UNIVERSITY OF BIRMINGHAM

THE PHYSIOLOGICAL ASSESSMENT OF SMALL AIRWAYS FUNCTION IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND THEIR UTILITY IN ASSESSING BRONCHODILATOR RESPONSIVENESS AND DURING ACUTE EXACERBATION EPISODES

by

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Abstract

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory disease that is linked to high mortality and morbidity. In COPD, the majority of airway resistance is located in the small airways. Studies have demonstrated that small airway dysfunction (SAD) has an important role in COPD pathophysiology. Few studies have shown that SAD can improve post-bronchodilator (BD) in some COPD patients, demonstrating the value of evaluating small airways as part of the bronchodilator responsiveness (BDR) assessment. Furthermore, there is evidence that SAD is worsened by inflammation associated with acute exacerbations of COPD (AECOPD), and it may improve as patients recover, indicating that small airway tests can be used to map and monitor recovery from AECOPD.

This thesis aimed to physiologically examine the small airway function in COPD and their utility in the assessment of bronchodilator responsiveness and during acute exacerbation of COPD.

Firstly, two cross-sectional studies were conducted using routinely collected lung function data of patients referred to the lung function unit as part of COPD screening to determine the prevalence of SAD in symptomatic ever-smokers and never-smokers. Secondly, to assess the utility of small airway tests in BDR assessment, a systematic literature review was carried out to identify the evidence of their use and a retrospective analysis of routinely collected lung function data of COPD patients was done to determine the use of MMEF as a measure of small airways (SA) in BDR assessment. Thirdly, to evaluate the utility of small airway tests during AECOPD, a systematic review of the literature to evaluate the evidence of their use in the acute setting was conducted.

Both cross-sectional studies of spirometric data found SAD in nearly all patients with established AO and 33-50% of patients without AO. This highlights that physiological

assessment of small airways might play an important role in managing COPD. The presence of SAD without AO in some symptomatic patients suspected of COPD indicates that this group may have early lung injuries and may benefit from being closely monitored to prevent COPD.

The systematic review of SA tests in BDR reported that previous studies showed that measures of SA were associated with notable changes following bronchodilator administration, but studies were few and included a small number of participants, warranting the need for a study to determine their utility. The BDR study demonstrated that BDR in MMEF is detected in 59.2% of COPD patients in the cohort, and importantly, was detected in nearly 37.9% of patients without BDR in FEV_1. This highlight that SA tests (particularly MMEF) could add to current spirometric measures used in the BDR assessment, providing insight into a clinical phenotype for patients displaying BDR in the SA alone, although further studies are needed to determine its clinical implications.

The systematic review of SA tests in AECOPD found six articles that showed that SA tests improved in correlation with FEV_1 during recovery from exacerbation. Notably, SA tests showed an earlier sign of change from exacerbation onset than FEV_1. These studies suggest that SA tests could be of value as a monitoring tool during AECOPD. Of the SA tests, FOT seems to be feasible and acceptable during AECOPD and may be useful for monitoring its recovery, although a comprehensive pilot study is needed to confirm this.

Publications arising from this work

Journal papers

Published:

- **Alobaidi NY**, Stockley JA, Stockley RA, Sapey E. **An overview of exacerbations of chronic obstructive pulmonary disease: Can tests of small airways' function guide diagnosis and management?.** *Ann Thorac Med*. 2020;15(2):54-63. doi:10.4103/atm.ATM_323_19
- **Alobaidi NY**, Almeshari M, Stockley JA, Sapey E, Edgar RG. **A Systematic Review of the Use of Physiological Tests Assessing the Acute Response to Treatment During Exacerbations of COPD (with a Focus on Small Airway Function)**. *COPD*. 2020;17(6):711-720. doi:10.1080/15412555.2020.1815183
- 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. Published 2021 Nov 11. doi:10.2147/COPD.S331995

In preparation:

- **Alobaidi N**, Almeshari M, Stockley JA, Stockley RA, Sapey E. **The utility of small airways tests in the assessment of bronchodilator responsiveness in COPD - A retrospective study.**
- **Alobaidi NY,** Almeshari MA, Stockley JA, Stockley RA, Sapey E. **Small airway dysfunction in symptomatic ever-smokers: A real-world retrospective study.**

- **Alobaidi NY**, Dhruv Parekh, Sapey E. **The utility of small airways tests during acute exacerbation of COPD – A protocol for pilot study**.
- **Alobaidi NY**, Almeshari MA, Stockley JA, Stockley RA, Sapey E. **Small airway dysfunction in symptomatic never-smokers: A retrospective study**.

Conference abstracts

Published:

- **Alobaidi N**, Almeshari M, Stockley J, Sapey E, Edgar R. A systematic review of the use of physiological tests assessing the acute response to treatment during exacerbations of COPD. *Eur Respir J*. 2020;56(suppl 64):156.
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List of abbreviations

AATD	Alpha-1 Antitrypsin Deficiency
AAT	Alpha-1 Antitrypsin
AECOPD	Acute exacerbation of COPD
AO	Airflow obstruction
ARTP	Association for Respiratory Technology & Physiology
ATS	American Thoracic Society
AX	area under the reactance curve
BAL	Bronchioalveolar lavage
BD	Bronchodilator
BDR	Bronchodilator Responsiveness
BiPAP	Bi-level positive airway pressure
BLT	Bilateral lung transplant
BMI	Body mass index
BTS	British Thoracic Society
CAT	COPD assessment test
CDI	convection-dependant inhomogeneity
CI	Confidence interval
COPD	Chronic Obstructive Pulmonary Disease
CPAP	Continuous positive airway pressure
CRF	Chronic Respiratory Failure
CRP	C-reactive protein
CT	Computed Tomography
CXR	Chest x-ray
DCDI	diffusion-convection-dependant inhomogeneity
DLCO	diffusing capacity of the lung for carbon monoxide
DPI	Dry powder inhalers
ECG	Electrocardiography
ECLIPSE	Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points
EFL	Expiratory Flow limitation
ERS	European Respiratory Society
ERV	Expiratory reserve volume
EXACT	Exacerbation of Chronic Pulmonary Disease Tool
FBC	Full blood count
FDA	Food and Drug Administration
FEF_{25-75}	forced expiratory flow between 25 and 75 of FVC
FEV_1	forced expiratory volume in one second
FEV_3	forced expiratory volume in 3 seconds
FL%	flow limitation percentage
FOT	Forced oscillometry technique

FRC	functional residual capacity
Fres	resonant frequency
FVC	forced vital capacity
GINA	Global Initiative for Asthma
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HR	Hazard ratio
hsCRP	High sensitivity C-reactive Protein
hs-cTnT	High-Sensitivity Cardiac Troponin T
IC	Inspiratory Capacity
ICS	Inhaled Corticosteroid
IOS	Impulse oscillometry
IQR	Interquartile ranges
IQR	Interquartile range
ISHLT	International society for heart and lung transplantation
KSA	Kingdom of Saudi Arabia
LABA	long-acting beta-2 agonists
LAMA	Long-acting muscarinic antagonists
LCI	Lung clearance index
LLN	Lower limit of normal
LTOT	Long-term oxygen therapy
LVRS	Lung volume reduction surgery
MBNW	Multiple Breath Nitrogen Washout
MBW	Multiple breath washout
MCID	Minimal clinically important difference
MEF_{25}	Maximal expiratory flow at 25% of FVC
MEF_{50}	Maximal expiratory flow at 50% of FVC
MEF_{75}	Maximal expiratory flow at 75% of FVC
MMEF	maximal mid-expiratory flow
MMEF/FVC	MMEF corrected for FVC
mMRC	modified Medical Research Council
NHS	National Health Service
NIH	national institute of health
NIPPV	Non-invasive positive pressure ventilation
NIPPV	Non-invasive positive pressure ventilation
NIV	Non-invasive ventilation
NIV	Non-invasive Ventilation
OR	Odds ratio
PBD	Post-bronchodilator
PEF	Peak Expiratory Flow
pMDI	pressurized metered dose inhalers
PR	Pulmonary Rehabilitation

PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PRM	Parametric response mapping
PRM^{fSAD}	functional small airway disease
PRO	Patient-reported outcome
ProBNP	B-Type Natriuretic Peptide
PROSPERO	International Prospective Register of Systematic Reviews
R^2	Coefficient of determination
R_{20}	resistance at frequency of 20hertz
R_5	resistance at frequency of 5hertz
R_{5-20}	difference between resistance at frequency of 5hertz and 20 hertz.
Raw	Airway resistance
RCT	Randomised Clinical Trial
R_{ex}	Airway resistance by body plethysmography during expiration
R_{in}	Airway resistance by body plethysmography during inspiration
Rrs	Respiratory resistance
Rrs_{exp}	resistance during expiration
Rrs_{insp}	resistance during inspiration
RT-PCR	Reverse transcription polymerase chain reaction
RV	Residual Volume
SA	Small airways
SABA	short-acting beta-2 agonists
SABD	Short-acting bronchodilators
S_{acin}	ventilation heterogeneity of the peripheral airways in the acinar zone
SAD	Small airway Dysfunction
SAF	Small airway function
SAMA	short-acting muscarinic antagonists
SBNW	Single Breath Nitrogen Washout
SBW	Single breath washout
S_{cond}	ventilation heterogeneity of the conducting airways
SD	Standard deviation
SD	Standard deviation
SEM	Standard error of mean
SF6	Sulphur hexafluoride
sGaw	Specific airway conductance
SGRQ	St George's Respiratory Questionnaire
SGS	systemic glucocorticoid steroids

SIII	The slope of Phase III
SLT	Single lung transplant
sR0.5	specific resistance of expiratory flow between +0.5 and –0.5L/s
sRaw	specific Raw
sReff	specific effective resistance
sRtot	specific total resistance
SVN	small volume jet nebulizers
TLC	Total lung capacity
UK	United Kingdom
VC	Vital capacity
WLS	weight least-square
X_5	reactance at frequency of 5hertz
Xrs	Respiratory reactance
Xrs_{exp}	reactance during expiration
Xrs_{insp}	reactance during inspiration
Z_5	respiratory impedance at frequency of 5 hertz
Zrs	Respiratory impedance
ΔXrs	expiratory flow limitation index

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1. INTRODUCTION

This chapter provides the background of the key topic areas explored in this PhD thesis: Chronic Obstructive Pulmonary Disease (COPD), exacerbations of COPD, small airway dysfunction (SAD), and measures of small airway function and their utility in the assessment of bronchodilator responsiveness (BDR) and during exacerbation periods.

Part of this chapter has been published in the Annals of Thoracic Medicine and titled **"An overview of exacerbations of chronic obstructive pulmonary disease: Can tests of small airways' function guide diagnosis and management?"** (see appendix 1.1.) (Alobaidi et al., 2020c).

1.1. Chronic Obstructive Pulmonary Disease

1.1.1. Definition and classification of disease severity

Chronic Obstructive Pulmonary Disease (COPD) is a chronic inflammatory disease that affects the lungs but also has significant systemic consequences (Sevenoaks and Stockley, 2006). The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines COPD as "a common preventable and treatable disease that is characterised by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases and influenced by host factors including abnormal lung development" (Global Initiative for Chronic Obstructive Lung Disease, 2022). A combination of damaged lung parenchyma and impaired small airways causes the airflow obstruction (AO) which defines COPD (Global Initiative for Chronic Obstructive Lung Disease, 2022), but COPD is heterogeneous, encompassing several clinical/pathological disorders including chronic bronchitis and emphysema. (Global Initiative for Chronic Obstructive Lung Disease, 2022). Chronic bronchitis is manifested clinically by symptoms of chronic cough for most days over three months in each of two years in a row after all other aetiologies have been ruled out (Des Jardins and Burton, 2019). Emphysema is a pathological diagnosis, recognized by the persistent dilatation of the airspaces distal to the terminal bronchioles, associated with bronchiole wall damage which is not associated with apparent fibrosis (Des Jardins and Burton, 2019). These disorders can co-occur in differing percentages among impacted subjects (Saetta et al., 2001). Figure 1.1. graphically shows the abnormalities in patients with chronic bronchitis and emphysema.

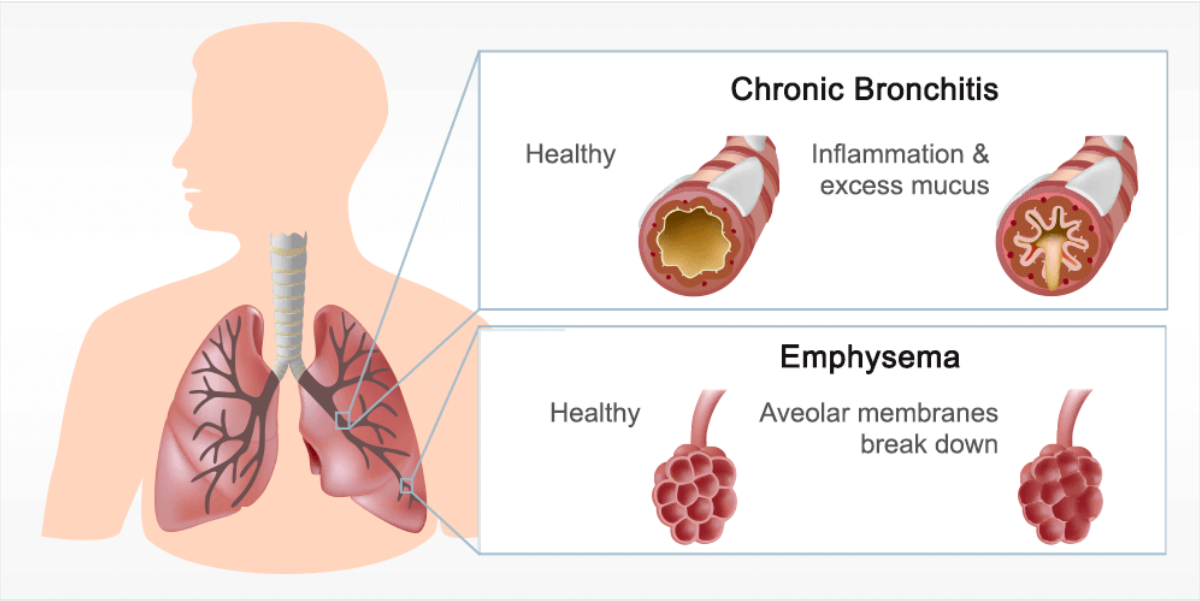

Figure 1.1. Illustration of the abnormalities in patients with chronic bronchitis and emphysema.

Legend: *This figure demonstrates airways with chronic bronchitis compared to healthy airways and alveoli with emphysema compared to healthy alveoli. This figure was reproduced with permission from Source: Asbestos.com. (The Mesothelioma Center, 2022)*

Diagnosing COPD is reliant on the presence of symptoms (breathlessness, chronic cough, sputum production and wheeze), precipitating factors associated with the disease, and post-bronchodilator (PBD) spirometry confirming AO (defined by forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) (FEV_1/FVC) ratio of <70%) (Global Initiative for Chronic Obstructive Lung Disease, 2022). According to the GOLD report, severity of AO in COPD is stratified into four stages (based on PBD FEV_1 % predicted): GOLD 1 ($FEV_1 \geq 80\%$ predicted); GOLD 2 ($FEV_1 \geq 50$ to < 80% predicted); GOLD 3 ($FEV_1 \geq 30$ to < 50% predicted); GOLD 4 (FEV_1 < 30% predicted) (Global Initiative for Chronic Obstructive Lung Disease, 2022). In 2011, GOLD developed a new approach in evaluating the severity of the disease referred to as the refined ABCD assessment tool and it was recommended that this approach should be used in guiding pharmacological treatments. The

refined ABCD assessment tool is multidimensional as it includes in addition to spirometric findings, the assessment of exacerbations' history and the impact of the disease on patients (assessed using modified Medical Research Council (mMRC) dyspnoea scale or COPD Assessment Test (CAT)) (Global Initiative for Chronic Obstructive Lung Disease, 2022). Following the evaluation of each aspect, patients will be categorised into any of the ABCD groups (see figure 1.2).

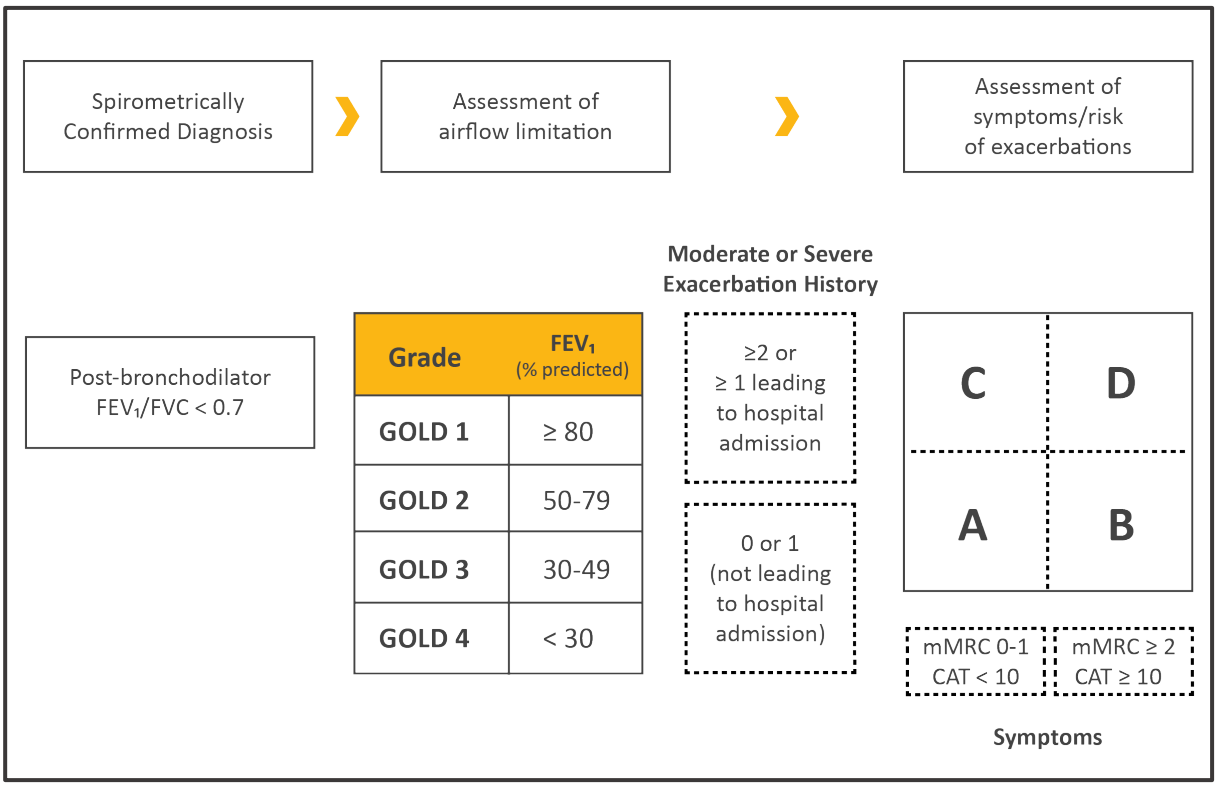

Figure 1.2. The refined ABCD assessment tool.

Legend: *This figure shows the ABCD assessment tool used to classify COPD patients, incorporating symptoms and exacerbation history. This figure was taken with permission from (Global Initiative for Chronic Obstructive Lung Disease, 2022).*

Abbreviations: *mMRC, modified Medical Research Council (dyspnea scale); CAT, COPD-assessment test.*

1.1.2. Aetiologies and precipitating factors

Globally, the most common aetiology of COPD is tobacco smoking (Global Initiative for Chronic Obstructive Lung Disease, 2022). Chronic current smokers and those with a past

smoking history of at least 20 pack-years are particularly at risk of developing COPD (van Durme et al., 2009). However, <50% of smokers develop the disease (Rennard and Vestbo, 2006), and non-smokers can also develop COPD (Salvi and Barnes, 2009), making cigarette smoke exposure, neither sufficient or necessary to cause disease. Non-smoking COPD is estimated to contribute to 25-45 of all cases of COPD (Salvi and Barnes, 2009), although we know very little about its pathogenesis apart from Alpha-1 Antitrypsin Deficiency (AATD). Precipitating factors contributing to non-smoking COPD include genetic susceptibility such as AATD (Global Initiative for Chronic Obstructive Lung Disease, 2022), environmental factors such as biomass fuel exposure and air pollution, all discussed below.

Genetic disorders may contribute to COPD, and AATD is the most commonly reported disorder. AATD is a genetic disorder featured by a decreased concentration of alpha-1 antitrypsin (AAT) in the blood (Stoller and Aboussouan, 2005). It is also featured by an autosomal and codominant inheritance pattern (Stoller and Aboussouan, 2005). AAT is a protein of the serpin family, encoded by the SERPINA1 gene on chromosome 14 at q31-32.3 (Jacobsson, 1955). AAT is mostly produced by hepatocytes and protects the body, including the lungs, from serine proteases (e.g. neutrophil elastase [NE] and protease 3 [PR3]) (Stoller and Aboussouan, 2005). The lower AAT levels in AATD patients are due to the mutation impacting the tertiary structure of AAT, which causes chains or polymers to form, inhibiting their secretion from the hepatocyte. A result of this is a disproportion between antiproteases and proteases, which results in protease damaging lung tissues, causing pathological changes such as emphysema; consequently, these patients are at a higher likelihood of COPD development (Global Initiative for Chronic Obstructive Lung Disease, 2022). The gene responsible for producing AAT contains two alleles that determine the genetic feature. Normal individuals have normal alleles, called M alleles, whereas AATD patients may have S

and/or Z alleles. Hence, these alleles are combined to describe the most common genotypes. In individuals with normal AAT, the genotype PiMM is observed, whereas those with AATD, PiZZ, PiMZ and PiSZ are mainly detected (Stoller and Aboussouan, 2005). PiZZ is the most common studied phenotype because it is associated with a severely low AAT compared to other genotypes, resulting in early-onset emphysema even in non-smokers (Piitulainen, Tornling and Eriksson, 1997). While patients with PiMZ and PiSZ genotypes have milder AATD and are less likely to develop lung diseases, exposure to risk factors such as smoking may increase their risk of developing COPD. AATD can also cause damage to other parts of the body, causing liver cirrhosis, vasculitis, hepatocellular carcinoma and panniculitis (Eriksson, Carlson and Velez, 1986; Fortin et al., 1991; Stoller and Piliang, 2008).

Environmental exposures have also been linked to COPD development. Work-related environmental exposure is estimated to account for about 15–20% of COPD cases (Loddenkemper et al., 2003). A meta-analysis by Po et al. demonstrated a significant relationship between COPD and biomass smoke exposure (Po, FitzGerald and Carlsten, 2011), highlighting that biomass exposure could cause damage to the lungs, leading to COPD. Importantly, COPD associated with biomass smoke exposure was associated with high mortality (Lopez et al., 2006). A study demonstrated that of individuals who died because of COPD in developing countries, approximately 50% have been exposed to biomass smoke during their lifetime (Lopez et al., 2006). Long-term exposure to air pollutants such as particulate matter, nitrogen dioxide, and ozone has also been shown to contribute to COPD (Liu et al., 2021; Shin et al., 2020).

Other risk factors may also predispose to COPD, such as ageing, socioeconomic status, childhood exposure, and other lung diseases such as asthma (Global Initiative for Chronic Obstructive Lung Disease, 2022). In the Global Initiative for Asthma (GINA),

asthma is defined as “heterogeneous disease, usually characterised 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, 2022). Asthmatic patients were found to be at greater risk of developing COPD than non-asthmatic patients in a large longitudinal study of 3099 participants (hazard ratio (HR), 12.5; 95% confidence interval (CI), 6.84 to 22.84) (Silva et al., 2004). Summary of the precipitating factors for COPD is provided in table 1.1.

Table 1.1. Precipitating factors linked with the development of COPD
Tobacco smoking Biomass smoke exposure Work-related exposure Air pollution Genetic factors (such as AATD) Intrauterine growth disorders Respiratory infections during childhood Low birth weight Low socioeconomic status Asthma Airway hyperresponsiveness Recurrent bronchopulmonary infections
Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; AATD, Alpha Antitrypsin Deficiency

1.1.3. Prevalence and impact

COPD is an important worldwide public health challenge (National Institute for Health and Care Excellence, 2019), affecting 251 million people globally (World Health Organization, 2021). Furthermore, COPD is a prominent and rising cause of mortality and morbidity. In 2019, COPD was found to be responsible for more than 3.2 million deaths (World Health Organization, 2021; World Health Organization, 2020), making it the third

prominent cause of mortality globally (World Health Organization, 2021). The prevalence of COPD is expected to increase year on year because of the continual exposure to precipitating factors and a globally ageing population (Mathers and Loncar, 2006). Population studies suggest COPD is seen in 10% of adults in Europe and the United States of America (Halbert et al., 2006). This suggests there should be 3 million people with COPD in the United Kingdom (UK), but there are merely 1 million with diagnosed disease, indicating two thirds of patients have undiagnosed disease (British Lung Foundation, no date).

Most diagnoses of COPD are made when people are in the sixth decade of life (National Institute for Health and Care Excellence, 2019), reflecting the slowly progressive nature of disease in most people (allowing lifestyle modification to mask functional deficits in lung health (Casanova et al., 2011)) but the prevalence of COPD rises with age and differs significantly by geographical area, reflecting socioeconomic deprivation (van Durme et al., 2009). Although COPD is more common in men, recently, the prevalence has increased in women, reflecting increases in smoking rates among women (National Institute for Health and Care Excellence, 2019).

In the UK, even though only a small number of COPD patients are hospitalised yearly, COPD is responsible for one in eight emergency department (ED) admissions (National Institute for Health and Care Excellence, 2019), making it the second paramount reason of ED admission in the UK (National Institute for Health and Care Excellence, 2019). COPD is also considered as one of the costliest in-patient disorders managed by the UK's National Health Service (NHS) (National Institute for Health and Care Excellence, 2019), approximately costing the economy £1.9 billion each year. COPD also accounts for 29% of the total cost of respiratory illnesses (British lung foundation, 2017).

In the Middle Eastern countries, COPD has become an important public health issue and despite this, it remains underdiagnosed and under-recognised (Ben Abdallah et al., 2011). Here, the most common risk factors for developing COPD are tobacco smoking, waterpipe smoking (also known as shisha), passive smoking, and other indoor and outdoor causes (Ben Abdallah et al., 2011). In the Kingdom of Saudi Arabia (KSA), evidence about the prevalence of COPD is still lacking. A cross-sectional analysis of 700 participants by Al Ghobain et al. showed that the overall prevalence of COPD in KSA is 4.2% (Al Ghobain et al., 2015). The authors also found that the diagnosis of COPD was related to older age, male gender and smoking status. However, the study was limited by the small sample size, the inclusion criteria (only including patients aged 40 years or older) and the population assessed (only assessing patients with COPD in GOLD 1 and 2). The study was also limited to one city, limiting the generalizability of the findings. Hence, to be more representative, large population-based studies are needed to determine the prevalence of COPD in KSA.

1.1.4. Disease mechanism

COPD is characterized by chronic inflammation, resulting in pathological changes in the tracheobronchial tree, such as mucous hypersecretion (chronic bronchitis), destruction of alveolar tissue (emphysema) and inflammation of the small airways (bronchiolitis), although their contribution to the disease varies depending on impacted individuals (Hogg and Timens, 2009).

In general, exposure to inhaled irritating particles such as cigarette smoking results in an inflammatory response in the lungs. This is present in all smokers, although it is not as intensified as in patients with established COPD. In the latter, the long-term exposure to these particles leads to the heightened inflammatory response. Despite that cigarette smoking is the

key precipitating factor to stimulating inflammatory responses, not all smokers develop COPD (Salvi and Barnes, 2009), indicating the importance of other factors such as genetics in COPD development. The mechanism by which non-smokers develop COPD appears to differ from the smoking-related COPD; however, little is known about the pathogenesis of non-smoking COPD, apart from the AATD. A number of mechanisms have been identified in the development of COPD, including exaggerated inflammation, an imbalance between proteases and antiproteases, and oxidative stress (Barnes, 2014). Notably, these mechanisms do not work independently but rather in concert, causing the disease to develop and worsen.

The role of inflammation is central in COPD as it affects the large and small airways as well as the lung parenchyma and worsens as the disease progresses (Barnes, 2014). Further worsening of inflammation may occur during acute episodes of deterioration in symptoms, known as exacerbations (Aaron et al., 2001; Biernacki, Kharitonov and Barnes, 2003). The inflammation can extend beyond the lungs and cause systemic inflammation that may lead to or exacerbate comorbid conditions (Barnes, 2010). Inflammation in COPD has shown to endure even when smoking is stopped, although the cause of this is still unclear, but studies have suggested that it could be caused by autoimmunity or self-perturbations in the lung microbiome (Lee et al., 2007; Sze et al., 2015). Innate and adaptive inflammatory responses are both involved in the pathogenesis of COPD (Barnes et al., 2015). Exposure to inhaled harmful particles triggers an innate immune response. As a result, macrophages and neutrophils are increased in the lungs, and the airway epithelium is stimulated (Brusselle, Joos and Bracke, 2011). There is mounting evidence that neutrophils and macrophages are the key inflammatory cells in COPD pathogenesis (Barnes, 2014; Stockley, 2002). A high level of neutrophils has been found in bronchial lavage (BAL) fluid (Martin et al., 1985; Keatings et al., 1996) and sputum collected from central airways (Stănescu et al., 1996; Rutgers et al.,

2000) in COPD patients. Moreover, a higher number of macrophages have been detected in lung parenchyma, sputum, and BAL of COPD patients (Barnes, 2014). In some COPD patients, level of eosinophils has been found to be increased in the sputum and the airways (Brightling et al., 2000), highlighting that these could reflect a phenotypic group of patients who may benefit from corticosteroids.

At a later stage of the disease, the adaptive immune response is stimulated, resulting in increased numbers of T lymphocytes and B lymphocytes in the lungs (Barnes et al., 2015). At this stage, CD8+ T cells, CD4+ T helper 1 cells rises in number in lungs (Barnes, 2008b). An increase in CD4+ T helper 17 cells is also observed during the adaptive immune response (McAleer and Kolls, 2014), leading to more heightened inflammation, resulting in a further higher level of neutrophils.

The level of several inflammatory mediators involved in inflammation and attracting inflammatory cells to the lungs is also increased in COPD compared to smoking controls (Barnes, 2008a). These include but not limited to Interleukin (IL)-8, IL-6, growth-related oncogene-a (GRO-a), Leukotriene B4 (LTB4), chemotactic protein-1 (MCP-1), Interferon-g inducible protein (IP-10), monokine-induced by interferon-g (Mig) and interferon-inducible T-cell a-chemoattractant (I-TAC). Other inflammatory mediators in the blood, including C-reactive protein (CRP) and fibrinogen, are elevated in COPD compared to healthy controls (Gan et al., 2004).

Another important mechanism in COPD pathogenesis is the imbalance between proteases (enzymes that damage connective tissues such as elastin fibre) and antiproteases (proteins work against the function of proteases) (Stockley, 1999). This imbalance happens due to the oxidants released from smoking or inflammatory cells (e.g. reactive oxygen species) that result in the inactivation of antiproteases and the production of proteases from

inflammatory cells in COPD patients (Barnes et al., 2015). Proteases implicated in COPD pathogenesis are mainly those secreted by neutrophils (e.g. NE, cathepsin G, and PR3) and macrophages (e.g. matrix metalloproteinases (MMP), MMP-9, MMP-12, and cathepsin B, K, L, and S). Therefore, this imbalance could lead to excessive mucous production, as seen in chronic bronchitis, or the destruction of alveoli in emphysema.

Moreover, oxidative stress, defined as an disproportion between oxidants and antioxidants, is central to COPD' pathogenesis, contributing to the majority of the disease pathological changes (Barnes et al., 2015). Cigarette smoking and the stimulation of inflammatory cells (especially neutrophils and macrophages) are the primary sources of oxidants in patients with COPD (Kirkham and Barnes, 2013). Oxidative stress is an important mechanism not only because it leads to injuries in the lungs but it also leads to amplified inflammation and worsens protease/antiprotease imbalance (Barnes et al., 2015).

The previously described pathogenic mechanisms lead to physiological impairments. First, the impairments in goblet cells and submucosal glands result in excessive mucous production, as seen in patients with chronic bronchitis (Global Initiative for Chronic Obstructive Lung Disease, 2022). Second, amplified inflammatory response and narrowing of airways causes AO in COPD, especially in the small airways, which is associated with a decreased FEV_1 and FEV_1/FVC (Barnes et al., 2015). The AO leads to the progressive accumulation of air in the lungs during expiration, leading to air trapping, which in turn results in hyperinflation (raised total lung capacity (TLC)) at rest (Barnes et al., 2015). The hyperinflation worsens with activity, resulting in a decreased inspiratory capacity (IC) (Guenette, Webb and O'Donnell, 2012). This leads to breathlessness, especially with exertion. Third, as results of the structural changes in the lungs, an abnormal gas exchange may happen at the advanced stage of the disease. This is featured by hypoxemia (low level of arterial

oxygen), hypercapnia (higher level of arterial carbon dioxide) and ventilation (V)/perfusion (Q) mismatch (Global Initiative for Chronic Obstructive Lung Disease, 2022). Fourth, some COPD patients may experience pulmonary hypertension because of hypoxic pulmonary vasoconstriction and structural changes in the pulmonary vasculature (Sakao, Voelkel and Tatsumi, 2014). Lastly, as a result of the inflammatory response and structural changes in the lungs, systematic impairments may be developed in some COPD patients, including cardiovascular diseases, skeletal muscle wasting, cachexia, depression and anxiety (Global Initiative for Chronic Obstructive Lung Disease, 2022)

1.1.5. Disease progression

COPD can be modified with acute acting therapies but is not a curable condition, and it is also preventable for most adults. COPD is a slowly progressive disease in most individuals (Casanova et al., 2011) but our understanding of the early stages of the disease is limited. This is because the majority of individuals with COPD are diagnosed with moderate to severe disease (as defined by spirometry) (Lindberg et al., 2006) and there has often been a significant delay between symptom onset and the performance of diagnostic spirometry for many individuals (Agusti et al., 2010; Vestbo et al., 2011). COPD varies in terms of its progression between individuals (Casanova et al., 2011) although most susceptible smokers experience a steady decline in lung function (Vestbo et al., 2011). In the ECLIPSE study, changes in FEV_1 were measured in COPD patients over three years period (Vestbo et al., 2011) and overall, the mean rate of decline in FEV_1 was 33ml/year, but there was substantial variability in the level of change. In 38% of the patients, FEV_1 decreased by approximately 40ml/year over the three years, the FEV_1 was relatively stable in 23% of patients, and in 8%, FEV_1 rose by more than 20ml/year. In this study, there was no relationship between the rate

of decline and age; but current smoking, milder AO and frequent exacerbations were more likely to be associated with a fast decline. The association of rate decline with milder AO indicates the importance of early diagnosis of COPD. However, due to the variability of spirometric measures, current recommendations suggest measuring FEV_1 at least over three time points a year part, meaning it takes years before fast declining patients are identified (Stockley et al., 2017a). The evaluation of declining lung function over three years period indicates that it may already be too late to intervene, as the patient's COPD may have already progressed to a more severe stage. This highlights the need for a better biomarker that could help detect disease progression in a shorter period. Such a biomarker should reflect not only physiological lung function but also other aspects of the disease mechanisms, such as inflammation.

1.1.6. Management of stable COPD

In COPD, in general, disease management is associated with improvement in patients' outcomes. In the GOLD report, the management goals for COPD patients are aimed at improving several outcomes (symptoms, health status and tolerability of exercise) and at decreasing the risks associated with the disease (preventing disease progression, exacerbations and mortality) (Global Initiative for Chronic Obstructive Lung Disease, 2022). The management of stable COPD includes several interventions, and they are detailed below.

1.1.6.1.Smoking Cessation

Smoking cessation is paramount to managing COPD as it has an impact on disease progression. An epidemiological study showed that smoking cessation has an effect on the decline of lung function, underlining the value of smoking cessation (Fletcher and Peto,

1977). Furthermore, in a large Randomised Clinical Trial (RCT), Anthonisen et al. showed that the rate of FEV_1 decline was substantially reduced in patients who stopped smoking (smoking cessation group) compared to those who are still smokers (control group) (Anthonisen et al., 1994). Another study demonstrated that smoking cessation is associated with improvement in pulmonary symptoms (Comstock et al., 2008). Smoking cessation also correlated with a decrease in hospitalization (Godtfredsen et al., 2002) and improvement in survival (Godtfredsen et al., 2008).

1.1.6.2.Vaccinations

Vaccination (especially Influenza) is also important in the management of COPD, as it decreases the risk of respiratory infections and its associated hospital admissions (Wongsurakiat et al., 2004). Influenza vaccination is also associated with lower risk of exacerbations (Poole et al., 2006) and death (Poole et al., 2006; Schembri et al., 2009; Nichol et al., 1994). Another vaccination recommended for COPD patients is the pneumococcal vaccine (e.g. Pneumococcal Conjugate vaccine [PCV13] and Pneumococcal Polysaccharide Vaccine [PPSV23]). The use of PCV13 and PPSV23 is associated with a lower likelihood of pneumonia in COPD patients (Bonten et al., 2015; Alfageme et al., 2006). The GOLD report recommends both vaccines for those 65 years and older, while PPSV23 is recommended for younger patients with COPD.

1.1.6.3.Pulmonary rehabilitation

Pulmonary rehabilitation (PR) is a vital part of managing COPD patients. PR is defined "a comprehensive intervention based on thorough patient assessment followed by patient-tailored therapies that include, but are not limited to, exercise training, education, self-

management intervention aiming at behaviour change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviours." (Spruit et al., 2013). The use of PR in stable COPD correlated with substantial amelioration in physical performance, health status and symptoms (McCarthy et al., 2015).

1.1.6.4.Pharmacological management

The pharmacological management for stable COPD patients should be tailored upon the patient's symptoms and exacerbation history (using the ABCD approach) (Global Initiative for Chronic Obstructive Lung Disease, 2022). Pharmacological treatments have been linked with ameliorated patient outcomes such as symptoms, health status and exacerbations (Burge et al., 2000; Anthonisen et al., 1994). Although several RCTs have not been conclusive on the effect of pharmacotherapy on lung function decline (Burge et al., 2000; Anthonisen et al., 1994; Vestbo et al., 1999; Pauwels et al., 1999), a recent meta-analysis of nine RCTs reported that active treatment arms compared to placebo arms was shown to improve the disease-associated decline lung function (Celli et al., 2021). The meta-analysis included studies with different interventions, such as long acting bronchodilators, inhaled corticosteroids (ICS) (Celli et al., 2021). The meta-analysis, including all treatments from nine RCTs, revealed that active treatment arms showed a decrease in the rate of FEV_1 decline by 5.0ml/year (95% confidence interval (CI), 0.8-9.1ml/year) compared with placebo arms. Further meta-analyses showed that compared to placebo arms, ICS and long-acting bronchodilator treatment arms resulted in decreases in FEV_1 decline of 4.9ml/year (95% Cl – 0.8, 10.6) and 7.3ml/year (95% Cl 4.1, 10.5), respectively. Accordingly, the recent GOLD report was updated, and emphasis was placed on finding patients who are likely to benefit and

exhibit improvement in lung function decline. Moreover, studies showed that pharmacological treatments are associated with a reduction in mortality (Rabe et al., 2020; Lipson et al., 2020). The common types of licensed COPD treatment are listed in Table 1.2.

Table 1.2. The common types of licensed COPD drugs

Drug class	Drug name	Formulation
SABA	Salbutamol	MDI, DPI and SVN
	Terbutaline sulfate	DPI and SVN
SAMA	Ipratropium bromide	MDI and SVN
LABA	Formoterol	MDI and DPI
	Indacaterol	DPI
	Salmeterol	MDI and DPI
LAMA	Tiotropium	DPI and SMI
	Aclidinium bromide	DPI
	Glycopyrronium bromide	DPI
	Umeclidinium	DPI
SABA + SAMA	Salbutamol + ipratropium	SVN
LABA + LAMA	Formoterol + aclidinium	DPI
	Formoterol + glycopyrronium	MDI
	Indacaterol + glycopyrronium	DPI
	Vilanterol + umeclidinium	DPI
	Oldaterol + tiotropium	SMI
LABA + ICS	Formoterol + beclometasone	DPI
	Formoterol + budesonide	MDI
	Salmeterol + fluticasone propionate	DPI
LABA + LAMA + ICS	Fluticasone + umeclidinium + vilanterol	DPI
	Beclometasone + formoterol + glycopyrronium	MDI
	Budesonide + formoterol + glycopyrrolate	MDI
Phosphodiestrase-4 inhibitors	Roflumilast	Oral
Mucolytic agents	Erdosteine	Oral
	Carbocisteine	Oral
	acetylcysteine	Oral

Legend: This table list the most common licensed COPD medications.
Abbreviations: SABA, short acting beta-2 agonist; SAMA, short acting muscarinic antagonist; LABA, long-acting beta-2 agonist; LAMA, long acting muscarinic antagonist; ICS, inhaled corticosteroid; MDI, metered dose inhalers; DBI, dry powder inhaler; SVN, small volume nebulizer.

Several pharmacological treatments have been used in COPD and each has a different mechanism of action as well as a different purpose of use. Bronchodilators are used to alleviate symptoms and improve lung function (Donnell et al., 2004), with beta-2 agonists and

muscarinic antagonists (both short-acting and long-acting) being the most commonly used. The use of bronchodilators has been demonstrated to decrease rates of exacerbations and hospitalizations (Kew, Mavergames and Walters, 2013). Using a combination of different bronchodilators may also be valuable in COPD (Nannini et al., 2013). In comparison to the use of monotherapy, combining long-acting beta-2 agonists (LABA) and long-acting muscarinic antagonists (LAMA) was associated with a higher amelioration in lung function (especially FEV_1), symptoms and quality of life (QOL) (Global Initiative for Chronic Obstructive Lung Disease, 2022). Other drugs used in managing stable COPD are anti-inflammatory drugs (such as inhaled corticosteroids (ICS)). The use of these drugs has been associated with a decrease in exacerbation rate. (Nannini et al., 2013); however, it is recommended to be used in combination with LABA (Global Initiative for Chronic Obstructive Lung Disease, 2022). Triple inhaled therapy (LABA, LAMA and ICS) also showed positive findings. In comparison to dual therapy, an RCT by Lipson et al. demonstrated that triple inhaled therapy resulted in a greater amelioration in lung function and a lower moderate or severe exacerbation rate (Lipson et al., 2018).

