.[8,9] There is no gold standard for BDR testing regimens and the type of medication, dosage, and time delay for post-assessment can vary, leading to difficulty in comparing results, although doses between 200 and 400 mcg of salbutamol via pMDI are suggested.[10–12] There are clear recommendations that patients should omit taking SABA for 4–6 hours before a baseline test; short-acting muscarinic antagonists (SAMA) for 12 hours before the test; long-acting beta2 agonists (LABA) for 24 hours before the test; Ultra-LABA for 36 hours before the test; long-acting muscarinic antagonists (LAMA) for 36–48 hours before the test.[2]

Different criteria have been suggested to define a "significant" BDR but a change in FEV_1 of at least 160 mL is usually recommended due to the effort-dependent variability of the test especially following repeated measures.[13] Significant BDR is defined as a change of over 12% from the baseline FEV_1 and an absolute increase of more than 200 mL by ATS/ERS,[14] and a change of over 15% from the baseline FEV_1 with an increase of 200 mL in volume by the British Thoracic Society (BTS).[15]

Although BDR is thought to be important to differentiate between asthma and COPD, studies have indicated that it may not be discriminatory.[16,17] BDR is seen in some patients with COPD, although this can have day-to-day variability.[18,19] BDR may be important in the diagnosis and prognosis of asthma,[20,21] but not all patients with diagnosed asthma have BDR. Nonetheless, in asthmatic patients with normal FEV_1, MMEF has been reported below normal values, indicating small airways dysfunction as part of the disease paradigm.[22] The usefulness of BDR in managing COPD patients is also unclear. Even in the absence of FEV_1 improvement, Vital Capacity and Inspiratory Capacity can increase following inhaled bronchodilator use and these improvements are reflected in reduced dyspnea and increased exercise performance.[23,24] This suggests that changes in FEV_1 may not be the only marker to capture a treatment response.

Studies using small airway tests to assess BDR have reported improvements in these lung function parameters post-therapy.[25,26] In COPD, there is evidence that small airways dysfunction might be the earliest pathological manifestation of disease (both pathologically and physiologically) and several studies reported a substantial loss of small airways or their function before the development of classical spirometric airflow obstruction.[27–29]

Pathological, physiological and radiological studies assessing the small airways recommend targeting them early in the course of COPD.[27–30] In both asthma and COPD, inhaled extra-fine particle treatments have been developed specifically to target the smaller airways[30] and more novel treatment trials are in progress. Understanding whether bronchodilator response can be assessed using tests of small airways function (SAF) would be important for clinical trials and assessing patient response to treatments.

The objective of this systematic review was to evaluate the current evidence of small airways response to short-acting inhaled bronchodilators in adults with asthma or COPD. Moreover, to evaluate the effectiveness of methods used in delivering aerosolized bronchodilators to the small airways and their function.

Materials and Methods

Protocol, Sources of Information and Search Strategy

The protocol was registered in PROSPERO (registration number CRD42020164140). The review was written in

accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[31] Through scoping, the following tests were selected to be included in the search, forced oscillometry (FOT), impulse oscillometry (IOS), forced expiratory flow at 50% of FVC (FEF_{50}), single breath washout (SBW) and multiple breath washout (MBW). A complete searching strategy is provided in the Supplementary File (S1).

Eligibility Criteria (PICO)

Studies were considered for inclusion to the review if the selected small airways tests were conducted on adults diagnosed with either asthma or COPD, where both FEV_1 and the change in small airways function due to BDR tests were reported. The eligibility criteria are detailed in Table 1.

Study Selection and Data Extraction

Search results were imported into EndNote 9.1 (Clarivate Analytics) and duplicates were removed. The screening was conducted using Rayyan software[32] to facilitate the screening between reviewers. Abstracts were screened blindly and independently by MAA and NYA using the predefined inclusion and exclusion criteria. Disagreements were resolved through discussion. Full-text articles were obtained and imported into EndNote by MAA and similar abstract screening method was used in screening full texts for suitability.

Using a custom, piloted data extraction form, data were extracted by MAA and NYA and then compared for consistency and accuracy. SAF tests used to assess the BDR, dose of medication, time interval after bronchodilator administration, characteristics of populations, smoking history, and devices used to assess BDR were extracted to aid the narrative synthesis of the studies. The categorization of the studies was based on the SAF test and the disease (asthma and COPD).

Quality Assessment

The quality assessment of included studies was undertaken blindly by two independent reviewers. The revised Cochrane risk of bias tool for randomized controlled trials (RCT) was used to assess the quality and likelihood of bias in the RCT studies included, with the risk of bias classified as high, some concern or low for each study.[33] The National Institute of Health (NIH) tool for quality assessment of cohort and cross-sectional studies was used to assess the quality of cohort and cross-sectional studies, with the quality classified as good, fair or poor.[34]

Data Synthesis

Meta-analysis was considered where homogeneous results were provided. Otherwise, data were drawn into figures.

Results

Study Selection

Through the electronic search, a total of 934 abstracts were identified, of which 817 were screened in the full-text phase and a total of 12 studies met the inclusion criteria. A PRISMA flow chart is shown in Figure 1.

Table 1 The PICO (Population, Intervention, Comparator, Outcome) and Study Design for the Systematic Review

PICO	Inclusion Criteria	Exclusion Criteria
Population	- Adult patients aged at least 18 years with a clinical diagnosis of COPD or Asthma	- Other chronic lung diseases such as cystic fibrosis.
		- Patients younger than 18 years old
Intervention	Small airways function (IOS, FOT, MMEF, FEF_{50}, MBW, SBW) response to BDR using short acting beta2 agonist (SABA) via various aerosol delivery devices.	
Comparator	BDR in conventional lung function (FEV_1)	
Outcome	Change in small airways function after administrating the bronchodilator therapy.	
Study design	Randomised Control Trials (RCT), Cohort, Cross-sectional, Longitudinal, Case-series >10 patients, Systematic reviews	Reviews, Editorials, Case series of <10 Patients, Case reports

Note: The Systematic review included the following inclusion and exclusion criteria, as described above.
Abbreviations: COPD, chronic obstructive pulmonary disease; IOS, impulse oscillometry; FOT, forced oscillometry; FEV_1, forced expiratory volume in 1 second; MMEF, mean mid-maximal expiratory flow; FEF_{50}, forced expiratory flow at 50% of FVC.

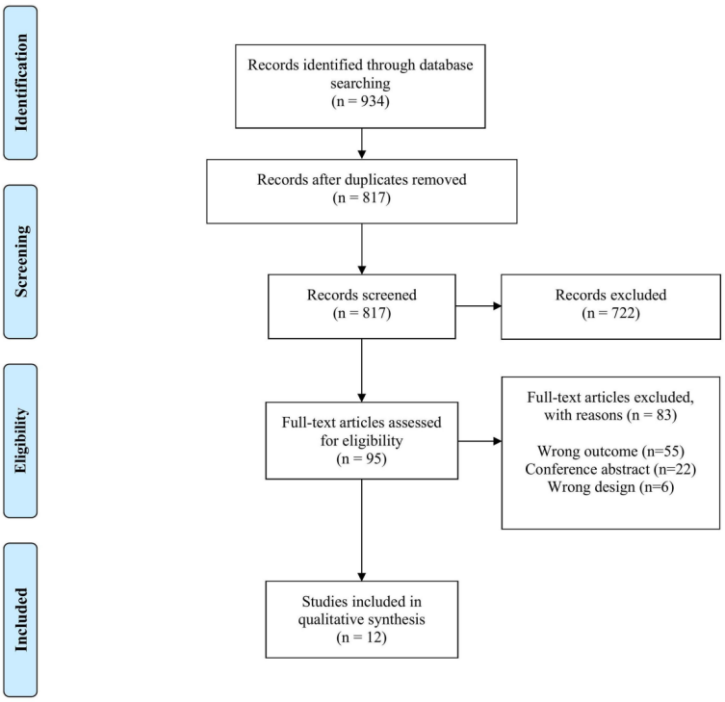


Figure 1 PRISMA flow chart showing the studies identification process from EMBASE and Medline databases.
Notes: Adapted from: Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097.[62] Creative Commons.

Study Characteristics

Ten studies included patients with asthma,[35–44] one study included COPD patients,[26] and one study included both asthmatic and COPD patients.[45] The total number of the participants included from all studies was 1104, of whom 941 were asthmatic, 64 COPD patients and 109 healthy control subjects. Studies were conducted in different countries from three continents. Three studies were conducted in the United Kingdom, two in the United States, and one study in each of the following countries: India, Iran, Italy, Japan, Korea, Lebanon, and Portugal. In Table 2, the main characteristics of each study are shown.