Other drugs have also been used in stable COPD management, such as methylxanthines, antibiotic and mucolytic. There are currently two methylxanthines available, theophylline and aminophylline. In a double-blind RCT, ZuWallack et al. found that theophylline combined with salmeterol significantly improved patients' symptoms and lung function compared to either drug alone (ZuWallack et al., 2001). In this study, there were significantly fewer side effects associated with salmeterol alone than with theophylline, suggesting that the side effects of theophylline could pose a challenge to their use. Furthermore, a low dose of theophylline combined with ICS did not result in a significant difference in improvement in exacerbation rates, health status, or lung function compared to a

placebo or placebo plus theophylline (Devereux et al., 2018; Jenkins et al., 2021). It is important to emphasize that methylxanthines may be associated with toxicity due to the narrow therapeutic range, although this depends on the dose. This makes them less favourable in COPD management. Antibiotics may also be used in stable COPD but prophylactically, and it was reported that their use may results in lower exacerbation rate (Albert et al., 2011; Herath et al., 2018) and an ameliorated health status (Herath et al., 2018). Mucolytics are used to help in sputum expectoration, and their administration may result in a decrease in exacerbations (Davies and Calverley, 2010).

1.1.6.5.Oxygen therapy and ventilatory support

Oxygen supplementation, especially long-term oxygen therapy (LTOT; defined by supplemental oxygen for ≥15 hours per day), has shown to be beneficial in the management of COPD (Global Initiative for Chronic Obstructive Lung Disease, 2022). A systematic review by Cranston et al. demonstrated that LTOT is associated with a higher survival rate in severe COPD with severe hypoxemia at rest (defined as arterial Pao2 <55mmhg) (Cranston et al., 2005). In the GOLD report, therefore, the use of LTOT is recommended for patients exhibiting severe hypoxemia (Global Initiative for Chronic Obstructive Lung Disease, 2022).

Non-invasive ventilatory (NIV) support is also a valuable intervention in managing COPD patients, particularly at home (Köhnlein et al., 2014). The non-invasive positive pressure ventilation (NIPPV) is the standard NIV support used in COPD management (Global Initiative for Chronic Obstructive Lung Disease, 2022). NIPPV can be provided in various modes, including continuous positive airway pressure (CPAP; a ventilatory mode that provides a continuously constant pressurized air) and bi-level positive airway pressure (BiPAP; a ventilatory mode that provides separate pressures at inspiration and expiration,

allowing the patients expire easily) (Masip, 2007). An RCT of 116 patients with persistent hypercapnia following COPD exacerbation revealed that BiPAP plus LTOT was associated with a decrease in the risk of death or readmission by 17% (95% CI, 0.1%-34.0%) compared to LTOT alone (Murphy et al., 2017). Furthermore, a longitudinal study by Melloni et al. demonstrated that the use of NIV support with and without LTOT resulted in a higher survival rate than LTOT alone (Melloni et al., 2018). In patients with COPD and obstructive sleep apnoea (also known as overlap syndrome), the use of CPAP resulted in lower hospital admission and lower mortality (Marin et al., 2010).

1.1.6.6.Interventional therapy

1.1.6.6.1. Surgical procedures

Surgical procedures, including lung volume reduction surgery (LVRS) and lung transplantation, might be beneficial in COPD management. However, their benefits may only be demonstrated in some COPD patients. Therefore, surgical procedures require careful selection for both surgical procedures and patients. LVRS is an invasive surgical intervention that lessens hyperinflation by excising portions of the lungs. In severe emphysema, LVRS is associated with better lung mechanics, decreased hyperinflation and ameliorated respiratory muscle (Cooper et al., 1995). LVRS has been demonstrated to be beneficial in patients with heterogeneous emphysema that is predominantly in the upper lobe (Zahid et al., 2011). Other studies have demonstrated that LVRS is linked to higher mortality in severe homogeneous emphysema (Fishman et al., 2003). This highlights the importance of the distribution of emphysema in selecting LVRS. This procedure, therefore, requires careful selection of patients.

Lung transplantation is considered as a final resort in managing end-stage lung diseases, with COPD responsible for more than 35% of lung transplantation (Chambers et al., 2017). A report from the International Society for Heart and Lung Transplantation (ISHLT) states that approximately 1,000 lung transplants are performed yearly for patients with severe COPD, with most of these are bilateral lung transplants (BLT) (Chambers et al., 2017). Lung transplant is associated with improvement in several outcomes, including health status and exercise performance (Global Initiative for Chronic Obstructive Lung Disease, 2022). Of note, patients with AATD related COPD had higher survival benefit than those with non-AATD COPD at 5-years and 10-years post lung transplant (Tanash et al., 2014). Patients with AATD related COPD are mostly diagnosed at a younger age and may decline faster and reach very severe stages while young. In contrast, non-AATD COPD patients (primarily associated with smoking) are mostly diagnosed at an older age. By the time they reach a severe stage and meet lung transplant criteria, they may have become older and have acquired more comorbid conditions. This could explain the rarity of lung transplantation in patients with smoking-related COPD. Additionally, it was found that a single lung transplant (SLT) resulted in a lower survival rate than BLT, especially for those under 60 years old, with a median survival of 7 years for BLT recipients and 5 years for those with a SLT recipient (Yusen et al., 2016). Despite advances in lung transplantation, the survival benefit of lung transplants is lower than that of other organs' transplants (Kotloff and Thabut, 2011). Moreover, lung transplant is associated with several complications, including acute rejection, bronchiolitis obliterans and infection (Global Initiative for Chronic Obstructive Lung Disease, 2022). Lung transplants are hampered by a lack of donors and high costs (Global Initiative for Chronic Obstructive Lung Disease, 2022), highlighting the need to carefully select patients in need of lung transplantation.

1.1.6.6.2. Bronchoscopic procedures

Various bronchoscopic procedures have been suggested to reduce thoracic lung volumes, resulting in a reduction in hyperinflation, and these procedures are less invasive compared to LVRS (Global Initiative for Chronic Obstructive Lung Disease, 2022). A commonly performed bronchoscopic procedure is endobronchial valve placement (EBV), which is linked to better lung function, symptoms, and health status (Criner et al., 2018). An RCT of 321 patients with heterogeneous emphysema showed that at 6-month after interventional therapy, FEV_1 and 6-minute walk distance ameliorated significantly in patients with EBV than those in the control group (Sciurba et al., 2010). However, whether these improvements are sustained is still unknown as studies have been short in duration. Hence, long-term studies are needed to determine the sustainability of improvements following EBV. Moreover, EBV is associated with serious side effects, such as pneumothorax (Global Initiative for Chronic Obstructive Lung Disease, 2022). With the availability of other bronchoscopic procedures such as lung volume reduction coil and vapour ablation, additional research is warranted to identify the optimal bronchoscopic technique that is less prone to complications.

1.2. Exacerbation of COPD

1.2.1. Definition and classification of severity

In many patients with COPD, periods of disease stability are punctuated with acute episodes of increased symptoms, termed exacerbations. In 1987, Anthonisen et al. defined exacerbation episodes by a deterioration of 3 key symptoms (breathlessness, sputum volume, and sputum purulence) (Anthonisen et al., 1987). In the recent GOLD report, an exacerbation

is defined as “an acute event characterised by a worsening of the patient’s respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication.” and their severities are defined by the treatment or level of care being given to COPD patients into mild, moderate, or severe (Global Initiative for Chronic Obstructive Lung Disease, 2022) (see table 1.3).

Table 1.3. Exacerbation severities and definition.	
Severity	***Definition***
Mild	Exacerbations managed with the use SABD only.
Moderate	Exacerbations managed with the use of SABD + antibiotic or/and oral corticosteroid.
Severe	Exacerbations results in hospitalization/ emergency room visit.
Abbreviations: SABD, short-acting bronchodilator	

There are limitations to these definitions. First, exacerbations are defined by symptoms. COPD is a heterogeneous condition, and patients describe variability in their daily burden of symptoms, making acute changes sometimes difficult to identify both at onset and conclusion (National Institute for Health and Care Excellence, 2019). The symptom-based definition does not provide any insight into pathology or treatment requirements apart from sputum purulence, which has been associated with bacterial infection and a clinical improvement when treated with antibiotics (Stockley et al., 2000). Second, patients with COPD suffer from co-morbidities; breathlessness and cough can be a manifestation of many conditions, including cardiac disease, anxiety, deconditioning, pneumonia, as well as COPD. The use of treatment or place of care provision to define severity also has limitations. COPD is more common with increasing age and often co-occurs with frailty. Age, frailty, and multi-morbid disease are risk factors for hospital admission, and some patients may require hospital care due to a low threshold for increased support rather than a severe respiratory event (Sapey et al., 2019).

1.2.2. Prevalence and impacts of exacerbations

Exacerbations are difficult to predict but can cluster together, with some patients being more prone to exacerbations (termed "frequent exacerbators") and exacerbations often occurring closely together (Le Rouzic et al., 2018). Frequent exacerbator phenotype is defined by the occurrence of ≥2 exacerbations per year (Le Rouzic et al., 2018) and approximately 75% of COPD patients suffered at least one exacerbation was identified by a large study of 49,286 COPD patients in the UK, with some patients found to have exacerbations more frequently (Raluy-Callado et al., 2015).

Exacerbations are important as they are associated with poor outcomes for patients, such as substantial mortality and morbidity. Among 16,016 COPD patients admitted for exacerbations, approximately 5% died while hospitalized, with older age, higher Charlson comorbidity index (CCI), respiratory acidosis, and the need for ventilatory support being the risk factors (Hartl et al., 2016). In this study, among patients discharged from the hospital post-exacerbation, 35.1% were readmitted. The risk factors for the 90-day readmission following an exacerbation were previous admissions, older age, higher CCI, high comorbid chronic pulmonary disease, and the need for ventilatory support. The study also showed that in comparison to non-readmitted patients, mortality was higher in readmitted patients (2.3% vs 13.4%). Exacerbations are also associated with other poor health outcomes such as myocardial infarctions (Donaldson et al., 2010). Furthermore, exacerbations are linked to a decrease in the QOL (Esteban et al., 2009; Cote, Dordelly and Celli, 2007), lung function (Celli et al., 2008) and exercise capacity (Cote, Dordelly and Celli, 2007). In a longitudinal study by Donaldson et al., exacerbation frequency was linked to declining FEV_1 over four years (Donaldson et al., 2002). In this study, the decline in FEV_1 was faster in frequent

exacerbators than infrequent exacerbators (40.1 ml/year [95% CI 38-42] vs 32.1 ml/year [95% CI 31-33]; see Figure 1.3). Exacerbations are also associated with significant healthcare utilization and cost (Punekar, Shukla and Müllerova, 2014). A retrospective study of 58,589 COPD patients by Punekar et al. showed that COPD management cost is higher in patients experiencing exacerbations compared to no exacerbations (Punekar, Shukla and Müllerova, 2014).

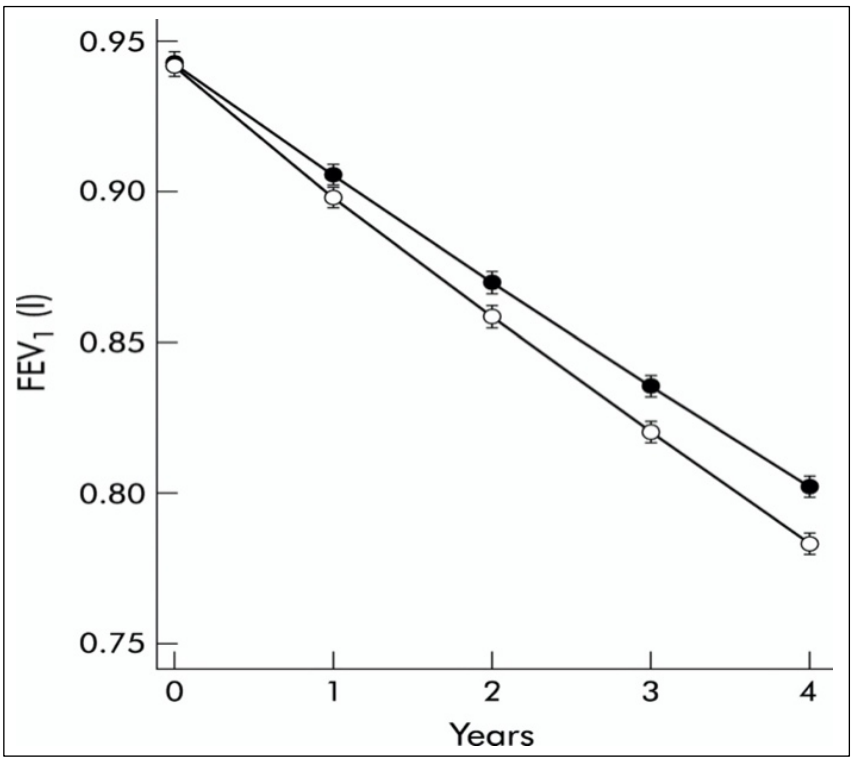

Figure 1.3. Lung function decline and exacerbation frequency.

Legend*: This figure shows when COPD patients with frequent exacerbation and infrequent exacerbation are compared, lung function (FEV_1) shows a rapid decline in patients with frequent exacerbation over 4 years. Open circles represent patients with frequent exacerbations while closed circle represent infrequent exacerbation. This figure was Reproduced from (Donaldson et al., 2002) with permission from BMJ Publishing Group Ltd.*

Abbreviations: *FEV_1, forced expiratory volume in the first second.*

Despite the significant impact of exacerbations, their pharmacological treatments have changed little over thirty years. This contrasts starkly with acute deteriorations of other chronic diseases, in which treatment advances have revolutionised outcomes.

1.2.3. Causes and pathogenesis of exacerbation

Exacerbations of COPD are associated with several potentially causative factors, including environmental changes and infections, which can be bacterial or viral. Studies indicate that approximately 50 to 70% of COPD exacerbations are caused by pulmonary infections (Ball, 1995), 10% are caused by environmental-related causes (Sunyer et al., 1993) and around 30% have no identifiable cause (Connors et al., 1996).

Potentially pathogenic bacteria have been identified in approximately 30 - 50% of sputum cultures in studies during exacerbations (Fagon et al., 1990; Monsó et al., 1995) and *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarhalis*, *Haemophilus parainfluenzae*, and *Pseudomonas aeruginosa* are the most common isolated (Monsó et al., 1995; Soler et al., 1998). Approximately 20 – 40% of exacerbations are associated with viruses detected by reverse transcription polymerase chain reaction (Seemungal et al., 2001). Rhinovirus is implicated in the majority of these episodes (Seemungal et al., 2000b) with a lower percentage associated with parainfluenza and adenoviruses. Of note, exacerbations caused by viral infections are associated with a protracted recovery (Seemungal et al., 2001), and a greater effect on healthcare utilization (Seemungal et al., 2000a). This probably reflects the limited treatment options for viral infections.

In spite of the importance of infections, environmental factors such as air pollution could be a cause of exacerbation. Approximately 10% of exacerbations are thought to be caused by environmental pollution (Sunyer et al., 1993), which is an increasing global health concern. A systematic review by Li et al. demonstrated that exposure to major environmental pollutants (especially for nitrogen dioxide and ozone) are associated with an increased risk of exacerbation (Li et al., 2016).

Most studies suggest inflammation is increased during exacerbations (Balbi et al., 1997; Hill et al., 1999) and just as with stable disease, most studies also report an increase in neutrophil counts in the bronchial walls and bronchial secretions during exacerbations (Bhowmik et al., 2000; Tsoumakidou et al., 2005). Eosinophilic airway inflammation has also been implicated in some COPD patients experiencing exacerbation (Couillard et al., 2017; Siddiqui et al., 2018). During exacerbation, a rise in airway inflammation leads to increased airway oedema, increased bronchial tone, and increased mucus secretion or plugging (O'Donnell and Parker, 2006), especially of the small airways. These airway changes result in increased airway resistance, worsening expiratory flow limitation (EFL) and V/Q mismatch (O'Donnell and Parker, 2006). The deterioration in EFL leads to increased air trapping and hyperinflation (which increases the work of breathing), as well as insufficient time to empty the lungs between the rapid and shallow breathing patterns present during exacerbations (see figure 1.4) (Woolhouse, Hill and Stockley, 2001).

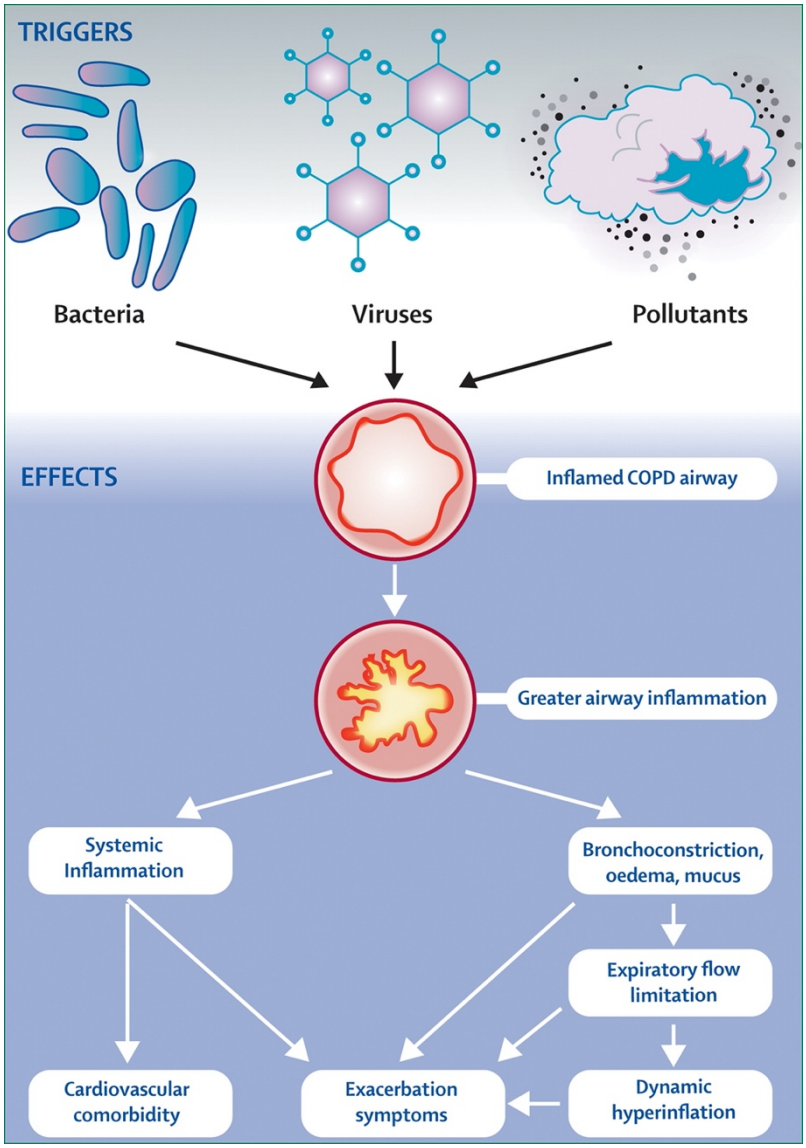

Figure 1.4. Schematic illustration of the pathophysiology of COPD exacerbation.

***Legend**: This figure was Reprinted from The Lancet, 370, Wedzicha et al., COPD exacerbations: defining their cause and prevention, 786 - 796., Copyright (2021), with permission from Elsevier (Wedzicha and Seemungal, 2007).*

***Abbreviations:** COPD, Chronic Obstructive Pulmonary Disease.*

To help identify potential causes of exacerbation, studies have focused on dividing exacerbating COPD patients into those with purulent or coloured sputum and those without. Although most describe a relationship with bacteria and sputum purulence (Miravitlles et al., 2012; Stockley et al., 2000), with sputum purulence being 94.4% sensitive and 77% specific for bacterial aetiology in one study (Stockley et al., 2000), other studies have not (Bafadhel et

al., 2011; Brusse-Keizer et al., 2009). More recently, Bafadhel et al. phenotyped COPD exacerbation into four biological groups: 55% of exacerbations were linked to bacteria, 29% to viruses, 28% to higher eosinophils levels in the sputum, and 14% to no notable inflammation (named pauci-inflammatory). Notably, these groups did not signify distinctions in outcomes such as symptom burden or clinical manifestation, including sputum purulence, which could not distinguish between aetiologies (Bafadhel et al., 2011).

1.2.4. Management of exacerbations

Minimising the harmful effect of the present exacerbation and preventing further occurrence of exacerbation are major goals of treatment for COPD patient during exacerbation across a number of guidelines (Global Initiative for Chronic Obstructive Lung Disease, 2022; National Institute for Health and Care Excellence, 2019; Khan et al., 2014). The management of an exacerbation varies depending on its severity (mild, moderate, or severe) (Global Initiative for Chronic Obstructive Lung Disease, 2022). The current management of COPD exacerbations does not really stratify patients by potential cause, and most patients receive a combination of bronchodilators, corticosteroids with or without antibiotics and the use of NIV for type 2 respiratory failure. However, there is increasing evidence that not all exacerbations are the same, both in cause, inflammatory infiltrate, and response to treatment.

Short-acting bronchodilators ((SABDs), either using beta-2 agonists, muscarinic antagonists or a combination of both) are the initial treatments for exacerbations to alleviate symptoms (Global Initiative for Chronic Obstructive Lung Disease, 2022). The use of antibiotic or systemic corticosteroid is also recommended in treating COPD exacerbation (Rodríguez-Roisin, 2006). The use of antibiotic to treat exacerbations has been assessed, and

it has been linked to a lower short-term mortality rate and sputum purulent by 77% and by 44%, respectively (Ram et al., 2006). In the recent GOLD report, antibiotic is recommended in patients with exacerbation whose symptoms suggest the likelihood of bacterial infection (such as a risen sputum volume and purulence) (Global Initiative for Chronic Obstructive Lung Disease, 2022). Systemic corticosteroids' use in exacerbations has been shown to be associated with amelioration in several outcomes, involving oxygenation (Davies, Angus and Calverley, 1999; Niewoehner et al., 1999), lung function (Aaron et al., 2003; Davies, Angus and Calverley, 1999; Niewoehner et al., 1999), duration of hospitalization (Davies, Angus and Calverley, 1999; Niewoehner et al., 1999), treatment failure (Alía et al., 2011; Niewoehner et al., 1999), and symptoms (Aaron et al., 2003). Additionally, in severe exacerbations, oxygen may be provided to treat hypoxemia during an exacerbation (Global Initiative for Chronic Obstructive Lung Disease, 2022). However, oxygen therapy may be associated with hypercapnia and acidosis if it is not titrated properly. Therefore, in the GOLD report, it is advised that supplemental oxygen levels be adjusted to a saturation of 88-92%. In case of life-threatening acute respiratory failure, patients should be firstly placed on NIV if there are no contraindications (Global Initiative for Chronic Obstructive Lung Disease, 2022). Invasive mechanical ventilation may be initiated if the patient failed NIV, or NIV is contraindicated (Global Initiative for Chronic Obstructive Lung Disease, 2022).

1.3. Assessment of exacerbation response in clinical trials

1.3.1. Exacerbation recovery

Exacerbations of COPD have both short-term clinical impacts and long-term clinical effects. Symptom recovery is shown to be variable following exacerbation episodes. In a cohort of 101 COPD patients, Seemungal et al. found that half of community-treated

exacerbations recover within a week but 14% take up to 35 days, and some patients do not appear to return to baseline (Seemungal et al., 2000a). Assessing response to treatment or recovery is crucial both when managing COPD patients during exacerbation and when evaluating novel putative therapies and symptoms, lung function and inflammatory changes are the most commonly used methods to assess exacerbation responses.

1.3.2. Evaluation of symptoms

As stated earlier, during an exacerbation, COPD patients exhibit an increase in dyspnoea and other symptoms, including cough with or without sputum production. These symptoms are commonly reported using patient-reported outcome (PRO) tools. PRO tools validated for exacerbations include St George's Respiratory Questionnaire (SGRQ), CAT, and Exacerbation of Chronic Pulmonary Disease Tool (EXACT), and these tools were developed in line with the Food and Drug Administration (FDA) regulatory guidance on the development and utility of PRO to assess treatment effect in clinical trials (Food and Drug Administration, 2009). The SGRQ is a 50-items questionnaire intended to assess health status in patient with obstructive lung diseases (Jones et al., 1992). In a study of 438 patients with exacerbation of chronic bronchitis, Spencer et al. evaluated the exacerbation response using SGRQ (Spencer and Jones, 2003) and found the most considerable improvements happened within four weeks. Although the SGRQ can identify exacerbation and recovery (Spencer and Jones, 2003), it is long, complex for patients to complete when acutely unwell, and requires a scoring algorithm to assess response. CAT is another questionnaire developed to assess the impact of the disease on health status, but shorter (only 8-items), far easier to complete and scored using simple addition (Jones et al., 2009). Mackay et al. studied CAT during COPD exacerbations in 161 patients in a community-based study and described a rise in respiratory

symptoms at exacerbation, relationship with markers of systemic inflammation and decline in FEV_1 (Mackay et al., 2012). CAT has also shown to be a reliable tool in monitoring changes during the recovery from COPD exacerbation (Jones et al., 2012).

EXACT is a 14-items tool used to recognise exacerbation, and is accepted as an exploratory outcome in clinical trials for exacerbations (Food and Drug Administration, 2014). It has also been validated for use in this setting (Choi et al., 2019). In RCT of 295 COPD patients, Choi et al. evaluated the utility of EXACT assessing the efficacy of acute therapy during exacerbation episode. In this study, EXACT was associated with greater improvement following exacerbation and significantly correlated with CAT ($r=0.8$, $p<0.01$). The authors concluded that EXACT is a reliable tool for evaluating the recovery of exacerbation in COPD (Choi et al., 2019). In another study, EXACT, CAT, SGRQ and other PROs were compared to find the most reliable measure for evaluating exacerbation and the recovery from exacerbation. The authors found that EXACT and CAT were the most responsive PRO tools (Nishimura et al., 2018). There are also a number of symptom diary cards that have been used in clinical studies (Seemungal et al., 2000a; Woolhouse, Hill and Stockley, 2001). These PRO tools seem to be useful during exacerbation; however, to assess exacerbation response using PROs, there needs to be a pre-exacerbation score to evaluate changes from the baseline which might limit its usage in clinical practice unless patients were under active follow up. While symptom scores are useful in assessing exacerbations recovery in COPD, studies have also utilised more objective measures such as the evaluation of lung function and inflammatory changes.

1.3.3. Evaluation of lung function

Spirometry, which is a commonly utilized lung function testing method in both diagnosing lung diseases and stratifying their severity, has been used in clinical trials during exacerbations of COPD. In the majority of these trials, FEV_1 is commonly the primary outcome as it is an accepted measure to assess lung function in clinical trials by the FDA (Food and Drug Administration, 2012). FEV_1 strongly correlates with recovery (Parker et al., 2005) but has only a weak association with symptoms (Nishimura et al., 2002). A longitudinal study by Johnson et al. reported that FEV_1 demonstrated statistically significant changes throughout the recovery period from an exacerbation, which correlated with symptoms and HRQOL (Johnson et al., 2007). Recently, an RCT by Zhang et al. assessed the safety and efficacy of different doses and frequencies (1mg Q6, 2mg Q6 and 4mg Q12) of Nebulised Budesonide in COPD exacerbation and found that FEV_1 demonstrated improvement more rapidly in the high dose group (4mg at Q12) (Zhang et al., 2020). However, studies showed that in the absence of a significant FEV_1 change, other physiological measures demonstrated significant changes in both exacerbation (Jetmalani et al., 2015) and stable COPD (O'Donnell, Revill and Webb, 2001; Schermer et al., 2007). This highlights that FEV_1 lack sensitivity in assessing treatment response. FEV_1 has also shown to have some limitations. Being a forced, effort-dependent manoeuvre, patients may struggle during episodes of increased breathlessness and even in the stable state, variability in measurements is common. For example, a study which only accepted measurements following three blows which technically acceptable (that is, they varied by less than ± 5% and by ± 0.1 L (Graham et al., 2019)) described a mean change of 22mls (standard deviation (SD) 170mls) in FEV_1 repeated after a twenty minute interval in health (Tweeddale et al., 1984).

Lung volumes measurements (including all capacities and volumes (Figure 1.5)) have also been used in the clinical trials to assess exacerbation response. Several methodologies have been applied to assess lung volumes, with body plethysmography, helium dilution and nitrogen washout being the most common. Lung volume measurements are widely available and have a known reference range. Inspiratory Capacity (IC) (the maximum volume inhaled from end-tidal exhalation) is the most common measurement of lung volumes and capacities used in clinical trials of exacerbation. IC can be calculated by subtracting expiratory reserve volume (ERV) from vital capacity (VC). IC has a strong association with symptoms, response to treatment, and recovery (Stevenson et al., 2005; Yetkin and Gunen, 2008). It has also been demonstrated that IC is better than FEV_1 in showing a correlation with dyspnea, QOL, and exercise tolerance both at baseline (Diaz et al., 2000; O'Donnell, Revill and Webb, 2001; O'Donnell and Webb, 1993) and after treatment (Boni et al., 2002; Donnell et al., 2004; O'Donnell, Lam and Webb, 1999). During the recovery from exacerbation, gas trapping reduces, and IC is increased (Parker et al., 2005). Thus, during an exacerbation, changes in lung hyperinflation (which is common in advanced COPD) can be assessed using IC. An observational study by Stevenson et al. assessed lung mechanics and dyspnea in COPD patients during exacerbation, and they found out that the significant change seen during exacerbation recovery was the improvement of lung volumes (especially IC) (Stevenson et al., 2005). In another observational study, Yetkin et al. evaluated the use of IC and FEV_1 in COPD patients to assess recovery from exacerbation (Yetkin and Gunen, 2008) and found IC improved more significantly than FEV_1. This suggest that IC may be a better measure than FEV_1 in COPD exacerbations. Although lung volumes can be obtained using several methodologies, they are not similar and lung volumes in patients with moderate-severe AO can be underestimated by dilution methods (Rodenstein and Stănescu, 1982). Moreover, lung

volumes measured by plethysmography can be overestimated if inaccurately measured (Rodenstein, Stănescu and Francis, 1982). Although it is less time consuming to obtain lung volumes using plethysmography, it is more expensive than other techniques. Furthermore, most techniques used to obtain lung volume measurements are effort dependent.

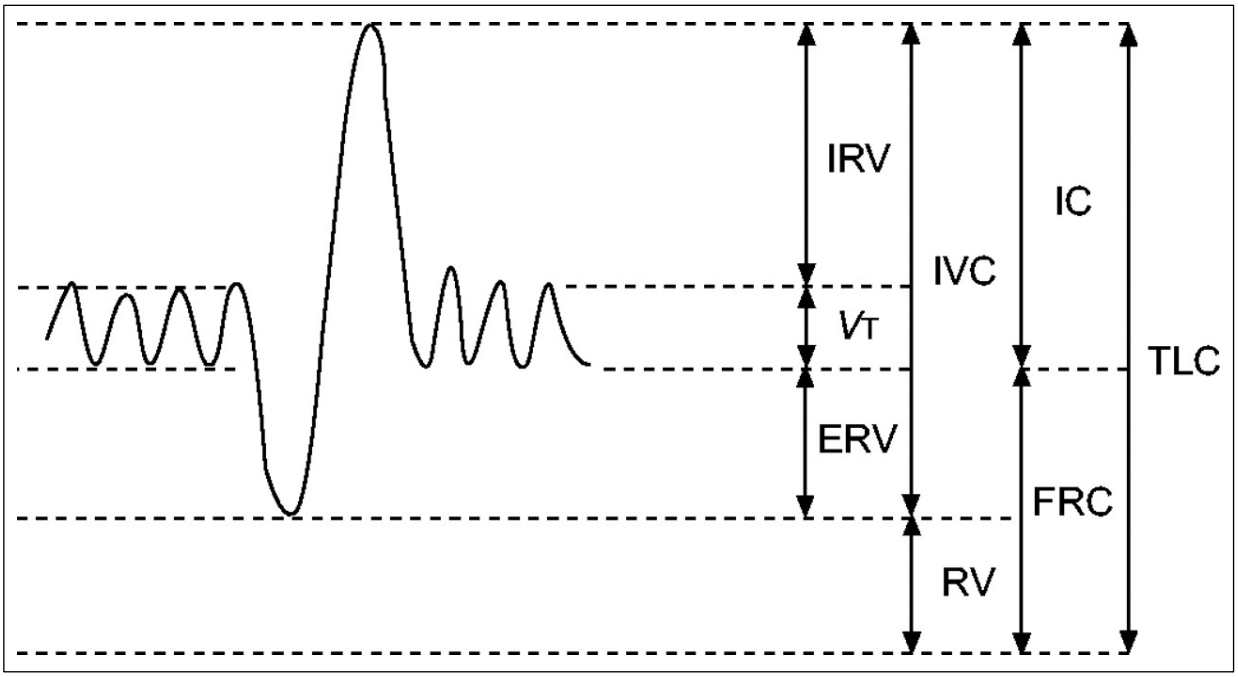

Figure 1.5. Lung volumes and capacities from a spirometry.

Legend: *This figure shows lung volumes and capacities obtained from a spirometry. Reproduced with permission of the © ERS 2021: European Respiratory Journal 26 (3) 511-522; DOI: 10.1183/09031936.05.00035005 Published 1 September 2005 (Wanger et al., 2005).*

Abbreviations: *IRV, inspiratory reserve volume; VT, tidal volume; ERV, expiratory reserve volume; IVC, inspiratory vital capacity; RV, residual volume; IC, Inspiratory capacity; FRC, Functional residual capacity; TLC, Total lung capacity.*

1.3.4. Evaluation of inflammatory changes

It is evident that inflammatory markers are intensified during exacerbations of COPD (Bhowmik et al., 2000). Hence, assessing their changes in this period might help in guiding therapies as well as monitoring recovery. Inflammation, in general, is assessed either using a blood sample (reflecting systematic inflammation) or a sputum sample (reflecting inflammation within airways). Inflammatory biomarkers have been used to evaluate the

recovery of COPD exacerbations, although not as primary endpoints in clinical trials. These include but are not limited to CRP, TNF-alpha, IL-6, IL-8, and neutrophils. A longitudinal study of 93 patients with exacerbation of COPD by Chang et al. showed improvements in sputum IL-8, myeloperoxidase (MPO) and neutrophils at day 4 of exacerbation, which was associated with improvement in symptoms and lung function (Chang et al., 2014). The study also showed that systematic inflammation (as measured by serum IL-6 and CRP) improved during the recovery from exacerbation. However, the systematic inflammation resolution occurred later in the exacerbation episode than airway inflammation resolution. Another longitudinal study of 73 patients with COPD exacerbation by Perera et al. reported that patients without symptom resolution had higher levels of serum CRP throughout recovery (Perera et al., 2007). The study also reported that patients with recurrent exacerbations had higher levels of serum CRP. These findings suggest that CRPs may be useful in both monitoring and predicting exacerbations. Fibrinogen has been proposed as a putative biomarker of risk of exacerbations, with higher levels associated with increased admissions (Duvoix et al., 2013). The phenotyping study by Bafadhel et al. demonstrated that some exacerbations are associated with high blood eosinophil levels (Bafadhel et al., 2011). In these patients, blood eosinophil has shown to be a useful biomarker in community-treated exacerbation, indicating that this biomarker could be valuable in guiding ICS treatment in COPD exacerbations (Bafadhel et al., 2012). Although inflammatory biomarkers could help identify and monitor exacerbation, they have limitations in clinical studies (Stockley et al., 2019). First, inflammation is not a feature of all exacerbations as some episodes are not associated with notable inflammation (Bafadhel et al., 2011), and second, they are extremely variable, especially in pulmonary secretions (Sapey et al., 2008). Lastly, without a “baseline” measure, it is difficult to assess whether the changes indicate exacerbation onset or recovery.

1.3.5. Conclusion

Although sputum volume and purulence can be observed during exacerbation, it is difficult to define a change in breathlessness and there are no objective biomarkers which can measure this. The limitations of the current tools to identify exacerbations or map recovery/response especially when dyspnoea is the only or main symptom have generated interest in other physiological tests which might provide more sensitive and specific measures, most notably tests of small airways function.

1.4. Small airways' dysfunction in COPD

Small airways are defined as airways of less than 2mm internal diameter (see figure 1.6.). Although COPD is defined by AO, there is evidence that SAD might be the earliest pathological manifestation (Hogg, Macklem and Thurlbeck, 1968; Hogg, McDonough and Suzuki, 2013; Stockley et al., 2017b). Studies by Hogg and co-authors revealed a significant loss of small airways preceding the onset of emphysema or established AO in patients with COPD (Hogg, Macklem and Thurlbeck, 1968; Hogg, McDonough and Suzuki, 2013). These findings were supported by physiological studies of small airways function (using Maximal Mid-expiratory flow (MMEF)). In a study of patients with AATD related COPD, SAD, measured by MMEF, preceded conventional spirometric evidence of COPD and all patients with spirometric evidence of COPD had evidence of severe SAD (only 17.5% of the predicted value), despite the AO being only moderate (65% of the predicted FEV_1 value) (Stockley et al., 2017b). A recent longitudinal study of 307 participants (without a history of COPD) showed that patients with low MMEF had a higher incidence of COPD than normal MMEF (38 patients, 41.8% vs 16 patients, 7.4%, respectively) (Kwon et al., 2020). Another study has shown that a reduction in small airways diameter was present in resected lungs of smokers

with AO (Bosken et al., 1990). Using a different physiologic measure of small airway function (oscillometry measures), another observational study demonstrated a progressive increments in SAD in COPD correlated with health status (Crisafulli et al., 2017). Therefore, the role of SAD in COPD is crucial and pathology in the small airways may demonstrate in physiological abnormalities (Hogg, McDonough and Suzuki, 2013; McDonough et al., 2011). AO, risen airway resistance, air trapping, and heterogeneity of ventilation may happen because of abnormalities in the small airways (McNulty and Usmani, 2014). Although the assessment of small airway function is challenging as these airways are not accessible, there are a number of different tests which have been suggested for the assessment of small airways function in COPD, including physiological and imaging studies.

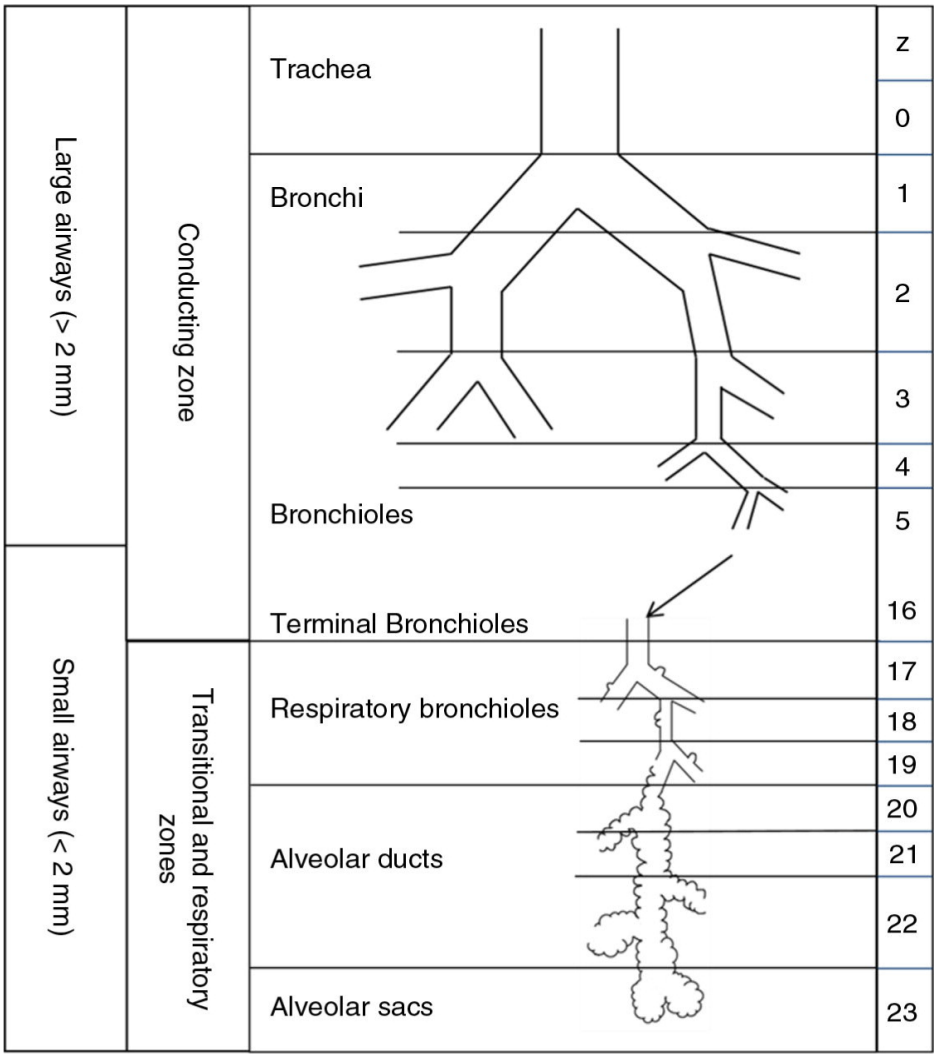

Figure 1.6. Structure of branching of airway generations.

Legend: *This figure was taken with permission from (McNulty and Usmani, 2014).*

Abbreviation: *mm, millimetre.*

1.5. Measuring small airway function

Assessing small airways may be important in obstructive lung diseases, especially if this is an early signal of lung tissue damage, and several methodologies have been used to assess their function. Expiratory flows (especially MMEF, which is also known as the forced expiratory flow between 25 and 75 of FVC (FEF_{25-75})), inert gas washout, plethysmographic airways resistance, oscillometry techniques, and computed tomography (CT) measures are the most commonly cited measures to assess small airway's function. However, none of these tests is accepted by the FDA as an outcome measure.