There were differences in the reported diagnostic criteria for asthma. In studies of asthma, four used Global Initiative of Asthma (GINA) guidelines[38,40,43] and one study used a specific criterion (stable asthma who showed at least 15% BDR after SABA inhalation within 12-month prior starting the study).[42] However, six of the studies that included asthmatic patients did not specify the diagnostic criteria.[35–37,39,41,44] In studies of COPD, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria were used for COPD diagnosis.[26,45] None of the included studies reported correction of MMEF in relation to FVC post-bronchodilation.

Only seven of the included studies defined the criteria for significance of BDR test. Those seven studies used the ATS/ERS criteria for defining significant BDR (≥12% and ≥200mL)[35,38–40,43–45] while in five, the criteria were not specified.[26,36,37,41,42]

There were different methods used in delivering aerosolized medications. Eight studies used pMDIs, two used small volume jet nebulizers (SVN), one used dry powder inhalers (DPI) and one used dosimeter. None of the included studies reported the use of extra-fine aerosol delivery devices such as vibrating mesh nebulizers. Only two studies compared modalities of delivering bronchodilators,

Table 2 Characteristics of Included Studies

Study ID	Study Design	Population	n= (M/F)	Age	SABA /Dose	Aerosol Device	BDR Time	SAF test	SAF Change	FEV_1 Change
Ohwada et al 2011[a]	Observational	Asthma	45 (12/33)	36.8±10.2	Salbutamol/ 200 mcg	pMDI + Spacer	15 min	MMEF(%)	6.7%±10.5	5.5%±8.1
								FEF_{50}(%)	33.3%±48.9	
Schecker et al 1993[b]	Randomized Controlled Trial	Asthma	20(16/4)	44±18	Pirbuterol/ 0.4 mg	pMDI	60 min	MMEF(%)	44.6%±8.6	31.1%±4.8
						Autohaler		MMEF(%)	45.6%±7	32%±5.8
Fakharian et al 2008[a]	Observational	Asthma	40(15/25)	43.1±12.99	Salbutamol/ 400 mcg	Asmyar (spacer)	10 min	MMEF(%)	16.3%±12.1	7.7%±5.1
								FEF_{50} (%)	13.5%±11.8	
			40(15/25)	43.1±12.99		Damyar (spacer)	10 min	MMEF(%)	16.1%±13.1	7.1%±5.9
								FEF_{50} (%)	14.4%±11.4	
Mariotta et al 2005[a]	Observational	Asthma (Intermittent)	108(68/40)	29.4±5.22	Salbutamol/ 200 mcg	pMDI	20 min	MMEF(%)	19.3%±17.9	5.03%±4.6
								FEF_{50} (%)	18.65%±16.2	
		Asthma (Persistent)	183(88/95)	31.07 ±10.48				MMEF(%)	28.9%±23.1	8.65%±5.9
								FEF_{50} (%)	27.1%±20.9	
		Control	38(24/14)	30.9±9.36				MMEF(%)	18.26%±9.3	3.4%±2.8
								FEF_{50} (%)	15.2%±8.9	
Rajkumar et al 2002[d]	Observational	Asthma	15(7/8)	31.8	Salbutamol/ 200 mcg	pMDI (Market Spacer)	NR	MMEF(%)	37.0%	19.0%
						pMDI (Homemade Spacer)		MMEF(%)	47.0%	22.7%
Castro et al 2015[a]	Observational	Asthma (-reversibility)	50(18/32)	61.2±11.9	Salbutamol/ 400 mcg	pMDI + Spacer	10 min	MMEF(%)	5.3%±10.9	3.9%±5.1
		Asthma (+reversibility)	50(28/22)	56.1±15.6				MMEF(%)	39.4%±62.6	18.5%±11.8

(*Continued*)

Table 2 (Continued).

Study ID	Study Design	Population	n= (M/F)	Age	SABA /Dose	Aerosol Device	BDR Time	SAF test	SAF Change	FEV_1 Change
El-Khatib et al 2014[a]	Observational	Asthma (Group 1)	44(21/23)	51±14	Salbutamol/ 2.5 mg	SVN	15–30 min	MMEF(L/s)	0.5±0.6	0.2L±0.3
								FEF_{50} (L/s)	0.7±0.9	
		Asthma (Group 2)	44(22/22)	52±13				MMEF(L/s)	0.2±0.4	0.2L±0.3
								FEF_{50} (L/s)	0.3±0.7	
		Asthma (Group 3)	44(23/21)	53±8				MMEF(L/s)	0.1±0.1	0.2L±0.2
								FEF_{50} (L/s)	0.1±0.2	
Lipworth et al 1997[c–e]	Observational	Asthma mild	10	31.7±8.7	Salbutamol/ 40mcg/kg	SVN	30 min	MMEF(L/s)	0.7 (0.0 to 0.1)	0.4L (−0.4 to 0.4)
		Asthma severe	10	52.9±15.2					0.3	0.4
		Control	10	20.6±1					0.7 (0.1 to 0.9)	0. 2 (−0.2 to 0.6)
Yagashi et al 2006[a]	Observational	Asthma	126(30/96)	45.1±13.9	Pirbuterol/ 0.8mg/	pMDI	30 min	R5(kPa/L/s)	−0.2±0.2	0.2L
								R5-R20(kPa/L/s)	−0.1±0.1	
								R20(kPa/L/s)	−0.1±0.1	
Nair et al 2011[c]	Observational	Asthma	82(28/54)	48.7±16.51	Salbutamol/ 400mcg	Accuhaler DPI	15 min	R5(%)	−33.0% (−42.6 to −25.0)	6.3% (5.0 to 7.6)
								R20(%)	−20.1% (−27.8 to −12.4)	
								X5(%)	−72.9% (−249.6 to 103.8)	
		Control	61(27/34)	28.2±10.13				R5(%)	−14.9% (−19.9 to −9.9)	2.25% (1.6 to 2.9)
								R20(%)	−15.7% (−21.0 to −10.4)	
								X5(%)	40.1% (−91.4 to 171.7)	

Park et al 2019[b]	Observational	COPD	40(36/4)	74.35±4.7	Salbutamol/ 200 mcg	pMDI	15 min	Fres(Hz)	−9.6%±2.1	6.3%±1.0
								R5(kPa/L/s)	−9.3%±1.8	
								R20(kPa/L/s)	−6.8%±1.6	
								R5-20(kPa/L/s)	−8.5%±1.6	
								X5(kPa/L/s)	−13.5%±3.2	
								AX(kPa/L/s)	−22.7%±4.5	
								MMEF(%)	8.3%±3.0	
								Fres(Hz)	−15.3%±2.6	9.2%±1.9
								R5(kPa/L/s)	−12.7%±2.7	
								R20(kPa/L/s)	−6.4%±2.6	
								R5-20 (kPa/L/s)	−10.3%±2.6	
								X5(kPa/L/s)	−5.9%±7.3	
								AX(kPa/L/s)	−22.9%±7.3	
								MMEF(%)	NR	
Borrill et al 2004[c]	Observational	COPD	24 (16/8)	63.6±7.1	Salbutamol/ 20 mcg	Dosimeter	15 min	R5(kPa/L/s)	− 9.0%(−14 to −4)	2.8%(0.8 to 4.9)
								R20(kPa/L/s)	−2.7%(−7 to −1.7)	
								X5(kPa/L/s)	−18.5%(−27.2 to −9.8)	
								Fres(Hz)	−11.1%(−15 to −7.2)	
								MMEF(L/s)	3.6%(−1.8 to 8.9)	
					Salbutamol/ 50 mcg			R5(kPa/L/s)	−16.7%(−22.5 to −10.8)	8%(5.2 to 10.4)
								R20(kPa/L/s)	−5.8%(−10.4 to - 2.2)	
								X5(kPa/L/s)	−32.0%(−47 to −16.9)	
								Fres(Hz)	−19.4%(−25 to −13.7)	
								MMEF(L/s)	12.9%(4.2 to 21.4)	
		Asthma	30 (23/7)	74.70±4.84						

(*Continued*)

Table 2 (Continued).