1.5.1. Expiratory flows

Flow measurements obtained from the expiratory curve of FVC manoeuvre, involve maximal expiratory flow at 25% of FVC (MEF_{25}), at 50% of FVC (MEF_{50}), at 75% of FVC (MEF_{75}), and MMEF (FEF_{25-75}) (see Figure 1.7). MMEF is the most widely studied tests of small airways and obtained by performing spirometry. In 1955, it was first presented as a sensitive measure of ventilation by Leuallen and Colleague (Leuallen and Fowler, 1955). MMEF has a wide normal range in clinical practice, which limits interpretation (Stanojevic et al., 2008). Nevertheless, several studies have demonstrated that MMEF is a valuable tool in identifying early disease. A cross-sectional study by Tsushima et al. reported that the percentage predicted MMEF was lower in participants with suggestive symptoms of COPD but had a normal FEV_1/FVC compared to healthy controls (Tsushima et al., 2006). Recently, Stockley et al. assessed MMEF, FEV_1, FEV_1/FVC ratio and health status in AATD patients

and found that a lower MMEF (<80%) is an early trait of lung pathology in these patients (Stockley et al., 2017b). The authors also found the decrease in MMEF is correlated with worse health status (assessed by SGRQ) and a rapid decline in lung function (FEV_1). More recently, a longitudinal study of 307 participants (no COPD history) by Kwon et al. investigated the use of MMEF in predicting the development of COPD and grouped patients into two groups (using the MMEF z-score as cut-off [-0.8435]): low MMEF (n=91) and normal MMEF (n=216) (Kwon et al., 2020). In this study, of all participants, 54 developed COPD following the ten-year follow-up, reporting a higher proportion of patients developing COPD in the low MMEF group than in the normal MMEF group (38 patients, 41.8% vs 16 patients, 7.4%; P<0.001). The study also reported that decreased MMEF is a significant risk factor for COPD development (HR, 3.308; 95% CI, 1.650-6.632). Although the assessment of MMEF may be informative about the presence of small airways impairment, MMEF relies on the FVC, and thus, it may be impacted by FVC changes. Therefore, to assess the changes of MMEF, it has been recommended to adjust it for lung volumes to overcome the reliance of MMEF on FVC (Cockcroft and Berscheid, 1980; Newball, 1975; Sherter, Connolly and Schilder, 1978). In a recent study, Mirsadraee et al. assessed the corrected MMEF for FVC (MMEF/FVC) in 77 smokers (40 COPD patients and 37 participants susceptible to COPD) and 32 non-smokers (Mirsadraee, Boskabady and Attaran, 2013). In this study, MMEF/FVC was decreased in the at-risk of COPD participants compared to the non-smoking participants, and MMEF/FVC strongly correlated with GOLD stages of COPD (r=0.82, p=0.0001). Their study also showed that MMEF/FVC compared to FEV_1 and FEV_1/FVC, had the largest area under the curve (0.849, p=0.001). The study suggests that MMEF/FVC may be useful in the early recognition of COPD. However, this was performed cross-sectionally; thus, it requires further longitudinal studies. It was reported that MMEF shows poor sensitivity if FEV_1/FVC

ratio is >75% (Gelb, Williams and Zamel, 1983). Another limitation of MMEF is the variability of the measurements. A large study of 3570 smokers and 5938 healthy individuals (never-smokers) by Hansen et al. used FEV_1/FVC, forced expiratory volume in three seconds (FEV_3)/FVC ratio (FEV_3/FVC), 1-FEV_3/FVC, and MMEF to determine which one is better at characterizing expiratory obstruction. They found that MMEF was the least accurate, especially in advancing age, while FEV_1/FVC, FEV_3/FVC and 1-FEV_3/FVC were the most accurate (Hansen, Sun and Wasserman, 2006). In spite of its drawbacks, MMEF may yet be a valuable parameter as an indicator of early AO before the diagnosis of COPD is made by conventional spirometric parameters (Stockley et al., 2017b).

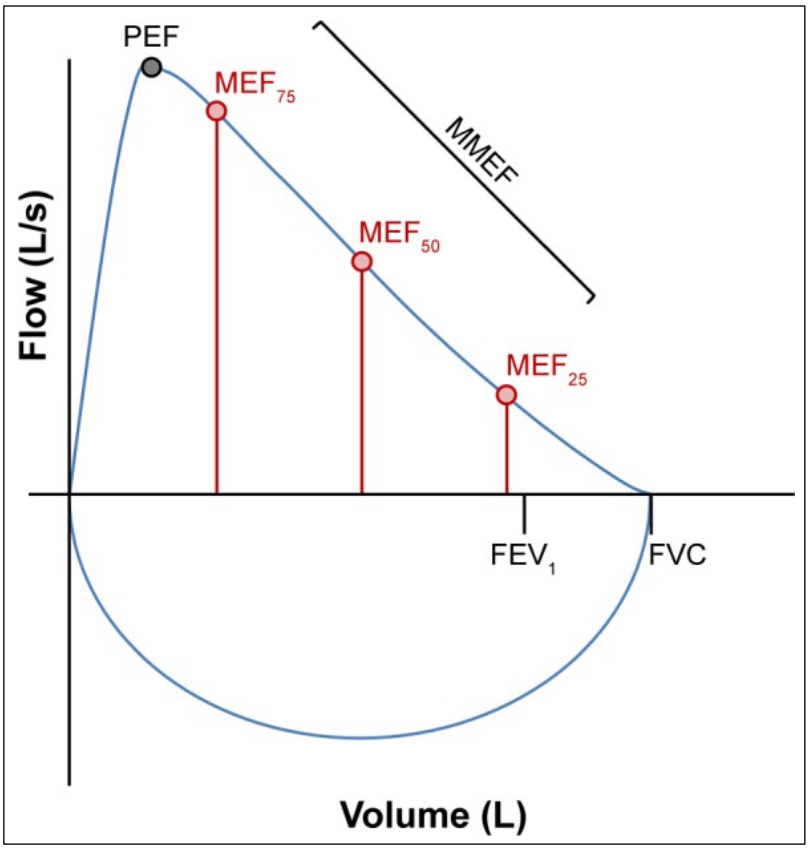

Figure 1.7. Flow/Volume loop of the forced expiratory manoeuvre obtained from a spirometry.

Legend: *This figure was taken from (Stockley et al., 2017a) with permission from Dove Medical Press.*

Abbreviations: *FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; MEF_{75}, maximal expiratory flow at 75% of FVC; MEF_{50}, maximal expiratory flow at 50% of FVC; MEF_{25}, maximal expiratory flow at 25% of FVC; MMEF, mid maximal expiratory flow; PEF, peak expiratory flow rate.*

1.5.2. Inert Gases washout:

Inert gases washout technique has a number of clinical applications and can be used to assess different lung volumes as well as ventilation inhomogeneity (defined as inequality of the ventilation distribution in the airways). This technique was firstly presented in 1949. Other gases such as helium and Sulphur hexafluoride (SF_6) can also be used, but a wash-in period is required. Nitrogen is the most commonly studied inert gas for washout technique, and there are two types: single breath nitrogen washout (SBNW) and multiple breath nitrogen washout (MBNW) (McNulty and Usmani, 2014).

1.5.2.1.Single breath nitrogen washout (SBNW):

SBNW involves breathing in 100% oxygen from Residual Volume (RV) to Total Lung Capacity (TLC) and then breathing out slowly (approximately flow of 0.5L/s) to RV (Anthonisen, Robertson and Ross, 1970). In SBNW, nitrogen concentration during the second expiratory phase can be divided into four stages, reflecting anatomical dead space (Phase I), the bronchial tree (Phase II), alveoli (Phase III) and airway closure (Phase IV) (see figure 1.8). Closing volume (CV), the amount of gas exhaled as small airways start to close, is measured (Dollfuss, Milic-Emili and Bates, 1967). Closing capacity (CC) can also be measured if RV is available, and it is obtained by adding RV and CV together. Validated reference ranges for SBNW parameters are available in clinical practice (Becklake et al., 1975) and in obstructive lung disease, CV is increased because of the earlier closure of the airways (152). It has been shown that abnormal CV can be seen in smokers even without AO (Buist and Ross, 1973). CV was found to be a valuable measure of early lung pathology than

FEV_1 in smokers (Garcia, Perez and Verbanck, 2012). However, the use of CV in COPD is questionable as a longitudinal study (9-11 years of follow up) of smokers by Buist et al. showed that those with abnormal CV, did not develop spirometrically defined AO (Buist et al., 1988).

The slope of phase III (S_{III}) is a useful marker of ventilation inhomogeneity and early recognition of COPD. In airway diseases, the impact of the disease on lung units is unequal, leading to inconsistencies in the ventilation of the lung subunits. These inconsistencies might happen in the conducting airways in which gas moves by convection (referred to as convection-dependant inhomogeneity (CDI)) (McNulty and Usmani, 2014). In the acinar airways, inconsistencies might happen when the diffusion-convection front appears (referred to as diffusion-convection-dependant inhomogeneity (DCDI)) (McNulty and Usmani, 2014). The ventilation inhomogeneity in the conducting airways could happen because of reduced airway diameter or decreased compliance in the lung units, wherein the acinar airways may happen because of structural differences between lung units (McNulty and Usmani, 2014). In airway diseases, as a result, impacted lung units mix poorly with inhaled oxygen, resulting in the higher nitrogen concentration and the longer time required to empty the nitrogen. This results in a rise in S_{III}. Oxhoj et al. evaluated VC, FEV_1, CV, CC, S_{III} in smokers, and found that S_{III} had the highest sensitivity of recognizing airway abnormalities (Oxhoj, Bake and Wilhelmsen, 1977). Furthermore, a recent study including COPD, smokers (no spirometric evidence of COPD) and non-smokers (healthy subjects) found that S_{III} was increased in most smokers compared to non-smokers (Gennimata et al., 2010). The study also reported that S_{III} had a progressive increase as severity increases, demonstrating a strong correlation between S_{III} and GOLD stages. Moreover, the study found that S_{III} had a significant correlation with

spirometric parameters (FEV_1, FEV_1/FVC, IC), diffusing capacity of the lung for carbon monoxide (DLCO), and dyspnoea scores.

A new technique of performing single breath inert gas washout has been established recently (Singer et al., 2013), using the differential distribution of two breathed in tracer gases (SF_6 and helium) (Husemann et al., 2014). A study by Husemann et al. showed that in COPD patients, this method has shown to be reproducible (Husemann et al., 2014). However, the method and its interpretation are still being studied, and more evaluation are needed before it can be used clinically.

Although SBNW is shown to be a sensitive measure in assessing SAD (Boeck et al., 2016), it is not specific as changes in the conducting airways might also impact the S_{III}. Moreover, S_{III} is not useful in finding the anatomical location of abnormalities (Verbanck, 2012). Despite that, the presence of normal S_{III} could be a useful indicator of the absence of SAD.

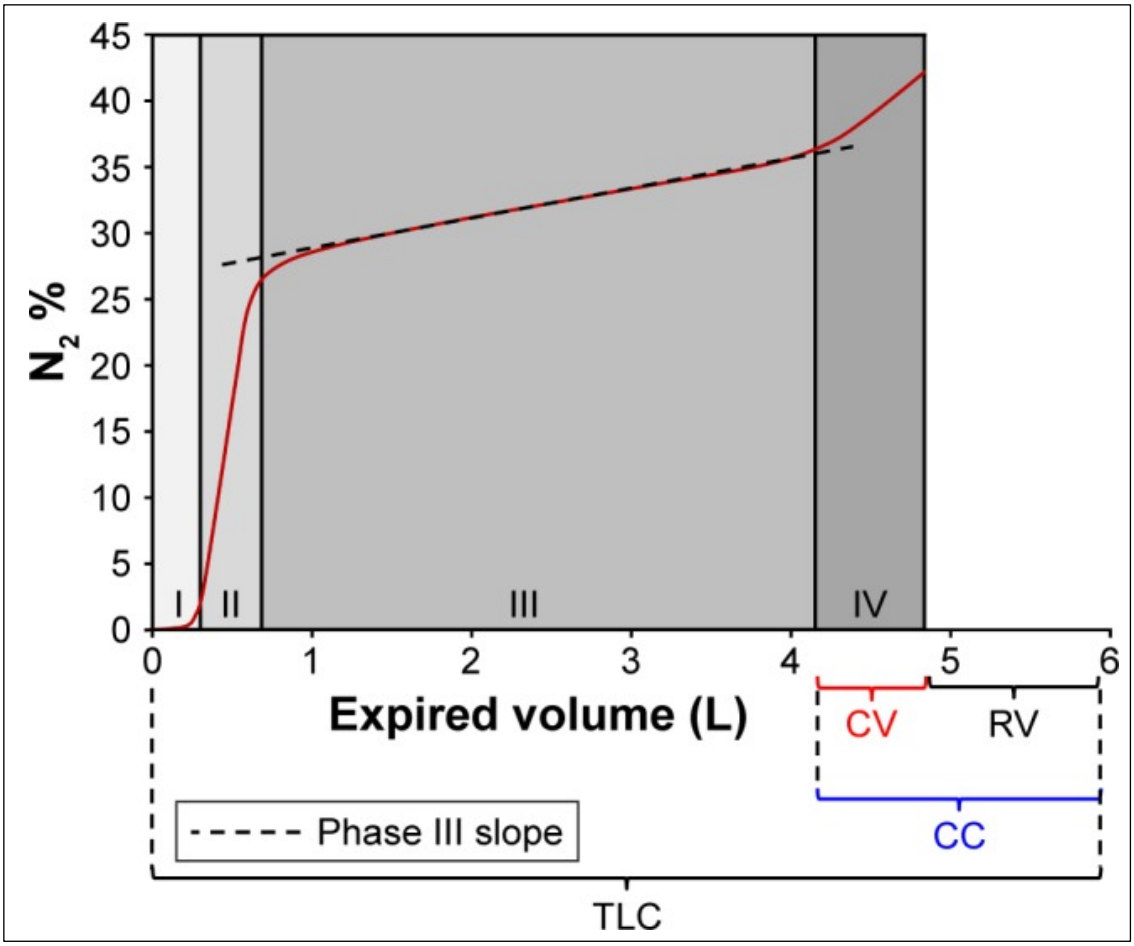

Figure 1.8. The four phases of SBNW.

Legend: *This figure demonstrates the four phases of the SBNW tests along with the closing volume (CV). If residual volume (RV) is obtained, closing capacity (CC) can be assessed. This Figure was taken from (Stockley et al., 2017a) with permission from Dove Medical Press.*

Abbreviations: *N_2, Nitrogen; CV, closing volume; RV, residual volume.*

1.5.2.2.Multiple breath nitrogen washout (MBNW)

MBNW is another inert gas washout method, performed by breathing 100% oxygen during tidal breathing. If tracer gases used, wash-in period will be performed. The test lasts until the inert gas's level reduction reaches $1/40^{th}$ of the initial level (about 2%) for three consecutive breaths (McNulty and Usmani, 2014) (see figure 1.9). In MBNW, three elements are used to identify gas mixing's efficiency and speed: respiratory rate, tidal volume and ventilation inhomogeneity (McNulty and Usmani, 2014). The assessment of ventilation

inhomogeneity can therefore be made inferentially when respiratory rate and tidal volume are relatively constant. In MBNW, the assessment of ventilation inhomogeneity in the lung is done by evaluating the number of lung turnovers needed to washout the inert gas to 1/40th of its starting level, termed lung clearance index (LCI) (McNulty and Usmani, 2014). LCI is measured by dividing the total volume of exhaled gas by the functional residual capacity (FRC) (McNulty and Usmani, 2014). LCI has been demonstrated as a reliable index of airways disease (Horsley et al., 2008). LCI is one of the first indices to decrease in children with cystic fibrosis (Kraemer et al., 2006), indicating that it can be used to detect anatomical change at an early stage. Recently, Fuchs et al. evaluated the usefulness of LCI to detect airway changes in AATD patients and found that LCI is increased before spirometric parameters become abnormal (Fuchs et al., 2016), suggesting that LCI may be valuable as measure of early lung disease. Nevertheless, further trials are needed to thoroughly assess the utility of LCI in COPD.

Intrinsic airway structure can also be identified by analyzing S_{III} of the multiple nitrogen washout curve, allowing the identification of discrimination of ventilation heterogeneity between the peripheral airways in the acinar zone ((S_{acin}) reflecting the contribution of DCDI) and the conducting airways ((S_{cond}) reflecting the contribution of CDI) (McNulty and Usmani, 2014). To obtain these indices, the slope should be normalized for the mean exhaled tracer gas concentration for each breath (Robinson et al., 2013). A recent study by Liu et al. assessed both S_{cond} and S_{acin} in COPD and non-smoker healthy subjects (Liu, Zhou and He, 2015). In this study, S_{cond} and S_{acin} were significantly increased in COPD patients, and both measures had significant correlation with traditional lung function. More recently, Verbanck et al. showed that both S_{acin} and S_{cond} are increased in COPD patients than in ever-smoking controls and never-smoking controls (Jarenbäck et al., 2016). The authors

also found that S_{acin} strongly correlate with DLCO and lung volumes while S_{cond} correlate with FEV_1 and sRaw. Moreover, studies indicate that S_{acin} might be a valuable measure of peripheral airways (Thompson et al., 2014; Verbanck, Schuermans and Vincken, 2010). Despite the usefulness of MBW, when compared to SBW, it is time consuming (especially tracer gases where wash-in period is required). Furthermore, due to the limited availability of the machines, MBW is not routinely utilised in clinical practice. Moreover, S_{cond} is not specific to small airways as they can be affected by abnormalities in the first generations of conducting airways. Using MBW to supplement spirometry, will help in resolving this problem. Although the technique is helpful in recognizing the location of airway disease, the modelling was done in healthy individuals. It is likely that in the disease state, convection-diffusion front is dissimilar, suggesting that the method may be inaccurate in terms of anatomical localisations.

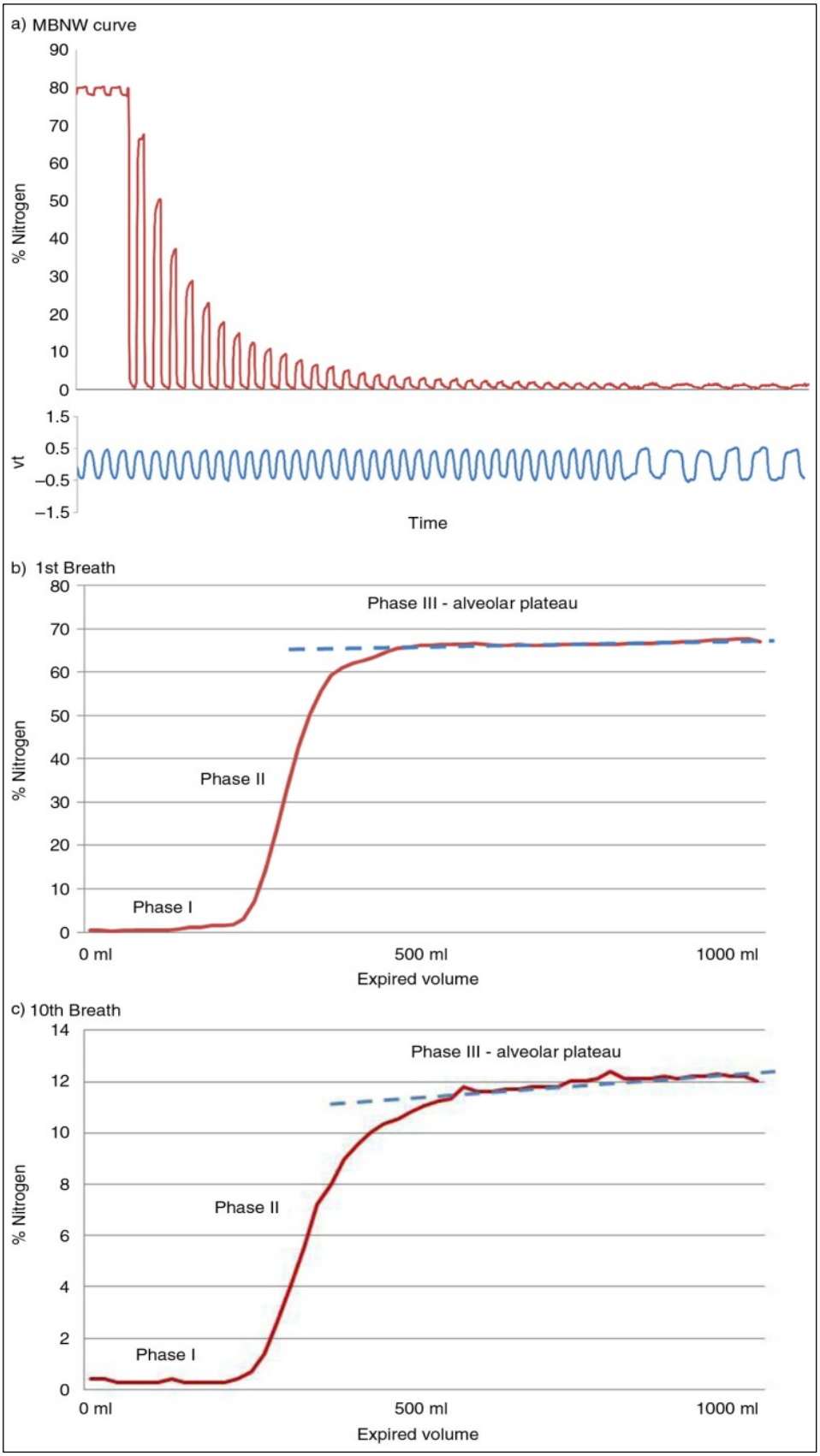

Figure 1.9. Illustration of the multiple breath nitrogen washout test.

Legend: *This figure demonstrates (a) Multiple breaths nitrogen washout curve. B) Specific breath showing Phase III slope (SnIII) from 1st breath C) specific breath showing phase III slope from 10th breath. This figure was taken from (McNulty and Usmani, 2014)*

Abbreviations: *Vt, Tidal volume.*

1.5.3. Plethysmographic measurement of airway resistance (Raw)

Assessments of airway function can be obtained by directly measuring airway resistance (Raw). Raw is obtained from body plethysmography technique and derived from the relationship between driving pressure and airflow in tidal breathing (Criée et al., 2011). In body plethysmography, the manoeuvre consists of several quiet breaths (to achieve a stable end-expiratory level prior to closing the shutter) and panting against shutter closed for 2-3 seconds. To minimise error and leaks, the panting should be a sequence of gentle pants at a frequency of 0.5 and 1.0Hz (Criée et al., 2011). After opening the shutter, the patient will be asked to perform two manoeuvres: first performing ERV, followed by a slow inspiratory VC (Figure 1.10) (Wanger et al., 2005). Although there is an agreed reference range for Raw in clinical practice, it is not regularly recorded or interpreted.

Specific Raw (sRaw), another measure of airway function, can also be assessed during tidal breathing (Stockley et al., 2017a). Using the sRaw loop, three measures are used to drive sRaw: a line of best fit of the resistance loop (called specific effective resistance (sReff)); the line linking the highest variance in shift volume (called specific total resistance (sRtot)); or infrequently, the line linking exhalation flow between -0.5 and $\pm$0.5L/s (sR0.5) (Stockley et al., 2017a). In healthy subjects, sRaw loop is linear, and these measures are approximately the same whereas, in AO, hysteresis of the sRaw loop is common and results in notable variances between sReff, sRtot and sR0.5 (see figure 1.11) (Stockley et al., 2017a). Recently, a study in COPD suggested that sReff and sRtot identify SAD and relate to symptoms of dyspnoea (Mahut et al., 2012).

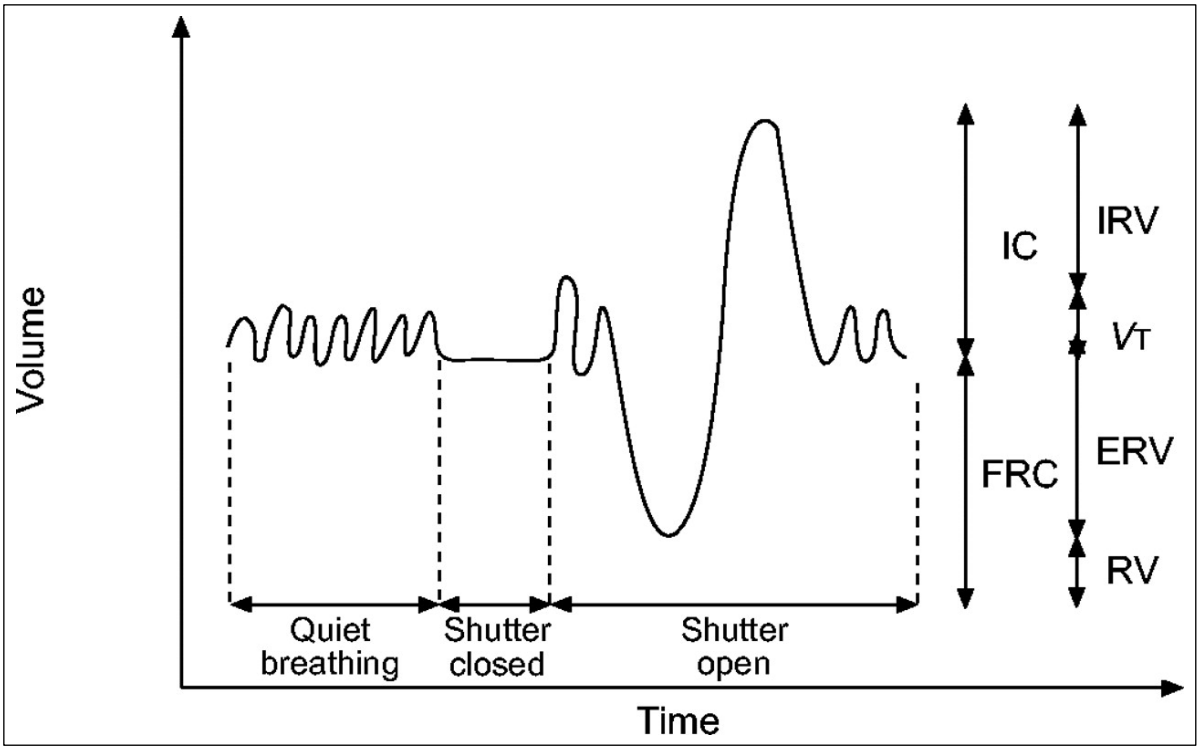

Figure 1.10. The technique of performing body plethysmography.

Legend*: This figure demonstrates the technique of performing body plethysmography. Reproduced with permission of the © ERS 2021: European Respiratory Journal 26 (3) 511-522; DOI: 10.1183/09031936.05.00035005 Published 1 September 2005 (Wanger et al., 2005).*

Abbreviations: *IRV, inspiratory reserve volume; VT, tidal volume; ERV, expiratory reserve volume; RV, residual volume; IC, Inspiratory capacity; FRC, Functional residual capacity.*

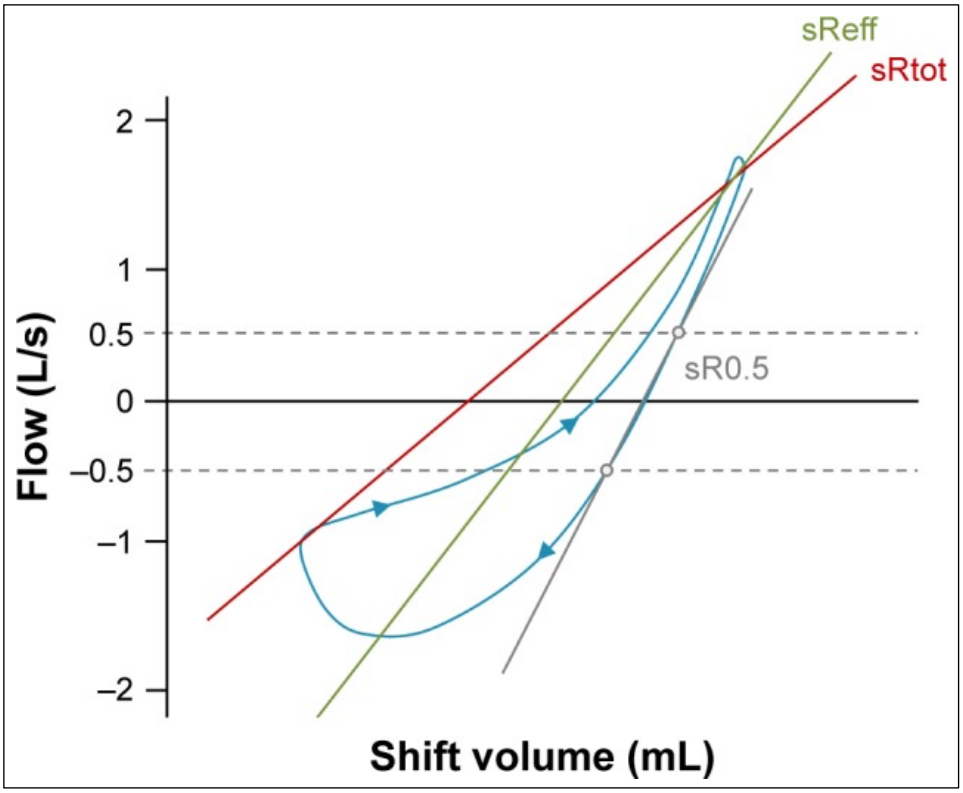

Figure 1.11. sRaw loop in patient with airflow obstruction.

Legend: *This figure demonstrates the differences in the methods of obtaining sRaw. The differences are caused by the hysteresis resulting from the airflow obstruction. This figure was taken from (Stockley et al., 2017a). with permission from Dove Medical Press.*

Abbreviations: *sReff, specific effective resistance; sRtot, specific total resistance; sR0.5, specific resistance of expiratory flow between ±0.5 and –0.5L/s.*

Specific airway conductance (sGaw) is another measure of airway function, which is the reciprocal measure of sRaw. sGaw is frequently recognised as a stronger parameter than Raw or sRaw because it has shown to have a linear association with lung volumes (Briscoe and Dubois, 1958). A study by Borrill et al. evaluated Raw, sGaw, and other lung functions (including FEV_1) in COPD to determine bronchodilator response (Borrill et al., 2005). In this study, to detect airway changes, Raw and sGaw showed greater sensitivity than FEV_1. However, both Raw and sGaw were less reproducible as they showed higher variabilities compared to FEV_1. Although a study has described significant decrease in Raw and sGaw in COPD patients with AATD (Duncan and Griffin, 1975), studies in COPD are small and sRaw

does not appear to rise substantially until moderate airflow limitation is established (Stockley et al., 2015). Furthermore, AO in the central airways may impact Raw or sGaw, and there is still uncertainty in the evidence of the usefulness of these measures in assessing small airways in COPD (Pellegrino et al., 2005).

1.5.4. Oscillometry Techniques

Oscillometry techniques are used to assess the mechanical characteristics of the lung known as respiratory impedance (Z_{rs}) in the respiratory tract non-invasively during tidal ventilation using various oscillation frequencies (between 5 and 35 Hz) (King et al., 2019). There are two forms of oscillometry techniques: Forced Oscillometry Technique (FOT) and Impulse oscillometry (IOS). In 1956, FOT was first introduced by DuBois and colleague as an assessment of lung function and it works by exerting sinusoidal sound waves produced by a loudspeaker passed into the lungs through a mouthpiece (Dubois et al., 1956). In 1975, a later version of FOT was developed with some differences in the application of oscillations named impulse oscillometry (IOS) (Michaelson, Grassman and Peters, 1975). The IOS uses oscillations in the form of pressure pulses, showing a quadrangular (square) sound wave (see figure 1.12). Validated reference ranges for oscillometry parameters are available in clinical practice (Oostveen et al., 2013).

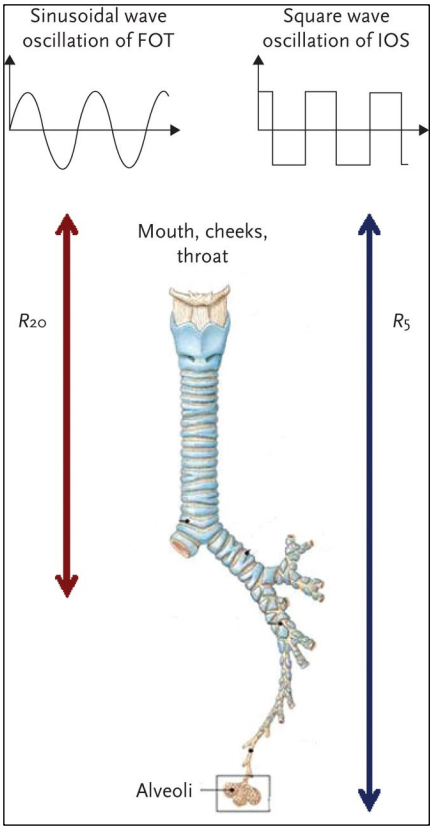

Figure 1.12. Comparison of FOT and IOS oscillation waves and distances travelled by distinct oscillation frequencies.

Legend: *This figure demonstrates the type of oscillation wave in FOT and IOS as well as how far oscillation frequency can go. Reproduced with permission of the © ERS 2021: Breathe 11 (1) 57-65; DOI: 10.1183/20734735.020514 Published 11 March 2015 (Brashier and Salvi, 2015).*

Abbreviations: *FOT, forced oscillation technique; IOS, impulse oscillometry.*

FOT and IOS use oscillating pressure differences to identify Z_{rs}, which is measured by the ratio of flow to pressure at different oscillation frequencies (Brashier and Salvi, 2015). Z_{rs} consists of the in-phase part called resistance (R_{rs}) and the out-phase part known as reactance (X_{rs}) (King et al., 2019). R_{rs} is amount of energy needed to disseminate oscillating pressures into the airways, and X_{rs} is the amount of recoil produced in response to the oscillations. In healthy individuals, R_{rs} is not affected by oscillation frequency, whereas in the presence of airway obstruction becomes affected (referred to as frequency-dependent) (King et al., 2019). Xrs is affected by oscillation frequency and refers to both the elastic and inertial

characteristics of the lung. X_{rs} is negative and mostly reflects the elastic characteristics in the lung at low frequencies (McNulty and Usmani, 2014). In contrast, at high frequencies, it is positive and reflects the inertial characteristics in the lung (McNulty and Usmani, 2014). At high frequencies (>15Hz), oscillations relate to R_{rs} of the central airways, while at low frequencies (such as 5Hz), oscillations enter into the peripheral part of the lung, reflecting R_{rs} of the entire lung (including small airways) (Figure 1.12).

When performing oscillometry techniques, several parameters that are useful in the assessment of small airways are obtained. R_{5-20}, which is the difference in the measurement of resistance at a frequency of 20 hertz (R_{20}) and resistance at a frequency of 5 hertz (R_5), has been used as an outcome measure that may identify resistance in the peripheral airway (Brashier and Salvi, 2015; Goldman, Saadeh and Ross, 2005). Reactance at 5 Hertz (X_5) is used to evaluate the structural characteristics of the lung parenchyma in the periphery and correlates with spirometric measures (Brashier and Salvi, 2015; Kolsum et al., 2009). The resonant frequency (Fres), defined as the frequency at which reactance is zero (the point where elastance and intertiance are equal), is also used as a measure (King et al., 2019). Measurement of the area under the curve of reactance (AX), which is the area between 5Hz and Fres, is also obtained. AX represents the elastic characteristics of whole respiratory system (involving the chest).

FOT may be sensitive to early changes in the small airways in smokers (Kolsum et al., 2009; Oppenheimer, Goldring and Berger, 2009) and may be valuable in monitoring COPD patients (Kamada, Kaneko and Tomioka, 2017). A cross-sectional study by Haruna et al. demonstrated that oscillometry parameters (R_{5-20} and X_5) had a significant correlation with FEV_1, dyspnoea and QOL (Haruna et al., 2010). Other studies have shown that FOT might help to distinguish between COPD and asthma (Das et al., 2014; Das et al., 2018) and maybe

more sensitive than spirometry following bronchodilator therapy (Saadeh et al., 2015) or bronchoprovocation tests (Kaminsky, 2012). FOT may also be a valuable tool for evaluating COPD patients during acute exacerbation (Jetmalani et al., 2015; Johnson et al., 2007). Recently, there have been significant advancements in FOT technology, and recent FOT devices are able to evaluate EFL and separate inspiratory/expiratory resistance and reactance. Recently, studies have suggested that IOS can identify SAD in COPD (Anderson and Lipworth, 2012; Ohishi et al., 2011; Tanaka, Fujii and Kitada, 2011). More recently, a cross-sectional study by Chaiwong et al. included 67 COPD patients, 50 chronic smokers (non-COPD) and 30 healthy participants to assess the use of IOS in diagnosing COPD. The authors found that AX, Fres, R_{5-20}, X_5, Z_5, R_5 showed a higher level of accuracy in diagnosing COPD, with AX showing the highest ability to diagnose COPD (Chaiwong et al., 2020). This study supports the use of IOS to supplement spirometry in the diagnosis of COPD. Figure 1.14 graphically shows the oscillometry parameters in patient with COPD. Although FOT/IOS are easy to perform and effort-independent, assessment can be challenging in the presence of artefacts such as swallowing or tongue movement. Therefore, patients should be provided proper coaching for accurate measurements.

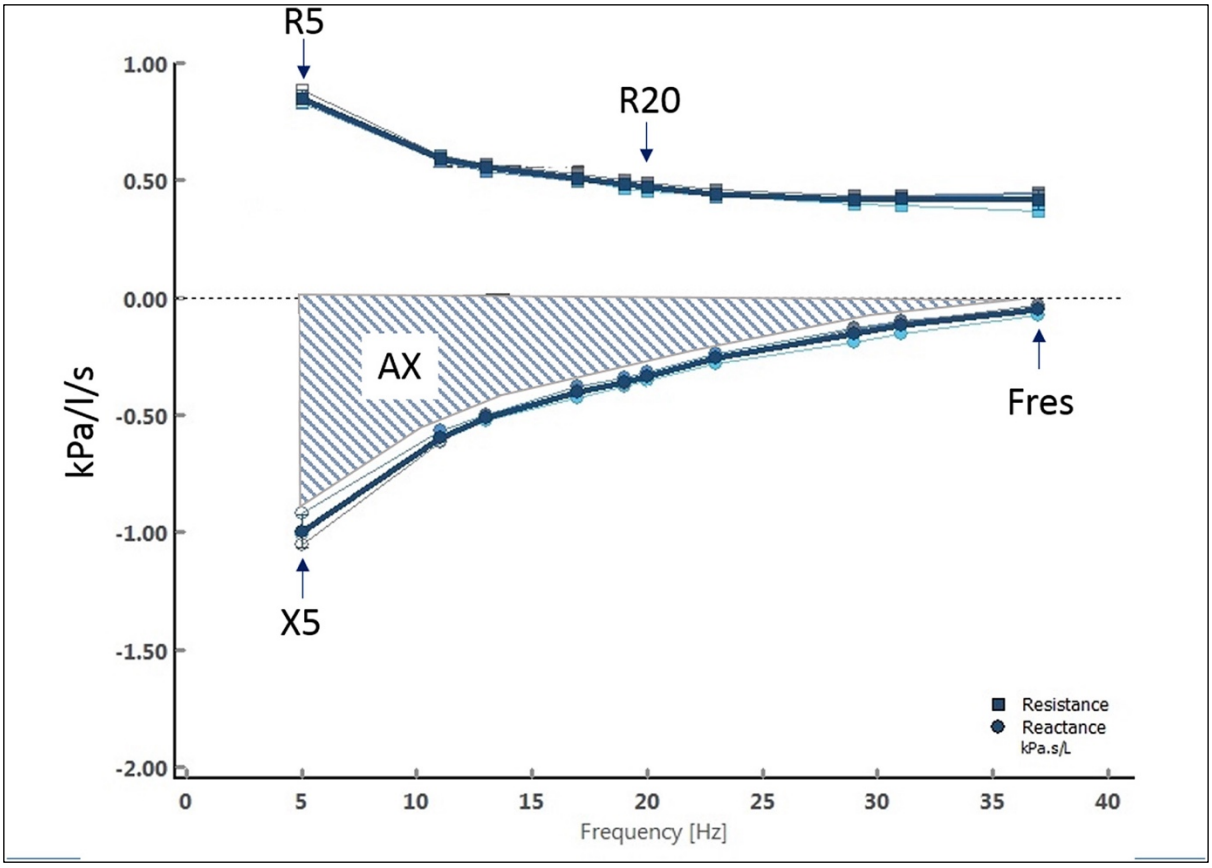

Figure 1.13. Impedance measurements (resistance and reactance) in IOS across several oscillation frequency in COPD patient.

Legend: *Reprinted from The Lancet, 139, Lipworth et al., What can we learn about COPD from impulse oscillometry?, 106-109, Copyright (2021), with permission from Elsevier (Lipworth and Jabbal, 2018).*

Abbreviations: *R5, resistance at a frequency of 5hz; X5, reactance at a frequency of 5hz; R20, resistance at a frequency of 20hz; AX, area under the curve of reactance; Fres, resonant frequency.*

1.5.5. Computed Tomography (CT)

Imaging of the chest can also provide an assessment of small airway function and CT is the most commonly cited imaging technique. CT scans of the lungs assess the presence and the distribution of emphysema, both visually, but more sensitively using density data from the images. Lung density evaluated at full inspiration, decreases with the amount of emphysema and is a highly sensitive measure of emphysema progression (Stolk et al., 2010). CT images are also increasingly being used to indirectly assess the presence of small airways disease, by

studying excess gas trapping at full expiration. Here, gas trapping is assumed to be a consequence of the loss or early closure of the peripheral airways. Parametric response mapping (PRM) analyses inspiratory and expiratory CT data, potentially identifying gas trapping caused by small airway disease alone (referred to as functional small airway disease (PRM^{fSAD})) through subtraction of defined emphysema. PRM^{fSAD} is shown to be a useful radiological finding of recognizing small airway abnormalities (Vasilescu et al., 2019). A longitudinal study by Bhat et al. showed an association between the decline in FEV_1 and PRM^{fSAD} (Bhatt et al., 2016). Despite the usefulness of CT, there are some limitations. Firstly, repeated assessment of CT measures is not possible because of the radiation exposure, limiting its use in monitoring COPD patients. Secondly, conducting and analysing CT scans needs a specialist centre; hence, very costly. Although there are studies that have utilised CT techniques (specifically PRM) to assess small airways (Dirksen et al., 2009; Stolk et al., 2010), these techniques still need to be fully validated to determine their clinical utility.

1.6. The rationale for the use of small airway test in the assessment of the bronchodilator responsiveness in COPD.

COPD is characterised by poor reversibility of the AO (Global Initiative for Chronic Obstructive Lung Disease, 2022). Bronchodilator responsiveness (BDR) using FEV_1 is seen in some patients with COPD (Tan et al., 2012; Albert et al., 2012), although it is widely used in the differentiation between asthma and COPD. However, the usefulness of BDR in COPD prognosis remains unclear. Furthermore, the BDR using FEV_1 was found to be continuously variable (Calverley et al., 2003); thus, this might limit its use as a marker of treatment responsiveness in COPD. Recently, it has been shown that even when FEV_1 does not improve, VC and IC increase, which correlate with reduced dyspnoea and better exercise

performance (Schermer et al., 2007; O'Donnell, Revill and Webb, 2001). This indicate that a positive BDR should not be determined by a single spirometric measure alone and additional physiological measures may be of value in understanding and managing COPD.

Studies have reported that demonstrated improvements in small airways tests following bronchodilator administration (Borrill et al., 2005; Wouters et al., 1989). IOS was used in three studies and demonstrated improvement in several parameters (R_5, Fres, X_5 and R_{5-20}) (Saadeh et al., 2015; Park et al., 2019; Borrill et al., 2005). In fact, the improvements of measures of small airways were greater than FEV_1. MMEF also showed improvement, which was greater than seen in FEV_1 (Park et al., 2019; Borrill et al., 2005).

Although studies assessing BDR using small airway tests were small, there is evidence that these tests may be valuable in the BDR assessment. As COPD is heterogeneous in aetiology, clinical features and disease progression, small airway responsiveness to bronchodilator might detect a subgroup of COPD patients that can be treated differently with increased therapeutic benefit using bronchodilators. However, a systematic review is needed to provide a definitive assessment of the current tests of small airway used in BDR, the bias contained within published studies and any comparison between them.

1.7. The rationale for and practicality of the tests of small airway function during exacerbation of COPD

The effect of exacerbation on small airways is likely to be amplified and therefore measuring small airways function during exacerbations may be of interest in identifying both the duration of the episode and the response to treatment. However, there are potential caveats to its use. In the study of AATD patients, all patients with moderate spirometric evidence of COPD had significant SAD (Stockley et al., 2017b). Another study of 40 COPD patients

reported similar findings, showing that in moderate COPD patients (FEV_1= 65%), there is a significant SAD (MMEF = 28%) (Mirsadraee, Boskabady and Attaran, 2013). These findings are similar to other studies including COPD patients (Piorunek et al., 2017; Pisi et al., 2015). Therefore, small airway's function would be greatly impaired even in the stable state and potentially only mild to moderate COPD patients may provide a detectable signal during an exacerbation.

As previously stated, the assessment of small airways function can be carried out using a number of tests, but whether these tests are clinically useful, or could be delivered during exacerbations of COPD has yet to be fully explored. To be clinically useful, tests should provide a pre-treatment measure which identifies the start, end and response to treatment of an exacerbation, is practical by the bedside and acceptable to patients. A summary of advantages and disadvantages of each test is presented in table 1.4.

Table 1.4. The use of tests of small airways function during exacerbation of COPD

Test	Outcome measured	Advantages	Disadvantages
Mid-Maximal Expiratory Flow	MMEF (FEF_{25-75})	1. Can be done at bedside 2. Widely accessible 3. Provide assessment of SAD	1. Very effort dependent 2. May be hard to do during exacerbation. 3. Poor reproducibility if not adjusted for lung volume
Single breath washout	S_{III}, CC, CV	1. Provide assessment of ventilation inhomogeneity 2. Quick to perform 3. Requires only tidal breathing if double trace gases method is used. 4. Can be done at bedside.	1. Conventional technique is effort-dependent 2. The new technique involving two inhaled tracers gases is not thoroughly investigated
Multiple breath washout	LCI, S_{cond}, S_{acin}	1. Provides assessment of ventilation in the acinar and small conducting airway. 2. Effort independent 3. Can be done at bedside	1. Time consuming 2. It may have variabilities
Plethysmographic measurement of resistance	Raw, sRaw, sGaw	1. Effort independent. 2. Quick technique to perform.	1. Method can pose technical challenges 2. Not specific to the function of peripheral airways 3. Cannot be done at bedside.
Oscillation techniques	R_5, R_{5-20}, X_5, AX, Fres	1. Quick to perform. 2. Effort independent. 3. Specific to small airway function 4. Clinically validated. 5. Can be done at bedside.	2. Specialised equipment
Computed Tomography	Air trapping, emphysema, PRM^{fSAD}	1. Provides direct evaluation of the presence of disease 2. Gold standard for detecting and phenotyping emphysema	1. High exposure to radiation 2. Costly 3. Cannot be done at bedside 4. Achieving consistent RV is difficult

Abbreviations: TGV, thoracic gas volume; RV, residual volume, MMEF, mid maximal expiratory flow; S_{III}, Slope of Phase 3; CC, closing capacity; CV, closing volume; LCI, lung clearance index; S_{cond}, ventilation inhomogeneity in conducting airways; S_{acin}, ventilation inhomogeneity in acinar zones; Raw, Airway resistance; sRaw, specific airway resistance; sGaw, specific airway conductance; R_5, resistance at oscillation frequency of 5 hertz; R_{5-20}, the difference of between resistance at 5 hertz and 20 hertz; X_5, reactance at oscillation frequency of 5 hertz; AX, area of reactance; Fres, resonant frequency; PRM^{fSAD}, parametric response mapping for functional small airway disease.

In general, studies utilising small airway tests in COPD exacerbation have been limited, both in the number of studies carried out and the number of patients recruited. Furthermore, the majority of these studies have been conducted during hospitalised exacerbations. Although two studies have included moderate exacerbation in their studies, most of the others have not specified the severity of exacerbation. In general, all studies did not specify the COPD severity of patients being examined; however, by assessing at the baseline FEV_1, most studies have assessed the small airways in moderate to severe COPD.

FOT and spirometry were used in an observational study to compare changes in COPD patients hospitalised with an exacerbation and demonstrated that inspiratory resistance was associated with a significant improvement in symptoms (Jetmalani et al., 2015). Inspiratory capacity and reactance by FOT have been shown to relate to exacerbation recovery (Johnson et al., 2007). Tests of small airways have also been used in several interventional studies including identifying a significant decrease in airway resistance by plethysmography after 14 days of treatment with systematic corticosteroid (Komlev et al., 2007) and identifying a significant improvement in MMEF at 10 and 30 days following treatment with erdosteine (Moretti and Ballabio, 2011). Another study compared treatment delivered via vibrating mesh nebuliser and small volume jet nebuliser using spirometry, body plethysmography, and IOS, demonstrating an improvement in spirometry, lung volume and airway impedance with recovery (Cushen et al., 2016).

Although studies using tests of small airways to assess exacerbation are small, there is consistent evidence that these tests offer the ability to map recovery (especially in milder to moderate disease). However, a systematic review is needed to provide a definitive assessment of the current tests of small airway used, the bias contained within published studies and any comparison between them. If any of these tests appeared sensitive to change during

exacerbation, a pilot study to see if test delivery is feasible and acceptable by the patient during exacerbation of COPD in the acute setting would be of great value. This might inform larger studies to determine if tests of small airways could be validated in exacerbations, and which tests might be the most informative, especially in episodes where dyspnoea is the sole symptom.

1.8. Hypotheses, Aims and objectives

The thesis evaluated three main hypotheses:

- **1st hypothesis**: SAD is a physiological feature of COPD and an early indicator of lung damage in the absence of AO.
- **2nd hypothesis**: SAD is improved post-bronchodilator (BD) in some COPD patients. Here, measure of small airways function will change following BD and will identify a subgroup of patients that might be managed differently.
- **3rd hypothesis**: SAD is worsened by the inflammation present during exacerbation. Measures of small airway function will change during AECOPD and mirror symptoms, functional status and systematic inflammation more closely than FEV_1.

The thesis was structured according to the pre-defined main hypotheses into three themes. Each theme consisted of two studies, which are detailed below:

Theme 1: The prevalence of small airway dysfunction in COPD and pre-COPD

Study 1: SAD in symptomatic ever-smokers: A retrospective real-world study.

Hypothesis: We hypothesized that physiological evidence of SAD, as assessed by MMEF, would be ubiquitous in patients with AO, preceding the development of AO. Furthermore, we hypothesized that patients with SAD without AO would have physiological indicators of the

risk of developing AO, even after the correction for potential confounders such as smoking history.

Aims:

- To investigate the prevalence of SAD in cigarette smokers with and without AO.
- To assess whether the presence of SAD without AO was associated with lower lung function measurements, which might suggest an increased risk of developing AO.
- To assess the relationships between SAD measures and AO severity in established COPD.
- To determine whether the presence of SAD was associated with lower lung function parameters (specifically FEV_1 and FEV_1/FVC ratio), even when potential confounders.

Study 2: SAD in symptomatic never-smokers: A retrospective real-world study.

Hypothesis: Physiological evidence of SAD, as assessed by MMEF, would be ubiquitous in patients with AO, as SAD preceded the development of AO. Moreover, patients with SAD who did not meet the physiological criteria for a diagnosis of AO would have physiological indicators of a heightened risk of AO, not seen in those without SAD.

Aims:

- To assess the prevalence of SAD in never-smokers with and without AO.
- To assess the baseline demographics and lung function across study groups.
- To evaluate the association of the MMEF z-score with the z-score of other spirometric measures.

Theme 2: The utility of small airways tests in BDR assessment in COPD.

Study 3: Small airways response to bronchodilator in adults with asthma or COPD: A systematic review

Hypothesis: existing evidence will support the use of small airway tests in BDR assessment for both asthma and COPD

Aim:

- To summarise the existing literature on small airways response to short-acting inhaled bronchodilators in asthma and COPD.

Objectives:

- To evaluate the current evidence of small airways response to short-acting inhaled bronchodilators in asthma and COPD.
- To evaluate the effectiveness of methods used in delivering aerosolised bronchodilators to the small airways and their function.

Study 4: The use of small airways test in bronchodilator response assessment in COPD - A retrospective study.

Hypothesis: A positive BDR within the SA, defined by a positive BDR in MMEF, would be common in COPD, seen in most COPD patients with a positive BDR defined by FEV_1, but would also be present in those without BDR in FEV_1. Moreover, we hypothesised that those with a positive BDR in SA alone would not be distinguishable in terms of demography, smoking exposure or severity of lung disease from those without positive BDR in SA. However, this might identify a subgroup of COPD patients who may benefit from more peripheral bronchodilator deposition using ultra-fine particles within inhalers, and therefore could form a group where screening was warranted to identify a treatable characteristic.

Aims:

- To determine the prevalence of positive BDR in MMEF, and its association with baseline demography, AO severity and smoking history.

- To assess the prevalence of positive BDR in MMEF with and without BDR in FEV_1.

Theme 3: The utility of small airways tests in acute exacerbation of COPD

Study 5: The use of physiological tests assessing the acute response to treatment during exacerbations of COPD (with a focus on small airway function) – A systematic review

Hypothesis: Existing evidence will support the use of small airways tests in exacerbation of COPD.

Aim:

- To summarize the findings of studies comparing a measure of small airways function to FEV_1 during exacerbations of COPD to inform whether these tests could be incorporated as a primary outcome for further studies within this

Objective:

- To assess treatment response using small airway tests in comparison to FEV_1 during exacerbation of COPD.

Study 6: The use of small airway tests in AECOPD: A prospective observational pilot study

Hypothesis: Small airway tests (FOT) is feasible and acceptable for patients hospitalised with AECOPD. The test also mirrors symptom scores, functional status, FEV_1 and systemic inflammation during exacerbation and the recovery period.

Aim:

- To assess the utility and acceptability of tests of small airways function during exacerbations of COPD in an observational pilot study.

Objectives:

- To determine if measures of SAD are more acceptable and feasible for patients hospitalised with an exacerbation of COPD compared to collecting FEV_1 and FVC.
- To assess if measures of SAD mirror changes in symptom scores, functional status, FEV_1 and systemic inflammation during resolution of an exacerbation of COPD.

Theme #1: The prevalence of small airway dysfunction in COPD and pre-COPD

2. Small airway dysfunction in symptomatic ever-smokers: a real-world retrospective study

This chapter utilized lung function data of ever-smoking participants to evaluate the prevalence of small airway dysfunction (SAD) in COPD and those at risk of developing COPD.

This chapter is a paper in preparation for submission to a journal for consideration to be published.

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

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2.1. Brief introduction:

As previously described, COPD is diagnosed based on subjective (respiratory symptoms, history of exposure to risk factors) and objective (physiologically confirmed airflow obstruction (AO)) assessments. According to the Global Initative for Obstructive Lung Disease (GOLD) report, AO is defined by Post-bronchodilator (PBD) forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio <70% with the severity classified by FEV_1 % predicted (Global Initiative for Chronic Obstructive Lung Disease, 2022). Other bodies recommend using the lower limit of normal (LLN) based on z-scores for FEV_1/FVC to define AO and FEV_1 z-score to stratify the severity of the disease as this is thought to be less biased at the extremes of age (Pellegrino et al., 2005; Quanjer et al., 2012).

COPD is a slowly progressive disease in most individuals (Vestbo et al., 2011) and FEV_1/FVC and FEV_1 lack the diagnostic sensitivity to identify early lung pathology (Herpel et al., 2006; Pennock, Rogers and McCaffree, 1981). As only a proportion of smokers develop COPD (Fletcher and Peto, 1977), identifying individuals with early lung damage who are most at risk of overt COPD would enable a focused effort to prevent pathological progression.

The role of small airways in COPD has been explored in several studies (McDonough et al., 2011; Hogg, McDonough and Suzuki, 2013; Bosken et al., 1990; Gennimata et al., 2010). Small airways loss preceded the development of emphysema and AO in pathological studies investigated by micro-computed tomographic radiology (McDonough et al., 2011; Hogg, McDonough and Suzuki, 2013; Hogg, Macklem and Thurlbeck, 1968). Further, in a longitudinal study of SAD in Alpha-1 Antitrypsin Deficiency (AATD) using Maximal Mid-Expiratory Flow (MMEF) (Stockley et al., 2017b), a reduced MMEF without AO was associated with worse health status and a faster subsequent decline in FEV_1 and appeared to precede the development of AO defined by conventional spirometry (Stockley et al., 2017b).

This, and other studies, suggest that measures of small airway function (especially MMEF) may be more sensitive to early damage than traditional spirometric measures (Tsushima et al., 2006; Mirsadraee, Boskabady and Attaran, 2013; Boeck et al., 2016; Verbanck, 2012; Oxhoj, Bake and Wilhelmsen, 1977).

We hypothesized that physiological evidence of SAD, as assessed by MMEF, would be ubiquitous in patients with AO, preceding the development of AO. Furthermore, we hypothesized that patients with SAD without AO would have physiological indicators of the risk of developing AO, even after the correction for potential confounders such as smoking history.

2.2. Aims:

- To investigate the prevalence of SAD in cigarette smokers with and without AO.
- To assess whether SAD without AO was associated with lower lung function measurements within the normal range, which might reflect an increased risk for developing AO, even when potential cofounders such as smoking were taken into account.
- To assess the relationships of SAD with AO severity in established COPD.
- To assess the relationship of measure of SAD with other spirometric measures.
- To determine whether the presence of SAD was associated with lower lung function parameters (specifically FEV_1 and FEV_1/FVC ratio), even when potential confounders were corrected for.

2.3. Methods and design:

2.3.1. Study design and setting

This was a retrospective, cross-sectional study of anonymized data from patients known to have or suspected of having COPD who underwent routine pulmonary function test at University Hospitals Birmingham NHS Foundation Trust, UK. The study included data obtained between 1st January 2016 and 30th April 2021 and all patients who had lung function during this period were screened for inclusion. The data study was approved by the Health Research Authority (REC Reference: 20/HRA/0203).

2.3.2. Eligibility criteria:

The study included all participants with:

1) Symptoms suggestive of COPD (breathlessness and/or a persistent cough)
2) Age 30 years or older
3) ≥10 pack-years history of cigarette smoking.
4) Either a confirmed diagnosis or were suspected as having COPD by a physician.
5) All traditional spirometric measures including MMEF were reported

Participants were excluded if they:

1) Had COPD related to AATD
2) A history/diagnosis of other chronic lung diseases
3) Significant structural changes in the lung (such as bronchiectasis) defined radiologically.

2.3.3. Study measures:

Patients' demographic data were collected. Smoking history included smoking status at the time of testing (ex-smoker or current smoker), pack-years history and years since

quitting smoking. The smoking exposure was also evaluated, and categorized into light (<20 pack-year history), moderate (20-40 pack-years history) and heavy (>40 pack-year history) (Lee et al., 2011). Regular medication use was documented.

All lung function parameters were assessed, including FEV_1, FVC, FEV_1/FVC, MMEF, forced expiratory volume in the first 3 seconds (FEV_3), MMEF/FVC, FEV_3/FVC. MMEF/FVC was obtained by dividing MMEF % predicted by FVC % predicted (Mirsadraee, Boskabady and Attaran, 2013). Lung function assessments used the Ultima PF™ Pulmonary Lung Function System (Medical Graphics UK Ltd, Tewkesbury, UK) and were performed in accordance with national guidelines (Sylvester et al., 2020).

The z-scores for MMEF and FEV_1/FVC were used to define abnormality and reflect SAD and AO, respectively. A cut-off of -0.8435 was chosen for abnormal MMEF z-score as this was shown to predict the development of COPD in a previous prospective study (Kwon et al., 2020). The conventional z-score of -1.645 was used for FEV_1/FVC to define AO, as this represents the LLN as defined in the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines (Pellegrino et al., 2005; Quanjer et al., 2012). Using these thresholds, participants were grouped according to the combination of SAD and AO: SAD-/AO- (no SAD and no AO), SAD+/AO- (SAD but no AO) and SAD+/AO+ (SAD and AO). Similarly, AO severity was also defined using FEV_1 z-score for consistency (Quanjer et al., 2014a), which includes 5 severity groups in comparison to the 4 severity groups included in the GOLD report.

MMEF z-score was compared with z-scores of other physiological measures where available.

2.3.4. Statistical Analysis:

Statistical analysis was performed using IBM Statistical Package for the Social Science (SPSS) software. Data were not normally distributed (assessed using Shapiro-wilk's test); hence, Kruskal-Wallis H tests were used throughout with the median and interquartile ranges (IQR) reported. Where Kruskal-Wallis H tests were significant, a post-hoc Dunn's test was applied. For variables used in group definitions (MMEF and FEV_1/FVC), no statistical analysis was conducted, except where the definition did not cause the variable to differ. Here, Mann-Whitney U tests was performed to determine the differences. Categorical variables were assessed using Chi-square or Fisher's exact test. The relationship of MMEF z-score with z-score of other physiological measures and whether smoking behaviors have impact on the relationships were assessed using weight least-square (WLS) regression. Coefficient of determination (r^2) for WLS regression was reported throughout. Curvilinear regression was used to determine the relationship between MMEF % predicted or MMEF/FVC with % predicted or ratio of other physiological measures, with r^2 for the curvilinear regression reported throughout.

Logistic regression was performed to identify factors associated with the presence of SAD. Significant variables in univariate analyses were included in the subsequent multivariate analysis. A $p<0.05$ was considered statistically significant throughout and p-values were adjusted using the Bonferroni method to account for multiple comparisons (Bonferroni, 1936). No power calculations were conducted for this pragmatic study.

2.4. Results:

2.4.1. Participant's selection:

On initial screening, the dataset included 2258 records. After assessing for eligibility, 1458 ever-smokers were included (see figure 2.1. for a flowchart including reasons for exclusion). These participants were placed into the three groups based on SAD and AO: SAD-/AO- (n=316); SAD+/AO- (n=335); and SAD+/AO+ (n=806).

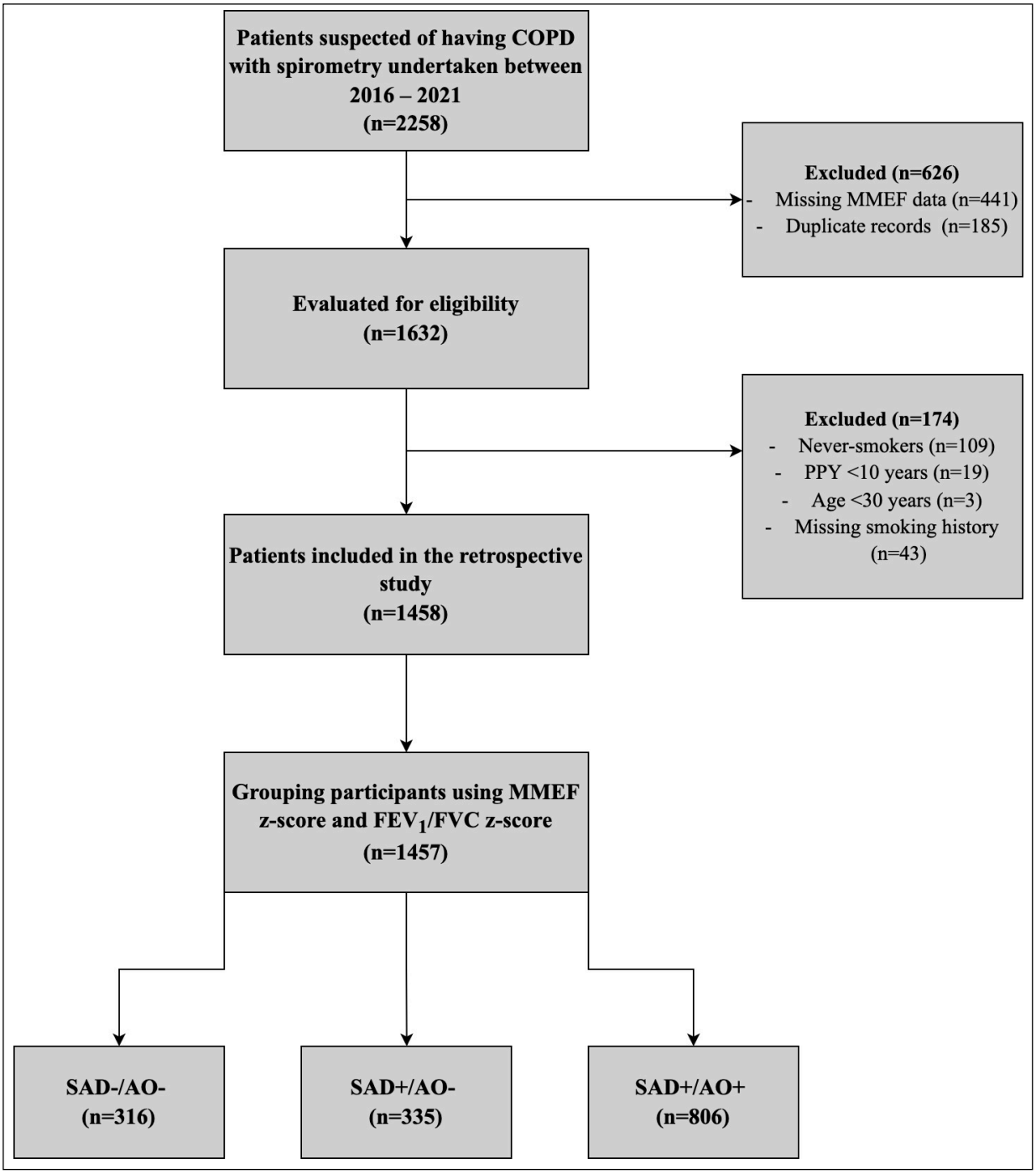

Figure 2.1. Flowchart of the retrospective study.

Legend: This figure shows the selection of patients according to eligibility criteria. One participant did not meet any of the group definition.
Abbreviations: COPD, chronic obstructive pulmonary disease; MMEF, maximal mid-expiratory flow; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; AO, airflow obstruction; SAD, small airway dysfunction.

2.4.2. Prevalence of SAD

All but one participant with AO had SAD (806/807; 99.9%). Of those without AO, 51.4% (335/650) had evidence of SAD.

2.4.2.1. Demographics and clinical characteristics:

Baseline demographics for the eligible participants and groups are shown in table 2.1. The average age was higher in SAD+/AO+ group (median 65 years) versus both SAD-/AO- group (median 63 years; p=0.049) and SAD+/AO- group (median 63 years; p=0.012). There were no differences in sex across groups. BMI was lower in SAD+/AO+ group than both SAD-/AO- group (median BMI 25.67 vs 30.20, p<0.001) and SAD+/AO- group (median BMI 28.94, p<0.001).

Participants in SAD-/AO- group had generally smoked less (less heavy smokers and a reduced pack-year history) compared to SAD+/AO- group and SAD+/AO+ group, with no differences between SAD+/AO- group and SAD+/AO+ group for smoking history (see figure 2.2.).

Patients in SAD+/AO+ group used more COPD-associated medications than those in SAD-/AO- group or SAD+/AO- group, including short-acting beta-2 agonists (SABA), inhaled corticosteroids (ICS)/ long-acting beta-2 agonists (LABA) and long-acting muscarinic antagonists (LAMA) (p<0.001 for all). Patients in SAD+/AO- group used more COPD medications (including SABA and ICS/LABA) than SAD-/AO- group (p<0.001 for all). Details of the medications used across groups are provided in appendix 2.1.

Table 2.1. Baseline demographics of the included participants.

Variable	Total n= 1458	SAD-/AO- *n = 316*	SAD+/AO- *n = 335*	SAD+/AO+ *n = 806*
Age (years)	64 (56.75 – 72)	63 (54.75 – 72)	63 (54.75 – 72)	65 (58 – 73)[*†]
Age (groups) (n, %)				
30 – 39	28 (1.9)	10 (3.2)	5 (1.5)	13 (1.6)
40 – 49	127 (8.7)	31 (9.8)	43 (12.9)	53 (6.6)[†]
50 – 59	336 (23.1)	82 (25.9)	79 (23.7)	175 (21.7)
60 – 69	479 (32.9)	98 (31)	102 (30.5)	278 (34.4)
≥70	487 (33.4)	95 (30.1)	105 (31.4)	288 (35.7)
Sex (male: female) n	744: 714	168: 148	150: 184	425: 382
Race (n, %)				
Caucasian	1382 (94.8)	286 (90.5)[‡§]	321 (96.1)	774 (94.8)
Black	22 (1.5)	9 (2.8)[†]	1 (0.3)	12 (1.5)
Asian	49 (3.4)	19 (6.0)[‡]	11 (3.3)	19 (2.3)
Others	5 (0.3)	2 (0.6)	1 (0.3)	2 (0.2)
Smoking status (n, %)				
Current smokers	842 (57.8)	163 (51.6)[‡]	197 (59)	482 (59.7)
Ex-smokers	616 (42.2)	153 (48.4)[‡]	137 (41)	325 (40.3)
Smoking exposure (n, %)				
Light	216 (14.8)	73 (23.1)[†‡]	43 (12.8)	100 (12.4)
Moderate	568 (39)	138 (43.7)	133 (39.7)	297 (36.8)
Heavy	673 (46.2)	105 (33.2)[†‡]	159 (47.5)	409 (50.7)
Pack year	40 (25 – 55)	31 (20 – 45)[†‡]	40 (26 – 55)	41 (28 – 59)
Years quit[§]	10 (3 – 20)	11 (4 – 24.50)[‡]	10 (4 – 20)	8 (3 – 15)
BMI (kg/m^2)	27.32 (23.09 – 31.95)	30.20 (25.34 – 34.71)	28.94 (25.33 – 34.07)	25.67 (21.88 – 29.82)[*†]

Legend: Data is presented as median and IQR, unless otherwise stated. [*] Significantly different from SAD-/AO-; [†]Significantly different from SAD+/AO-; [‡]Significantly different from SAD+/AO+; [§]only assessed in ex-smokers. For adjusted p-value, significance level was set at <0.05.

Abbreviations: IQR, interquartile range; BMI, body mass index; SAD, small airway dysfunction; AO, airflow obstruction; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; MMEF, maximal mid-expiratory flow.

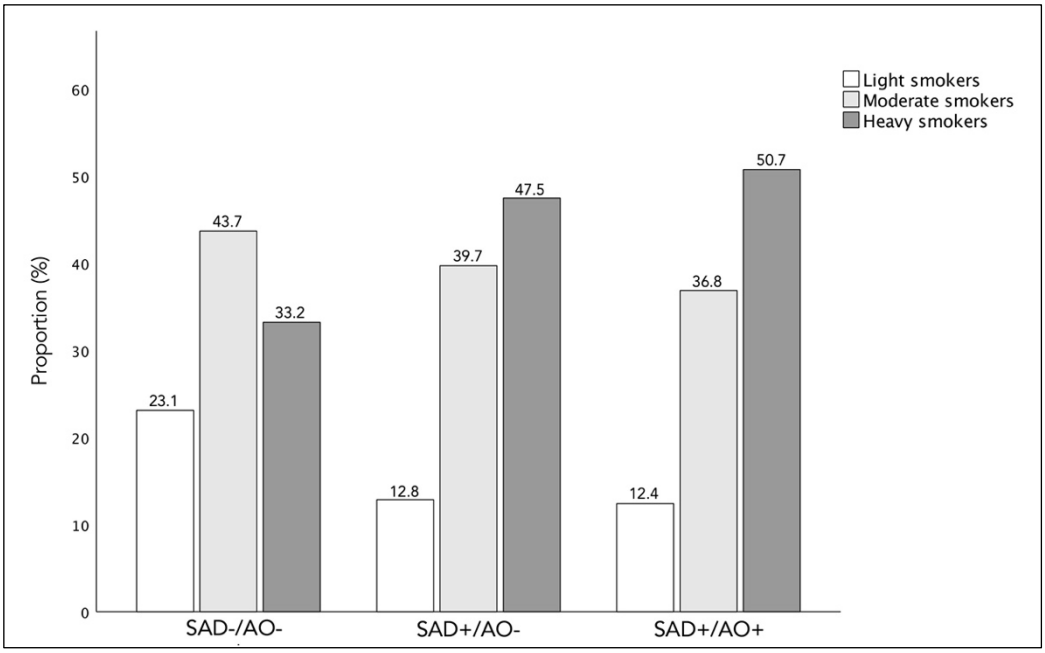

Figure 2.2. The proportion of participants being light, moderate or heavy smokers.

Legend: The bar chart demonstrates the percentage of light, moderate or heavy smokers across study groups.
Abbreviations: SAD, small airway dysfunction; AO, airflow obstruction.

2.4.3. Physiological assessment of lung function

Table 2.2. shows the baseline spirometric measures across groups. All spirometric measures were lower in SAD+/AO- group than SAD-/AO- group ($p<0.001$).

SAD+/AO+ group had lower lung function ($p<0.001$ for all comparisons) than both SAD+/AO- group and SAD-/AO- group. FVC z-score and FVC % predicted did not differ between SAD+/AO+ group and SAD+/AO- group. The distribution of MMEF z-score, FEV_1 z-score, FEV_1/FVC z-score and FVC z-score across groups are shown graphically in figure 2.3. The distribution of MMEF % predicted, MMEF/FVC ratio, FEV_1 % predicted, FVC % predicted, FEV_1/FVC ratio and FEV_3/FVC ratio across groups are shown in appendix 2.2.

Table 2.2. Baseline spirometric measures of the included participants.

Variable	Total *n = 1458*	SAD-/AO- *n = 316*	SAD+/AO- *n = 335*	SAD+/AO+ *n = 806*
FEV_1				
z-score	-2.09 (-3.16 – -1.11)	-0.44 (-1.00 – 0.20)	-1.67 (-2.26 – -1.18)*	-2.97 (-3.70 – -2.12)*†
% Predicted	67.05 (47.65 – 84.12)	93.68 (85.60 – 103.92)	74.05 (64.50 – 82.43)*	50.91 (37.25 – 66.36)*†
FVC				
z-score	-0.50 (-1.15 – 0.20)	-0.50 (-1.15 – 0.20)†‡	-1.34 (-2.02 – -0.63)	-1.19 (-2.02 – -0.35)
% Predicted	84.43 (71.96 – 96.75)	93.16 (83.37 – 103.37)†‡	80.44 (70.60 – 91.37)	82.05 (69.22 – 95.38)
FEV_1/FVC§				
z-score	-1.93 (-3.34 – -0.63)	0.09 (-0.30 – 0.46)	-1.00 (-1.33 – -0.60)*	-3.18 (-4.11 – -2.34)
%	63 (48 – 74)	79 (76 – 83)	71 (68 – 75)*	50 (39 – 59)
MMEF§				
z-score	-1.96 (-2.80 – -1.01)	-0.16 (-0.49 – 0.25)	-1.37 (-1.67 – -1.11)	-2.72 (-3.2 – -2.18)†
% Predicted	40.56 (21.08 – 67.58)	95.25 (83 – 110.51)	56.02 (47.76 – 63.70)	22.74 (14.80 – 33.76)†
MMEF/FVC	48.28 (27.25 – 79.86)	104.80 (90.10 – 122.99)	68.02 (59.16 – 79.86)*	28.73 (19.90 – 40.47)*†
FEV_3/FVC	85.44 (74.22 – 92.26)	94.65 (92.10 – 96.83)	90.75 (87.73 – 93.46)*	75.13 (64.70 – 82.67)*†

Legend: Data is presented as median and IQR. * Significantly different from SAD-/AO-; †Significantly different from SAD+/AO-; ‡Significantly different from SAD+/AO+; §statistical test was only done for differences between groups where a definition did cause the variable to differ.

Abbreviations: IQR, interquartile range; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; MMEF, mid maximal expiratory flow; FEV_3, forced expiratory volume in 3 seconds; SAD, small airway dysfunction.

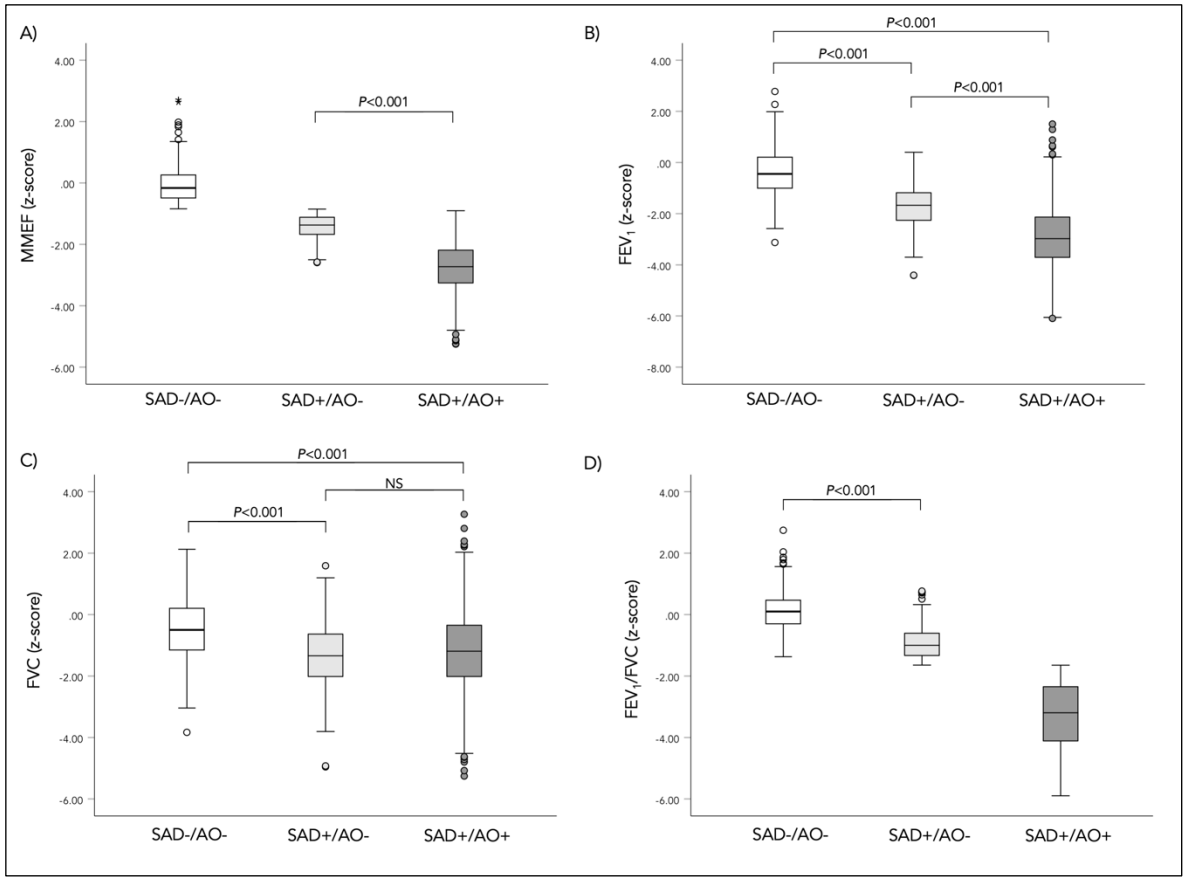

Figure 2.3. Distribution of spirometric measures across study groups.
Legend: A box plot demonstrating the distribution of z-scores of spirometric measures across groups. The plot shows median, interquartile range, minimum and maximum. A) The distribution of MMEF z-score across groups. B) The distribution of FEV_1/FVC z-score across groups. C) The distribution of FEV_1 z-score across groups. D) The distribution of FVC z-score across groups. For figures A and D, statistical test was only done for differences between groups where a definition did cause the variable to differ, and the reported p-values are for the Mann-Whitney U test. For figures B and C, the presented p-values are for post-hoc Dunn's test, and the Kruskal Wallis tests p-values for both figures were <0.001.
Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; MMEF, maximal mid-expiratory flow; SAD, small airway dysfunction; AO, airflow obstruction.

2.4.4. The relationship of SAD with AO severity

Participants with AO were grouped according to AO severity using FEV_1 z-scores and the 5 severity rankings described previously (Quanjer et al., 2014a). Table 2.3. summarizes baseline demographics and lung function of these participants. In this cohort, patients with very severe disease were younger than those with lesser severity ($p<0.001$ for all comparisons). There were no differences between subgroups in sex or ethnicity, although BMI was lower in patients with very severe disease compared to moderately severe patients

(median BMI 23.43 vs 26.99, p=0.006). Of note, smoking status and pack-year history did not differ across severity groups but those with the most severe disease had stopped smoking later than the other groups. Severe and very severe patients used more medications than mild, moderate and moderately severe patients, including SABA, ICS/ LABA and LAMA ($p<0.001$ for all) as shown in appendix 2.3.

FVC and FEV_3/FVC decreased as disease severity increased ($p<0.001$) in a stepwise manner. Similarly, SAD, as measured by MMEF z-score, also worsened in a stepwise manner as the severity of AO increased ($p<0.005$; see figure 2.4.). Of note, even in mild AO, the MMEF % predicted was substantially impaired (median 40.5% and 41.9% for MMEF/FVC). The distributions of MMEF % predicted and MMEF/FVC across severity are shown graphically in appendix 2.4.

Table 2.3. Baseline demographics and spirometric measures across severity

Variable	Mild *n = 177*	Moderate *n = 111*	Moderately severe *n = 120*	Severe *n = 263*	Very severe *n = 135*
Age (years)	65 (57 – 75)	67 (60 – 75)	67 (58.50 – 74)	69 (61 – 73)	59 (53 – 64)[*†‡§]
Age (groups) (n, %)					
30 – 39	4 (2.2)	4 (3.6)	0 (0)	2 (0.8)	3 (2.2)
40 – 49	15 (8.4)	5 (4.5)	10 (8.3)	8 (3)	15 (11.1)[^]
50 – 59	36 (20.2)	18 (16.2)	20 (16.7)	47 (17.9)	54 (40)[*†‡§]
60 – 69	60 (33.7)	36 (32.4)	45 (37.5)	89 (33.8)	49 (36.3)
≥70	63 (35.4)	48 (43.2)	45 (37.5)	117 (44.5)	14 (10.4)[*†‡§]
Sex (male: female) n	92: 86	50: 61	72: 48	138: 125	73: 62
Race (n, %)					
Caucasian	170 (95.5)	109 (98.2)	111 (92.5)	253 (96.2)	131 (97)
Black	4 (2.2)	0 (0)	4 (3.3)	4 (1.5)	0 (0)
Asian	3 (1.7)	2 (1.8)	5 (4.1)	5 (1.9)	4 (3)
Others	1 (0.6)	0 (0)	0 (0)	1 (0.4)	0 (0)
Smoking status (n, %)					
Current smokers	113 (63.5)	59 (53.2)	72 (60)	159 (60.5)	79 (58.5)
Ex-smokers	65 (36.5)	52 (46.8)	48 (40)	104 (39.5)	56 (41.5)
Smoking exposure (n, %)					
Light	20 (11.2)	19 (17.1)	18 (15)	16 (6.1)[†‡]	28 (20.7)[§]
Moderate	79 (44.4)	35 (31.5)	35 (29.2)	100 (38)	48 (35.6)
Heavy	79 (44.4)	57 (51.4)	67 (55.8)	147 (55.9)	59 (43.7)
Pack year	40 (26.75 – 55)	41 (25 – 53)	43 (29 – 60)	44 (30 – 62)	38 (23 – 63)
Years quit	12 (3 – 21.50)	9 (3 – 16)	9 (2.25 – 19.50)	7 (3 – 14)	5 (2 – 10)[*]
BMI (kg/m^2)	25.78 (22.96 – 28.68)	26.17 (21.29 – 30.42)	26.99 (22.85 – 30.36)	25.52 (21.92 – 30.66)	23.43 (19.62 – 28.73)[‡]
Spirometric measures					
FEV$_1$[#]					
z-score	-1.48 (-1.80 – -1.07)	-2.27 (-2.37 – -2.13)	-2.77 (-2.89 – -2.63)	-3.45 (-3.72 – -3.26)	-4.42 (-4.83 – -4.21)

% Predicted	77.77 (72.63 – 84.63)	63.18 (59.72 – 67.59)	55.27 (50.21 – 59.36)	40.40 (35.66 – 46.95)	27.26 (22.72 – 33.28)
FVC					
z-score	0.20 (-0.38 – 0.72)	-0.98 (-1.24 – -0.38)*	-1.25 (-1.66 – -0.69)*	-1.79 (-2.26 – -1.04)*†‡	-2.54 (-3.28 – -1.73)*†‡§
% Predicted	103.77 (94.99 – 111.71)	85.41 (81.28 – 95.04)*	81.92 (74.64 – 90.89)*	72.31 (65.25 – 84.53)*†‡	63.83 (53.33 – 74.67)*†‡§
FEV_1/FVC					
z-score	-2.20 (-2.66 – -1.89)	-2.37 (3.02 – -2.15)	-3.00 (-3.53 – -2.48)*†	-3.78 (-4.25 – -3.16)*†‡	-4.65 (-5.02 – -4.18)*†‡§
%	60 (55 – 64)	57 (52 – 62)	52 (46 – 58)*†	43 (36 – 51)*†‡	34 (28 – 41)*†‡§
MMEF					
z-score	-1.94 (-2.18 – -1.69)	-2.28 (-2.57 – -2.07)*	-2.56 (-2.82 – -2.32)*†	-3.01 (-3.26 – -2.78)*†‡	-3.77 (-4.11 – -3.52)*†‡§
% Predicted	40.50 (33.74 – 48.48)	32.50 (26.49 – 38.56)*	25.76 (21.40 – 29.61)*†	17.60 (13.95 – 21.62)*†‡	10.32 (8.76 – 13.67)*†‡§
MMEF/FVC	41.93 (30.95 – 48.58)	38.11 (29.23 – 47.09)	31.61 (24.04 – 40.27)*†	23.28 (18.08 – 31.43)*†‡	15.68 (13.26 – 22.33)*†‡§
FEV_3/FVC	81.75 (77.01 – 85.47)	80.82 (75.51 – 86.22)	77.78 (70.26 – 83.24)*	70.51 (61.30 – 77.44)*†‡	61.14 (51.51 – 70.12)*†‡§

Legends: Data is presented as median and IQR unless otherwise stated. Severity of AO are stratified using FEV_1 z-score.
*Significantly different from mild, †Significantly different from moderate, ‡Significantly different from moderately severe, §Significantly different from severe, #statistical tests were not done because variable was used to define groups.
Abbreviations: IQR, interquartile range; BMI, body mass index; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; MMEF, maximal mid-expiratory flow; FEV_3, forced expiratory volume in 3 seconds; AO, airflow obstruction.