Study ID	Study Design	Population	n= (M/F)	Age	SABA /Dose	Aerosol Device	BDR Time	SAF test	SAF Change	FEV_1 Change
					Salbutamol/ 100 mcg			R5(kPa/L/s)	−16%(−23.3 to −8.6)	10.2%(7.4 to 12.9)
								R20(kPa/L/s)	−4.6%(−11.6 to 2.3)	
								X5(kPa/L/s)	−26.7%(−42.7 to −10.7)	
								Fres(Hz)	−17.9%(−23.3 to −12.4)	
								MMEF(L/s)	13.6%(5.2 to 22.1)	
					Salbutamol/ 200 mcg			R5(kPa/L/s)	−17.9%(−25.5 to −10.3)	11.9%(8.6 to 15.1)
								R20(kPa/L/s)	−6.2%(−13 to 0.6)	
								X5(kPa/L/s)	−28.6%(−45.9 to −11.3)	
								Fres(Hz)	−20.7%(−25.8 to - 12.4)	
								MMEF(L/s)	21.3%(11.1 to 31.6)	
					Salbutamol/ 400 mcg			R5(kPa/L/s)	−20%(−28.3 to −11.6)	13.7%(10.2 to 17.2)
								R20(kPa/L/s)	−7.4%(−13.9 to −0.9)	
								X5(kPa/L/s)	−32.8%(−48.8 to −16.8)	
								Fres(Hz)	−22.7%(−29.1 to −16.3)	
								MMEF(L/s)	19.3%(7.9 to 30.7)	
					Salbutamol/ 800 mcg			R5(kPa/L/s)	−22.4%(−29.3 to −15.4)	16.3%(12.2 to 20.4)
								R20(kPa/L/s)	−11.0%(−17.4 to −4.6)	
								X5(kPa/L/s)	−36.2%(−49.6 to −22.8)	
								Fres(Hz)	−23.3%(−29.0 to −17.5)	
								MMEF(L/s)	25.0%(11.8 to 38.2)	
								AX(cmH_2O)	−0.10±0.3	
								R15(cmH_2O)	−0.008±0.1	

Notes: For each study, the population, numbers of participants by gender, average age of participant, SABA used, device for BDR, time from delivery to measurement, small airway function test (SAF), change in that test and change in FEV_1 is reported. Change in SAF and FEV_1 is reported in percent predicted or in units as reported in the table [a]Changes reported in mean ± standard deviation (SD). [b]Changes reported in mean ± standard error of mean (SEM). [c]Changes reported in mean (95% CI). [d]Mean was only reported for this study. [e]Measure of variance was not reported for severe asthmatic group.

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; MMEF, mean mid-maximal expiratory flow; FEF_{50}, forced expiratory flow at 50% of FVC; Fres, resonant frequency; R5, resistance at 5 Hz; R20, resistance at 20 Hz; R5–20, resistance between 5 and 20 Hz; X5, reactance at 5 Hz; AX, area of reactance curve (between X5 and Fres).

which was a comparison between spacers.[36,41] One study compared two types of inhalers: a standard pMDI and an Autohaler (a breath-actuated pMDI).[42] All studies used SABA, of which 10 used salbutamol and 2 used pirbuterol. Dosages were also different between studies but mostly ranged between 200 and 400 mcg of salbutamol or equivalent. Tests used for assessing SAF were spirometry (MMEF, FEF_{50}) in 10 studies and oscillometry in four. None of the included studies reported using MBW or SBW technique.

There were also differences in reporting the outcomes of BDR response. Absolute change of the parameters was reported in three of the studies[35,37,44] whereas the change in % predicted in one study.[39] The percentage of change was reported in eight studies,[26,36,38,40–43,45] but most did not indicate if the percentage of change was derived from the absolute values or % predicted. Of the studies reporting percentage of a change, only two[38,40] reported the method of obtaining % change using absolute values with the following conventional formula: [(post-treatment – pre-treatment)/pre-treatments] *100.

Meta-analysis was not considered feasible due to non-conformity of studies with respect to demographics, disease severity stages, methods used in delivering bronchodilators, drug type/dose, the time intervals between bronchodilation administration and tests differing between studies. A feature of all the studies, however, was the wide spread of patient responses, with large measures of variance across studies, suggesting marked heterogeneity between individuals and their responses.

Quality Assessment

The revised Cochrane risk of bias tool was used for one study, which was the only RCT.[42] Here, there was an overall high risk of bias, but there was a low risk of bias around deviation from the intervention or the measurement of the outcome.

The rest of the studies were assessed with the NIH tool for observational cohort and cross-sectional studies. The questions in all domains (D) of the NIH tool were answerable except that of D8, which relates to exposure to the outcome and was considered not applicable to the included studies. The assessment showed an overall good quality in 6 studies,[26,35,40,43–45] fair quality in two[38,39] and poor quality in three.[36,37,41] A graph of NIH quality assessment is shown in the Supplementary File (S2).

Result of Individual Studies

Spirometry (MMEF, FEF_{50})

Asthma

Eight of the 12 studies reported BDR of MMEF, FEF_{50} or both in asthmatic patients.[35–38,40–43] Ohwada et al[40] recruited 45 non-smoking patients diagnosed with asthma but treatment-naive. The BDR assessment was carried out using 200 mcg of salbutamol via pMDI and spacer. Fifteen minutes after inhaling the salbutamol, patients were reassessed. All results are reported as mean and standard deviation (±SD). A non-significant change of 6.7±10.5% change in MMEF was described. In contrast, a significant change in FEF_{50} of 33.3±48.9% was found and statistically significant ($p = 0.001$) as well as a 5.7±8.1% change ($p = 0.004$) in FEV_1. However, the change of FEV_1 did not meet the ATS/ERS criterion for significant BDR.

Schecker et al[42] assessed two types of inhalers to determine if device influenced the medication deposition or response, the standard pMDI and the Autohaler. Patients were tested on two separate days to assess consistency with both devices. Pirbuterol 0.4 mg was used as the bronchodilator and spirometry results were reported after 60 minutes. Similar changes in both devices were found for MMEF and FEV_1. A mean change in MMEF of 44.6 ±8.6% was reported using a standard pMDI and 45.6±7.0 using the Autohaler. Mean change in FEV_1 was 31.1±4.8% using a standard pMDI and 32.0±5.8 using the Autohaler, meeting ATS/ERS criteria for significant BDR for both inhalers, although there were no significant differences between the two devices for results for either MMEF or FEV_1.

Fakharian et al[36] conducted a study to compare the BDR of 2 spacers (Asmyar and Damyar). The authors reported the change in MMEF and FEF_{50} 10 minutes after administering 400 mcg of salbutamol and included only non-smokers with mild to moderate asthma. The change in MMEF and FEF_{50} using Asmyar was 16.3 ±12.1% and 13.5±11.8%, respectively whereas, in Damyar, the change was 16.1±13.1% and 14.4±11.4%, respectively. The change in FEV_1 was reported to be 7.7 ±5.1% in Asmyar and 7.10±5.91% in Damyar. There were no differences between the spacers for any of the indices and subjects did not meet the ATS/ERS criteria for BDR in FEV_1.

Mariotta et al[38] reported MMEF and FEF_{50} in asthmatic patients (with either intermittent or persistent symptoms) and control subjects. The 3 groups were tested for

BDR with 200 mcg of salbutamol and had spirometry test assessed after 20 minutes. The authors reported a mean change in MMEF of 19.3±17.9%, 28.9±23.1% and 18.3 ±9.3% in intermittent, persistent and control, respectively. FEF_{50} change was reported to be 18.7±16.2%, 27.1±20.9% and 15.2±8.9% and FEV_1 change was reported to be 5.0 ±4.6%, 8.7±5.9% and 3.4±2.8% for the same groups. However, once again, the changes of FEV_1 did not meet the ATS/ERS criteria for BDR in any group.

Rajkumar et al[41] studied the difference between commercial and home-made spacers. Percentage of change in MMEF was reported after administering 200 mcg of salbutamol but the time to post-bronchodilator testing was not reported. In this study, although the mean % change was reported, measure of variance was not. The change of MMEF was 37.0% and 47.1% when using commercial spacers versus home-made, respectively. FEV_1 change was 19.0% and 22.7% for commercial and home-made spacers, respectively, which is (on average) above the 12% threshold of the ATS/ERS BDR criterion for both groups. There was no difference in response between the two spacers.

Castro et al[43] included asthmatic patients with a confirmed history of airway reversibility consistent with the ATS/ERS 2005 guidelines as well as matched asthmatic patients without evidence of airway reversibility. Smoking patients, those under 20 years of age and patients who had a recent exacerbation of asthma were excluded from the study. Salbutamol (400 mcg) was used to assess BDR, and testing was completed ten minutes post-bronchodilator. The mean change (±SD) in MMEF in the patients with a history of reversibility was 39.4±62.6% opposed to those without reversibility 5.3±10.9%. The average FEV_1 change (±SD) was 18.5±11.8% and 3.9±5.1% in patients with reversible and non-reversible airflow, respectively, confirming that the group with previously noted reversibility once again met the ATS/ERS criterion for BDR as a % change.