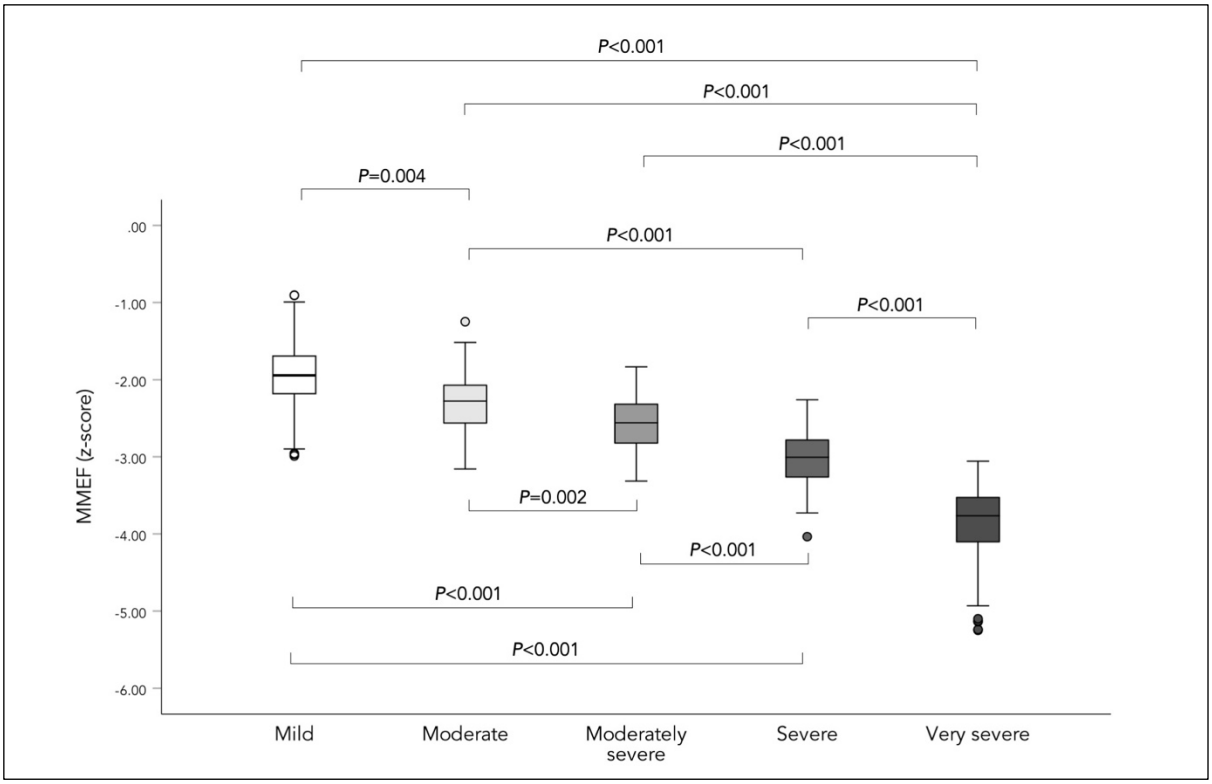

Figure 2.4. Distribution of MMEF z-score across airflow obstruction severity.
Legend: A box plot demonstrating the distribution of MMEF z-score across airflow obstruction severity. The plot shows median, interquartile range, minimum and maximum. AO severity was assessed using FEV_1 z-score. The presented p-values are for post-hoc Dunn's test, and the Kruskal Wallis test's p-values for figure were <0.001.
Abbreviations: MMEF, maximal mid-expiratory flow; AO, airflow obstruction

2.4.5. The relationship of MMEF with other lung function parameters

In the WLS regression, MMEF z-score demonstrated a strong relationship with FEV_1 (r^2= 0.90, p<0.001) and FEV_1/FVC z-score (r^2= 0.86, p<0.001), but a weaker relationship with FVC z-score (r^2= 0.17, p<0.001). Figure 2.5. is a scatter plot of the relationship between MMEF z-score and FEV_1 z-score and Figure 2.6. is a scatter plot of the relationship between MMEF z-score and FEV_1/FVC z-score. MMEF z-score also demonstrated strong relationship with FEV_3/FVC % (r^2= 0.69, p<0.001; see figure 2.7.)

In the multiple WLS regression analyses (accounting for pack-year history), MMEF z-score showed strong relationship with FEV_1 z-score (r^2= 0.90, p<0.001) and FEV_1/FVC (r^2=

0.86, p<0.001), and weak relationship with FVC z-score (r^2= 0.18, p<0.001). Here, pack-years was not a statistically significant predictor in any of the regression models.

In the multiple WLS regression analysis for ex-smokers (accounting for years since quitting smoking), MMEF z-score showed strong relationship with FEV_1 z-score (r^2= 0.89, p<0.001) and FEV_1/FVC z-score (r^2= 0.88, p<0.001), and weak relationship with FVC z-score (r^2= 0.22, p<0.001). Years since quitting was significant predictor in all models (p<0.001 for all, except in the model for FEV_1 z-score p=0.017).

In a curvilinear regression, MMEF % predicted and MMEF/FVC ratio also showed strong association with other spirometric measures, presented in appendix 2.5. The relationships of MMEF % predicted and MMEF/FVC with FEV_1/FVC and FEV_1 % predicted are graphically shown in appendix 2.6.

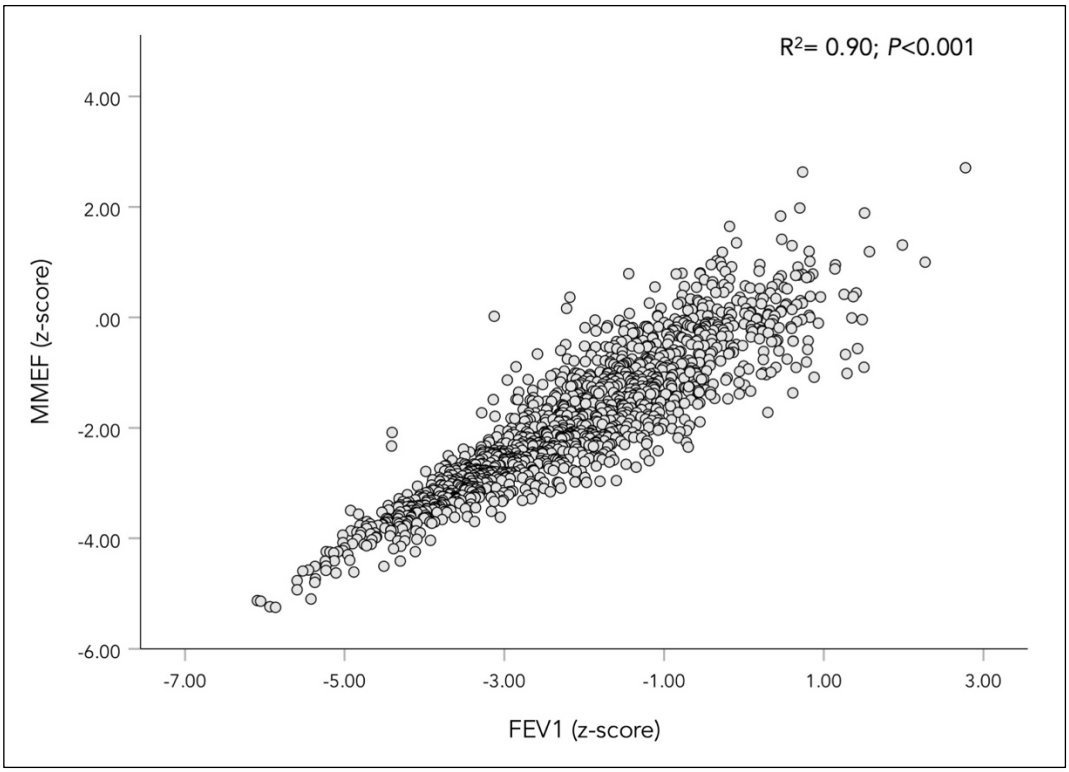

Figure 2.5. FEV_1 z-score plotted against MMEF z-score.
Legend: A scatter plot showing the relationship between MMEF z-score and FEV_1z-score. The coefficient of determination (r^2) for the WLS regression is shown in the figure along with its p value.
Abbreviations: MMEF, maximal mid-expiratory flow; FEV_1, forced expired volume in the first second; WLS, weight-least square.

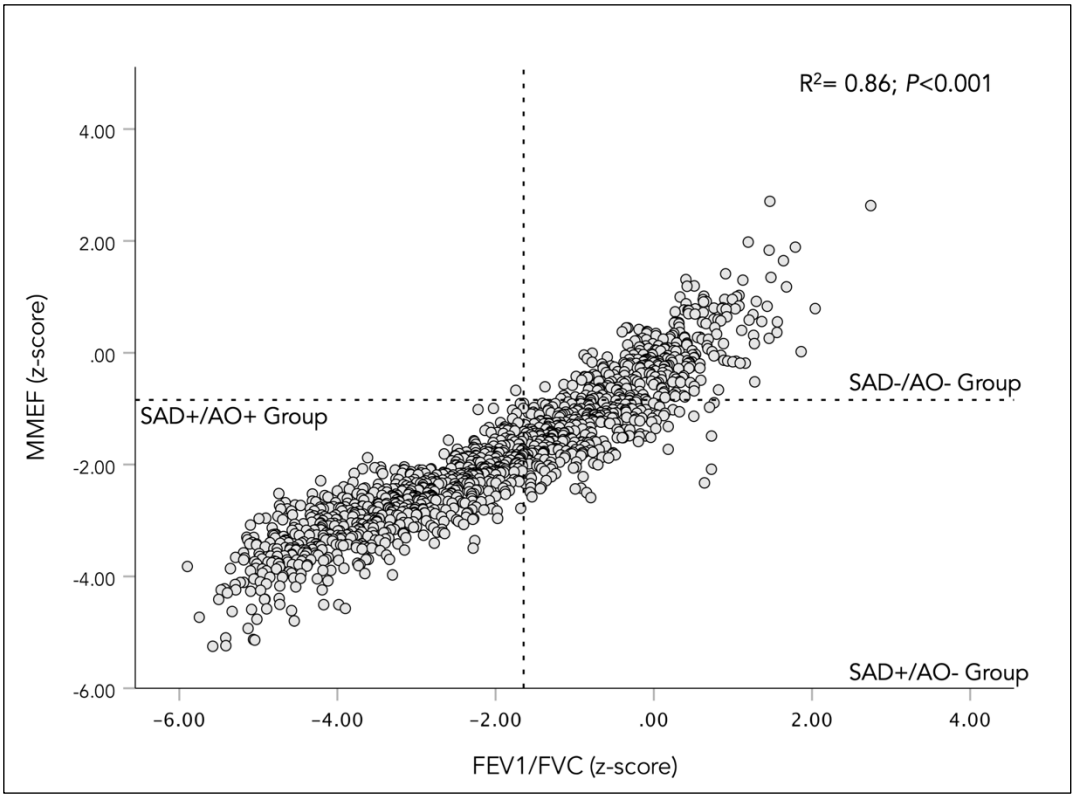

Figure 2.6. FEV_1/FVC z-score plotted against MMEF z-score.
Legend: A scatter plot showing the relationship between MMEF z-score and FEV_1/FVC z-score. The plot is divided according to groups definition. The coefficient of determination (r^2) for the WLS regression is shown in the figure along with its p value.
Abbreviations: MMEF, maximal mid-expiratory flow; FEV_1, forced expired volume in the first second; FVC, forced vital capacity; SAD, small airway dysfunction; AO, airflow obstruction; WLS, weight-least square.

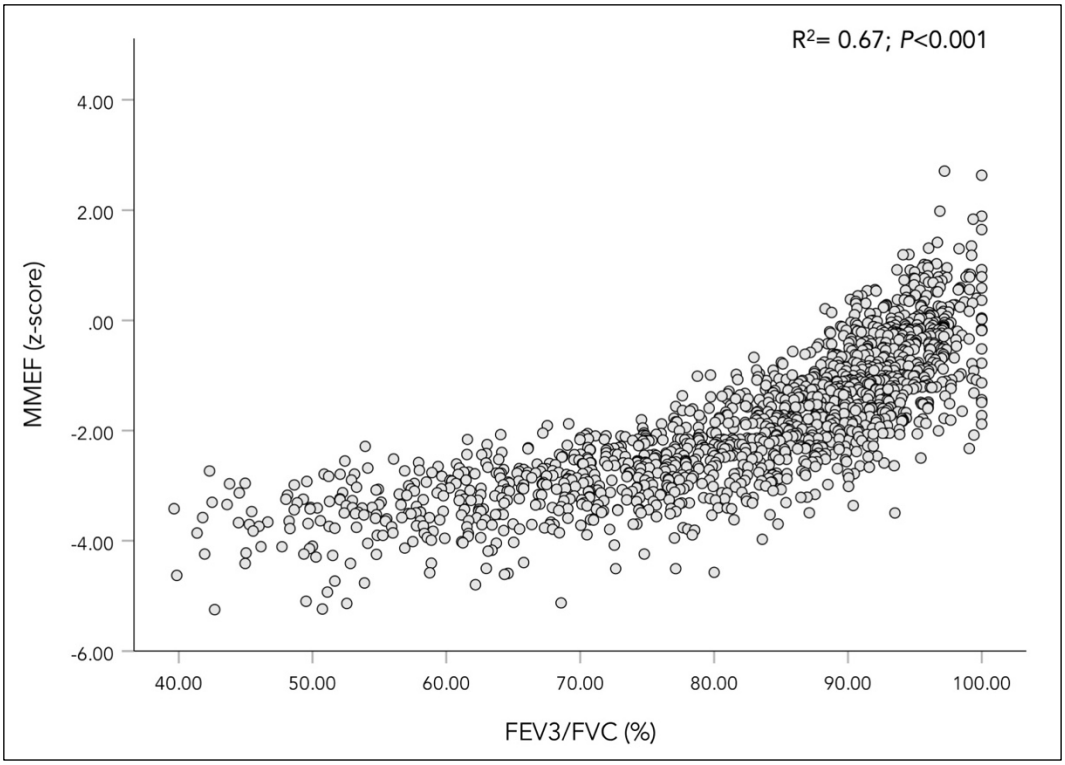

Figure 2.7. FEV_3/FVC plotted against MMEF z-score.
Legend: A scatter plot showing the relationship between MMEF z-score and FEV_3/FVC. The coefficient of determination (r^2) for the curvilinear regression is shown in the figure along with its p value.
Abbreviations: MMEF, maximal mid-expiratory flow; FEV_3, forced expired volume in three seconds; FVC, forced vital capacity.

2.4.6. The association of the presence of SAD with low FEV_1 and FEV_1/FVC

An initial regression model including all participants was built to assess whether the presence of SAD was associated with a lower FEV_1 and FEV_1/FVC after correcting for potential confounders (see Table 2.4.). In the univariate analysis, age, BMI, pack-years, smoking status, FEV_1 z-score, FVC z-score and FEV_1/FVC z-score were significant factors for the presence of SAD. All were included in the multivariate analysis except FVC z-score because of the multi-collinearity with other spirometric measures. The multivariate analysis demonstrated that increasing FEV_1 z-score and FEV_1/FVC z-score was associated with a lower likelihood of having SAD. In the multivariate analysis, age, BMI, smoking status and pack-years were not significant factors associated with the presence of SAD.

Table 2.4. Logistic regression of the association of the presence of SAD with low FEV_1 and FEV_1/FVC.

Variable	Univariate			Multivariate*		
	OR	**CI 95%**	**p value**	**OR**	**CI 95%**	**p value**
Age	1.014	1.003 – 1.026	**0.015**	0.976	0.939 – 1.015	0.231
BMI	0.947	0.931 – 0.964	**<0.001**	1.041	0.978 – 1.108	0.204
Pack-years	1.013	1.007 – 1.018	**<0.001**	0.988	0.978 – 1.003	0.132
Smoking status†						
Current smokers	1.380	1.074 – 1.772	**0.012**	1.857	0.699 – 4.930	0.214
Sex‡						
Female	1.117	0.87 – 1.43	0.38			
FEV_1 z-score	0.125	0.098 – 0.160	**<0.001**	0.007	0.002 – 0.023	**<0.001**
FEV_1/FVC z-score	0.037	0.0243 – 0.0583	**<0.001**	0.0003	0.00006 – 0.002	**<0.001**
FVC z-score	0.586	0.522 – 0.658	**<0.001**			

Legend: This tables demonstrate the logistic regression of the association of the presence of SAD with low FEV_1 and FEV_1/FVC in all included participants. * The multivariate regression model showed a Nagelkerke $R^2 = 0.948$ and Hosmer-Lemeshow goodness of fit p value=1.00. † The reference category was ex-smokers. ‡ The reference category was male. The presence of SAD defined by MMEF z-score <0.8435.
Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; MMEF, maximal mid-expiratory flow.

An alternative regression model was built to assess whether the presence of SAD in the absence of AO was associated with a lower FEV_1 and FEV_1/FVC after adjusting for potential confounders (see Table 2.5.). In the univariate analysis, pack-years, sex, FEV_1 z-score and FEV_1/FVC z-score were significant factors for the presence of SAD. All significant variables were included in the multivariate analysis except FVC z-score because of the multi-collinearity with other spirometric measures. The multivariate analysis demonstrated that females had a 33.22 times higher odds ratio of having SAD compared to than males. The multivariate analysis also showed that increasing FEV_1 z-score and FEV_1/FVC z-score was associated with a lower likelihood of exhibiting SAD, demonstrating that the presence of SAD was associated with a lower FEV_1 z-score and FEV_1/FVC z-score even when in the normal range. Of the significant factors in univariate analysis, pack-years was no longer significant in the multivariate analysis.

Table 2.5. Logistic regression of the association of the presence of SAD with low FEV_1 and FEV_1/FVC in the absence of AO

Variable	Univariate			Multivariate*		
	OR	**CI 95%**	**P value**	**OR**	**CI 95%**	**P value**
Age	1.004	0.991 – 1.018	0.55			
BMI	1.000	0.979 – 1.021	0.98			
Pack-years	1.009	1.003 – 1.015	**0.002**	0.988	0.971 – 1.005	0.168
Smoking status†						
Current smokers	1.340	0.983 – 1.827	0.064			
Sex‡						
Female	1.383	1.016 – 1.883	**0.039**	33.225	8.194 – 134.723	**<0.001**
FEV_1 z-score	0.136	0.100 – 0.185	**<0.001**	0.001	0.00008 – 0.005	**<0.001**
FEV_1/FVC z-score	0.043	0.027 – 0.068	**<0.001**	0.00001	0.000001 – 0.0003	**<0.001**
FVC z-score	0.449	0.377 – 0.536	**<0.001**			

Legend: This tables demonstrate the logistic regression of the association of the presence of SAD with low FEV_1 and FEV_1/FVC in participants without AO. * The multivariate regression model showed a Nagelkerke $R^2 = 0.942$ and Hosmer-Lemeshow p value=0.999. † The reference category was ex-smokers. ‡ The reference category was male. The presence of SAD defined by MMEF z-score <0.8435.

Abbreviations: SAD, small airway dysfunction; AO, airflow obstruction; OR, odds ratio; CI, confidence interval; BMI, body mass index; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; MMEF, maximal mid-expiratory flow.

2.5. Discussion:

This retrospective study provides data about the prevalence of SAD (assessed using MMEF z-score) in smokers suspected of having COPD. The current paper highlights four important points.

Firstly, SAD is a constant feature of those who have developed AO confirmed by a low MMEF, with and without correction for FVC.

Secondly, there was a significant degree of SAD even in mild AO, suggesting a substantial disruption of small airways function prior to crossing the AO diagnostic criteria. Indeed, once AO is established, there was a strong association between MMEF z-score and both FEV_1 z-score and FEV_1/FVC z-score across AO severity groups.

Thirdly, evidence of SAD is common in symptomatic ever-smokers even without AO (affecting around 50% of participants without AO) and is associated with lower lung function parameters (even whilst in the normal range) compared with those without SAD. This suggests that even when routine spirometry appears "normal", those with SAD may have physiology which is declining faster than seen in health. Our data suggests that such patients may form a cohort which would benefit from close monitoring, to ascertain if this will lead to COPD and to mitigate such outcomes.

Fourthly, the relationship between MMEF and FEV_1 and FEV_1/FVC was maintained even following adjustment for smoking history, indicating it was independent of cigarette load. Further, the logistic regression demonstrated that the presence of SAD was associated with lower FEV_1 and FEV_1/FVC, irrespective of other potential confounders. This suggests there are a group of smokers who are pathophysiologically different, consistent with a "susceptible" cohort. Further study is needed to understand the mechanisms underpinning this potential susceptibility.

In the regression model of those without AO, sex was related to SAD, with females 33 times more likely to have SAD, albeit the OR was associated with a wide CI 95%. Despite the higher OR in the present study, a recent study by Xiao et al. reported a consistent finding confirming a sex difference (Xiao et al., 2020). Xiao used an abnormality of at least two out of three spirometric measures (MMEF, forced expiratory flow at 50% and 75%) to define SAD, with a cut-off of 65% predicted. The differences in selected definitions could explain the differences in OR between Xiao et al. and the present study.

In the current study, age was greater in SAD+/AO+ group than SAD-/AO- group and SAD+/AO- group, but was reduced in those with very severe AO compared to all other severities of AO. In a complex disease such as COPD, decline rates are variable. Age (as a surrogate of time) might account for some of the differences in baseline lung function between SAD+/AO- group and SAD+/AO+ group but of note, age was not a significant factor accounting for the presence of SAD in multivariate regression modelling. The contribution of ageing can only be confirmed by longitudinal follow up, which would also enhance our understanding of the relationship between small and large airways function in COPD and might support new monitoring and treatment strategies.

Smoking exposures were similar between SAD+/AO- group and SAD+/AO+ group, did not differ across increasing AO severity (as grouped by FEV_1 z-score) and was not associated with SAD in multivariate analysis. These results suggest that smoking exposure alone cannot explain the physiological differences between groups. Tsushima et al. reported similar findings, demonstrating that smokers with COPD had similar pack-year history compared to those designated at-risk of COPD (Tsushima et al., 2006), although Mirsadraee et al. suggested this reflected a lower smoke exposure (Mirsadraee, Boskabady and Attaran, 2013). This latter study used GOLD criteria and percent predicted to define groups while our

study used the z-scores to define abnormality reflecting both AO and SAD. The physiological criteria used may account for some differences in findings.

The use of FEV_3/FVC has been of value to detect mild lung injury in the absence of classical AO (Morris, Coz and Starosta, 2013). Morris et al. reported that, compared to those with normal FEV_3/FVC, patients with a lower ratio had lower FEV_1, higher Residual Volume (RV)/Total Lung Capacity (TLC), higher RV, higher TLC and lower transfer factor for carbon monoxide (TLco), potentially highlighting the presence of early physiological impairment including air trapping and impaired gas exchange (Morris, Coz and Starosta, 2013). Our study demonstrated that FEV_3/FVC was lower in SAD+/AO- group than SAD-/AO- group and was strongly associated with the MMEF z-score, providing further support that the MMEF z-score is detecting early lung pathology in this group. MMEF/FVC has also been used in the early detection of COPD (Mirsadraee, Boskabady and Attaran, 2013) and again this measure was also lower in SAD+/AO- group, further supporting the MMEF z-score.

Several other studies have assessed SAD (using MMEF) in COPD. MMEF % predicted was lower (though not necessarily abnormal) in patients at risk of developing COPD (Tsushima et al., 2006). Correction of MMEF for FVC also identifies early pathological changes prior to COPD development (Mirsadraee, Boskabady and Attaran, 2013) and expiratory flow rates (including MMEF) detected abnormality in those with normal FEV_1/FVC (Gelb et al., 2021). Our findings, together with these and other studies promote MMEF (expressed as either % predicted or z-score) as a valuable marker of SAD before classically defined AO manifests (Kwon et al., 2020; Mirsadraee, Boskabady and Attaran, 2013; Stockley et al., 2017b; Tsushima et al., 2006; Gelb et al., 2021).

Concerns about the use of MMEF in clinical management have been raised, for example, in a large cross-sectional study using MMEF z-score (Quanjer et al., 2014b). This study concluded that MMEF did not provide additional information to current spirometric measures used in clinical practice, which contrasts with the close relationship demonstrated in the current study. However, the study by Quanjer et al. included a large and mixed population of participants including a variety of lung diseases. The lack of utility of a test in general population does not negate its use in selected population, a concept supported in a study of a highly selected population (AATD), where low MMEF % predicted in the absence of classical AO was associated with a reduced health status and a subsequent faster decline in lung function (Stockley et al., 2017b). In addition, this study suggested that SAD appeared to precede the development of macroscopic emphysema, which is a classic component of the PiZZ genetic variant.

A 10-year longitudinal study demonstrated that non-AATD patients with low MMEF z-score had a higher incidence rate of developing COPD than those with normal MMEF z-score (41.8% vs 7.4%, $P< 0.001$) (Kwon et al., 2020). These authors used a different normality cut-off for MMEF z-score (<-0.8453) than that used by Quanjer et al. (<-1.654), suggesting that the z-score cut-off may be critical for its utility. Our study only included ever-smokers and used MMEF z-score and FEV_1/FVC z-scores to define SAD and AO, respectively. We chose a "normality" cut-off of -0.8453 for the MMEF z-score as this has been shown to predict future COPD development (Kwon et al., 2020). In addition, we used a normality cut-off of -1.654 in FEV_1/FVC z-score to define AO as this reduces false-positive results related to aging (Swanney et al., 2008).

Our study provides evidence to support the use of MMEF (expressed as z-score) as an assessment tool in patients at risk of developing COPD. We suggest that patients with MMEF

< -0.8453 should be considered a phenotypic group that likely reflects SAD. This group of patients should be monitored and early preventive measures (most importantly, smoking cessation) should be considered. Moreover, pharmacological treatments such as extra-fine particles inhalers may be of use in this group, as these inhalers have shown to reach higher deposition in the small airways (Pirina et al., 2018; van den Berge et al., 2021; Usmani et al., 2020). Other tests of small airways have also demonstrated to be of value in the early detection of COPD (Boeck et al., 2016; Oxhoj, Bake and Wilhelmsen, 1977; Piorunek et al., 2017). In the current study, we chose MMEF to define small airway abnormality because of its availability in routine physiological assessment.

Our study has limitations. This was a cross-sectional study but the value of MMEF z-score as a monitoring tool has also been demonstrated longitudinally (Kwon et al., 2020) and our study provided a larger sample confirming the presence of low MMEF in smokers with and without AO. MMEF is a highly variable spirometric measure but we used MMEF z-score to optimize the interpretive accuracy. This was also a retrospective study, meaning that available data was limited to routine lung function tests, although this is more representative of the real-world approach to such strategies. We used -0.8453 z-score cut-off to define SAD, which is different to the traditional -1.645 LLN for lung function parameters, including MMEF. However, this cut-off has also been used by others and shown to predict COPD development (Kwon et al., 2020). Finally, the majority of patients were of white ethnicity. Therefore, more studies are required to determine how representative these findings might be of diverse ethnic communities.

2.6. Conclusion:

SAD (defined by a low MMEF z-score) is a feature present in patients with AO and also in symptomatic ever-smokers in the absence of AO. These findings highlight the potential importance of MMEF in the detection of the early pathological features of COPD. Closely monitoring patients with low MMEF and considering early interventions may be central to improving health and prognosis.

3. Small airway dysfunction in symptomatic never-smokers: A retrospective study

In this chapter, I examined the prevalence of small airway dysfunction in COPD and those at risk of developing COPD utilizing lung function data of symptomatic never-smoking participants.

3.1. Brief introduction:

Chronic Obstructive Pulmonary Disease (COPD) is primarily caused by cigarette smoking (Global Initiative for Chronic Obstructive Lung Disease, 2022). However, not all smokers developed the disease (Fletcher and Peto, 1977), and COPD can be seen in never-smokers. Never-smokers are estimated to make up 25-45% of COPD cases (Salvi and Barnes, 2009), emphasizing the disease's relevance in this population. Several predisposing factors could be responsible for never-smoking COPD, including environmental exposures and genetic susceptibility (Global Initiative for Chronic Obstructive Lung Disease, 2022). While clinical manifestations of COPD in never-smokers were similar to those in ever-smokers, physiological measures were found to be different (Tan et al., 2015), likely indicating the disease's different pathophysiological processes between the two populations.

Diagnoses and severity stratification of COPD is made using the traditional spirometric measures (FEV_1/FVC and FEV_1). Notwithstanding their relevance in the diagnosis, these measures have not shown to be valuable in detecting early diseases (Herpel et al., 2006; Pennock, Rogers and McCaffree, 1981). Early detection of COPD may avert additional lung harm, preventing COPD development (Han et al., 2020). For this reason, a new term has been proposed by Han et al., “pre-COPD”, to recognize individuals with symptoms suggestive of COPD in the absence of airflow obstruction (AO) with or without identified structural or functional impairments who may or may not progress to AO over time (Han et al., 2020). As several predisposing factors could contribute to COPD in never-smokers, it would be helpful to have a physiological measure that helps recognize those with pre-COPD, allowing an earlier intervention that can halt progression to established COPD.

Studies have demonstrated that small airways represent an essential part of the pathophysiological process in COPD (Bosken et al., 1990; Hogg, Macklem and Thurlbeck,

1968; Hogg, McDonough and Suzuki, 2013). Furthermore, small airways dysfunction (SAD) seemed to occur before the development of emphysema (Stockley et al., 2017b) and AO (Kwon et al., 2020). Several physiological measures have been suggested to assess small airways, with Maximal Mid-Expiratory Flow (MMEF) being the most studied (Stockley et al., 2017a; McNulty and Usmani, 2014). Studies have demonstrated that MMEF is a valuable early lung pathology marker that likely reflects SAD (Kwon et al., 2020; Mirsadraee, Boskabady and Attaran, 2013; Stockley et al., 2017b; Tsushima et al., 2006).

Studies assessing small airways in never-smokers suspected of having COPD have been small. A recent study of never-smoking Alpha-1 Antitrypsin Deficiency (AATD) patients by Stockley et al. demonstrated that the presence of SAD without AO, as measured by low MMEF, correlated with poor health status and ensuing FEV_1 decline (Stockley et al., 2017b). In a longitudinal study, Kwon et al. found that low MMEF was linked to a greater risk of COPD development in non-AATD patients (Kwon et al., 2020); notably, never-smokers had a lower risk of developing COPD than occasional smokers and long-term smokers. This highlights that the pathophysiological process may also be different in the early stages between never-smokers and ever-smokers. However, the prevalence of SAD in those with and without AO has never been assessed in never-smoking non-AATD participants. Therefore, the present study was conducted to evaluate the prevalence of SAD (measured by MMEF z-score) in never-smokers suspected of having COPD.

We hypothesized that physiological evidence of SAD, as assessed by MMEF, would be ubiquitous in patients with AO, as SAD preceded the development of AO. Moreover, patients with SAD who did not meet the physiological criteria for a diagnosis of AO would have physiological indicators of a heightened risk of AO, not seen in those without SAD.

3.2. Aims:

- To examine assess the prevalence of SAD in never-smokers with and without AO.
- To assess the baseline demographics and lung function across study groups
- To evaluate the association of the MMEF z-score with the z-score of other spirometric measures

3.3. Methods and design

3.3.1. Study design and setting

This was a retrospective, cross-sectional observational study of routinely collected lung function data from symptomatic never-smokers who underwent pulmonary function test as part of COPD screening. The collated lung function data were obtained from the University Hospitals Birmingham NHS Foundation Trust, UK between 1st January 2016 and 30th April 2021. The study was approved by the Health Research Authority (REC Reference: 20/HRA/0203).

3.3.2. Eligibility criteria

Participants were eligible for inclusion in the study provided they met the following criteria:

1. Had suggestive symptoms of COPD (including breathlessness and/or continuous cough)
2. Were aged 30 years and older
3. Had never smoked
4. Had all traditional spirometric measures available, including MMEF.

Participants were not included in the study if they:

1. Had history of AATD.

2. A history/ diagnosis of other chronic pulmonary disorders.
3. Substantial radiological structural abnormalities in the lung (like bronchiectasis), reckoned by radiology reports.

3.3.3. Study Measures

Clinical data were collated including age, sex, body mass index (BMI) and ethnicity. Current medications use was also curated. All reported lung function measures captured on spirometry were recorded for analysis. This included FEV_1, FVC, FEV_1/FVC. Measures of the small airways were also collated, involving MMEF and MMEF corrected for FVC (MMEF/FVC) (Mirsadraee, Boskabady and Attaran, 2013). FEV_3/FVC was also gathered and evaluated as previous studies have suggested that this measure may be useful in detecting mild injuries of the lungs prior to established AO (Morris, Coz and Starosta, 2013). Lung function parameters were obtained using the Ultima PF^{TM} Pulmonary Lung Function System (Medical Graphics UK Ltd, Tewkesbury, UK), following the Association for Respiratory Technology and Physiology/British Thoracic Society guidelines (Sylvester et al., 2020).

In this study, a cut-off of -0.8435 for MMEF z-score was used to identify an abnormality reflecting SAD (Kwon et al., 2020), whereas a cut-off of -1.645 for FEV_1/FVC was used for AO, as described in other study (Quanjer et al., 2012). Accordingly, participants were grouped into SAD-/AO- group (no SAD and no AO), SAD+/AO- group (SAD but no AO) and SAD+/AO+ (SAD and AO). The relationship of MMEF z-score with z-scores of other physiological measures were assessed where available.

3.3.4. Statistical analysis

The IBM Statistical Package for the Social Sciences (SPSS) software was used for statistical analysis. The data distribution was evaluated using Shapiro-Wilk's test, showing non-normally distributed variables, and hence, all continuous variables were reported as median and interquartile ranges (IQR). The Kruskal-Wallis H test and Dunn's test were used for groups comparisons. For variables used in group definitions (MMEF and FEV_1/FVC), no statistical analysis was conducted, except where the definition did not cause the variable to differ. Here, Mann-Whitney U tests was performed to determine the differences. Weight least-square (WLS) regression was used to assess the relationship of MMEF with spirometric measures. Coefficient of determination (r^2) for WLS regression was reported throughout. Curvilinear regression was used to determine the relationship between MMEF % predicted or MMEF/FVC with % predicted or ratio of other physiological measures, with r^2 for the curvilinear regression reported throughout. For multiple comparisons, statistical significance values were adjusted by the Bonferroni correction (Bonferroni, 1936) and p value <0.05 was considered statistically significant.

3.4. Results

3.4.1. Participant's selection

The lung function dataset collected within the study censor period comprised 2258 records. After checking for eligibility, 109 never-smokers were included in the study (see figure 3.1.). Included participants were divided into subgroups according to the presence of SAD and/or AO: SAD-/AO- group (n=43; 39.4%); SAD+/AO- group (n=22; 20.1%); and SAD+/AO+ (n=44; 40.3%).

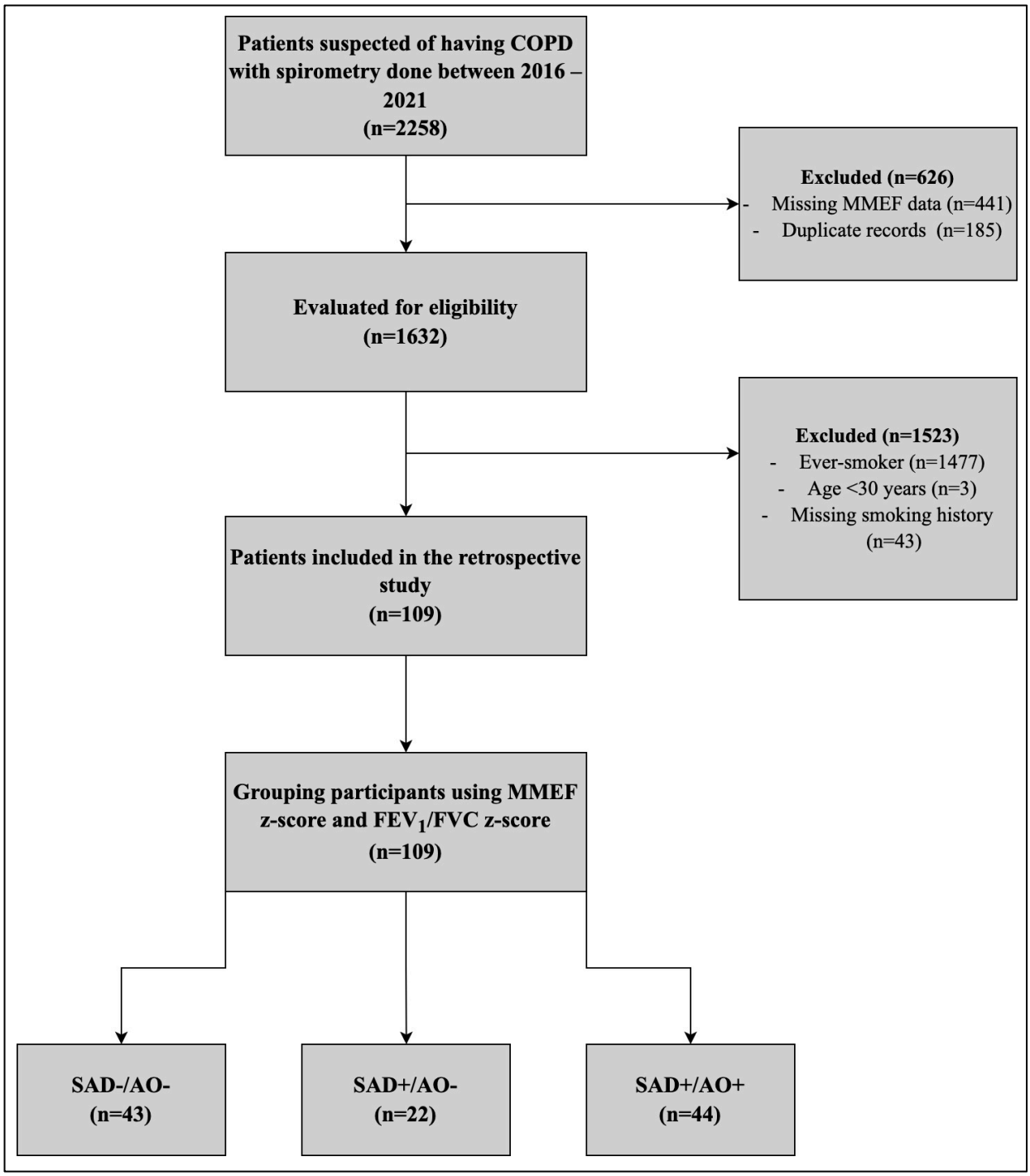

Figure 3.1. Flowchart of the retrospective study.
Abbreviations: COPD, chronic obstructive pulmonary disease; MMEF, maximal mid-expiratory flow; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; SAD, small airway dysfunction; AO, airflow obstruction.

3.4.2. Prevalence of SAD

SAD was prevalent in all patients with AO (44/44; 100%). SAD was also prevalent in 33.8% (22/65) of those without AO.

3.4.3. Baseline demographics and lung function

Table 3.1. presents the baseline demographics for all participants and groups. Apart from the use of some medications, no differences in baseline demographics were found. The use of SABA was significantly higher in SAD+/AO+ group than SAD/AO- group (72.7% vs 40.9%, p=0.004) and SAD-/AO- group (72.7% vs 39.5%, p =0.004). The use of ICS/LABA was significantly lower in SAD-/AO- group than SAD+/AO- group (2.3% vs 38.6%, p<0.001) and SAD+/AO+ (2.3% vs 37.6%, p<0.001), whereas it was similar between SAD+/AO- group and SAD+/AO+ group.

Table 3.1. Baseline demographics of the included participants

Variable	Total n= 109	SAD-/AO- *n = 43*	SAD+/AO- *n = 22*	SAD+/AO+ *n = 44*
Age (years)	69 (60 – 74.50)	69 (61 – 74)	69.50 (60.50 – 78)	58 (58.50 – 74.75)
Sex (male: female) (n, %)	54 (49.5): 55 (50.5)	21 (48.8): 22 (51.2)	7 (31.8): 15 (68.1)	26 (59.1): 18 (40.9)
Race (n, %)				
Caucasian	94 (86.2)	36 (83.7)	20 (90.9)	38 (86.4)
Black	5 (4.6)	2 (4.7)	0 (0)	3 (6.8)
Asian	9 (8.3)	4 (9.3)	2 (9.1)	3 (6.8)
Unspecified	1 (0.9)	1 (2.3)	0 (0)	0 (0)
BMI (kg/m2)	28.51 (23.95 – 32.09)	29.32 (25.10 – 33.46)	28.83 (24.62 – 32.77)	26.75 (21.91 – 31.77)
Medications (n, %)				
SABA	58 (53.2)	17 (39.5)	9 (40.9)	32 (72.7)[*#]
SAMA	3 (2.8)	0 (0)	0 (0)	3 (6.8)
ICS	12 (11)	7 (16.3)	1 (4.5)	4 (9.1)
LABA	1 (0.9)	0 (0)	0 (0)	1 (2.3)
ICS/LABA	26 (23.9)	1 (2.3)[#¶]	8 (38.6)	17 (37.6)
LAMA	18 (16.5)	3 (7)	4 (18.2)	11 (25)
LABA/LAMA	1 (0.9)	0 (0)	0 (0)	1 (2.3)
Systematic CS	6 (5.5)	1 (2.3)	2 (9.1)	3 (6.8)
Montelukast	3 (2.8)	1 (2.3)	0 (0)	2 (4.5)
CV Medications	48 (44)	21 (48.8)	8 (36.4)	19 (43.2)
GI Medications	29 (26.6)	13 (30.2)	4 (18.2)	12 (27.3)
Domiciliary Oxygen	1 (0.9)	0 (0)	0 (0)	1 (2.3)
Mucolytic	5 (4.6)	1 (2.3)	1 (4.5)	3 (6.8)
Theophylline	1 (0.9)	0 (0)	0 (0)	1 (2.3)

Legend: Data is presented as median and IQR, unless otherwise stated. [*] Significantly different from SAD-/AO-; [#] Significantly different from SAD+/AO-; [¶] Significantly different from SAD+/AO+
Abbreviations: SD, standard deviation; IQR, interquartile range; BMI, body mass index; SABA, short-acting beta-2 agonist; SAMA, short-acting muscarinic antagonist; ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist; CS, corticosteroid; CV, Cardiovascular; GI, gastrointestinal; SAD, small airway dysfunction; AO, airflow obstruction.

The baseline spirometric parameters across groups are presented in table 3.2. All spirometric parameters ([$p<0.001$ for all measures and comparisons]) were lower in SAD+/AO+ group than SAD-/AO- group, except FVC % predicted and FVC z-score. All spirometric measures were lower in SAD+/AO+ group than SAD+/AO- group ($p<0.001$), except FEV_1 z-score, FEV_1 % predicted, FVC z-score and FVC % predicted.

In SAD+/AO- group, all spirometric measures were lower than SAD-/AO- group (FEV_1 z-score [$p<0.001$], FEV_1/FVC z-score [$p=0.004$], FVC z-score [$p=0.009$], FEV_1 % predicted [$p<0.001$], FVC % predicted [$p=0.005$], FEV_1/FVC [$p=0.03$], FEV_3/FVC [$p<0.01$]). The distribution of MMEF z-score, FEV_1 z-score, FEV_1/FVC z-score and FVC z-score across groups are shown in figure 3.2. The distribution of MMEF % predicted, FEV_1 % predicted, FEV_1/FVC ratio and MMEF/FVC ratio across groups are demonstrated in appendix 3.1.