Figure 2 summarizes these results by showing the average % change and the absolute change of MMEF and FEF_{50} in comparison to FEV_1 and FVC in asthmatic patients. For all studies, there was a greater average % change in tests of SAD than FEV_1.

El-Khatib et al[35] designed a study to compare the effectiveness of using Heliox to reduce viscosity compared to medical air when nebulizing bronchodilators. The authors randomized asthma patients in a cross-over design so that each patient received albuterol 2.5mg using one or other method for nebulization on 2 different days (thus acting as their own control). Patients were grouped based on their baseline FEV_1 results (all % predicted: ≥80% (Group 1), <80% to >50% (Group 2) and ≤50% (Group 3)) and absolute values of change were reported. Using medical air, mean changes of 0.54L/s±0.63 in MMEF and 0.67L/s±0.91 in FEF_{50} were reported in group 1. In group 2, a mean change in MMEF and FEF_{50} were 0.20L/s±0.43 and 0.33L/s±0.68, respectively. In group 3, mean changes in MMEF and FEF_{50} were 0.10L/s±0.13 and 0.09L/s

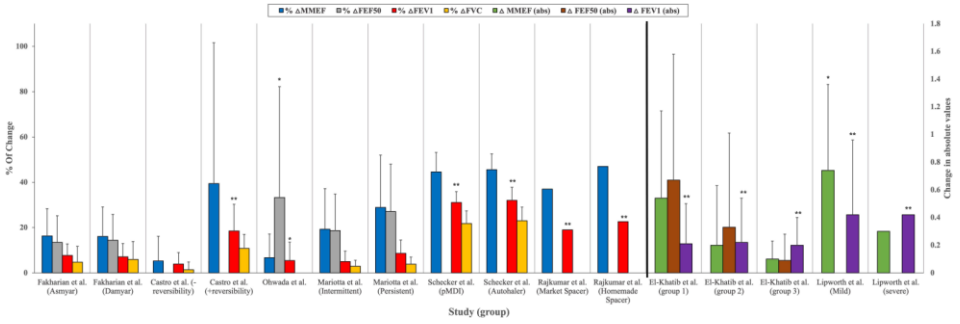


Figure 2 The average percentage change and absolute change in MMEF, FEF_{50}, FEV_1 and FVC across asthma studies.
Notes: Left vertical axis is % of change in MMEF, FEF_{50}, FEV_1 and FVC in asthmatic patients. Right Vertical axis is absolute change in MMEF, FEF_{50}, FEV_1. Data presented are means ± standard deviation (SD). Included data has been taken and adapted from Fakhrian et al,[35] Castro et al,[43] Ohwada et al,[40] Mariotta et al,[38] Schecker et al,[42] Rajkumar et al,[41] Elkhatib et al,[36] and Lipworth et al.[37] Measure of variances is not displayed in the error bars for Rajkumar et al[41] and severe asthmatic patients in Lipworth et al[37] because SD was not reported. *BDR is statistically significant. **BDR is clinically significant according to ATS/ERS criteria.
Abbreviations: MMEF, mean mid-maximal expiratory flow; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; FEF_{50}, forced expiratory flow at 50% of FVC.

±0.19, respectively. The mean change of FEV_1 was reported to be 0.21L±0.29 in Group 1, 0.22L±0.32 in Group 2 and 0.20L±0.20 in Group 3 which, on average, met the ATS/ERS criteria for significant BDR in all groups.

Lipworth et al[37] conducted a study to assess the lungs' absorption of nebulized salbutamol (using a weight adjusted dose of 40mcg/kg) with lung physiology measured at baseline and 30 minutes after treatment. The authors recruited participants with mild and severe asthma as well as healthy controls. Thirty participants were included, with 10 in each group. Of note, 95% confidence intervals were only reported for the healthy controls and mild groups, with no explanation as to why these data were omitted in the severe asthma group. The mean change of MMEF in L/s (95% CI) was reported as 0.74 (0.04 to 0.93) in mild patient, 0.30 in severe patients and 0.69 (0.09 to 0.88) in the control group. The mean change in FEV_1 (95% CI) was 0.42L (−0.38 to 0.39) in mild patients, 0.42L in severe patients and 0.22L (−0.18 to 0.59) in the control group, meeting average ATS/ERS criteria for significant BDR in all groups. In Figure 2, the mean change of MMEF (L/s) and FEF_{50} (L/s) in comparison to FEV_1 (L) is shown in the asthmatic patients from the studies by El-Khatib et al[38] and Lipworth et al.[40]

Across all studies in asthma, BDR as measured using small airways tests appeared to show a greater difference than FEV_1 (especially in milder disease) but had higher variability. In studies that assessed BDR in asthmatic subjects, only 5/10 studies met the ATS/ERS criteria for BDR of FEV_1.[35,37,41–43]

COPD

Two studies reported BDR using MMEF in COPD patients.[26,45] Borrill et al[26] recruited 24 patients with COPD to compare IOS, airway resistance measured by body plethysmography and spirometry (including MMEF) to find the most reliable method for evaluating BDR. In this study, short-acting bronchodilators, long-acting beta2 agonists and tiotropium were withheld for 6 hours, 12 hours and 24 hours, respectively prior to the study day. Salbutamol (administered via dosimeter) was given in ascending doses of 20mcg, 50mcg, 100mcg, 200mcg, 400mcg and 800mcg, to assess the BDR and lung function was reassessed 15 minutes after each dose. In this study, MMEF showed statistically significant improvements ($p < 0.05$) at doses of 200mcg and 400mcg with mean (95% CI) of 21.3% (11.1 to 31.6) and 19.3% (7.9 to 30.7), respectively. In contrast, the mean change of FEV_1 showed statistically significant improvement ($p < 0.05$) starting from a dose of 100mcg, showing % change of 10.2% (7.4 to 12.9) and 11.9% (8.6 to 15.1) after a dose of 100mcg and 200mcg, respectively. However, the ATS/ERS criteria for significant BDR with FEV_1 were only met at a dose of 400mcg and 800mcg: average 13.7% (10.2 to 17.2) and 16.3% (12.2 to 20.4), respectively. Figure 3 summarizes these % changes in MMEF and FEV_1 using the different doses of salbutamol.

A recent prospective study by Park et al[45] was conducted to assess BDR using IOS compared to spirometry in 40 elderly patients with COPD. In this study, patients were required to have no change in their prescribed medications for at least 4 weeks before the study but there were no details of when or if medications were paused prior to measurements. Albuterol was administered as two puffs of 100mcg via pMDI to assess BDR and the time interval between the inhalation and post-bronchodilator measurements was 15 minutes. The authors performed IOS before spirometry in all patients. In this study, the COPD patients were compared with 30 asthmatic patients and MMEF (referred to in the study as FEF_{25-75}) was also used to assess the BDR. Following administration of albuterol, the mean change in MMEF was 8.6% (SEM 3.0). The mean change in FEV_1 of 6.3% predicted (1.0 SEM) did not reach the ATS/ERS criteria for BDR. It was not reported if any changes reached statistical significance.

Oscillometry (R5, R5-20, X5, AX, Fres)

Asthma

Three studies reported the BDR using oscillometry.[39,44,45] Yaegashi et al[44] retrospectively analysed data from asthmatic patients who underwent both spirometry and oscillometry. Patients with COPD or any other disorder of airflow obstruction that was not diagnosed as asthma were excluded as were patients with a smoking history of more than 10 pack years. Pirbuterol 0.8 mg was administered via pMDI, but spacer use was not reported. BDR tests were carried out 30 minutes after the administration of the bronchodilator. The mean change (±SD) was reported in kPa/L/s to be (−0.16±0.16, −0.06±0.11, −0.06 ±0.08) in resistance at 5Hz (R5), R5-20 (the difference between R5 and R20) and resistance at 20Hz (R20), respectively. Statistical analysis was not performed to assess the relevance of the changes. Changes in other common oscillometry parameters such as reactance at 5Hz (X5) were not reported. The mean change in FEV_1

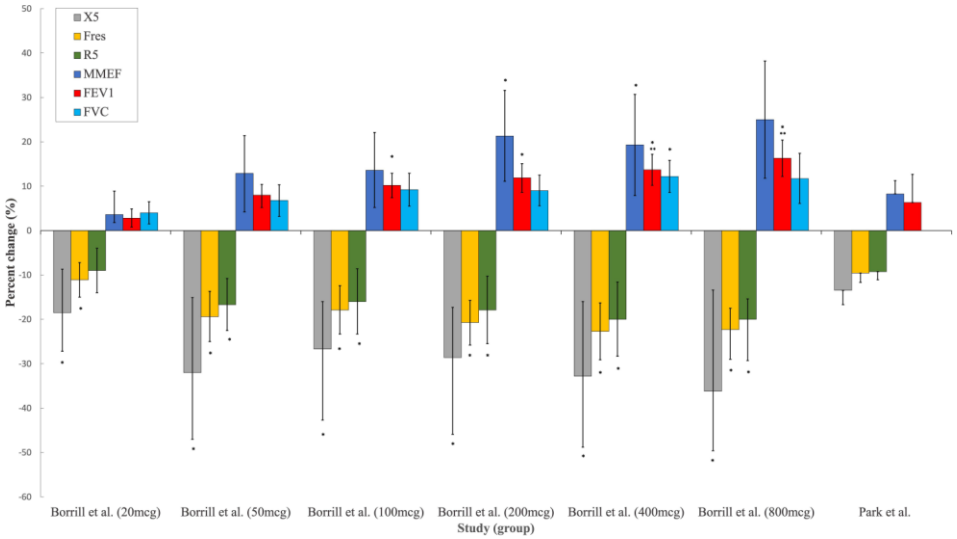


Figure 3 The % of change in spirometry indices (MMEF, FEV_1, and FVC) and in oscillometry indices (X5, Fres, and R5) in COPD patients.
Notes: Vertical axis is % of change in spirometry indices and oscillometry indices across different doses of salbutamol Borrill et al.[26] Data presented in the figure are mean (95% CI) for Borrill et al[26] and mean and standard error for Park et al[45] *BDR is statistically significant. **BDR is clinically significant according to ATS/ERS criteria.
Abbreviations: MMEF, mean mid-maximal expiratory flow; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; mcg, microgram. X5, reactance at 5 hertz; Fres, resonant frequency; R5, resistance at 5 hertz; FEV_1, forced expiratory volume in 1 second.

was 0.20±0.25L, meeting average ATS/ERS criteria for significant BDR.

Nair et al[39] conducted a study to compare the BDR in asthmatic and healthy controls using spirometry and oscillometry before and 15 minutes after using Salbutamol 400 mcg delivered via an Accuhaler (DPI). In the asthma group, the mean % change (95% CI) after administering salbutamol was −33.8 (−25.0 to −42.6), −20.1 (−12.4 to −27.8) and −73.0 (−103.8 to −249.7) in R5, R20 and X5, respectively. In the control group, the mean % change (95% CI) was −14.9 (−10.0 to −19.9), −15.7 (−10.4 to −21.0), and 40.09 (171.7 to −91.4) in R5, R20 and X5, respectively. A mean % change (95% CI) of 6.34% (7.6 to 5.0) in FEV_1 in the asthma group and 2.3% (3.0 to 1.6) in the healthy controls were found, thus not meeting ATS/ERS criteria for significant BDR. Baseline values and post-bronchodilator values were reported as % predicted. The change was reported as the % of change of from baseline in both oscillometry and spirometry.

In Park et al,[45] the authors also recruited 30 elderly patients with asthma. BDR was reported as the mean (±SEM) percentage change in the absolute values for the following IOS parameters; resonant frequency (Fres), R5, R20, R5-20, X5 and area of reactance (AX). Results were as follows: −15.3% ± 2.6 in Fres, −12.7% ± 2.7 in R5, −6.4% ± 2.6 in R20, −10.3% ± 2.6 in R5-R20, −5.9% ± 7.3 in X5, and −22.9% ± 7.3 in AX. In comparison, the % change in FEV_1 was reported as 9.2%±1.9. In Figure 4, a bar chart of the percentage of change is provided.

COPD

Two studies reported BDR using oscillometry in COPD patients.[26,45] Borrill et al[26] compared different lung function tests to determine the most reliable method for identifying BDR in COPD. In this study, IOS parameters R5, R20, X5 and Fres (abbreviated in the study to RF) were evaluated following the administration of ascending doses of salbutamol. X5 and Fres showed statistically significant improvements after 20mcg, but only after 50mcg in R5. Although R20 showed changes at all doses, they were not statistically significant (see Table 2). The changes of IOS parameters showed significant improvements across several doses, as shown in Figure 3. As described previously, FEV_1 also showed statistically significant changes after 100mcg but only met the ATS/ERS criteria for significant of BDR after 400mcg and 800mcg. In this study, all IOS

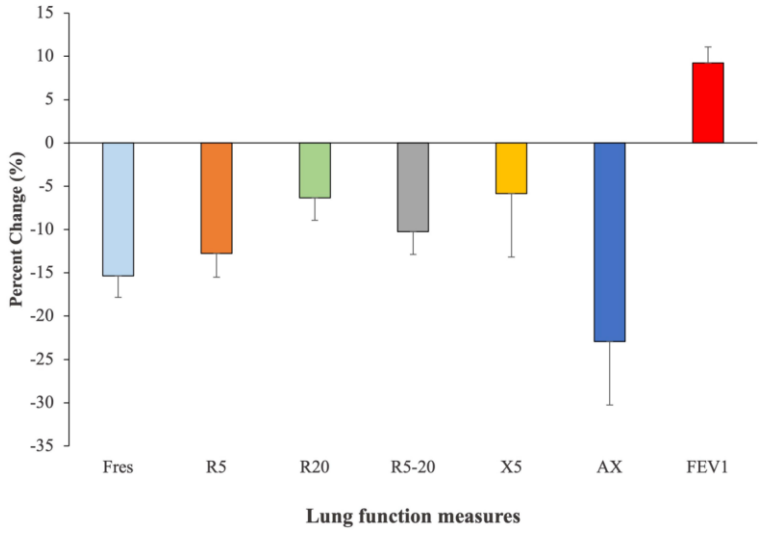


Figure 4 The percentage change of IOS parameters and FEV_1 in Asthmatic patients following BDR.
Notes: Vertical axis is % of change in oscillometry parameters in comparison to FEV_1 in asthmatic patients. Data is adapted from Park et al.[45] Data presented in the figure are the mean % change (± standard error of mean (SEM)).
Abbreviations: X5, reactance at 5 hertz; Fres, resonant frequency; R5, resistance at 5 hertz; R20, resistance at 20Hertz; R5-20, the difference between R5 and R20; AX, area of reactance; FEV_1, forced expiratory volume in 1 second.

parameters showed higher variability compared to FEV_1, with Fres being the least variable.

As previously described, Park et al[45] conducted a prospective study to assess the use of IOS in demonstrating BDR and its role as an alternative to spirometry in 40 patients with COPD. The authors reported Fres, R5, R20, R5-20, X5 and AX. In this study, although statistical significance for the changes was not reported, IOS parameters showed notable mean % change. The mean % change (SEM) for X5, AX and Fres was −13.5 (3.2), −22.7 (4.5) and −9.6 (2.1), respectively. The mean % change (SEM) for R5, R20 and R5-20 was −9.3 (1.8), −6.8 (1.6) and −8.5 (1.6), respectively. In contrast, FEV_1 had a mean % change of 6.3 (1.0), although the ATS/ERS BDR significance level was not met (see Figure 3).

Discussion

To the best of our knowledge, this the first systematic review to consider evidence for tests of SAF to assess BDR in asthmatic and COPD patients. The studies included varied in design and patient demographics. In most of the studies, the diagnoses of asthma and COPD followed GINA and GOLD criteria, although the diagnostic criteria were not formally reported in other studies. There was heterogeneity of the small airways tests used, the devices, and the reported outcomes. Furthermore, in most of the studies, different bronchodilators, delivery systems, doses, interval times and measurements were used. Hence, it is challenging to draw any conclusion to address whether tests of small airways could be used in the assessment of BDR. Moreover, the high study heterogeneity prohibited a meta-analysis.

In general, there is no clear consensus on how BDR tests should be conducted despite a number of published guidelines. Indeed, most of the studies included in this review had different methodologies for assessing BDR, which limits the certainty of evidence. As there are specific cut-off values for BDR significance, there should be a clear test procedure including aerosol device, time between tests, medication, and dosage. Moreover, the criteria of reporting the change are not clear. The ATS guidelines suggest reporting the absolute change and percentage of change but did not indicate where the percentage is derived, ie, % predicted or absolute values.[2] In the latest Association for Respiratory Technology & Physiology (ARTP), UK statement on pulmonary function testing, it

was highlighted that there are six different methods for calculating the BDR change.[46] Nevertheless, it was proposed that the use of z-score or change of % predicted should be used as it may avoid age, height, and sex bias of the results.[46]

In six of the studies,[35,36,38,40,43,44] means were reported despite the data being clearly skewed, weakening the evidence presented in this review. This variance is due to the inherent variability of SAF tests and to the effort-dependence in spirometry. In such cases, median and interquartile range should have been used.