Table 3.2. Baseline spirometric measures of included participants

Variable	Total *n = 109*	SAD-/AO- *n = 43*	SAD+/AO- *n = 22*	SAD+/AO+ *n = 44*
FEV_1				
z-score	-1.41 (-2.74 – -0.33)	-0.19 (-0.69 – 0.21)[#¶]	-1.90 (-2.07 – -1.26)	-2.83 (-3.23 – -1.83)
% predicted	78.86 (56.00 – 95.21)	98.23 (90.27 – 104.22)[#¶]	70.67 (61.30 – 81.60)	55.25 (43.47 – 69.81)
FVC				
z-score	-0.78 (-1.65 – 0.06)	-0.39 (-1.04 – 0.15)[#]	-1.44 (-1.78 – - 0.53)	-1.01 (-1.92 – -0.02)
% predicted	88.96 (74.10 – 101.26)	93.91 (86.66 – 104.33)[#]	78.08 (66.15 – 91.33)	84.70 (70.33 – 101.95)
FEV_1/FVC[&]				
z-score	-1.10 (-2.51 – 0.15)	0.28 (-0.07 – 0.84)	-1.06 (-1.20 – -0.77)[*]	-2.84 (-3.66 – -2.38)
%	70 (58 – 79)	80 (78 – 85)	70 (68 – 73.25)[*]	54 (43 – 61)
MMEF[&]				
z-score	-1.20 (-2.24 – -0.04)	0.13 (-0.29 – 0.61)	-1.33 (-1.59 – - 0.99)	-2.55 (-3.06 – -2.02)[#]
% predicted	57.84 (30.99 – 100.86)	106.57 (88.56 – 127.06)	57.51 (46.68 – 64.35)	28.01 (17.56 – 34.92)[#]
MMEF/FVC				
%	65.78 (37.52 – 111.14)	114.83 (98.63 – 134.83)	66.33 (63.22 – 70.53)[*]	31.32 (21.95 – 45.62)[*#]
FEV_3/FVC				
%	90.62 (81.39 – 94.97)	95.32 (93.12 – 97.50)	91.40 (88.30 – 92.94)[*]	77.43 (97.14 – 83.94)[*#]

Notes: Data are presented as median and IQR. [*]Significantly different from SAD-/AO-; [#] Significantly different from SAD+/AO-; [¶] Significantly different from SAD+/AO+; [&]statistical test was only done for differences between groups where a definition did cause the variable to differ.

Abbreviations: IQR, interquartile range; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; MMEF, maximal mid-expiratory flow; FEV_3, forced expiratory volume in 3 seconds; SAD, small airway dysfunction; AO, airflow obstruction.

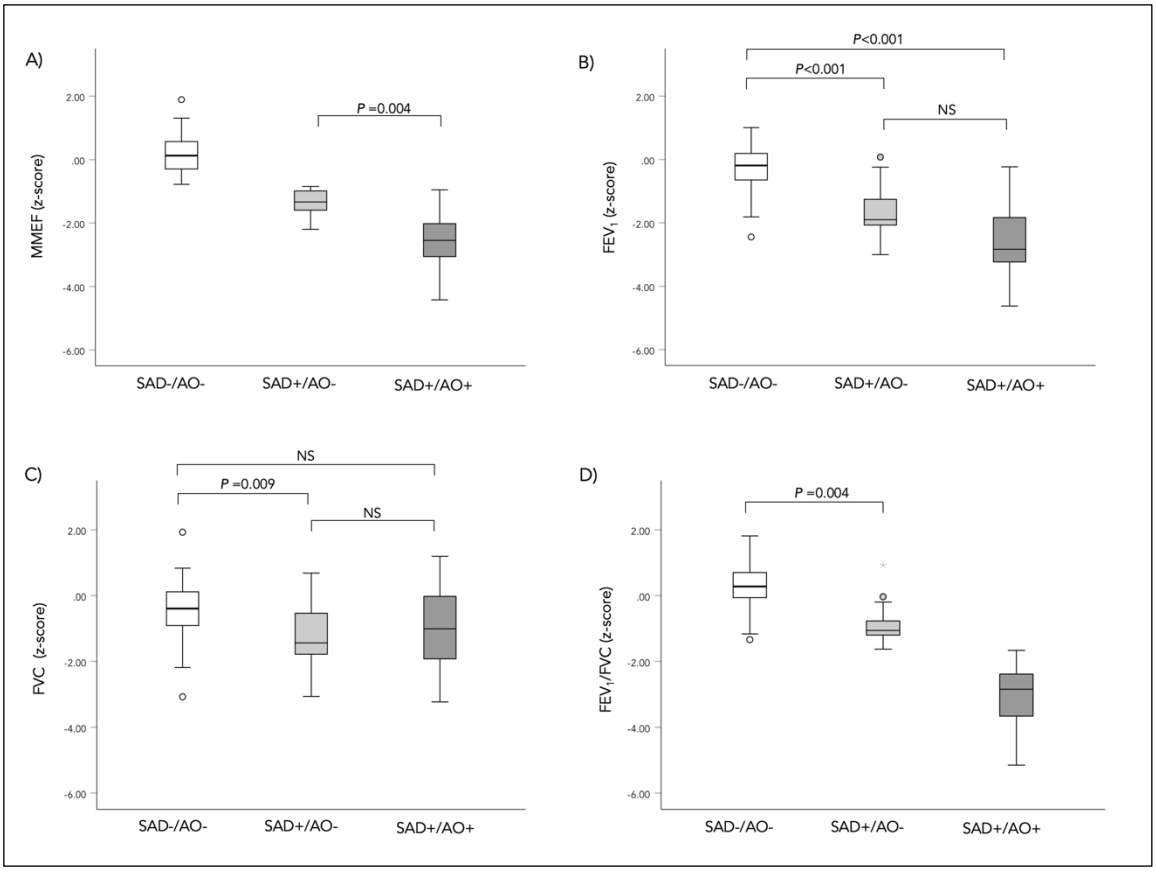

Figure 3.2. Distribution of spirometric measures across study groups.
Legend: A box plot demonstrating the distribution of z-scores of spirometric measures across groups. The plot shows median, interquartile range, minimum and maximum. A) The distribution of MMEF z-score across groups. B) The distribution of FEV_1/FVC z-score across groups. C) The distribution of FEV_1 z-score across groups. D) The distribution of FVC z-score across groups. For figures A and D, statistical test was only done for differences between groups where a definition did cause the variable to differ, and the reported p-values are for the Mann-Whitney U test. For figures B and C, the presented p-values are for post-hoc Dunn's test, and the Kruskal Wallis tests p-values for figure B and figure C were <0.001 and 0.008, respectively.
Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; MMEF, maximal mid-expiratory flow; SAD, small airway dysfunction; AO, airflow obstruction.

3.4.4. The relationship of MMEF z-score with spirometric measures

In the WLS regression, MMEF z-score was strongly related to FEV_1 z-score (r^2= 0.77, p<0.005) and FEV_1/FVC z-score (r^2= 0.85, p<0.005), whereas it was weakly related with FVC z-score (r^2= 0.12, p<0.005). Figure 3.3. shows a scatter plot of the correlation between MMEF z-score FEV_1 z-score. Figure 3.4. shows a scatter plot of the correlation between MMEF z-score and FEV_1/FVC z-score. FEV_3/FVC was also strongly associated with MMEF z-score (r^2=0.87; p<0.001, see figure 3.5.).

Using the curvilinear regression, the relationship of MMEF % predicted with % predicted or % of other spirometric measures are shown in appendix 3.2.

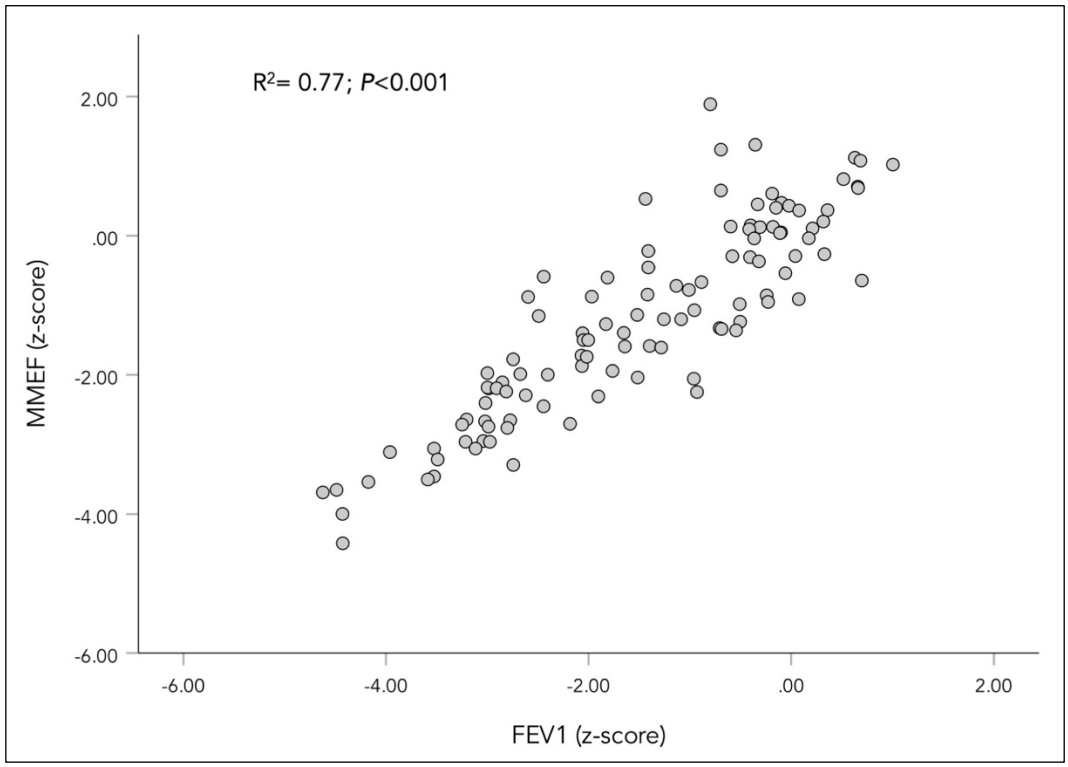

Figure 3.3. FEV_1 z-score plotted against MMEF z-score.
Legend: A scatter plot demonstrating the relationship between MMEF z-score and FEV_1 z-score. The coefficient of determination (r^2) for the WLS regression is shown in the figure along with its p value.
Abbreviations: MMEF, maximal mid-expiratory flow; FEV_1, forced expired volume in the first second; WLS, weight-least square.

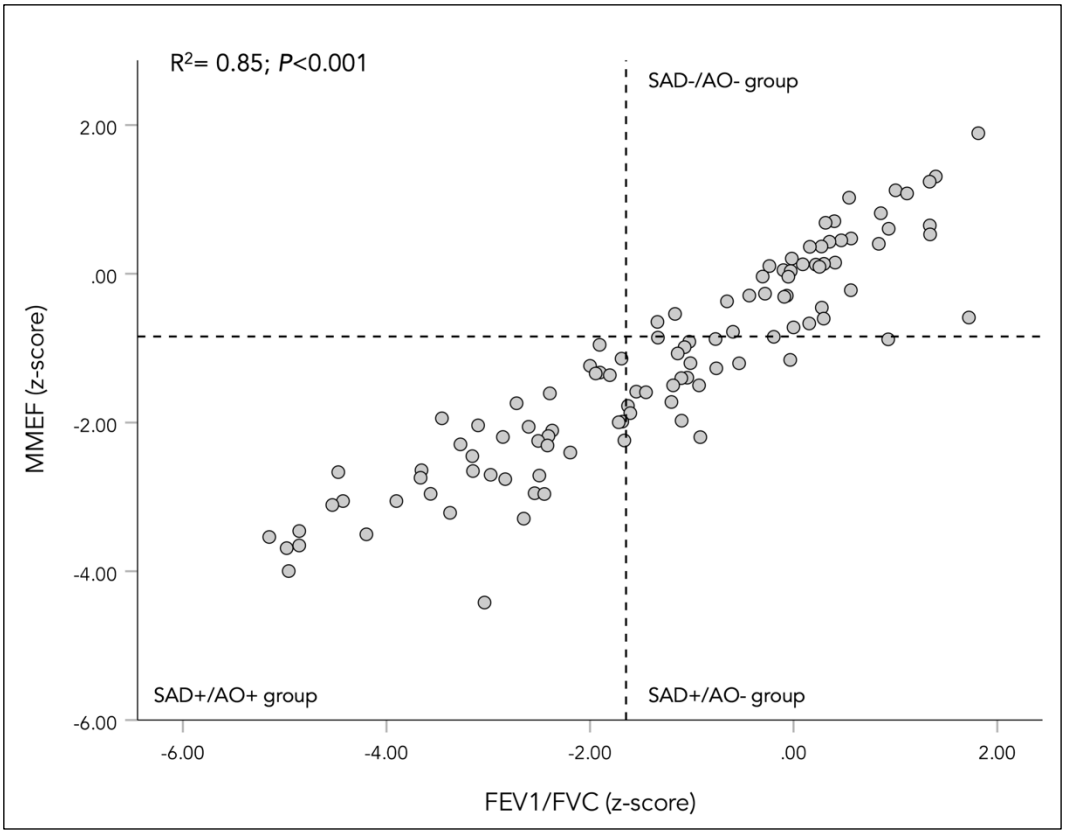

Figure 3.4. FEV_1/FVC z-score plotted against MMEF z-score.
Legend: A scatter plot showing the relationship between MMEF z-score and FEV_1/FVC z-score. The plot is divided according to groups definition. The coefficient of determination (r^2) for the WLS regression is shown in the figure along with its p value.
Abbreviations: MMEF, maximal mid-expiratory flow; FEV_1, forced expired volume in the first second; FVC, forced vital capacity; SAD, small airways dysfunction; AO, airflow obstruction; WLS, weight-least square.

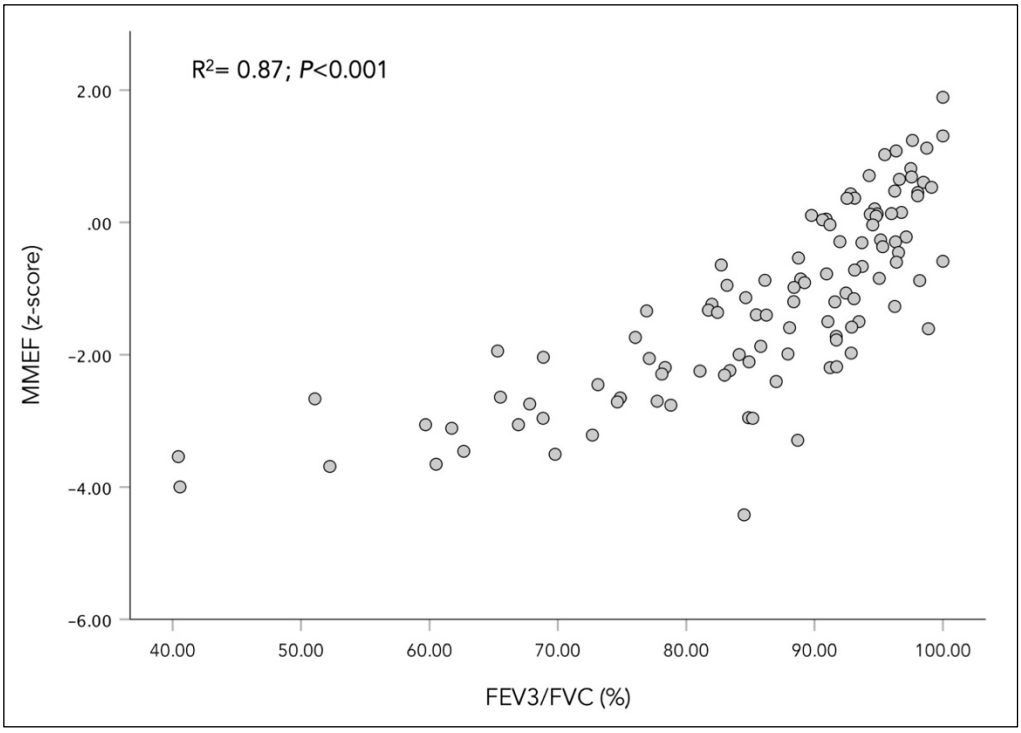

Figure 3.5. FEV_3/FVC plotted against MMEF z-score.
Legend: A scatter plot showing the relationship between MMEF z-score and FEV_1/FVC z-score. The plot is divided according to groups definition. The coefficient of determination (r^2) for the curvilinear regression is shown in the figure along with its p value.
Abbreviations: MMEF, maximal mid-expiratory flow; FEV_3, forced expired volume in three seconds; FVC, forced vital capacity.

3.5. Discussion:

This cross-sectional study of symptomatic never-smokers demonstrated four main findings. First, AO, an essential hallmark of COPD, was prevalent in a group of never-smoking participants, detected in 40% of symptomatic never-smokers in the current cohort. Second, SAD (determined by low MMEF z-score) was common in this cohort, seen in 60% of patients overall, including 40% with AO and 20% without AO. Third, patients with SAD but without AO had lower lung function (although within normal range) across all parameters than those without AO or SAD, including FEV_1, FVC and FEV_1/FVC. Fourth, there were no differences in demography between groups, except the use of some inhaled medications. Notably, SAD+/AO- group had similar inhaled ICS/LABA use to SAD+/AO+ group.

The presence of AO in 40% of never-smokers highlights the importance of factors other than smoking that contributes to COPD and emphasizes the need for screening for other risk factors that account for non-smoking COPD. History of exposure to other risk factors was not provided in this study, apart from the absence of AATD. Hence, it is unclear what contributed to COPD development in the current study, but previous studies have demonstrated that biomass fuel exposure (Sana et al., 2018), occupational exposures (Lytras et al., 2018) and history of early life respiratory infections (de Marco et al., 2011) could be responsible for never-smoking COPD. Moreover, the present study has demonstrated that AO is always accompanied by reduced MMEF, suggestive of SAD, seen in all patients with AO, similar to the ever-smoking finding in the previous chapter. The presence of SAD in all patients with AO highlights the vital role of the small airway in the pathological process, and hence, management may be beneficial in targeting these airways. However, it is unclear at what stage of disease these management strategies would be beneficial, and thus, this requires a randomized controlled trial to be determined.

The fact that SAD is detected in patients without AO and that it is associated with lower lung function indices (even though within the normal range) than those without SAD or AO indicates that those with SAD alone may have lung physiology that is accelerating faster than those with normal spirometry. In the recent study of symptomatic participants suspected of having COPD, Kwon et al. showed that the MMEF z-score of <-0.8435 significantly predicted COPD development over ten years (Kwon et al., 2020). Given that SAD appears to precede COPD (Hogg, McDonough and Suzuki, 2013; Stockley et al., 2017b), patients with low MMEF z-score in Kwon et al. possibly have had SAD that have worsened due to the continual exposure to risk factors, leading to the development of AO. For this reason, their cut-off was used in the present study to define SAD presence. Therefore, our finding and

Kwon et al. suggest patients with SAD alone may indicate the presence of pre-COPD and should be more closely monitored to identify those with ongoing damage leading to COPD, which could potentially help mitigate the condition.

In the present study, all spirometric measures were lower in SAD+/AO- group than in SAD-/AO- group and higher in SAD+/AO- group than SAD+/AO+ group, except FVC and FEV_1. FVC was only different between SAD+/AO- group and SAD-/AO- group, but not SAD+/AO+ group. Previous studies have described that FVC does not show an association with other spirometric measures (Stockley et al., 2017b), and this was also seen in the current study. FVC has also been shown to be of little value in predicting COPD development (Kwon et al., 2020), limiting its use in discovering early disease. FEV_1 was higher in SAD-/AO- group than SAD+/AO- group and SAD+/AO+ group, but no statistical difference was seen between SAD+/AO- group and SAD+/AO+ group despite the median being lower in the latter, which is likely due to the small sample size in SAD+/AO- group.

The FEV_3/FVC ratio was found to detect mild lung injury in patients without AO in a large study of 13,302 patients (Morris, Coz and Starosta, 2013). In this study, patients with low FEV_3/FVC had worse lung function measures (lower FEV_1, higher Residual Volume (RV)/Total Lung Capacity (TLC), higher RV, higher TLC and lower transfer factor for carbon monoxide (TLco)) than those with normal FEV_1/FVC and FEV_3/FVC and better lung function than those with established AO. Therefore, the presence low FEV_3/FVC alone is likely indicative of early physiological impairments, such as air trapping and poor gas exchange. In the present study, SAD+/AO- group had a lower FEV_3/FVC (although within normal range) than SAD-/AO- group and higher than SAD+/AO+ group. Given the strong correlation between the MMEF z-score and FEV_3/FVC in the present study, this signifies

patients in SAD+/AO- group may have an abnormality reflecting earlier lung injury before established AO.

The MMEF/FVC was shown to be helpful in detecting patients at risk for COPD (symptomatic participants without AO) (Mirsadraee, Boskabady and Attaran, 2013). In this study, some symptomatic patients had low MMEF/FVC (defined by <80%) without AO (defined by FEV1/FVC <70%). The current study found that SAD+/AO- group had a lower MMEF/FVC than those in SAD-/AO- group and higher than in SAD+/AO+ group, further supporting that using the pre-defined cut-off, MMEF z-score could potentially identify early lung pathology before AO can be detected.

In the present study, although the median age for patients with SAD alone was higher than for those with AO and SAD, it was not statistically different, which could be because of the small sample size. Median age was similar in patients with SAD alone to those without SAD or AO. Identifying age-related decline rates can only be determined with a longitudinal follow-up study, but these results demonstrate that age is unlikely to explain differences in lung decline, and other factors could account for the acceleration of decline lung function in SAD+/AO- group and SAD+/AO+ group. Detailed histories of the trajectories or exposures of the patients in the current cohort are unknown. Therefore, a longitudinal study using more comprehensive patient histories is needed to determine the factors responsible for the presence of SAD alone in never-smokers and whether they differ between those with SAD alone and those with AO.

From the study of ever-smoking participants in the previous chapter, females were more likely to suffer from SAD without AO. In the current study, females were more likely to have SAD but no AO, although statistically insignificant, which could be due to the

underpowered sample size. Hence, further studies are needed to confirm whether never-smoking females are at greater risk of SAD alone than males.

All medications were not different between groups, except SABA and ICS/LABA. SAD+/AO+ group had higher use of SABA than SAD-/AO- group and SAD+/AO- group, but no differences between SAD-/AO- group and SAD+/AO- group. The use of ICS/LABA was as high in SAD+/AO- group as SAD+/AO+ group, despite no AO in SAD+/AO- group and the recommendation by NICE guidelines that the use of ICS/LABA should be for those with spirometrically confirmed AO (National Institute for Health and Care Excellence, 2019). Therefore, the absence of AO in SAD+/AO- group raises concern regarding the reason for prescribing such high levels of ICS/LABA. ICS/LABA contains high dose of ICS and characterized by high potency, and associated with adverse effects, including community-acquired pneumonia, glucose dysregulation and adrenal suppression (Ejiofor and Turner, 2013). There are two possible reasons why patients in SAD+/AO- group are on ICS/LABA. First, the current study used the LLN to define AO, whereas the fixed 70% cut-off is still used in clinical practice. This could explain that some patients were given ICS/LABA following the confirmation of AO using the fixed cut-off. Second, it is possible that some of these patients have other conditions that may have caused their symptoms at some time of their lives, which may have impacted them from performing a maximal effort for spirometry, possibly leading to the misclassification of patients to being COPD. Thus, these patients have been prescribed ICS/LABA, but this cannot be confirmed due to the retrospective nature of routinely collected data, which lacks longitudinal data. Hence, a longitudinal retrospective study is required to confirm whether these patients' previous spirometry results were requested for symptoms because of other conditions.

The use of MMEF in the clinical decision making has not been widely adopted, in part due to a large retrospective study by Quanjer et al. (Quanjer et al., 2014b) which showed that MMEF was not of value as an addition to current spirometric measures in clinical practice. However, there are some factors which should be considered. First, the study was conducted in an unselected population and the fact that a test may not be useful in an unselected population does not mean that it would not be useful in a specific population. In support of this concept, recent studies of a highly selected population demonstrated positive findings, supporting MMEF use in either % predicted or z-score (Kwon et al., 2020; Stockley et al., 2017b). Stockley et al. found low MMEF % predicted in AATD patients without AO was related to lower health status and accelerated decline in lung function (Stockley et al., 2017b). Kwon et al. showed that in symptomatic non-AATD participants without AO, those with a low MMEF z-score had a higher probability of developing COPD compared to those with a normal MMEF z-score (Kwon et al., 2020). Second, Quanjer et al. used a wider range (z-score of -1.654) for abnormality in MMEF. The cut off selected for abnormality may also affect the case mix of patients included in each group. Third, the close relationship of the MMEF z-score with the traditional spirometric measures, similar to previous studies (Stockley et al., 2017b), contrasts with Quanjer et al. and highlights that the MMEF z-score has the potential to supplement other spirometric measures particularly at detecting those at risk of developing COPD. In the present study, we only included never-smoking participants suspected of having COPD and used z-scores for MMEF and FEV_1/FVC to define abnormality, reflecting SAD and AO, respectively. The cut-off of -0.8453 used to define SAD was selected because it was able to predict COPD development (Kwon et al., 2020). For FEV_1/FVC z-score, we selected a cut-off of -1.654 to define airflow obstruction as this decreases the false-positive findings caused by aging (Quanjer et al., 2012).

Few studies have assessed the small airways in never-smokers. A longitudinal study of never-smoking AATD participants by Stockley et al. showed that SAD (described by low MMEF %predicted) without AO was associated with poorer health status and consequent decline in FEV_1 (Stockley et al., 2017b). In a recent longitudinal retrospective study of non-AATD patients with different smoking statuses (including never-smokers), Kwon et al. demonstrated that patients with low MMEF z-score were associated with a higher chance of developing COPD after accounting for several confounders, including smoking status (hazard ratio (HR), 3.308; 95% confidence interval (CI), 1.650 – 6.632; $p<0.001$) (Kwon et al., 2020). In this study, the risk of developing COPD was greater in occasional smokers (HR, 4.586; 95% CI, 1.913- 10.993; $p<0.001$) and long-term smokers (HR, 2.179; 95% CI, 1.115- 4.258; $p=0.023$) than never-smokers. This suggests that cigarette smoking appears to accelerate lung function decline than other factors associated with never-smokers. Thus, the pathophysiological process seems to be different in the early stages between never-smokers and ever-smokers. However, Kwon and colleagues did not report the number of never-smokers who developed COPD as well as their baseline demographics. Therefore, it remains unclear if other factors (i.e. age) might have impacted the finding of the low-risk COPD development in never-smokers. Moreover, it would be more informative to conduct a longitudinal study of never-smokers with low MMEF who develop COPD to determine baseline demographics, including the history of exposure to risk factors.

The present study differs from the longitudinal study by Kwon et al (Kwon et al., 2020). In their study, Kwon et al. used the MMEF z-score to evaluate whether an abnormal MMEF z-score in patients without COPD can predict COPD development over a period of time, showing that the cut-off they used is of value in predicting COPD. This highlights that the cut-off likely indicates early lung impairments, reflecting the presence of SAD in those

with an abnormal MMEF z-score. Using the same cut-off used by Kwon et al. to pragmatically define the presence of SAD, the present study included never-smoking participants known to have or suspected of having COPD to determine the prevalence of SAD with and without AO, demonstrating that SAD is prevalent among never-smokers with and without AO.

The present study provides data to support the use of MMEF z-score in never-smokers at risk for developing COPD. Potentially, MMEF z-score <-0.8453 could be utilized to screen symptomatic patients who have never smoked for lung physiology that likely reflect SAD, leading to further investigations to identify potentially mitigating factors. In never-smokers, several risk factors may account for COPD development, such as occupational or domestic exposure to inhaled toxins or passive smoking. Therefore, assessing these risk factors and avoiding them may help obviate further lung harm resulting in overt COPD.

Our study has several limitations. Our pragmatic study included all available lung function tests between the censor period, but only identified a relatively small sample size, and a lack of power could account for some non-significant results. Therefore, further larger studies are required to confirm our findings in never-smokers. Although MMEF is variable, we used it to assess SAD because of its accessibility. In the present study, the use of the z-score for MMEF lessened its variability. To define an abnormality of the MMEF z-score, a cut-off was used that differed from the GLI's lower limit of normal; however, the cut-off used was shown to predict COPD (Kwon et al., 2020). It is important to point out that the study was conducted retrospectively using real-world data; consequently, some data may not be available for evaluation. Lastly, our study was cross-sectional; however, the relevance of the MMEF z-score as a screening measure has been shown in a long-term study (Kwon et al., 2020).

3.6. Conclusion:

The present study demonstrated that SAD (identified by a low MMEF z-score) is an attribute seen in all never-smokers with AO and can also be found in those without AO. Our findings suggest MMEF may have a role in identifying early lung pathology in never smokers, although it is unclear if this leads to the development of AO in these subjects. Although larger and more comprehensive studies are required to confirm our conclusion, observing participants with low MMEF and intervening early might result in amelioration of their overall health status, and importantly, it may halt them from developing COPD.

Theme #2: The utility of small airways tests in BDR assessment in COPD

4. Small airways response to bronchodilators in adults with asthma or COPD: a systematic review

This was a collaborative work conducted by me and another co-author (Mohammed Almeshari, a PhD student at the institute), where we both made an equal contribution. An abstract of this review was also presented at the British Thoracic Society (BTS) winter meeting (Almeshari et al., 2021a) (see Appendix 4.1)

This chapter has also been published in the International Journal of COPD and titled **"Small airways response to bronchodilators in adults with asthma or COPD: a systematic review"** (Almeshari et al., 2021b) (see Appendix 4.2).

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Authors contribution: N.Y. Alobaidi conceived, designed the study, performed the initial search, assessed the eligibility of the included studies, performed the quality assessment for the included studies, performed data acquisition and wrote the COPD part of the initial manuscript in all sections and approved the final version. M.A. Almeshari conceived, designed the study, performed the initial search, assessed the eligibility of the included studies, performed the quality assessment for the included studies, performed data acquisition and wrote the asthma part of the initial manuscript in all sections and approved final version. E. Sapey designed and planned the study and revised the manuscript and approved final version. O. Usmani assisted in designing and planning the study and

approved final version. R.A. Stockley revised the manuscript and approved final version. J.A. Stockley revised the manuscript and approved final version.

4.1. Introduction

Testing for bronchodilator responsiveness (BDR) is currently included in the diagnosis of asthma and can help in differentiating asthma from 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 (SAD) is prevalent in both asthma and COPD (Usmani et al., 2016; Higham et al., 2019). Spirometry is the current gold standard to diagnose airways obstruction (Pellegrino et al., 2005; Global Initiative for Chronic Obstructive Lung Disease, 2022) and Maximal Mid-Expiratory Flow (MMEF), also known as Forced Expiratory Flow between 25-75% of FVC (FEF_{25-75}) is the index parameter most commonly used to evaluate small airways function by spirometry (McNulty and Usmani, 2014; Singh et al., 2020; Stockley et al., 2017a). 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 beta-2 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). 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., 2005).

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 beta-2 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, Alexander and McHardy, 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., 2019). BDR is seen in some patients with COPD, although this can have day-to-day variability (Tan et al., 2012; Albert 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 SAD as part of the disease paradigm (Almeshari et al., 2020). 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 (O'Donnell, Revill and Webb, 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 (Borrill et al., 2005; Wouters et al., 1989). In COPD, there is evidence that SAD 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, Macklem and Thurlbeck, 1968; Stockley et al., 2017b).

Pathological, physiological and radiological studies assessing the small airways recommend targeting them early in the course of COPD (Bosken et al., 1990; Hogg, Macklem and Thurlbeck, 1968; Stockley et al., 2017b; Papi et al., 2018). 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.

4.2. Aim

To assess the current evidence of BDR using SAF in asthma and COPD.

4.3. Objectives

- To evaluate the current evidence of small airways response to short-acting inhaled bronchodilators in adults with asthma or COPD.
- To evaluate the effectiveness of methods used in delivering aerosolized bronchodilators to the small airways and their function.

4.4. Methods and design

4.4.1. Protocol and registration

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 (Liberati et al., 2009).

4.4.2. Eligibility criteria

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 SAF 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 COPD or Asthma	- Other chronic lung diseases such as cystic fibrosis. - Patients younger than 18 years old
Intervention	SAF (IOS, FOT, MMEF, FEF_{50}, MBW, SBW) response to BDR using SABA via various aerosol delivery devices.	
Comparator	BDR in conventional lung function (FEV_1)	
Outcome	Change in SAF after administrating the bronchodilator therapy.	
Study design	Randomised Control Trials, Cohort, Cross-sectional, Longitudinal, Case-series >10 patients, Systematic reviews	Reviews, Editorials, Case series of <10 Patients, Case reports

Notes: The systematic review included that met the inclusion and exclusion criteria, as described above.
Abbreviations: COPD, chronic obstructive pulmonary disease; SAF, small airway function; 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; SABA, short acting beta-2 agonist.

4.4.3. Search strategy

Through scoping, the following tests were selected to be included in the search, MMEF, Forced Oscillometry (FOT), Impulse Oscillometry (IOS), Forced Expiratory Flow at 50% of FVC (MEF_{50}), Single Breath Washout (SBW) and Multiple Breath Washout (MBW). The following electronic databases will be searches from inception up to January 2020: EMBASE, MEDLINE, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science (Abstracts & Proceedings). A complete searching strategy is provided in appendix 4.3.

4.4.4. Study selection

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 and similar abstract screening method was used in screening full texts for suitability.

4.4.5. Data extraction

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)

4.4.6. Risk of bias and 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 RCTs 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 (NHLBI, 2021).

4.4.7. Data synthesis

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

4.5. Results

4.5.1. Characteristics of included studies

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. The excluded articles in the full-text phase are listed in the online supplemental material (S.2) with reasons for exclusion.

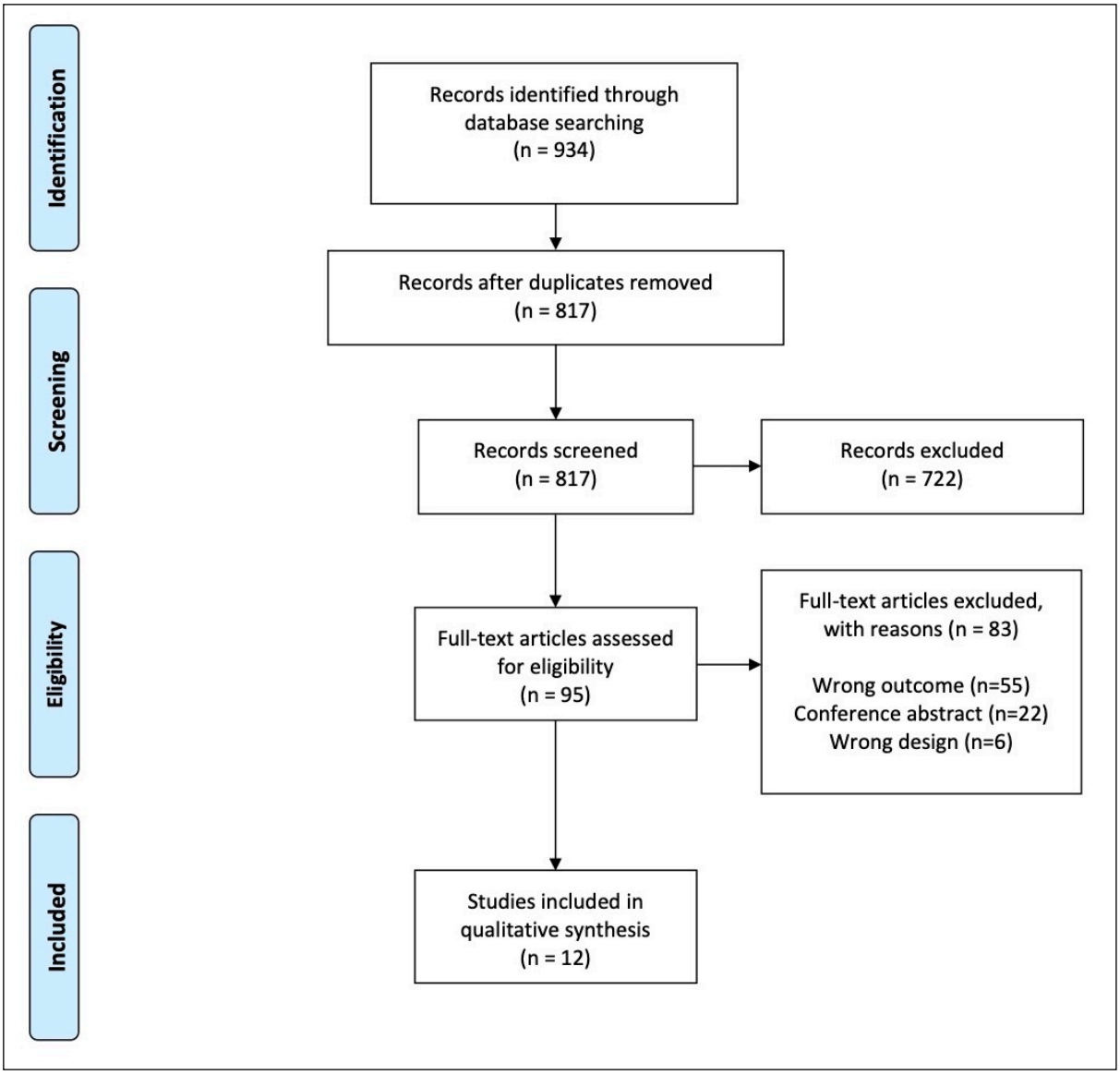

Figure 4.1. PRISMA flow chart showing the studies identification process from EMBASE and Medline databases. This figure was adapted from Moher et al (Moher et al., 2009).

Ten studies included patients with asthma (El-Khatib et al., 2014; Fakharian et al., 2008; Lipworth and Clark, 1997; Mariotta et al., 2005; Nair, Ward and Lipworth, 2011; Ohwada et al., 2011; Rajkumar, Vatsa and Gaur, 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.

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, Ward and Lipworth, 2011; Rajkumar, Vatsa and Gaur, 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, Ward and Lipworth, 2011; 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, Vatsa and Gaur, 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, Vatsa and Gaur, 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, Ward and Lipworth, 2011). 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, Vatsa and Gaur, 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.

Table 4.2. 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
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)
Yaegashi 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	
		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]	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)	
					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	

Legend: For each study, the population, numbers of participants by gender, average age of participant, SABA used, device for BDR, time from delivery to measurement, SAF test were 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; 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 25-75% 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

4.5.2. Quality assessment of included studies

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, Ward and Lipworth, 2011) and poor quality in three (Fakharian et al., 2008; Lipworth and Clark, 1997; Rajkumar, Vatsa and Gaur, 2002). A graph of NIH quality assessment is shown in appendix 4.4.

4.5.3. Results of individual studies

4.5.3.1. Spirometry (MMEF, FEF_{50})

4.5.3.1.1. 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, Vatsa and Gaur, 2002; Schecker et al., 1993; Tavares e Castro et al., 2015). Ohwada et al. recruited 45 non-smoking patients diagnosed with asthma but treatment-naïve (Ohwada et al., 2011). 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 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. assessed two types of inhalers to determine if device influenced the medication deposition or response; the standard pMDI and the Autohaler (Schecker et al., 1993). 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. conducted a study to compare the BDR of 2 spacers (Asmyar and Damyar) (Fakharian et al., 2008). 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. reported MMEF and FEF_{50} in asthmatic patients (with either intermittent or persistent symptoms) and control subjects (Mariotta et al., 2005). 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. studied the difference between commercial and home-made spacers (Rajkumar, Vatsa and Gaur, 2002). 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. 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 (Tavares e Castro et al., 2015). 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 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 SAF than FEV_1.

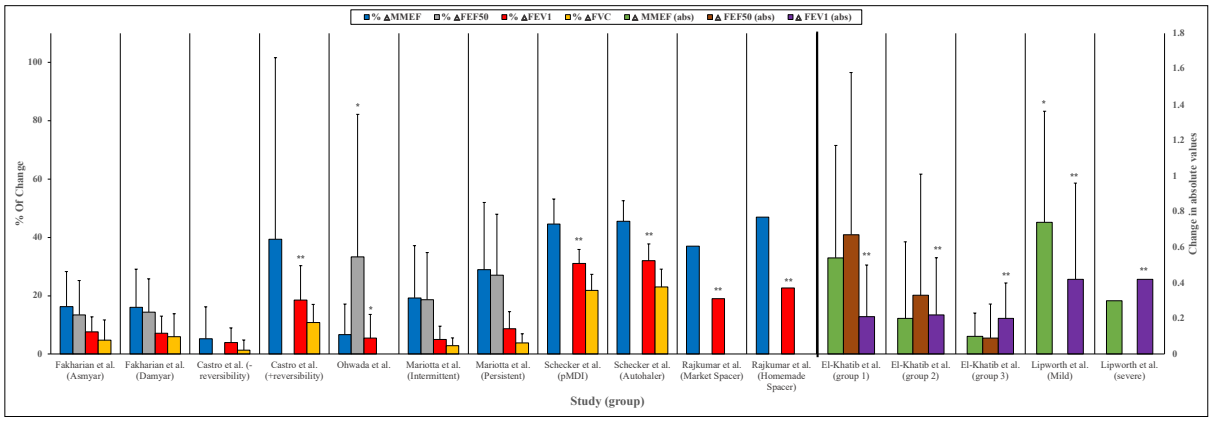

Figure 4.2. The average percentage change and absolute change in MMEF, FEF_{50}, FEV_1 and FVC across asthma studies.

Legend. 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 mean ± standard deviation (SD). Included data has been taken and adapted from Fakharian et al. (Fakharian et al., 2008), Castro et al. (Tavares e Castro et al., 2015), Ohwada et al. (Ohwada et al., 2011), Mariotta et al. (Mariotta et al., 2005), Schecker et al. (Schecker et al., 1993), Rajkumar et al. (Rajkumar, Vatsa and Gaur, 2002), El-khatib et al. (El-Khatib et al., 2014), and Lipworth et al. (Lipworth and Clark, 1997). measure of variances is not displayed in the error bar for Rajkumar et al. (Rajkumar, Vatsa and Gaur, 2002). and severe asthmatic in Lipworth et al. (Lipworth and Clark, 1997). because SD was not reported. * = BDR is statistically significant. ** = BDR is clinically significant according to ATS/ERS criteria.
Abbreviations: MMEF, Maximal Mid-expiratory flow; FEV_1, forced expiratory volume in 1 second; FVC forced vital capacity; FEF_{50}, forced expiratory flow at 50% of FVC.