Current asthma guidelines, such as the BTS and GINA include BDR of FEV_1 to diagnose asthma and differentiate it from other respiratory diseases such as COPD. However, the criteria to identify BDR (>12% and >200 mL) in FEV_1 is not always observed in asthmatic patients.[17] In addition, this level of BDR has also been reported in patient with COPD.[17] Furthermore, the assessment of BDR using FEV_1 demonstrates high inter-patient and intra-patient variability in asthmatic and COPD patients, limiting its specificity or sensitivity in discriminating COPD from asthma.[47,48] It has been proposed that the use of grading in assessing the BDR is more valuable than using a simple cutoff value as evidence shows that BDR relates to clinical outcomes such as exacerbation rates or quality of life.[49,50] FEV_1 is considered an assessment of larger airways function, although it can reflect major small airway dysfunction/loss. Evidence shows that small airways are affected in asthma[51] and dysfunction at this site increases with GINA-based severity.[52]

The reported studies suggested differences in BDR between larger and small airways, depending on disease severity. In general, in mild to moderate disease, small airways showed greater BDR expressed as a change in L/s than overall airways (assessed by FEV_1 in L). In severe cases, a different pattern was seen with larger airways reflecting higher BDR, suggesting a fixed obstruction, loss of the small airways or a decrease in aerosol delivery to the small airways due to an increased obstruction in the large airways. These findings also align with the hypothesis that small airways are affected early[53] in obstructive lung diseases and SAF tests should, therefore, be considered in their assessment.

In the studies of asthmatic patients, higher variance in BDR results were seen most in MMEF and FEF_{50} compared to FEV_1. Using MMEF, the small airways response to bronchodilator showed greater changes than FEV_1 in COPD patients and, in one study, it was shown that the changes were greater in higher BD doses.[26] In one study, however, MMEF changes had higher variability than FEV_1.[26] Therefore, the variability seen in studies using MMEF and FEF_{50} may impose a challenge to implement these measures in the assessment of BDR. Moreover, when assessing the BDR in MMEF, current guidelines suggest correction to the FVC (which influences the MMEF),[2] yet none of the included studies have reported this correction. The need to correct MMEF to FVC makes its use in the BDR assessment challenging.

As for FEV_1, obtaining MMEF and FEF_{50} requires a maximal inspiration followed by a forced maximal expiration, which is effort-dependent and the maneuver itself can result in changes in airway tone.[54,55] Oscillometry can overcome this limitation, as this test is effort-independent. In asthmatic patients, oscillometry showed a decrease in all resistance parameters (R5, R20, R5-R20, relating to total, large and small airways resistance, respectively) after the administration of a bronchodilator. The greatest change seen was in the total resistance (R5) in the two studies that reported this technique in asthma, indicating the reversibility nature of the airways in asthmatic patients including the small airways. However, there are inconsistencies in how results are reported. For example, Nair et al,[39] reported only the % of predicted values for oscillometry, leading to some values being >400% and limiting the ability to compare these results to other published literature which have used different parameters.

In COPD, IOS was used in two studies, demonstrating BDR and improvement in X5, R5, Fres, R5-20 and AX, with X5 and AX showing the most pronounced improvements compared to other IOS parameters. In the study by Borrill et al[26] the % change of R5, X5, and Fres was greater than FEV_1 across all doses given to patients but there was not data to support the clinical implications of the changes seen. In the study by Park et al,[45] all IOS parameters (including R5-20) demonstrated greater % changes compared FEV_1, with the greatest seen in AX and X5. In this study, however, the changes of IOS parameters were lower compared to the findings in Borrill et al, which may be because of differences in aerosol delivery methods (pMDI vs Dosimeter) or differences in patient demography with this study including an older population. In oscillometry, higher oscillation frequencies (>15Hz) do not penetrate the small airways, which play a central role in the pathophysiology of COPD.[27,28] As resistance at higher frequency relates to the larger airways it was shown to be unrelated to the obstruction in COPD

and explains why R20 did not show significant changes in these studies. The changes of X5, AX and Fres may be associated with the improvement of small airway patency, resulting in a reduction in hyperinflation and, hence, lung volume, consequently leading to an increase in lung compliance.

In summary, these studies suggest that oscillometry may detect significant BDR that is not detected by changes in FEV_1. However, in the study by Borrill et al,[26] IOS parameters had both a higher within test and within day variability than FEV_1 and, therefore, were less reproducible. In this study, only 24 COPD patients were included, and further larger studies are needed to determine the variabilities of these measurements. In general, oscillometry lacks knowledge of sensitivity as well as the reference ranges for multi-ethnic adults.[56] Moreover, using different devices may affect oscillometry results.[51] Although new oscillometry devices can separate inspiratory and expiratory parameters (which may provide an evaluation of expiratory flow limitation), oscillometry is relatively expensive compared to spirometry and may require training. Therefore, these limitations may generally hinder the utilization of oscillometry in clinical practice. Although some studies have suggested different BDR threshold for some oscillometry parameters,[56–58] the evidence of recognized BDR guidelines is still lacking. Thus, oscillometry is less attractive for BDR assessment compared to traditional spirometry measures (FEV_1 and FVC), which has been solely used and engrained into clinical practice.

Although the systematic protocol did not plan to assess the differences in BDR between asthma and COPD, Park et al[45] compared BDR by IOS for COPD and asthmatic patients with no statistical differences found between these groups. However, findings are limited as, firstly, due to the narrow demography of included patients (older than 70 years in both groups), which might impede discrimination between the two diseases.[52] Secondly, in the post-hoc analysis, they grouped asthma and ACOS together despite the clinical differences between the conditions,[59] meaning it is not possible to draw conclusions on the comparison of BDR in asthma versus COPD.

Limitations and Implication for Research and Clinical Practice

This systematic review is limited by the small number of included studies, the differences in studies design, the use of different small airway tests and the different outcomes reported. Other differences also limit the evidence presented in this review, such as the use of different medications, doses, drug delivery devices and time interval to testing. Many factors have been reported that may alter the deposition of aerosolized drugs and there are differences in efficiencies among them.[60] Time interval between bronchodilator administration and testing has been reported to be an important aspect in assessing the lung function[61] and yet there is no consistency between the studies reported here. Collectively, these limitations make comparison across the included studies impossible. Studies also did not report the demographics of participants in detail, with most not reporting ethnicity. We found that there is a statistically significant BDR demonstrated for both the small and larger airways in both asthmatic and COPD patients, but the implications are obscure. More research is needed to assess and quantify the response to extra-fine particle bronchodilators that are thought to have a greater role in the peripheral airways. However, there is a real need to define the sensitivity of the tests and, moreover, to understand what is a clinically important change for tests of SAF. This would include further assessment of whether/when agreed BDR in small airways might be important and associated with a demonstrable clinical or research benefit. Furthermore, asthma and COPD are both heterogeneous diseases in terms of pathology, clinical phenotype, and disease progression. Therefore, it is possible that small airway responsiveness in COPD may identify a subgroup of patients, namely those with patent though impaired small airways rather than those who have lost small airways. Such patients could be managed differently as they are likely to have increased therapeutic benefit using bronchodilators.

Conclusion

In asthma and COPD, there is evidence supporting the potential use of BDR measured using tests of SAF. However, the evidence to date is limited by the lack of consensus as to which bronchodilator should be used, at what dose, by which delivery mode, the time interval between drug administration, how to report BDR test results and the clinical impact of any change (minimal clinically important difference). Oscillometry is effort-independent and, hence, could be a method of choice but it remains limited due to the lack of reference ranges for multi-ethnic adults, variability, and sensitivity to change as well as limited knowledge on the clinical impact with respect to a significant BDR. MMEF is highly variable but has shown some potential, especially in mild

asthma but is unlikely to be clinically useful in assessing BDR without the recommended isovolumetric correction, which is a far more specialized technique. Oscillometry may also be useful, particularly for patients who are unable to perform spirometry, but the difference in hardware, the use of different frequencies (in the higher range) and the different units in which the parameters are reported are all major challenges in the development of standardized guidelines for assessing BDR. Moreover, SAF techniques that are not integral to basic spirometry require additional costs that are usually much higher than the cost of a spirometer. For these reasons, tests of SAF are currently less attractive for the assessment of BDR than the traditional spirometry parameters FEV_1 and FVC, which are deeply ingrained in general clinical practice. There is a need for robust evidence of a clear benefit to using SAF tests instead of or as an adjunct to the FEV_1 along with published guidelines that define a significant BDR before there is any chance of their adoption into routine practice.