El-Khatib et al. designed a study to compare the effectiveness of using Heliox to reduce viscosity compared to medical air when nebulizing bronchodilators (El-Khatib et al., 2014). 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. 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 (Lipworth and Clark, 1997). 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. (El-Khatib et al., 2014) and Lipworth et al. (Lipworth and Clark, 1997).

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, Vatsa and Gaur, 2002; Schecker et al., 1993; Tavares e Castro et al., 2015).

4.5.3.1.2. COPD

Two studies reported BDR using MMEF in COPD patients (Borrill et al., 2005; Park et al., 2019). Borrill et al. 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 (Borrill et al., 2005). 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 4.3. summarizes these % changes in MMEF and FEV_1 using the different doses of salbutamol.

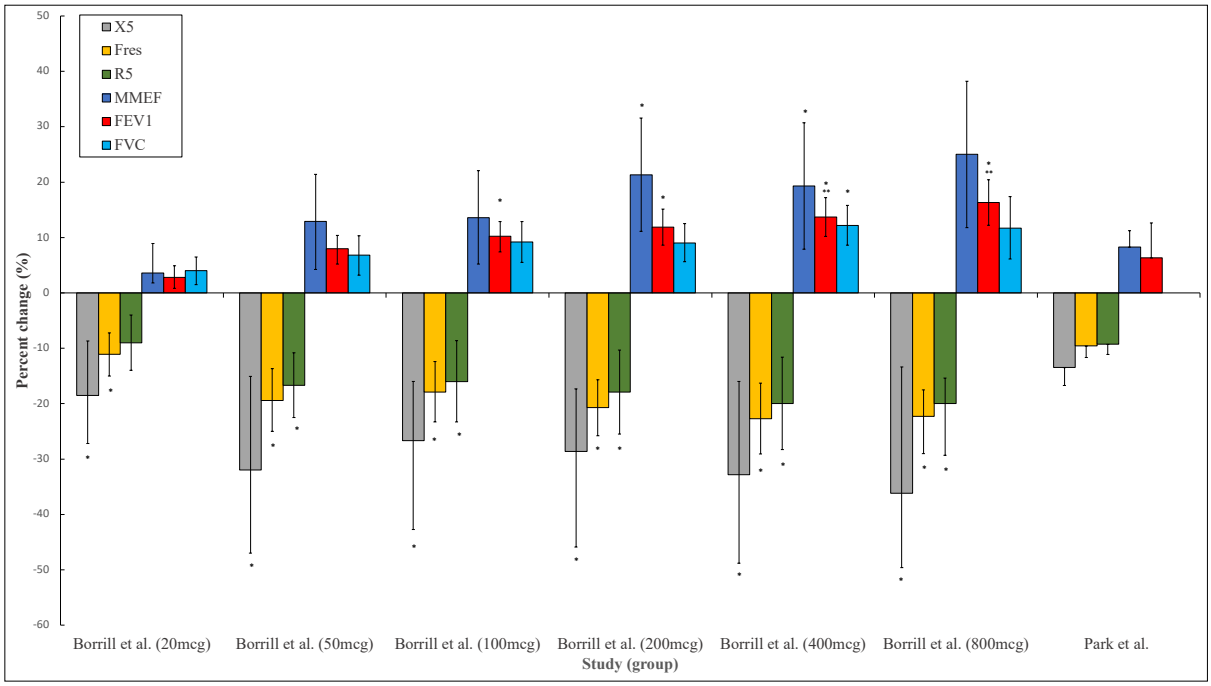

Figure 4.3. The % change of in spirometric indices (MMEF, FEV_1 and FVC) and in oscillometry indices (X5, Fres, R5) in COPD patients.

Legend. Vertical axis is % of change in spirometric indices and oscillometry indices in comparison to FEV_1 in COPD patients across different doses of salbutamol in Borril et al. (Borrill et al., 2005) and in a single dose in Park et al. (Park et al., 2019) Data presented in the figure are Mean (95% CI) for Borrill et al. (Borrill et al., 2005) and mean and standard error of mean for Park et al. (Park et al., 2019) * = BDR is statistically significant. ** = BDR is clinically significant according to ATS/ERS criteria.
Abbreviations: X5, reactance at 5 hertz; Fres, resonant frequency; R5, resistance at 5 hertz; FEV_1, forced expiratory volume in 1 second; mcg, microgram; FVC, forced vital capacity; MMEF, maximal mid-expiratory flow.

A recent prospective study by Park et al. was conducted to assess BDR using IOS compared to spirometry in 40 elderly patients with COPD (Park et al., 2019). 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.

4.5.3.2. Oscillometry (R_5, R_{5-20}, X_5, AX, Fres)

4.5.3.2.1. Asthma

Three studies reported the BDR using oscillometry (Nair, Ward and Lipworth, 2011; Park et al., 2019; Yaegashi et al., 2007). Yaegashi et al. retrospectively analysed data from asthmatic patients who underwent both spirometry and oscillometry (Yaegashi et al., 2007). 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 (R_5), R_{5-20} (the difference between R_5 and R_{20}) and resistance at 20Hz (R_{20}), respectively. Statistical analysis was not performed to assess the relevance of the changes. Changes in other common oscillometry parameters such as reactance at 5Hz (X_5) 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. 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) (Nair, Ward and Lipworth, 2011). 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 R_5, R_{20} and X_5, 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 R_5, R_{20} and X_5, 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., authors also recruited 30 elderly patients with asthma (Park et al., 2019). BDR was reported as the mean (±SEM) percentage change in the absolute values for the following IOS parameters; resonant frequency (Fres), R_5, R_{20}, R_{5-20}, X_5 and area of reactance (AX). Results were as follows: −15.3% ± 2.6 in Fres, −12.7% ± 2.7 in R_5, −6.4% ± 2.6 in R_{20}, −10.3% ± 2.6 in R_{5-20}, −5.9% ± 7.3 in X_5, and −22.9% ± 7.3 in AX. In comparison, the % change in FEV_1 was reported as 9.2%±1.9. In figure 4.4, a bar chart of the percentage of change is provided.

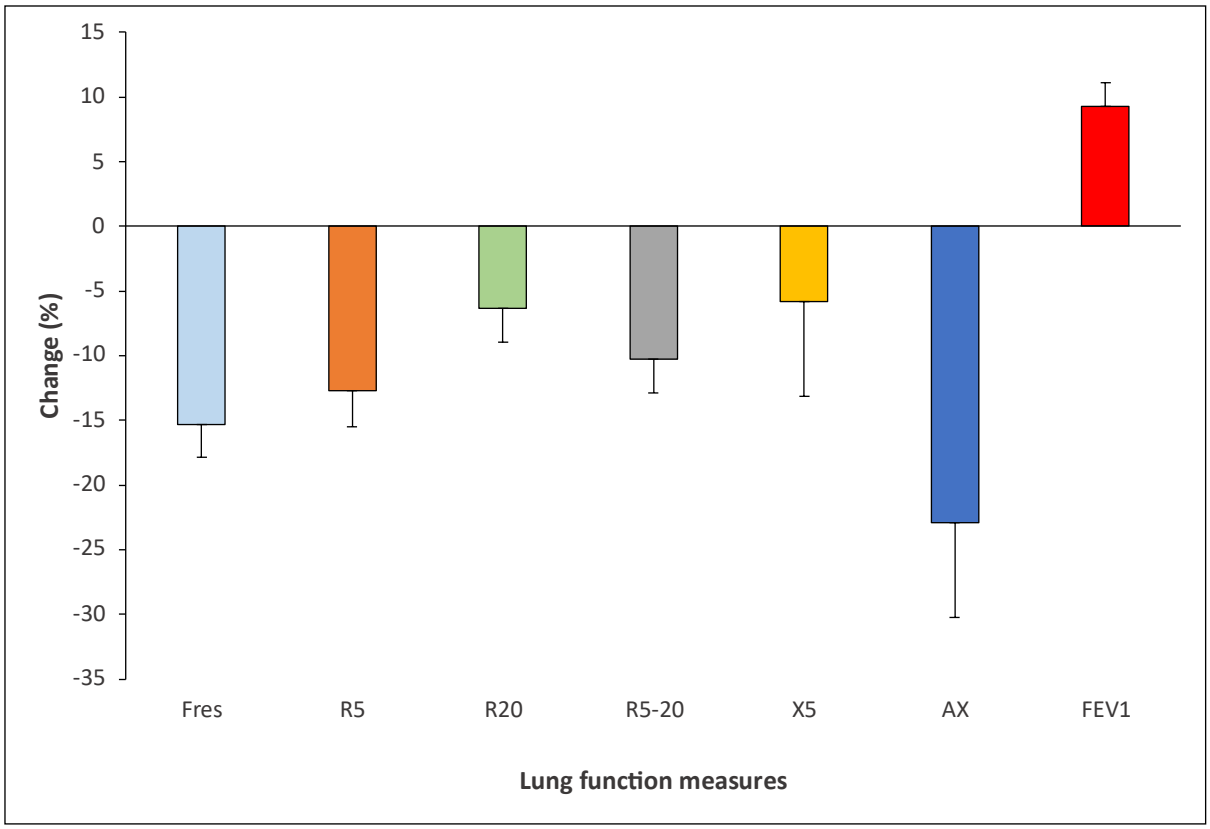

Figure 4.4. The percentage change of IOS parameters and FEV_1 in Asthmatic patients following BDR

Legend: Vertical axis is % 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: X_5, reactance at 5 hertz; Fres, resonant frequency; R_5, resistance at 5 hertz; R_{20}, resistance at 20Hertz; $R_{5\text{-}20}$, the difference between R5 and R20; AX, area of reactance; FEV_1, forced expiratory volume in 1 second

4.5.3.2.2. COPD

Two studies reported BDR using oscillometry in COPD patients (Borrill et al., 2005; Park et al., 2019). Borrill et al. compared different lung function tests to determine the most reliable method for identifying BDR in COPD (Borrill et al., 2005). 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. X_5 and Fres showed statistically significant

improvements after 20mcg, but only after 50mcg in R_5. Although R_{20} showed changes at all doses, they were not statistically significant (see table 4.2.). The changes of IOS parameters showed significant improvements across several doses, as shown in figure 4.3. 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 parameters showed higher variability compared to FEV_1, with Fres being the least variable.

As previously described, Park et al. 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 (Park et al., 2019). The authors reported Fres, R_5, R_{20}, R_{5-20}, X_5 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 X_5, AX and Fres was -13.5 (3.2), -22.7 (4.5) and -9.6 (2.1), respectively. The mean % change (SEM) for R_5, R_{20} and R_{5-20} 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 4.5.).

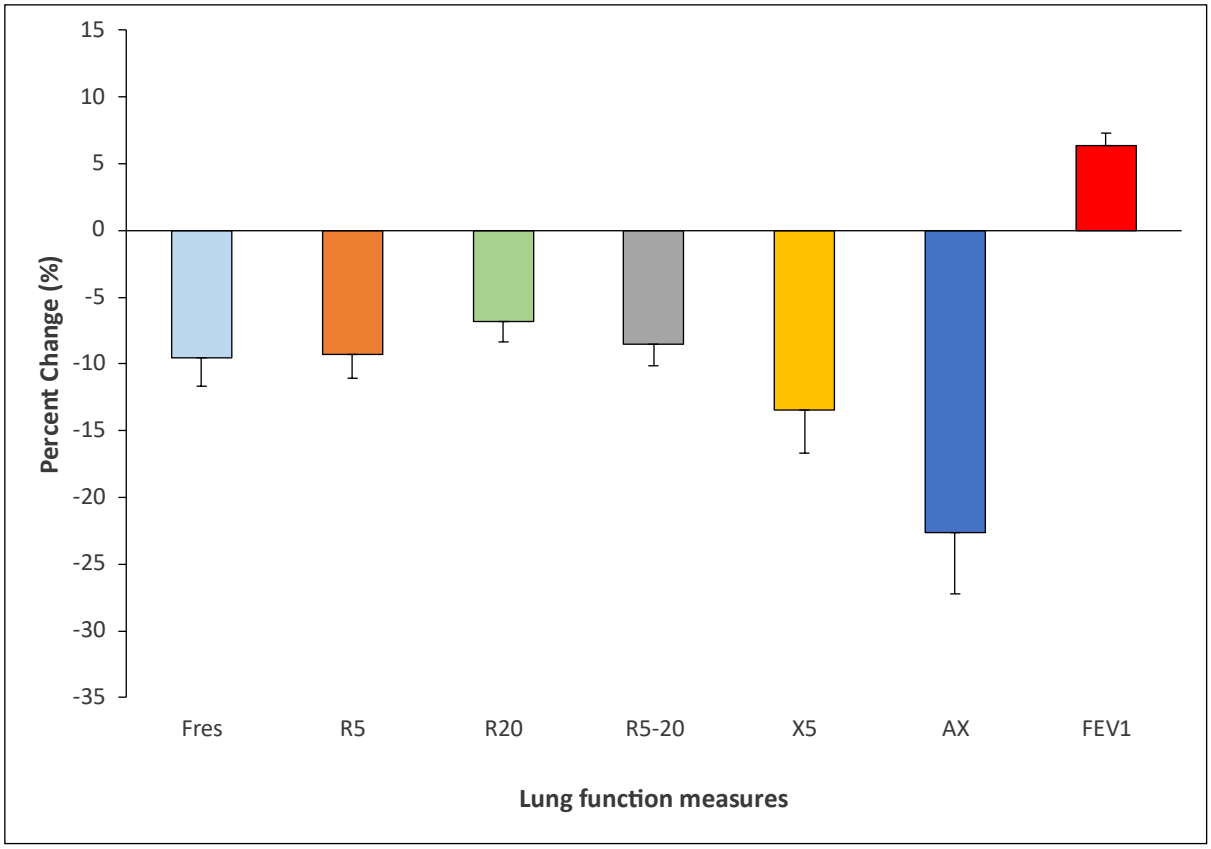

Figure 4.5. The percentage change of IOS parameters and FEV_1 in COPD patients following BDR

Legend: Vertical axis is % of change in oscillometry parameters in comparison to FEV_1 in COPD 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: X_5, reactance at 5 hertz; Fres, resonant frequency; R_5, resistance at 5 hertz; R_{20}, resistance at 20Hertz; R_{5-20}, the difference between R_5 and R_{20}; AX, area of reactance; FEV_1, forced expiratory volume in 1 second

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/ERS 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, means were reported despite the data being clearly skewed, weakening the evidence presented in this review (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). 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., 2019). In addition, this level of BDR has also been reported

in patient with COPD (Janson et al., 2019). 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 its evidence shows how it relates to clinical outcomes such as exacerbation rates or quality of life (Hansen et al., 2019; Ioachimescu et al., 2021). 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).

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 in obstructive lung diseases (Jiang et al., 2019) 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 (Borrill et al., 2005). In one study, however, MMEF changes had higher variability than FEV_1 (Borrill et al., 2005). 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 (R_5, R_{20}, R_{5-20}, relating to total, large and small airways resistance, respectively) after the administration of a bronchodilator. The greatest change seen was in the total resistance (R_5) 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 reported only the % of predicted values for oscillometry (Nair, Ward and Lipworth, 2011), 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 X_5, R_5, Fres, R_{5-20} and AX, with X_5 and AX showing the most pronounced improvements compared to other IOS parameters. In the study by Borrill et al., the % change of R_5, X_5, 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 (Borrill et al., 2005). In the study by Park et al., all IOS parameters (including R_{5-20}) demonstrated greater % changes compared FEV_1, with the greatest seen in AX and X_5 (Park et al., 2019). 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, Macklem and Thurlbeck, 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 R_{20} did not show significant changes in these studies. The changes of X_5, 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., IOS parameters had both a higher within test and within day variability than FEV_1 and, therefore, were less reproducible (Borrill et al., 2005). 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, Woodcock and Singh, 2004; Houghton, Woodcock and Singh, 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. compared BDR by IOS for COPD and asthmatic patients with no statistical differences found between these groups (Park et al., 2019). 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. 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.

5. The utility of tests of small airways in bronchodilator response assessment in COPD: A retrospective study

This chapter utilized lung function data of ever-smoking COPD patients to evaluate the utility of tests of small airways in the bronchodilator responsiveness (BDR) assessment.

This chapter is a paper in preparation for submission to a journal for consideration to be published.

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

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5.1. Brief Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a chronic inflammatory disease characterised by poorly reversible airflow limitation (Global Initiative for Chronic Obstructive Lung Disease, 2022). Bronchodilator responsiveness (BDR) can be used to help distinguish between COPD and asthma (Mackay et al., 2012; National Institute for Health and Care Excellence, 2019; Global Initiative for Chronic Obstructive Lung Disease, 2022; Global Initiative for Asthma, 2022) and is a valuable indicator of prognosis in asthma (Galant et al., 2011), although it is increasingly recognised that some patients with COPD also display BDR (Albert et al., 2012; Tan et al., 2012; Tashkin et al., 2008). The usefulness of BDR in COPD remains unclear (Anthonisen et al., 2005) but BDR in both FEV_1 and FVC can identify subjects with less emphysema, a more exacerbations and greater lung function decline but a lower mortality risk than subjects with no BDR (Fortis et al., 2019).

The assessment of BDR usually depends on the measurement of the forced expiratory volume in the first second (FEV_1) although definitions of BDR can vary between guidelines. A BDR is commonly defined by an increase in percent change of $\geq$12% and in absolute change of $\geq$200ml (Pellegrino et al., 2005). Studies have shown that vital capacity and inspiratory capacity can increase in the absence of a positive FEV_1 response (O'Donnell, Revill and Webb, 2001; Schermer et al., 2007), indicating that a BDR should not be determined by a single spirometric measure alone and additional physiological measures may be of value in understanding and managing COPD.

Physiological and pathological studies have demonstrated that small airways dysfunction (SAD) is an important feature of COPD (Bosken et al., 1990; Hogg, McDonough and Suzuki, 2013; Stockley et al., 2017b). Maximal Mid-Expiratory Flow (MMEF) is the most widely reported measure of small airway function and has become a valuable marker of

SAD, especially in the detection of early stages of COPD (Kwon et al., 2020; Stockley et al., 2017b; Tsushima et al., 2006).

A recent systematic review reported that studies exploring the use of tests of small airways (SA) in BDR assessment in COPD are few and involve small number of participants (Almeshari et al., 2021b). Despite this, the studies reported that BDR as defined by tests of SA could potentially identify specific groups of patients and suggested that, with the advent of ultra-fine particles inhalers, there may be specific treatment options for those with BDR detected in the SA (Borrill et al., 2005; Park et al., 2019). Further studies were suggested to determine the potential utility of tests of SA in defining BDR in COPD.

We hypothesised that a BDR within the SA (defined by a BDR in MMEF) would be common in COPD, seen in most COPD patients with a BDR defined by FEV_1, but also in some without BDR in FEV_1. Moreover, we hypothesised that those with a BDR in the SA alone would not be distinguishable in terms of demography, smoking exposure or severity of disease from those without BDR in the SA. However, this might potentially identify a subgroup of COPD patients who may benefit from more peripheral bronchodilator deposition using ultra-fine particles inhalers and could, therefore, form a group where screening was warranted to identify a differently treatable characteristic.

5.2. Aims

- To determine the prevalence of significant BDR in MMEF.
- To assess the prevalence of significant BDR in MMEF with and without significant BDR in FEV_1, and its association with baseline demography, airflow obstruction (AO) severity and smoking history.

5.3. Methods

5.3.1. Study design and setting

This was a retrospective study of historical lung function data from COPD patients who underwent pulmonary function testing at the University Hospitals Birmingham NHS Foundation Trust, UK. The study utilised data collected between January 2016 and April 2021. The study was approved by the Health Research Authority (REC Reference: 20/HRA/0203).

5.3.2. Eligibility criteria

The study included participants if they had the following:

1) Confirmed diagnosis of COPD (post-bronchodilator (BD) FEV_1/FVC ratio < lower limit of normal (LLN))
2) Aged 30 years and over
3) Ten or more pack-years history of smoking
4) Pre- and post-BD spirometric measures, including MMEF.

Participants were excluded if they had COPD related to AATD, other factors which might alter the interpretation of lung function tests, a clinician defined history/diagnosis of other chronic lung diseases, or significant radiological bronchiectasis.

5.3.3. Study measures

Patient demographics were collected, including age, sex, body mass index (BMI), ethnicity and smoking history, which included current smoking status (ex- or current smokers), pack-years and years since quitting and long-term medications.

Pre- and post-BD lung function parameters were documented, including FEV_1, FVC, FEV_1/FVC, MMEF, MMEF adjusted for FVC (MMEF/FVC), forced expiratory volume exhaled in the first 3 seconds (FEV_3) and FEV_3/FVC. Using post-BD FEV_1 % predicted, we evaluated AO severity using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (Global Initiative for Chronic Obstructive Lung Disease, 2022). Lung function parameters were obtained using the Ultima PF^{TM} Pulmonary Lung Function System (Medical Graphics UK Ltd, Tewkesbury, UK), performed following the Association for Respiratory Technology and Physiology/British Thoracic Society guidelines (Sylvester et al., 2020).

BDR was evaluated 20 minutes after the administration of 2.5 mg of salbutamol by a jet nebulizer. The assessment of BDR included the evaluation percent change (% change), which was calculated using the following formula:

Significant BDR in FEV_1 was defined according to American Thoracic Society/ European Respiratory Society criteria (increase of $\geq$12 in % change and $\geq$200ml) (Pellegrino et al., 2005). Significant BDR in MMEF was defined as an increase of $\geq$30 in % change, based on previous studies (Levine et al., 2016; Shim, 1989).

In an initial analysis, patients were divided into two groups according to their BDR significance in MMEF:

- Patients with BDR in MMEF
- Patients without BDR in MMEF

Using the pre-defined BDR definition of FEV_1 and MMEF, patients were further classified into three groups according to their BDR features:

- Group 1 (BDR in FEV_1 and MMEF),

- Group 2 (BDR in MMEF but not in FEV_1),
- Group 3 (no BDR in either FEV_1 or MMEF).

5.3.4. Statistical analysis

The Shapiro–Wilk normality test was used, which confirmed the data was non-normally distributed and median and interquartile was reported for all variables. The Kruskal-Wallis H was performed, and if it demonstrated statistical significance difference, pairwise comparisons using Dunn's test were conducted to determine differences. For variables used in group definitions (change in MMEF and FEV_1), no statistical analysis was conducted, except where the definition did not cause the variable to differ. Here, Mann-Whitney U tests was performed to determine the differences. Categorical variables were evaluated using Chi-square or Fisher's exact test. Using the Bonferroni method, adjustment for p-values was made to account for multiple comparisons (Bonferroni, 1936). IBM SPSS software was used for all statistical analyses.

5.4. Results

5.4.1. Participant's selection

There were 2285 lung function recordings taken for patients with COPD within the timeframe but after eligibility evaluation, 314 were included in the study (see figure 5.1 for a flow diagram providing details of reasons for exclusion). Initially, patients were grouped into those with BDR in MMEF (n=186) and those without BDR in MMEF (n=128). Including the BDR response in FEV_1 with MMEF: BDR in FEV_1 and MMEF (Group 1; n=107), BDR in MMEF alone (Group 2; n=79) and no BDR in either measure (Group 3; n=128). All patients with a BDR in FEV_1 had a BDR in MMEF.

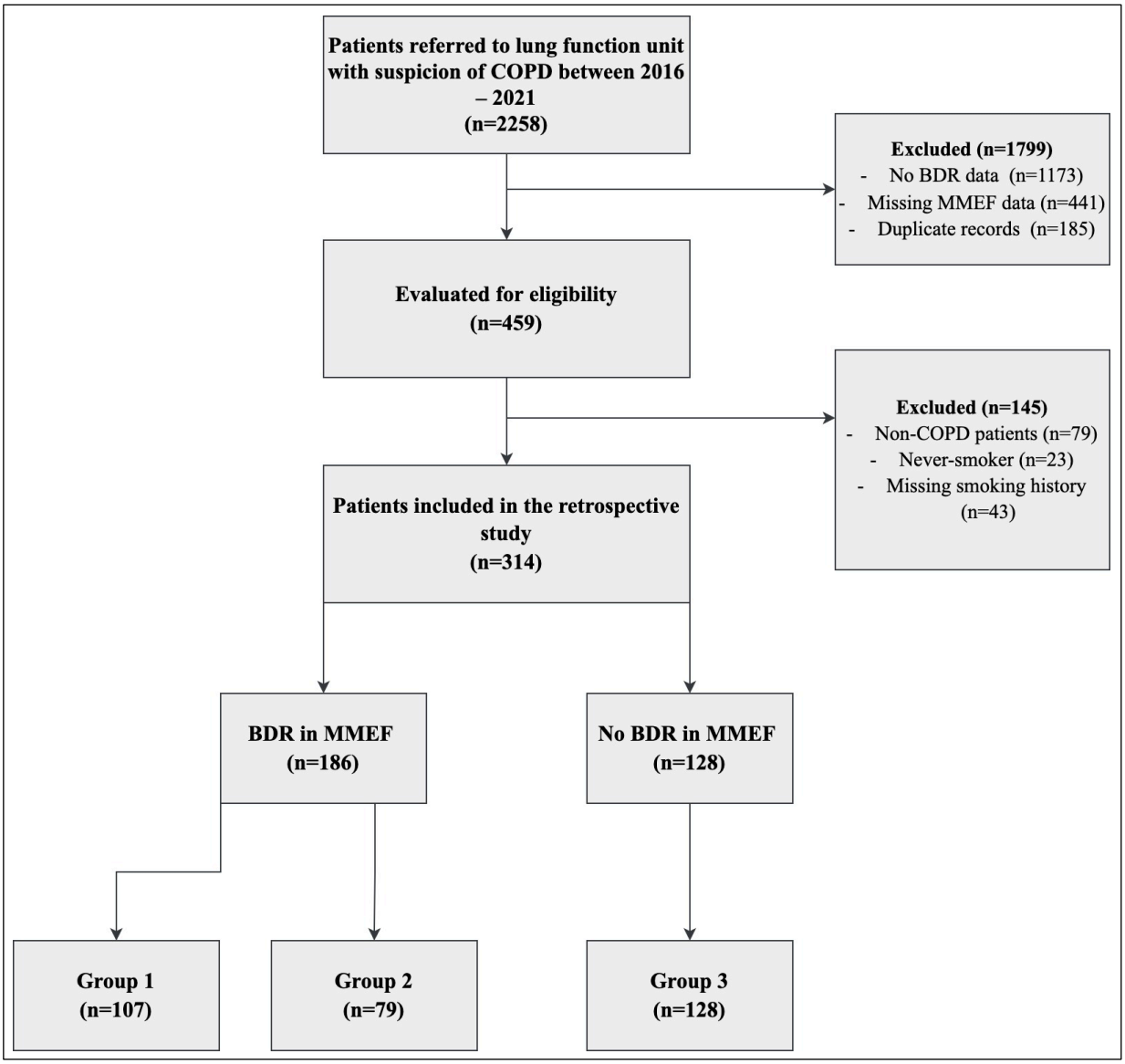

Figure 5.1. Flowchart of the study.
Legend: This figure demonstrates the selection process for patients according to eligibility criteria.
Abbreviations: COPD, chronic obstructive pulmonary disease; MMEF, maximal mid-expiratory flow; FEV_1, forced expiratory volume in 1 second; BDR, bronchodilator response; Group 1, those with BDR in FEV_1 and MMEF; Group 2, those with BDR in MMEF alone; Group 3, those with no BDR in either FEV_1 or MMEF.

5.4.2. Prevalence of BDR in MMEF

Of the 312 included patients, 59.2% demonstrated a BDR in MMEF. Of whom, 57.5% had BDR in FEV_1.

5.4.3. Prevalence of BDR in MMEF with and without BDR in FEV_1

In a further analysis, grouping patients into those with BDR in FEV_1 and MMEF; MMEF alone; or no BDR in either measure confirmed that all patients with a BDR in FEV_1 had BDR in MMEF (group 1). Of those without BDR for FEV_1, 37.98% (79/208) had a positive BDR for MMEF alone (group 2).

5.4.3.1. Baseline demographics

Baseline characteristics of the patients in each of the 3 groups are summarized in table 5.1. Apart from age (younger patients in group 1 than in group 2 [median age 60 vs 67, p=0.040] and group 3 [median age 60 vs 67, p=0.003]) and BMI (higher in group 1 than in group 3 [median 27.77 vs 25.81, p=0.015]), there were no differences in baseline demographics across groups.

Table 5.1. Baseline demographics across groups.

Variable	Group 1 n=107	Group 2 n=79	Group 3 n=128
Age	60 (54 – 71)[‡§]	67 (56 – 73)	67 (58 – 74)
Sex (n, %)			
Male	71 (67)	40 (50.6)	67 (51.9)
Female	35 (33)	39 (49.4)	62 (48.1)
BMI (kg/m^2)	27.75 (23.94 – 31.63)[§]	25.89 (22.77 – 31.22)	25.82 (22.13 – 29.69)
Smoking status (n, %)			
Current smoker	62 (58.5)	50 (63.3)	81 (62.8)
Ex-smoker	44 (41.5)	29 (36.7)	48 (37.2)
Pack-years	38 (25 – 52)	42 (26 – 54)	40 (25 – 57)
Years quit	7 (2 – 12)	12 (3 – 18)	10 (2 – 20)
Medications (n, %)			
SABA or SAMA	62 (58.5)	44 (55.7)	75 (58.1)
SABA + SAMA	0 (0)	1 (1.3)	2 (1.6)
LABA or LAMA	27 (25.5)	16 (20.3)	32 (24.8)
LABA + LAMA	1 (0.9)	2 (2.5)	3 (2.3)
ICS	5 (4.7)	7 (8.9)	6 (4.7)
LABA + ICS	12 (11.3)	10 (12.7)	18 (14)

Legend: Data are presented as median (IQR) or n (%). Group 1, positive BDR in FEV_1 and MMEF; group 2, positive BDR in MMEF alone; group 3, no positive BDR in either measure. [*] This was only assessed in ex-smokers, [†] significantly different from group 1, [‡] significantly different from group 2, [§] significantly different from group 3.

Abbreviations: BMI, body mass index; SABA, short-acting beta-2 agonist; SAMA, short-acting muscarinic antagonist; ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist; FEV_1, forced expiratory volume in one second; MMEF, maximal mid-expiratory flow.

5.4.3.2.Lung function and bronchodilator response

Table 5.2. describes the baseline spirometric measures, post-BD spirometric measures and the post-BD change for the BDR groups. In general, patients in groups 1 and 2 had lower baseline lung function measures (lower FEV_1 % predicted and lower FVC % predicted [$p<0.001$ for both variables]) than group 3. The distribution of baseline FEV_1 % predicted, FVC % predicted and FEV_1/FVC ratio groups are graphically shown in Figure 5.2.

Groups 1 and 2 also had greater BDR (including FEV_1, FVC, MMEF, MMEF/FVC and FEV_3 [$p<0.001$ for all variables]) than group 3, whereas patients in group 2 had less BDR than in group 1 ($p<0.001$).

GOLD stages were not different across the three groups, except GOLD II which was less prevalent in group 2 than group 1.

Table 5.2. Baseline and post-BD spirometric measures and post-BD changes across groups.

Variable	Group 1 n=107	Group 2 n=79	Group 3 n=128
FEV_1			
Baseline (L)	1.50 (1.21 – 2.02)	1.22 (0.89 – 1.90)*‡	1.47 (1.15 – 2.08)
Baseline (% predicted)	51.11 (40.82 – 62.13)	51.02 (38.02 – 70.66)	60.28 (49.85 – 73.40)*†
Post-BD (L)	1.86 (1.58 – 2.39)†‡	1.37 (1.04 – 2.05)	1.57 (1.20 – 2.12)
Post-BD (% predicted)	63.67 (55.84 – 72.94)	56.12 (43.48 – 76.79)	62.16 (49.30 – 73.72)
Post-BD change (L)$^{\#}$	0.33 (0.28 – 0.44)	0.16 (0.13 – 0.19)	0.05 (0 – 0.10)†
Post-BD change (% predicted)$^{\#}$	11.29 (9.36 – 14.46)	6.12 (5.15 – 7.52)	1.96 (0 – 3.60)†
%Change of initial$^{\#}$	21.34 (17.48 – 32.65)	11.51 (9.50 – 15.38)	3.60 (0 – 6.43)†
FVC			
Baseline (L)	3.17 (2.39 – 3.72)	2.64 (2.07 – 3.30)	3.03 (2.40 – 3.80)
Baseline (% predicted)	80.47 (69.25 – 90.31)	79.63 (69.68 – 91.45)	88.94 (79.33 – 104.54)*†
Post-BD (L)	3.67 (2.91 – 4.21)†‡	3.05 (2.46 – 3.65)	3.12 (2.42 – 3.93)
Post-BD (% predicted)	91.56 (80.99 – 104.18)	89.77 (77.97 – 102.86)	92.28 (81.89 – 104.41)
Post-BD change (L)	0.47 (0.29 – 0.67)	0.33 (0.20 – 0.46)*	0.07 (-0.01 – 0.18)*†
Post-BD change (% predicted)	11.95 (7.53 – 18.62)	9.55 (6.06 – 13.51)*	1.84 (-0.51 – 5.17)*†
%Change of initial	16.06 (8.60 – 27.40)	11.97 (6.53 – 17.28)*	2.34 (-0.49 – 5.81)*†
FEV_1/FVC			
Baseline (%)	52 (45 – 57)	52 (41 – 59)	53 (46 – 60)
Post-BD (%)	55 (49 – 61)	53 (41 – 59)	54 (44 – 60)
Post-BD change (%)	3 (0 – 6)†‡	0 (-1 – 2)	0 (-2 – 2)
MMEF			
Baseline (L/s)	0.62 (0.47 – 0.77)†	0.45 (0.32 – 0.83)	0.57 (0.39 – 0.90)
Baseline (% predicted)	23.50 (18.80 – 29.67)	23.24 (13.84 – 37.52)	26.90 (18.94 – 36.85)
Post-BD (L/s)	1.12 (0.87 – 1.43)†‡	0.64 (0.44 – 1.17)	0.59 (0.41 – 0.99)
Post-BD (% predicted)	43 (32.83 – 55.09)†‡	34.48 (21.53 – 53.77)	28.14 (21.51 – 40.20)
Post-BD change (L/s)$^{\#}$	0.47 (0.32 – 0.65)	0.21 (0.15 – 0.35)*	0.05 (0 – 0.10)
Post-BD change (% predicted)$^{\#}$	17.91 (12.63 – 26.09)	10.49 (6.44 – 15.04)*	2.63 (0 – 4.56)

%Change of initial[#]	76.24 (57.54 – 96.88)	42.34 (35.44 – 53.57)[*]	11.77 (0 – 20)
MMEF/FVC			
Baseline (%)	30.23 (25.27 – 38.15)	30.69 (20.45 – 40.54)	29.67 (22.54 – 42.22)
Post-BD (%)	47.54 (36.82 – 61.38)	41.15 (24.10 -52.97)[*]	31.34 (24.93 – 42.80)[*†]
Post-BD change (% predicted)	16.48 (10.52 – 21.70)	8.99 (5.14 – 12.54)[*]	2.13 (-0.39 – 4.22)[*†]
FEV_3			
Baseline (L)	2.26 (1.89 – 2.87)	1.87 (1.42 – 2.58)[*‡]	2.18 (1.74 – 2.88)
Post-BD (L)	2.74 (2.27 – 3.31)[†‡]	2.06 (1.67 – 2.81)	2.28 (1.78 – 2.91)
Post-BD change (L)	0.42 (0.32 – 0.53)	0.22 (0.19 – 0.29)[*]	0.07 (0.01 – 0.12)[*†]
%Change of initial	17.92 (13.50 – 23.85)	10.99 (8.53 – 15.38)[*]	3.24 (0.68 – 5.19)[*†]
FEV_3/FVC			
Baseline (%)	77.14 (71.92 – 81.57)	76.57 (64.02 – 82.19)	76.74 (70.03 – 83.07)
Post-BD (%)	79.28 (72.67 – 83.33)	77.84 (67.67 – 82.98)	76.84 (68.82 – 83.07)
Post-BD change (%)	1.51 (-0.98 – 3.89)[‡]	0.10 (-3.04 – 3.32)	0.33 (-2.50 – 2.53)
GOLD stages (n, %)			
GOLD I	16 (15.1)	13 (16.5)	18 (14)
GOLD II	70 (66)[†]	35 (44.3)	78 (60.5)
GOLD III	19 (17.9)	25 (31.6)	28 (21.7)
GOLD IV	1 (0.9)	6 (7.6)	5 (3.9)

Legend: Data are presented as either median (IQR) or n (%). Group 1, positive BDR in FEV_1 and MMEF; group 2, positive BDR in MMEF alone; group 3, no positive BDR in either measure; [*] significantly different from group 1; [†] significantly different from group 2; [‡] significantly different from group 3. [#] statistical test was only done for differences between groups where a definition did cause the variable to differ.

Abbreviations: FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; MMEF, maximal mid-expiratory flow; FEV_3, forced expiratory volume in 3 seconds; BDR, bronchodilator response; BD, bronchodilator.

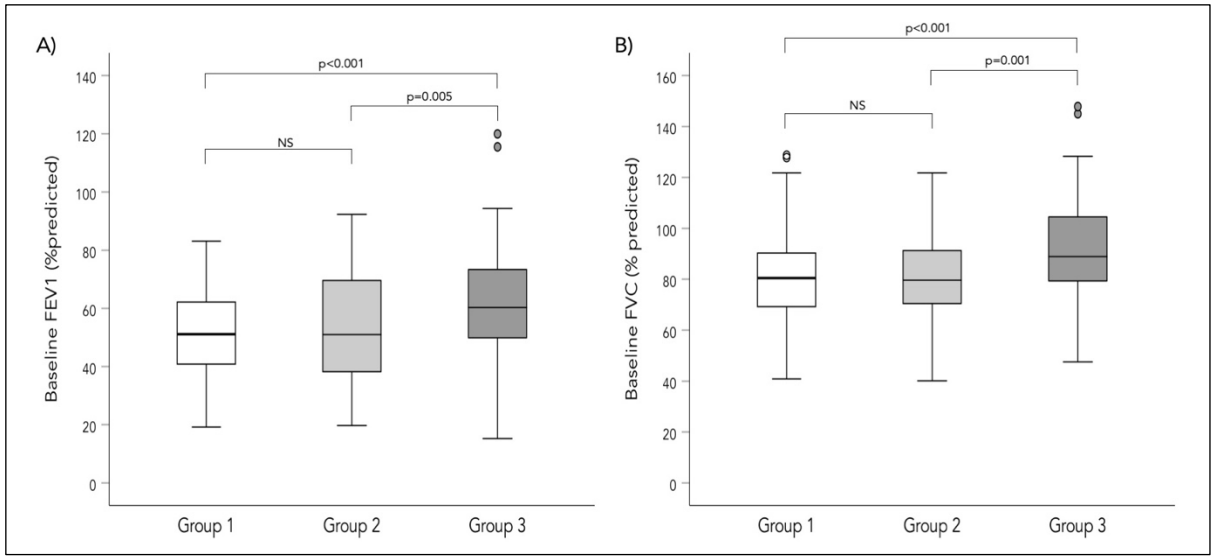

Figure 5.2. Baseline spirometric measures across groups.
Legend: This figure demonstrates the distribution of baseline spirometric measures across groups. A) Baseline FEV_1 % predicted. B) Baseline FVC % predicted. The presented p-values are for post-hoc Dunn's test, and the Kruskal Wallis tests p-values for both figures were <0.001
Abbreviations: MMEF, maximal mid-expiratory flow; FEV_1, forced expired volume in the first second; FVC, forced vital capacity; Group 1, positive BDR in FEV_1 and MMEF; group 2, positive BDR in MMEF alone; group 3, no positive BDR in either measure.

5.5. Discussion

The present study provides data of BDR using the commonly reported measures from spirometry (FEV_1) and a widely recognised measure of SAD (MMEF) in ever-smoking COPD patients and emphasises three key points.

Firstly, BDR in the MMEF is common in COPD, detected in 59% of COPD patients in this cohort.

Secondly, BDR in MMEF is observed in all patients with BDR FEV_1, signifying that the change in MMEF represents a physiological improvement that likely reflects improvement in SA patency. However, comprehensive studies, including the assessment of static lung volumes and gas transfer, are needed to support this.

Thirdly, BDR in MMEF is also present in some patients without BDR in FEV_1, indicating a potential utility of MMEF as an additional test in global lung BDR assessment.

Here, the post-BD change (though crossing our threshold for BDR in MMEF) was less than that seen in those with BDR in both MMEF and FEV_1, which may subsequently have less effect on FEV_1 than seen when with greater improvement in MMEF. This highlights that bronchodilator therapy (particularly those targeting small airways) would likely benefit such patients even if no significant change was seen in FEV_1. However, exploring this further requires prospective studies to determine whether the response in MMEF alone represents a detectable clinical effect.

The present study found that baseline demographics, including age, smoking exposure and AO severity, were not different in those with BDR in MMEF alone and those without BDR in either measure, which is in line with the study hypothesis. This highlights that although BDR in the MMEF alone could not be predicted by any baseline demography, the MMEF changes seen in these patients indicate that these likely reflect a physiological improvement and could be of value as it may form a group with differently treatable traits. However, whether these improvements are of benefit to symptoms is currently unclear as such measures were not collected routinely and hence, requires further study for confirmation.

Grouping patients with BDR in MMEF into those with and without BDR in FEV_1 was not related to baseline spirometric measures, except FEV_1 and FVC % predicted, which were lower in those exhibiting MMEF BDR (groups 1 and 2) than those without BDR in either measure (group 3). The findings indicate that having a lower baseline FEV_1 and FVC will likely increase the chances of patients exhibiting BDR in MMEF, whether alone or with BDR in FEV_1. Our findings for those with BDR in FEV_1 and MMEF confirm previous studies using similar BDR criteria for FEV_1 (Janson et al., 2019; Marín et al., 2014). The similar baseline FEV_1 and FVC seen in groups 1 and 2, with BDR in FEV_1 only seen in group 1,

highlights that the differences in improvements could indicate improvement in different regions of the lung. However, only a comprehensive study would confirm this.

In the current study, patients in group 1 were younger than groups 2 and 3, which may explain why positive BDR in FEV_1 was not observed in groups 2 and 3. However, previous studies found no associations between age and BDR in FEV_1 (Marín et al., 2014; Albert et al., 2012) even after adjusting for baseline FEV_1 (Janson et al., 2019). The reason for this difference is unclear but could be due to the diagnostic criteria for COPD as previous studies used FEV_1/FVC <70% to define AO, while the current study used the LLN (i.e., z-score <-1.645). The smaller and focused sample size in the present study may reflect this difference.

Higher BMI was found in patients with BDR in FEV_1 and MMEF than those without BDR in either measure, as in previous studies (Tashkin et al., 2008; Marín et al., 2014). Whether this reflects a weight-related effect on spirometric measures or a marker of deteriorating health and lung function is complex and requires prospective study of this interaction to explore putative reasons.