Abbreviations

COPD, chronic obstructive pulmonary disease; ATS, American Thoracic Society; ERS, European Thoracic Society; FVC, forced vital capacity; FEV_1, forced expiratory volume in the first second; MMEF, maximal mid-expiratory flow; SABA, short-acting beta2 agonists; BDR, bronchodilator response; pMDI, pressurized metered dose inhalers; SAMA, short-acting muscarinic antagonists; SAF, small airways function; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; FOT, forced oscillometry; IOS, impulse oscillometry; FEF_{25-75}, forced expiratory flow between 25% and 75% of FVC; FEF_{50}, forced expiratory flow at 50% of FVC; SBW, single breath washout; RCT, randomized controlled trials; GINA, Global Initiative of Asthma; GOLD, Global Initiative for Chronic Obstructive Lung Disease; SVN, small volume jet nebulizers; DPI, dry powder inhalers; SD, standard deviation; R5, resistance at 5Hz; R5-R20, the difference between R5 and R20; R20, resistance at 20Hz; X5, reactance at 5Hz; Fres, resonant frequency; AX, area of reactance; ARTP, Association for Respiratory Technology & Physiology.

Disclosure

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8.4.3 Protocol Registry In PROSPERO

Citation

Mohammed Almeshari, Nowaf Alobaidi, Elizabeth Sapey, Omar Usmani. Small airways reversibility in asthma and COPD: a systematic review. PROSPERO 2020 CRD42020164140 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020164140

Review question

What is the amount of reversibility in physiological small airway function using different types of aerosol devices in adults with asthma or COPD?

Searches

The following electronic databases will be searches from inception up to January 2020:
EMBASE
MEDLINE
CINAHL
Cochrane Central Register of Controlled Trials (CENTRAL)
Web of Science (Abstracts & Proceedings) up to 5 years
Hand searching of references of the selected articles

Types of study to be included

Included types of studies:

RCTs

Cohort

Cross-sectional

Longitudinal

Case-series >10 pt.s

Systematic reviews

Exclusion:

Review articles

case controls

background articles

Condition or domain being studied

Physiological small airways reversibility in asthma and COPD

Participants/population

Adults (>18 years) with either Asthma or COPD

Intervention(s), exposure(s)

Small airways function (IOS, FOT, MBW, MMEF, FEF50, SBW) reversibility using short acting beta agonist (SABA) via various aerosol delivery devices.

Comparator(s)/control
Reversibility in conventional lung function (FEV1)

Main outcome(s) [1 change]

The percentage of change in small airways function after administrating the bronchodilator therapy.

Measures of effect

Within 1 hour post inhalation therapy.

Additional outcome(s) [1 change]

Effectiveness of aerosol therapy devices by the percentage of change in both large and small airways function

Measures of effect

Percentage of change.

Data extraction (selection and coding)
Two reviewers will independently screen title and abstract for inclusion against the inclusion and exclusion criteria listed above. Disagreement will be resolved through discussion and the third reviewer will resolve when necessary.
Full-text will be screened using the same independent process of two reviewers and a third where disagreement persists after discussion. There will be documented reasons for exclusion that will be reported. This process will be reported using PRISMA flow diagram.
Data extraction will be undertaken using an electronic data capture form. This will include but not be limited to will be on study design, patient characteristics, interventions, comparator, and outcomes. Data extraction will be done by one reviewer and checked for accuracy by a second reviewer with disagreement being checked by a third member of the team. Study's author will be contacted directly if data are ambiguous or missing.

Risk of bias (quality) assessment
All the final selected studies will be assessed for risk of bias using a pre-specified tool depending on the study design.
The reviewers will independently check each selected article to minimize bias.
Disagreement will be resolved using a third review. Information from the risk of bias assessments will be utilized when
synthesizing the data to explain differences in study results and to comment upon the reliability of conclusion that arise

from the analysis.

RCT: Cochrane RoB 2.0

Cohort: Newcastle Ottawa Scale

Cross-sectional: ARHQ Methodology Checklist for Cross-sectional study

Systematic reviews: AMSTAR

Case-series: JBI Critical Appraisal Checklist for Case Series

Strategy for data synthesis [2 changes]

Studies will be grouped based on the small airways function test used (Oscillation, FVC maneuver, MBW). A narrative synthesis will be carried out to assess the percentage of change in small airways function by assessing the difference before and after brochodilation therapy and the devices used to deliver the medication and how it relates to the reversibility measure (FEV1) being used at the moment. This will help in getting more insight on small airways function reversibility compared to large airways and how effective are aerosol devices in treating large and small airways. Quantitative synthesis will be carried out to assess the amount of change between different small airways function (e.g. R5, X5, Sacin, MMEF) after bronchodilator and comparing it to the change in FEV1.

Analysis of subgroups or subsets

Where necessary data are available, subgroup analysis will be used to assess the effectiveness of aerosol delivery devices, adapters, types of propellant used.

Contact details for further information

Mohammed Almeshari
mxa1066@student.bham.ac.uk

Organisational affiliation of the review

University of Birmingham
https://www.birmingham.ac.uk

Review team members and their organisational affiliations [1 change]

Mr Mohammed Almeshari. University of Birmingham
Mr Nowaf Alobaidi. University of Birmingham
Dr Elizabeth Sapey. Univeristy of Birmingham
Dr Omar Usmani. Imperial College London

Type and method of review

Systematic review

Anticipated or actual start date

27 January 2020

Anticipated completion date

29 May 2020

Funding sources/sponsors

King Saud University

King Saud Bin Abdulaziz University for Health Sciences

University of Birmingham

Imperial College London

Conflicts of interest

Language
English

Country
England

Stage of review [1 change]

Review Completed published

Details of final report/publication(s) or preprints if available [1 change]

Almeshari MA, Alobaidi NY, Sapey E, Usmani O, Stockley RA, Stockley JA. Small Airways Response to Bronchodilators in Adults with Asthma or COPD: A Systematic Review. Int J Chron Obstruct Pulmon Dis. 2021;16:3065-3082

https://doi.org/10.2147/COPD.S331995
https://doi.org/10.2147/COPD.S331995

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Asthma; Humans; Pulmonary Disease, Chronic Obstructive

Date of registration in PROSPERO
27 February 2020

Date of first submission
01 February 2020

Stage of review at time of this submission
The review has not started

Stage	Started	Completed
Preliminary searches	No	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Revision note
Adding the publication information.

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.
The record owner confirms that they will update the status of the review when it is completed and will add

publication details in due course.

Versions

27 February 2020
24 January 2022

8.4.4: PRISMA checklist			
Section/topic	**#**	**Checklist item**	**Reported on page #**
TITLE			
Title	**1**	**Identify the report as a systematic review, meta-analysis, or both.**	**1**
ABSTRACT			
Structured summary	**2**	**Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.**	**2**
INTRODUCTION			
Rationale	**3**	**Describe the rationale for the review in the context of what is already known.**	**4**
Objectives	**4**	**Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).**	**5**
METHODS			
Protocol and registration	**5**	**Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.**	**5**
Eligibility criteria	**6**	**Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.**	**6**
Information sources	**7**	**Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional**	**6**

		studies) in the search and date last searched.	
Search	**8**	**Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.**	**S.3**
Study selection	**9**	**State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).**	**6**
Data collection process	**10**	**Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.**	**6**
Data items	**11**	**List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.**	**6**
Risk of bias in individual studies	**12**	**Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.**	**7**
Summary measures	**13**	**State the principal summary measures (e.g., risk ratio, difference in means).**	**n/a**
Synthesis of results	**14**	**Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.**	**n/a**
Risk of bias across studies	**15**	**Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).**	**7**
Additional analyses	**16**	**Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.**	**N/A**
RESULTS			

Study selection	**17**	**Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.**	**8**
Study characteristics	**18**	**For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.**	**8**
Risk of bias within studies	**19**	**Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).**	**9**
Results of individual studies	**20**	**For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.**	**9**
Synthesis of results	**21**	**Present results of each meta-analysis done, including confidence intervals and measures of consistency.**	**14**
Risk of bias across studies	**22**	**Present results of any assessment of risk of bias across studies (see Item 15).**	**14**
Additional analysis	**23**	**Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).**	**N/A**
DISCUSSION			
Summary of evidence	**24**	**Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).**	**15**
Limitations	**25**	**Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).**	**15**
Conclusions	**26**	**Provide a general interpretation of the results in the context of other evidence, and implications for future research.**	**17**
FUNDING			

Funding	**27**	**Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.**	**1**

8.4.5 Search Strategy

MEDLINE:

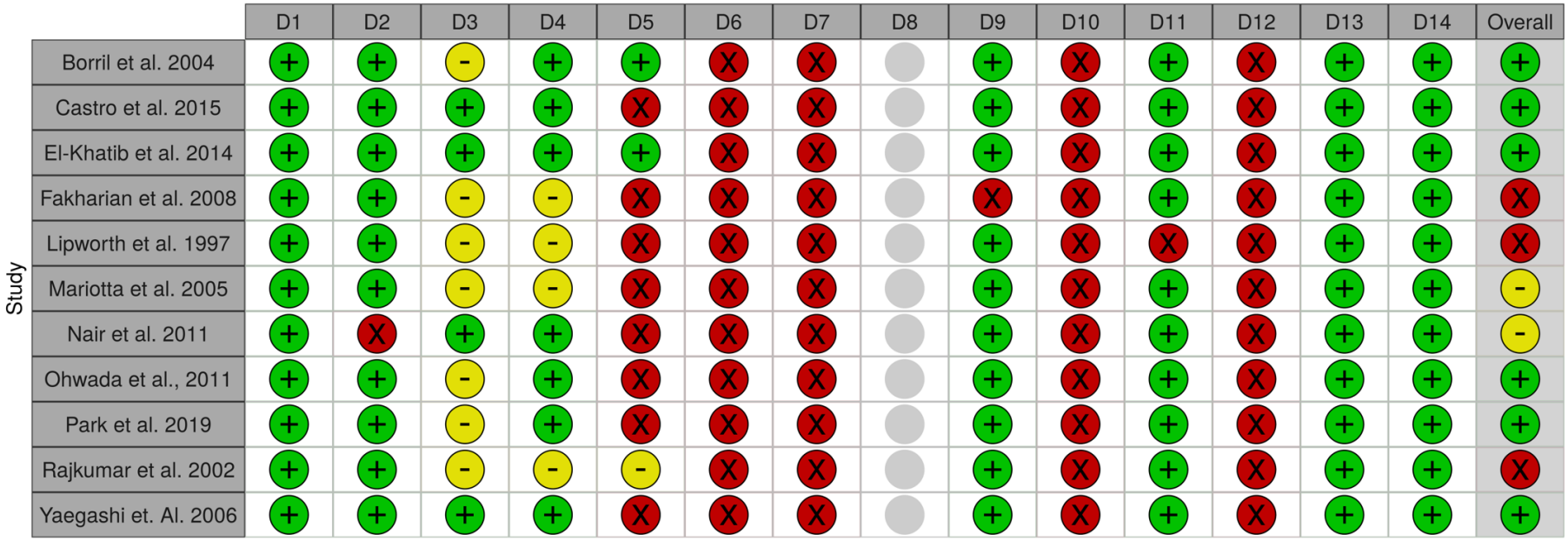
1. exp adult/
2. airway*.ti,ab.
3. exp chronic obstructive lung disease/
4. exp airway obstruction/
5. exp asthma/
6. asthma*.ti,ab.
7. COPD*.ti,ab.
8. exp emphysema/
9. exp Bronchitis, Chronic/
10. exp Pulmonary Disease, Chronic Obstructive/
11. exp Pulmonary Emphysema/
12. Small airway dysfunction*.ab,ti.
13. SAD.ab,ti.
14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. 1 and 14
16. MMEF.ti,ab.
17. fef25-75.mp.
18. FEF 25 - 75.mp.
19. fef50.mp.
20. MBW.ti,ab.
21. breath washout.ti,ab.
22. impulse oscill*.ti,ab.
23. forced oscill*.ti,ab.
24. ios.ti,ab.
25. fot.ti,ab.
26. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
27. exp Bronchodilator Agents/
28. exp Albuterol/
29. salbutamol.mp.
30. 27 or 28 or 29
31. exp Forced Expiratory Volume/
32. exp Respiratory Function Tests/
33. FEV1.ti,ab.
34. spirome*.ti,ab.
35. exp Forced Vital Capacity/
36. FVC.ti,ab.
37. 31 or 32 or 33 or 34 or 35 or 36
38. change*.ti,ab.
39. reversibility.ti,ab.
40. BDT.ti,ab.
41. BDR.ti,ab.

42. AR.ti,ab.
43. bronchodilator test.ti,ab.
44. respons*.ti,ab.
45. 38 or 39 or 40 or 41 or 42 or 43 or 44
46. 15 and 26 and 30 and 37 and 45

Embase:
1. exp adult/
2. airway*.ti,ab.
3. exp chronic obstructive lung disease/
4. exp airway obstruction/
5. exp small airway disease/
6. exp asthma/
7. asthma*.ti,ab.
8. COPD*.ti,ab.
9. exp emphysema/
10. exp chronic bronchitis/
11. Small airway dysfunction*.ab,ti.
12. SAD.ab,ti.
13. 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. 1 and 13
15. exp maximal mid expiratory flow/
16. MMEF.ti,ab.
17. FEF 25 - 75.ti,ab.
18. FEF25-75.ti,ab.
19. FEF50.ti,ab.
20. exp forced expiratory flow/
21. exp lung clearance/
22. MBW.ti,ab.
23. breath washout.ti,ab.
24. impulse oscill*.ti,ab.
25. forced oscill*.ti,ab.
26. ios.ti,ab.
27. fot.ti,ab.
28. 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29. exp salbutamol/
30. exp beta 2 adrenergic receptor stimulating agent/
31. exp bronchodilating agent/
32. 29 or 30 or 31
33. exp forced expiratory volume/
34. exp lung function/
35. FEV1.ti,ab.
36. Spirometry.ti,ab.
37. FVC.ti,ab.
38. exp Forced Vital Capacity/

39. 33 or 34 or 35 or 36 or 37 or 38
40. change*.ti,ab.
41. reversibility.ti,ab.
42. BDT.ti,ab.
43. AR.ti,ab.
44. bronchodilator test.ti,ab.
45. BDR.ti,ab.
46. respons*.ti,ab.
47. 40 or 41 or 42 or 43 or 44 or 45 or 46
48. 14 and 28 and 32 and 39 and 47

8.4.6 Quality Assessment Graph



D1: Was the research question or objective in this paper clearly stated?
D2: Was the study population clearly specified and defined?
D3: Was the participation rate of eligible persons at least 50%?
D4: Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?
D5: Was a sample size justification, power description, or variance and effect estimates provided?
D6: For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?
D7: Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?
D8: For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome?
D9: Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
D10: Was the exposure(s) assessed more than once over time?
D11: Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
D12: Were the outcome assessors blinded to the exposure status of participants?
D13: Was loss to follow-up after baseline 20% or less?
D14: Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

8.5.1 Published Abstract in Respiratory Care Journal

RESPIRATORY CARE

The Bronchodilator Response in $FEF_{25-75\%}$ Compared to FEV_1 in Assessing Asthma

Mohammed A Almeshari, Nowaf Y Alobaidi, James Stockley and Elizabeth Sapey

Respiratory Care October 2021, 66 (Suppl 10) 3608514;

Abstract

Background: Asthma is a common, chronic heterogeneous disease. Tests of large airways function (FEV_1) are commonly used to diagnose/monitor disease and bronchodilator responsiveness (BDR: measured by a change in FEV_1) is considered the hallmark of asthma. Small airways (<2 mm in diameter) dysfunction (SAD) has been described in asthma, but it is unclear how common BDR in the small airways is in asthma. The aim of this study was to compare BDR in the small airways compared to FEV_1.

Methods: A retrospective analysis of patients attending a secondary referral hospital in the Midlands, United Kingdom, including non-smoking adults (>18 y) referred to the pulmonary function laboratory as part of an asthma assessment between January 2016 and April 2021. BDR was assessed 20 min after the administration of 2.5 mg of salbutamol using a jet nebulizer. Changes in FEV_1 and FEF_{25-75} were assessed. The study was approved by the Research Ethics Committee and the Health Research Authority of the NHS (20/WM/0024).

Results: 219 patients were identified for this initial analysis. The population consisted of 104 (47.5%) males and the mean age was 44.7 y ± 18.9 with a BMI of 28.2 ± 6.5. 28 (12.8%) demonstrated airflow limitation in pre-BDR tests. The mean difference in pre and post bronchodilator %predicted FEV_1 was 9.7 (95% CI = 8.7-10.8) and 22.3 (95% CI = 19.7-24.9) %predicted FEF_{25-75}; ($P < 0.01$ for both). In total 73 (33.3%) demonstrated BDR in FEV_1, 101 (46.1%) in FEF_{25-75}. All of those with significant BDR response in FEV_1 had a significant response in FEF_{25-75}. The BDR in FEF_{25-75} was noted to be the lowest in severe cases, with no distinctive differences in other patients' characteristics.

Conclusions: This study confirms the presence of BDR in more adults with asthma using measures of small airways function than FEV_1. It is unclear whether this represents a separate phenotype of asthma.