Smoking history, including smoking status, pack-years and years since quitting, was not different between those with and without positive BDR in FEV_1. This likely indicates that smoking exposure per se does not affect the BDR of FEV_1 in COPD nor the BDR of MMEF alone, highlighting that smoking exposure cannot explain the differences in physiological improvements. Our findings are thus supportive of previous studies that smoking exposure did not predict the BDR in FEV_1 (Marín et al., 2014; Janson et al., 2019).

In routine lung function, the inclusion of MMEF has been challenging because of the wide variation found in a non-characterized general population (Quanjer et al., 2014b). However, recent studies have demonstrated its utility, particularly in the early detection of COPD (Stockley et al., 2017b; Kwon et al., 2020) and an essential predictor of COPD

development (Kwon et al., 2020). These studies indicate that MMEF is of value in selected patient group and to answer specific questions reflecting present and future disease phenotype. Therefore, the current study is a proof-of-concept to assess whether BDR in MMEF detect patients showing physiological improvements in the SA following a bronchodilator. A cut-off of 30% to define a BDR in MMEF was pragmatically chosen, due to its previous use in other studies (Shim, 1989; Levine et al., 2016).

In COPD, BDR in MMEF has only been assessed in two studies (Park et al., 2019; Borrill et al., 2005). In the first, 24 COPD patients showed notable improvement of MMEF (mean % change of 21.3 and 19.3) after 200ug and 400ug of salbutamol, respectively (Borrill et al., 2005). Park et al. in the second study showed less improvement in MMEF (mean % change of 8.25) after administering 200ug salbutamol (Park et al., 2019). In both studies, MMEF demonstrated changes after bronchodilator administration, as in the present study. However, our study (by pragmatic design/definition) demonstrated larger changes in MMEF that was accompanied by a BDR response of FEV_1 in some patients and was able to identify others with BDR in MMEF alone.

It is important to emphasise that post-BD MMEF changes demonstrated a greater variance than post-BD FEV_1 changes, which is consistent with the study by Borril and colleagues (Borrill et al., 2005). This raises a challenge in the interpretation of such changes of MMEF in the BDR assessment. The criteria we used to determine improvement in MMEF have been proposed by others (Shim, 1989; Levine et al., 2016) and are certainly consistent with BDR of FEV_1 in group 1 and would thus indicate a real change also in group 2 although why this diverges from the FEV_1 response is currently unknown. However, as previously stated, this definition identifies a group of COPD patients who may have important physiological improvements in the SA and hence, may reflect a phenotype that benefits from

more peripheral bronchodilator deposition using ultra-fine particles inhalers, although the clinical benefit will require further specific study.

The strength of our study is it is the first to provide data about BDR in the SA in identifying physiological COPD phenotype. However, it is important to recognize weaknesses. First, due to the study's retrospective design, the data were limited to those routinely quantified. Therefore, more comprehensive studies that incorporate symptoms and other physiological parameters are required to determine the clinical importance of the findings. Second, we chose a BDR in MMEF representing a BDR in the SA because of its availability in routine physiological assessment. However, it is recognised that MMEF is a highly variable spirometric measure, and it is also, in part, dependent on FVC. Therefore, correcting MMEF for lung volumes is recommended (Cockcroft and Berscheid, 1980; Sherter, Connolly and Schilder, 1978). The correction was recommended because MMEF failed to show a significant change after bronchodilator administration when FVC changed (Cockcroft and Berscheid, 1980; Sherter, Connolly and Schilder, 1978). In our study, the % change of MMEF in group 2 was greater than 30%, suggesting that this concern was not a factor in the current study. In group 3, the median change in FEV_1 and FVC were 3.6 and 2.3, respectively; thus, some of these patients might experience a significant change in MMEF once FVC was corrected for. However, this is unlikely to affect our conclusions that BDR in MMEF could identify a response that was not captured by FEV_1. Third, as there is no agreed threshold for a BDR in MMEF, we pragmatically used a cut-off of 30% based on previous studies (Shim, 1989; Levine et al., 2016). Finally, long-term studies are needed to confirm the reliability of BDR in MMEF alone as a clinical phenotype in COPD and its implications.

5.6. Conclusion

This cross-sectional study identified that positive BDR of the SA (using MMEF) is common in COPD and is present in all patients exhibiting BDR in FEV_1, supporting the potential utility of MMEF in BDR assessment. BDR of the SA is also seen in some COPD patients even in the absence of an accepted response in FEV_1, which may identify a group of patients that have a different pathophysiology, prognosis and potential treatment strategy. Therefore, assessing BDR using MMEF may also play a role in the management of COPD.

Theme #3: The utility of small airways tests in acute exacerbation of COPD

6. The use of physiological tests assessing the acute response to treatment during exacerbations of COPD (with a focus on small airway function) – A systematic review

This systematic review was performed to provide information about small airway tests' use in this acute setting. An abstract of this review was also presented at the European Respiratory Society Congress (Alobaidi et al., 2020a) (see appendix 6.1).

This chapter has also been published in the Journal of COPD and titled **"The use of physiological tests assessing the acute response to treatment during exacerbations of COPD (with a focus on small airway function) – A systematic review"** (Alobaidi et al., 2020b) (see appendix 6.2).

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Authors contribution: N.Y. Alobaidi conceived, designed the study, performed the initial search, assessed the eligibility of the included studies, performed the quality assessment for the included studies, performed data acquisition and wrote the initial manuscript and approved the final version. M.A. Almeshari assessed the eligibility of the included studies and performed the quality assessment for the included studies and approved the final version. E. Sapey designed and planned the study and revised the manuscript and approved the final version. J.A. Stockley revised the manuscript and approved the final version. R.G. Edgar assessed the eligibility of the included studies and revised the manuscript and approved the final version.

6.1. Introduction

Recently, the United Kingdom national COPD audit data identified difficulties in diagnosing exacerbations and poor care during exacerbations as significant, unfulfilled health needs (Stone RA, 2018). Methods of diagnosing COPD exacerbations and assessing the response to treatment currently rely on self-reported symptoms in clinical practice and spirometry in research studies. Commonly, the forced expiratory volume in the first second (FEV_1) has been the primary physiological outcome measure for clinical trials during exacerbation. However, this forced respiratory manoeuvre is variable (even during stable COPD) (Tweeddale et al., 1984) and insensitive to change over time (Pride, 2001), making it a poor biomarker for exacerbations. For example, bronchodilators have been shown to decrease hyperinflation, lessen the work of breathing and improve symptoms in the absence of a significant spirometric response (Newton, O'Donnell and Forkert, 2002).

Tests of small airway function might provide more sensitive and specific measures during exacerbations but there are a number of physiological measurements that have been proposed as measures of small airways function and a number of different devices available for each measurement (McNulty and Usmani, 2014; Singh et al., 2020; Stockley et al., 2017a). The reported measurements include (but are not limited to) Maximal Mid-Expiratory flow (MMEF), nitrogen washout tests, Forced oscillation technique (FOT) and plethysmographc airway resistance (Raw).

While there remain some debate about the specificity of certain tests to evaluate small airways function (King et al., 2019), studies suggest that tests of small airways may be better able to identify physiological responses to treatment compared with conventional spirometric measures (Borrill et al., 2005). However, it is unclear

whether such tests would be clinically valuable during an exacerbation of COPD as there are no previous comprehensive reviews of the evidence in this area.

6.2. Aim

To summarize the findings of studies comparing a measure of small airways function to FEV_1 during exacerbations of COPD to inform whether these tests could be incorporated as a primary outcome for further studies within this population.

6.3. Objective

To assess treatment response using small airway tests in comparison to FEV_1 during exacerbation of COPD.

6.4. Methods and design

6.4.1. Protocol and registration

The systematic review protocol was prepared following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009) and registered on PROSPERO (registration number: CRD42019131939).

6.4.2. Eligibility criteria

6.4.2.1. Study design

Randomized controlled trials (RCT), non-randomized interventional studies, observational studies, case series and uncontrolled studies of ≥10 that compared at least one small airway test with FEV_1 at both exacerbation onset (this was clinician-defined exacerbation) and a follow-up measurement up to and including two months after exacerbation onset.

6.4.2.2.Type of participants:

Adult patients older than 18 years with a clinical diagnosis of COPD during exacerbation with no limitation on either COPD or exacerbation severity were included. Studies of COPD patients not experiencing an exacerbation (therefore, stable) were excluded. Studies of patients with a primary diagnosis of other lung diseases, including asthma, were also excluded.

6.4.2.3.Intervention and comparator

Studies were included if they contained at least one of the following commonly used tests of small airways in comparison to FEV_1: FOT, MMEF, Raw by body plethysmography and nitrogen washout tests.

6.4.2.4.Outcome

Tests of small airways which included but (were not limited to) FOT, IOS, MMEF, Raw by body plethysmography, and nitrogen washout tests.

6.4.3. Search strategy

A comprehensive search was conducted using MEDLINE (via Ovid), EMBASE (via Ovid), CINAHL, and the Cochrane Central Register of Controlled Trials (CENTRAL).

Different search strategies were used for each database (shown in appendix 6.3). ClinicalTrials.gov was used to search for completed and ongoing clinical trials. Where possible, articles not in English were translated. References lists of peer-reviewed published articles was also manually searched for additional references. Search results were downloaded to Rayyan (Ouzzani et al., 2016) and duplicates were removed.

6.4.4. Study selection

Two authors independently screened studies to assess eligibility for inclusion in the study according to the pre-specified inclusion and exclusion criteria (NYA and MAA). Disagreements were resolved through the third reviewer (RGE). Full-text studies were screened and reviewed by two independent reviewers using the pre-specified inclusion and exclusion criteria (NYA and MAA). Disagreement was resolved through discussion with a third reviewer (RGE) and reasons for exclusion recorded. Study selection was done through Rayyan (Ouzzani et al., 2016). The selection process was reported using the PRISMA flow diagram (see figure 6.1).

6.4.5. Data extraction

For each included study, data were extracted using customized electronic data extraction form, which was piloted by two reviewers (NYA and MAA) before the data extraction phase. Data extraction was completed by one reviewer (NYA) and checked for accuracy by a second reviewer (MAA). Corresponding authors were contacted if data were ambiguous or missing.

6.4.6. Risk of bias and quality assessment

Risk of bias was assessed using two quality assessment tools. RCTs were evaluated with the revised Cochrane tool for assessing the risk of bias in RCT (Sterne et al., 2019), with the risk of bias classified as high, some concern or low for each study. Non-randomized studies were assessed using National Institute of Health (NIH) Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group (NHLBI, 2021), with the quality classified as good, fair or poor. Two reviewers independently checked each selected article (NYA and MAA). Disagreement was resolved through discussion.

6.4.7. Data synthesis

Outcomes of the included studies were compared and a narrative analysis was performed. Due to the high degree of heterogeneity (with different tests of small airways, different definitions of exacerbations used and different outcome measures), a meta-analysis of included studies was not possible.

6.5. Results

6.5.1. Characteristics of included studies

Of 1436 citations (excluding duplicates), 154 relevant studies met inclusion criteria. Thirteen were non-English articles (four German, two Russian, two Chinese, one Korean, one Polish, one Bulgarian and one French) but were included for full text screening. After the full-text screening, seven articles were eligible to be included in the review and 147 were excluded with exclusion reasons documented. Of the seven articles included, only one was not in English and was written in Russian (Komlev et al., 2007) (See figure 6.1).

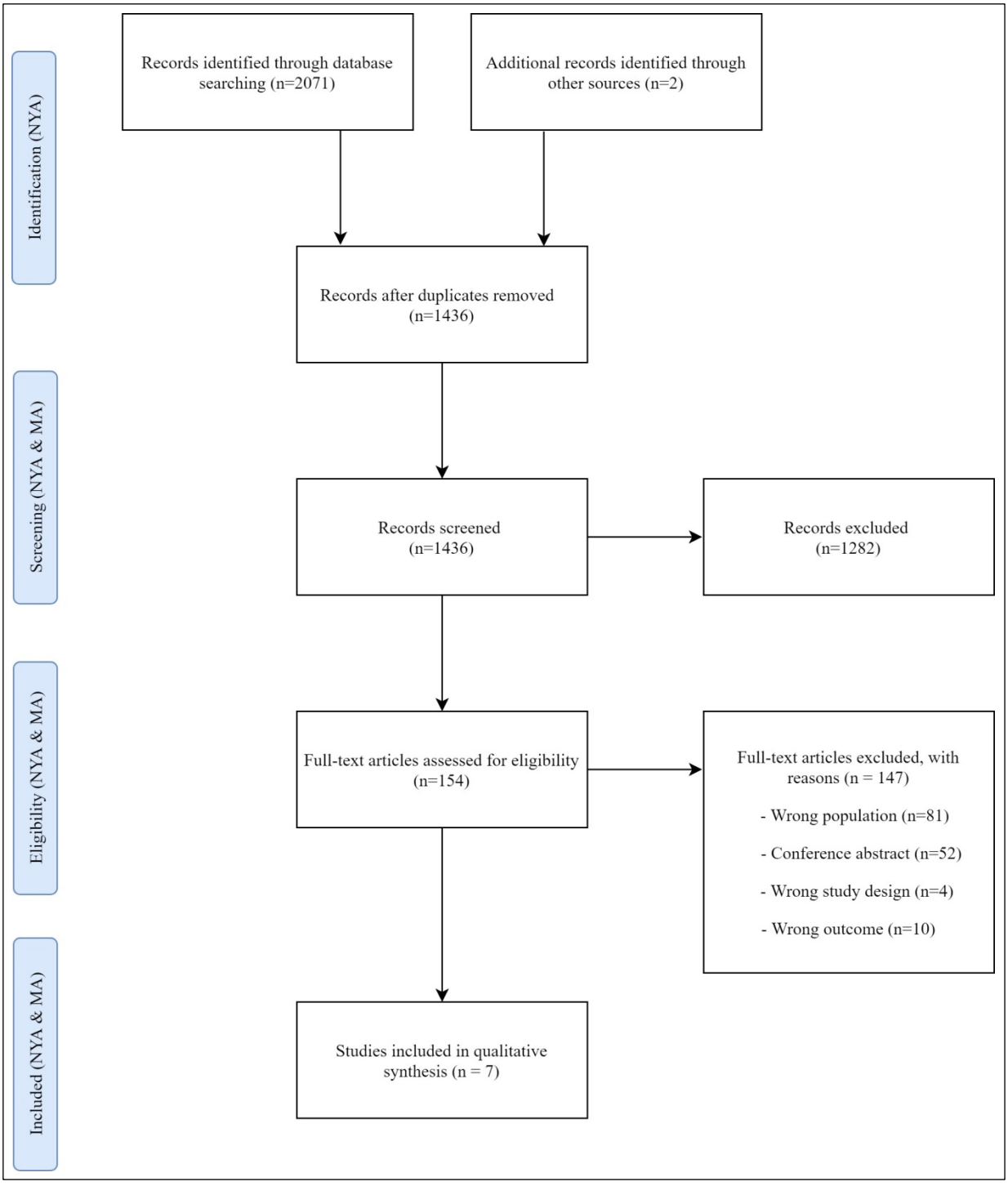

Figure 6.1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram (Moher et al., 2009)

Of the included studies, six studies were non-randomized (Parker et al., 2005; Johnson et al., 2007; Stevenson et al., 2005; Yetkin and Gunen, 2008; Jetmalani et al., 2015; Komlev

et al., 2007), and one was RCT (Sahn, Baird and Sahn, 1978). Five studies were hospitalized exacerbations (Johnson et al., 2007; Stevenson et al., 2005; Yetkin and Gunen, 2008; Jetmalani et al., 2015; Komlev et al., 2007), one included both hospitalized and community exacerbations (Parker et al., 2005), and one included community exacerbations only (Sahn, Baird and Sahn, 1978). Different definitions of exacerbation were used in most studies and they are reported in Table 6.1. The duration of included studies ranged from 5 to 60 days, with a median time of 14 days (Interquartile Range (IQR) 8 to 42). The sample size across all studies ranged between 20 to 87 participants, with a median size of 29 participants (IQR 22.5 to 52.5). The characteristics and the main findings of the seven included studies are detailed in table 6.2.

Table 6.1. Definition of exacerbation in the included studies:

1st Author (year)	Definition of exacerbation
Stevenson et al., 2005	An increase in at least two major symptoms: dyspnoea, sputum purulence, or increased sputum volume, sufficient to require hospitalization.
Sahn et al., 1978	Not explained
Yetkin et al., 2008	Episodes of worsening breathlessness and/or wheezing, often accompanied by greater volume or purulence of sputum and increased cough
Parker et al., 2005	According to the criteria adopted by the Canadian Thoracic Society, ‘‘a sustained worsening of dyspnoea, cough or sputum production leading to an increase in the use of maintenance medication and/or supplementation with additional medications’’
Komlev et al., 2007	An increase in cough, an increase in the amount of sputum and a change in its character, an increase in shortness of breath and a decrease in exercise tolerance, moderate signs of intoxication syndrome that requires therapy.
Jetmalani et al., 2015	GOLD definition “an acute event characterized by a worsening of the patient’s respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication”
Johnson et al., 2007	Increased breathlessness for at least 24 hours with at least two criteria of increased cough frequency or severity, increased sputum volume or purulence or increased wheeze.

Legend: This table demonstrates how exacerbations were defined among included studies. Each row provides the definition of exacerbations used in the stated study. Although they have defined exacerbations differently, most of the studies’ definitions met current international guidelines of exacerbation

Table 6.2. Detailed description of included studies							
1st Author (Year)	Study design	Mean age, COPD and exacerbation severity	Subjects	Name of SA test	Assessed measures (unit)	Detailed description of the study	Summary of the findings
Stevenson et al., (2005)	Longitudinal observational study.	Age: 70 years COPD: Moderate-severe. Exacerbation: Severe	*N*= 22	IOS	R_5, X_5 (kPa/L/s)	Duration: 42 days Measurements: Day 1, day 2, day 3, discharge day and day 42. Treatment: Routine care (nebulized salbutamol and ipratropium bromide (5mg and 0.5 mg) and oral CS (30mg daily for 1 week), and most patients received antibiotics).	• FEV_1 (L) showed significant improvement in day 2 ($p<0.05$), discharge day ($p<0.05$), and day 42 ($p<0.05$). However, MCID was not met until day 42. • R_5 did not show any significant improvement throughout the treatment period. • X_5 showed significant improvement at discharge day ($p<0.001$) and day 42 ($p<0.001$)
Sahn et al. (1978)	Longitudinal RCT.	Age: 62.9 years COPD:* Exacerbation: Moderate	*N*= 23	MMEF	MMEF (L/s)	Duration: 7 days Measurements: day 0, day 2, day 7 Treatment: High dose of Amoxicillin (1000mg) vs standard dose (500mg).	• MMEF and FEV_1 both before and after treatment showed significant Improvement during the treatment period. ($p<0.05$). • Moreover, the improvement in FEV_1 met MCID criteria.
Yetkin et al., (2008) (Yetkin and Gunen, 2008)	Longitudinal observational study.	Age: 63 years COPD: Moderate-severe Exacerbation: Severe	*N*= 87	MMEF	MMEF (reported as FEF_{25-75}) (% and L/s))	Duration: 9 days (2 SD) Measurements: Admission Day and discharge day. Treatment: Routine Care (inhaled salbutamol and ipratropium bromide, intravenous (IV) theophylline and prednisolone (40mg/day) and antibiotic)	• MMEF and FEV_1 both showed significant improvement after treatment of exacerbation ($p <0.05$). • FEV_1 changes did not meet the MCID criteria.
Parker et al., (2005)	Longitudinal observational study.	Age: 65 years COPD: Severe.	*N*= 20	MMEF	MMEF (reported as FEF_{25-75})	Duration: 60 days	• FEV_1 showed significant improvement at day 14 and day

		Exacerbation: Moderate and severe			(L-s-1))	Measurements: Admission day, day 7, day 14, day 30 and day 60. Treatment: Routine care (inpatients were treated according to the Canadian Thoracic Society (could include bronchodilators, Corticosteroid (CS) and antibiotic) and outpatients was treated by the family physician (mainly antibiotic)	30 ($p<0.05$) and more significant improvement seen at day 60 ($p<0.01$). • Moreover, changes in FEV_1 at day 14, 30 and 60 met the MCID criteria. • MMEF did not show any significant improvement throughout the study period. • sRaw showed significant improvement both during treatment period and most significant changes were at day 14 and 60 ($p<0.05$).
				Raw by Body plethysmography	sRaw (%)		
Komlev et al., (2007)	Longitudinal interventional study.	Age: Not reported COPD: Moderate-severe Exacerbation: Severe	*N*= 66	MMEF	MMEF (reported as FEF_{25-75}) (% Predicted)	Duration: 14 days Measurements: admission day and day 14 Treatment: Dexamethasone 24-32mg IV Twice daily.	• FEV_1 and MMEF improved significantly only in group 1 ($p<0.05$). • Raw inspiratory did not show any improvement in both groups. • Raw expiratory improved significantly in both groups ($p<0.05$)
				Raw by Body plethysmography	R_{in}, R_{ex} (kPa/L/s)		
Jetmalani et al., (2015)	Longitudinal observational study.	Age: 63 years COPD: Moderate-severe. Exacerbation: Severe	*N*= 29	FOT	Resistance (Rrs, Rrs_{insp}, Rrs_{Exp}), Reactance (Xrs, Xrs_{insp}, Xrs_{exp}, ΔXrs) (cmH_2O-s-L^{-1})	Duration: 5 days (1 SD) Measurements: Admission Day and prior to discharge. Treatment: Routine care (terbutaline, budesonide and oral CS).	• Both expiratory flow limitation (EFL) and Non-EFL patients did not have significant improvement in FEV_1. • Resistance parameters (Rrs, Rrs_{insp}, Rrs_{Exp}) did not show any significant improvement in both groups.

							• Reactance parameters (Xrs, Xrs_{insp}, Xrs_{exp}, ΔXrs) only showed significant improvement in EFL patients ($p<0.05$)
Johnson et al., (2007) (Johnson et al., 2007)	Longitudinal observational study.	Age: 63.1 years COPD: Moderate-severe. Exacerbation: Severe.	*N*= 39	FOT	Resistance (Rrs, Rrs_{insp}, Rrs_{Exp}), Reactance (Xrs, Xrs_{insp}, Xrs_{exp}, FL%) (kPa/L/s)	Duration: 6 weeks (42 days) Measurements: <48 hours of admission, after one week and after 6 weeks. Treatment: Routine care (not specified)	• FEV_1 (L), FEV_1 (% predicted) showed significant improvement in visit 2 ($p<0.005$) and visit 3 ($p<0.001$). These changes met MCID criteria. • Resistance parameters of FOT (Rrs, Rrs_{insp}, Rrs_{exp}) did not show any significant improvement in both visit 2 and visit 3. Reactance parameters of FOT (Xrs, Xrs_{insp}, Xrs_{exp}, Flow Limitation% (FL% represents the proportion of breaths for which ΔXrs indicated flow limitation) showed significant improvement in both visit 2 and 3 ($p<0.05$)

Legend: COPD severity was assessed using GOLD guideline as per the FEV_1% predicted. Exacerbation severity was assessed using GOLD guideline (Mild: treated with short acting bronchodilators (SABDs) only, Moderate: treated with SABDs + antibiotic and/or oral CS, Severe: require hospitalization or ER visits).
* FEV_1% predicted is not reported; therefore, COPD severity could not be determined.
Abbreviations: COPD, Chronic Obstructive Pulmonary Disease (COPD); IOS, impulse oscillometry; FEV_1, Forced Expiratory volume in the first second; MCID, minimal clinically important difference; RCT, randomized clinical trial; R_5, total respiratory resistance; X_5, total respiratory reactance; MMEF, Maximal Mid-Expiratory flow; $FEF_{25-75\%}$, forced expiratory flow between 25% and 75% of the forced vital capacity; CS, corticosteroid; FOT, forced oscillation technique; Rrs, total respiratory resistance, Xrs, total respiratory reactance; Rrs_{insp}, resistance during inspiration; Rrs_{exp}, resistance during expiration; Xrs_{insp}, reactance during inspiration; Xrs_{insp}, reactance during expiration; ΔXrs, expiratory flow limitation index; EFL, expiratory flow limitation; FL%, flow limitation percentage; Raw, airway resistance; sRaw, specific airway resistance; R_{ex}, resistance during expiration; R_{in}, resistance during inspiration.

Of the seven included articles three studies used FOT (Johnson et al., 2007; Jetmalani et al., 2015; Stevenson et al., 2005), four studies used MMEF (Parker et al., 2005; Sahn, Baird and Sahn, 1978; Yetkin and Gunen, 2008; Komlev et al., 2007) and two studies used Raw by body plethysmography (Parker et al., 2005; Komlev et al., 2007). Using small airways tests and FEV_1, treatment response was assessed in all of the included studies. However, included studies varied in how they reported response to treatment. Some studies reported pre- and post-measure (Sahn, Baird and Sahn, 1978; Stevenson et al., 2005; Yetkin and Gunen, 2008; Jetmalani et al., 2015; Komlev et al., 2007) while, in the others, pre-measure and the changes in the outcome measured were reported (Parker et al., 2005; Johnson et al., 2007).

6.5.2. Quality assessment of included studies

All non-randomized studies had clearly stated their objective, research question and eligibility criteria. However, three of the studies did not justify the sample size of the study (Yetkin and Gunen, 2008; Jetmalani et al., 2015; Komlev et al., 2007), although two had the highest number of participants among the included studies (Yetkin and Gunen, 2008; Komlev et al., 2007). Participants of the included studies were representative of the general population of interest in all of the studies. Four of the studies had a number of visits where measurements were taken (Parker et al., 2005; Sahn, Baird and Sahn, 1978; Johnson et al., 2007; Stevenson et al., 2005). One study was felt to be of good quality (Johnson et al., 2007), two of fair quality (Yetkin and Gunen, 2008; Komlev et al., 2007) and three of poor quality (Parker et al., 2005; Stevenson et al., 2005; Jetmalani et al., 2015) (as shown in table 6.3.). The risk of bias of the only included RCT (Sahn, Baird and Sahn, 1978) was found to be high (as shown in table 6.4.).

Table 6.3. NIH quality assessment tool of included non-randomized studies.

NIH Quality assessment	Yetkin et al., 2007	Jetmalani et al., 2015	Parker et al., 2005	Johnson et al., 2007	Stevenson et al., 2006	Komlev et al., 2007
Was the study question or objective clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes
Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	Yes	Yes	Yes	Yes	Yes
Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	Yes	Yes	Yes	Yes	Yes
Were all eligible participants that met the prespecified entry criteria enrolled?	CD	CD	CD	CD	CD	CD
Was the sample size sufficiently large to provide confidence in the findings?	Yes	CD	No	Yes	No	Yes
Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	Yes	Yes	Yes	Yes	Yes
Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes
Were the people assessing the outcomes blinded to the participants' exposures/interventions?	NA	NA	NA	NA	NA	NA
Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	CD	No/NA	Yes/CD	Yes/Yes	Yes/Yes	CD
Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	Yes	Yes	Yes	Yes	Yes
Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	Yes	Yes	CD	Yes	Yes	CD
If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	CD	CD	CD	CD	CD	CD
Overall Quality rating	**Fair Quality**	**Poor Quality**	**Poor Quality**	**Good Quality**	**Poor Quality**	**Fair Quality**

Legend: Quality assessment was done using NIH tool. Each question was assessed by two reviewers separately (NYA. and MA), and overall rating was blindly determined. Results were then discussed, and Conflicts in questions and overall rating resolved through discussion. The overall quality rating for included studies is the agreed rating between reviewers.
Abbreviations: CD, cannot determine; NA, not applicable.

Table 6.4. Risk of bias assessment of the included RCT

Study ID	Randomization Process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
Sahn et al., 1978	High	High	High	Some concerns	Some concerns	**High risk of bias**

Legend: Risk of bias was evaluated using Revised Cochrane tool for RCT. The tool assesses risk of bias on several domains: Randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported results. The risk of bias was evaluated as recommended: high risk, some concerns, or low risk. Each domain was assessed by two reviewers independently (NYA and MA). Conflict in domains and overall risk of bias were resolved through discussion.

6.5.3. Results of individual studies

6.5.3.1. Forced oscillation technique (FOT)

FOT was used to assess treatment response in COPD exacerbation in three observational studies. Impulse oscillometry (Jaeger MasterScreen (IOS)), which is a later version of FOT, was used in one study. Stevenson et al. used IOS and FEV_1 to assess treatment response during exacerbation in a longitudinal study. Here, after the baseline assessment (day 1 of the exacerbation), IOS and FEV_1 were repeated at day 2, day 3, discharge day and day 42 (Stevenson et al., 2005). The median length of hospital stay was 7 days (range 3-10 days). The authors only reported R_5 (total respiratory resistance) and X_5 (total respiratory reactance), with both reported as mean $\pm$ standard deviation (SD). R_5 did not show any improvement during the treatment period. X_5 showed an average improvement of 26% from baseline (-0.42 ± 0.03 kPa/L/s) to discharge day (-0.31 ± 0.03 kPa/L/s; $p<0.001$) and a 33% improvement from baseline to day 42 (-0.28 ± 0.04 kPa/L/s; $p<0.01$). FEV_1 also improved during the treatment period from a mean of 1.03 ± 0.08L at baseline to 1.08 ± 0.08L ($p<0.05$) at day 2 with no changes at day 3. At discharge, FEV_1 increased to 1.12 ± 0.09L ($p<0.05$) (an average of 8% improvement) but this did not meet the accepted Minimal Clinically Important Difference ((MCID) of at least 100ml) for FEV_1 (Jones et al., 2014). The 100ml MCID was not observed until day 42 (1.26 ± 0.10L; $p<0.01$), where there was an average 22% improvement from baseline.

Jetmalani et al. who used an in-house-built FOT device at 6Hz, assessed if expiratory flow limitation ((EFL) representing a physiological condition in which expiratory flow cannot rise by increasing respiratory effort (Tantucci and Grassi, 1999)) related to symptoms during hospitalized exacerbations of COPD (Jetmalani et al., 2015). The authors categorized patients into two groups: those with EFL at admission and those with no EFL at admission. They

performed assessments on admission and prior to discharge, with mean length of stay being 5 days (±1 SD). All FOT results were reported as mean ±SD. Resistance parameters (Rrs (total respiratory resistance), Rrs_{insp} (resistance during inspiration), Rrs_{exp} (resistance during expiration)) did not change in either group. Reactance parameters improved in the EFL group prior to discharge. Although Xrs_{insp} (reactance during inspiration) showed improvement (increasing from -3.73 ± 0.97 $cmH_2O \cdot s \cdot L^{-1}$ to -2.90 ± 0.87 $cmH_2O \cdot s \cdot L^{-1}$, p=0.01), Xrs (total respiratory resistance), Xrs_{exp} (reactance during expiration), ΔXrs (expiratory flow limitation index, which is used to measure EFL (Xrs_{insp} - Xrs_{exp})) demonstrated the most pronounced improvement (Xrs increased from -7.37 ± 2.27 $cmH_2O \cdot s \cdot L^{-1}$ to -4.41 ± 1.92 $cmH_2O \cdot s \cdot L^{-1}$ (p=0.008), Xrs_{exp} from -8.70 ± 3.19 $cmH_2O \cdot s \cdot L^{-1}$ to -5.12 ± 2.33 $cmH_2O \cdot s \cdot L^{-1}$ (p=0.008), and ΔXrs from 4.97 ± 2.64 $cmH_2O \cdot s \cdot L^{-1}$ to 2.21 ±1.51 $cmH_2O \cdot s \cdot L^{-1}$ (p=0.008)). FEV_1 did not change in either group.

Johnson et al. used FOT (with an oscillation frequency of 5Hz) and FEV_1 to assess treatment response across three visits (<48 hours of admission, after one week and after 6 weeks) (Johnson et al., 2007). All results are reported as mean and standard error of mean (SEM). No significant changes were seen in resistance parameters (Rrs, Rrs_{insp}, Rrs_{exp}) across timepoints. Following one week of admission, mean Xrs_{insp} increased by 13% (4.5 SEM) ($p<0.05$); Xrs by 27.9% (7 SEM) and Xrs_{exp} 31.5% (7.8 SEM) ($p<0.001$ for both). After 6 weeks, Xrs_{insp} increased by 27.4% (6.7 SEM) ($p<0.001$), Xrs by 35.2% (8.9 SEM) and Xrs_{exp} by 37.1% (10.0 SEM) ($p<0.005$ for both). FL% (flow limitation percentage, which represents the proportion of breaths for which ΔXrs indicated the flow limitation) improved at visit two (decreasing by 19.2 ± 6.1%, $P<0.005$) and decreasing by 19.5 ± 7%, ($p<0.05$) at visit 3. FEV_1 also improved, meeting the MCID criterion at visit two (improvement of 0.153L ± 0.046 (6.4 ± 1.7%; $p<0.005$)) and three (0.274L ± 0.064 (11.4 ± 2.3%; $p<0.001$)). When expressed as a percentage change, reactance parameters improved more than FEV_1.

6.5.3.2.MMEF

MMEF was used in four studies. Sahn et al. (who included only male patients in their RCT) used MMEF and FEV_1 to assess the response to high (1000mg three times a day (TID)) or standard (500mg TID) dose amoxicillin during an episode of acute bronchitis in patients with COPD (reflecting the terminology of exacerbations at that time) (Sahn, Baird and Sahn, 1978). However, they reported the results as only one mean and SD irrespective of the different doses of antibiotic being given. MMEF and FEV_1 (pre- and post-bronchodilator) were collected at day 0, day 2 and day 7 with MMEF changing throughout the treatment period ($p<0.05$). At day 2, pre-bronchodilator MMEF increased from 1.25 ± 0.26 L/s to 1.46 ± 0.28L/s ($p<0.05$) but there was no difference in pre-bronchodilator MMEF when day 7 (1.39 ± 0.29L/s) was compared to baseline. Post bronchodilator MMEF improved only at day 7, where it rose from 1.35 ± 0.28L/s to 1.67 ± 0.32 L/s ($p<0.05$) (an average 24% increase). FEV_1 also improved during the treatment period, meeting the MCID criterion. Pre-bronchodilator FEV_1 increased from 1.65 ± 0.22L to 1.82 ± 0.22L at day 2 and to 1.81 ± 0.23L at day 7 ($p<0.05$). Post-bronchodilator FEV_1 rose from 1.80 ± 0.23L to 1.94 ± 0.22L ($p<0.05$) at day 2 and to 1.98 ± 0.23L ($p<0.05$) at day 7 (an average 10% increase).

MMEF was also used in two observational studies. Yetkin et al. used MMEF (termed FEF_{25-75} in their study (L/s and %)) and FEV_1 to assess treatment response during an exacerbation, collecting readings on admission day and discharge day (mean length of stay 9 days $\pm$ 2) (Yetkin and Gunen, 2008). All results were reported as mean and SD. MMEF and FEV_1 changed at discharge ($p<0.05$): MMEF increased from 0.43 ± 0.14L/s to 0.52 ± 0.14L/s ($p <0.05$) (an average 20% increase) and FEV_1 increased from 1.14 ± 0.29L to 1.22 ± 0.32L, (p-value <0.05) (an average 7% increase), which FEV_1 did not meet the MCID.

Parker et al. assessed both Inspiratory Capacity (IC) and MMEF in comparison to FEV_1 to evaluate the severity and recovery of acute exacerbations of COPD in a longitudinal study with multiple visits (admission day, day 7, day 14, day 30 and day 60) (Parker et al., 2005). All results were reported as mean and SEM. MMEF did not show any change throughout the treatment period. In contrast, FEV_1 improved during the recovery period of the exacerbation although changes above the MCID criterion were only seen from day 14 (FEV_1 increased by 0.12 ± 0.06L at day 14, 0.13 ± 0.06L at day 30 ($p<0.05$) and by 0.24 ± 0.06L at day 60 ($p<0.01$))

In an interventional study, Komlev et al. also used MMEF and FEV_1, assessing the effect of systemic glucocorticoid steroids (SGS) during acute exacerbations of COPD from admission to day 14 of treatment (Komlev et al., 2007). All results were reported as mean and SD. In their study, MMEF demonstrated improvements at day 14 (rose from 15.7 ±7.0% to 21.5 ± 14%, $p<0.05$; an average improvement of 37%). FEV_1 also demonstrated improvements (increased from 41.1 ± 14% to 50.1 ± 16%, $p<0.05$; an average 22% increase). They also separated patients into two groups: group 1 (>15% change in FEV_1 at day 14 of SGS) and group 2 (<15% changes in FEV_1 at day 14 of SGS). At day 14, group 1 demonstrated improvements in MMEF and FEV_1 ($p<0.05$) with no change in group 2. In group 1, MMEF increased from 12.4 ± 7.0% predicted to 28.8 ±18.0% predicted at day 14 of SGS treatment ($p<0.05$), and FEV_1 increased from 34.2 ± 11.0% to 60.5 ± 14.0%. Although it could not be determined whether the improvement in FEV_1 met MCID criteria as actual values were not given, a 25% change represents a clinically relevant change.

6.5.3.3.Raw by Body Plethysmography

Raw obtained by body plethysmography was used to assess treatment response in two studies. Parker et al. reported MMEF, FEV_1 and specific airway resistance (sRaw) in their observational study at admission, day 7, day 14, day 30 and day 60 (as described previously) (Parker et al., 2005). All results were reported as mean and SEM. Although sRaw decreased at day 7 and day 30, it only demonstrated significant improvement at day 14 and day 60 ($p<0.05$). Compared to the baseline assessment, sRaw changed by 133 ± 57% and 128 ± 51% at day 14 and 60, respectively ($p<0.05$) with FEV_1 improving most at day 60 ($p<0.01$).

As described previously, Komlev et al. assessed airway resistance during inspiration (R_{in}) and expiration (R_{ex}) at admission day and day 14 of SGS (Komlev et al., 2007). All results were reported as mean and SD. R_{ex} showed significant improvement (decreasing from 1.05 ± 0.66kPa/L/s to 0.76 ± 0.5kPa/L/s; $p<0.05$), while R_{in} did not. When separated into the two groups, R_{in} did not change at day 14 in either group. In contrast, R_{ex} decreased in both group 1 (from 1.02 ± 0.5kPa/L/s to 0.57 ± 0.4kPa/L/s; $p<0.05$) and group 2 (from 1.06 ± 0.7kPa/L/s to 0.84 ± 0.5kPa/L/s; $p<0.05$), with FEV_1 improving only in group 1 ($p<0.05$).

6.6. Discussion:

This is the first systematic review evaluating the use of physiological tests of small airway function during exacerbations of COPD. The aim of this review was to assess whether there was sufficient evidence to incorporate measures of small airways function as a primary outcome for studies of COPD exacerbations. In summary, the small number of studies, low participant numbers, study heterogeneity and general mixed quality of the studies limits any conclusions about the utility of these tests during exacerbations. However, in most studies, there were early signals of small airways measurement change following the diagnosis and

treatment of an exacerbation. This was reported (albeit not consistently) for FOT, MMEF and sRaw, often at an increased magnitude or prior to an FEV_1 change. This suggests further studies are warranted to determine if these physiological tests provide information about the early recovery phase of exacerbations. However, more information is needed to determine population reference ranges, which test should be used in which setting and which devices provide comparable results.

Exacerbations are common and serious events and are associated with reductions in quality of life, health status and lung function (Seemungal et al., 1998). Diagnostic tools and treatment approaches have not changed significantly for over 30 years (Sapey et al., 2019) but there is great interest in testing new therapies to prevent or treat exacerbations and finding more sensitive and specific tools to diagnose exacerbations and map their recovery. It is increasingly recognized that small airways dysfunction and damage is an early feature of COPD (Hogg, 2004; Stockley et al., 2017b) and these processes may also be implicated in exacerbations (Papi et al., 2006; O'Donnell and Parker, 2006). Exacerbations are usually associated with an increase in airway inflammation, impacting on small airways through airway narrowing, mucus hypersecretion and sometimes plugging (Papi et al., 2006; O'Donnell and Parker, 2006). In light of this, small airways tests have been proposed as potential tools that could be used in studies of COPD (Singh, 2017).

In general, published studies of tests of small airways function during exacerbations were small and heterogeneous, using different small airway tests and different definitions of an exacerbation. The methodological quality of these studies was variable and mainly of fair to poor quality. There was only one study of good quality (Johnson et al., 2007), with two of fair quality (Yetkin and Gunen, 2008; Komlev et al., 2007), three of poor quality (Parker et al., 2005; Stevenson et al., 2005; Jetmalani et al., 2015) and one trial rated as having a high

risk of bias (Sahn, Baird and Sahn, 1978). Small airways tests along with FEV_1 demonstrated improvement following the recovery from exacerbation in the majority of the included studies but different studies reported improvements at different time points, even with the same test.

Despite these important limitations, there were suggestions of an earlier signal of change from exacerbation onset in the tests of small airways compared to FEV_1. For example, for FOT: while Stevenson et al. reported a difference in FEV_1 across all time points, there was only an average improvement of 8% in FEV_1 at discharge in contrast to an average improvement of 26% in X_5 (with average length of stay 7 days) (Stevenson et al., 2005). Johnson et al. reported improvements in FEV_1 as well as FOT, with FOT having a greater percentage change than FEV_1 (Johnson et al., 2007). Jetmalani et al. did not find a difference in FEV_1 at discharge (day 5) despite describing difference in measures of FOT (Jetmalani et al., 2015). For MMEF, Sahn et al. described an average increase of 24% in MMEF but only a 10% increase in FEV_1 at day 7 post-exacerbation (Sahn, Baird and Sahn, 1978). Komlev et al. reported a greater percentage increase in MMEF than FEV_1 at day 14 post-exacerbation and improvements in R_{ex} (Komlev et al., 2007). Yetkin et al. described a 20% increase in MMEF but only a 7% increase in FEV_1 between admission and hospital discharge (with an average admission length of 9 days) (Yetkin and Gunen, 2008). Parker et al. described no significant change in MMEF or FEV_1 within the first two weeks following exacerbation onset but significant improvements in FEV_1 and sRaw after day 14 (Parker et al., 2005). When interpreting these data, the variance of results should be carefully considered alongside the average percentage change, but these results support some small airways signal during exacerbations for at least some COPD patients.

Although tests of small airway and FEV_1 seems to mirror each other in terms of physiological improvement, (especially in the later recovery phases of an exacerbation),

obtaining FEV_1 measurement can be challenging (as spirometry is a maximal forced manoeuvre) (Global Initiative for Chronic Obstructive Lung Disease, 2022) compared to some small airways' tests (for example, IOS, FOT) where patients perform tidal breathing. Furthermore, patients during exacerbation may be too unwell to perform spirometry. Potentially, FOT may be a more acceptable test to perform at the bedside but, unfortunately, the included studies did not report completeness of data at each testing time for each test. Therefore, it is unclear if patients were more likely to complete tidal breathing assessments as opposed to forced manoeuvres.

Three studies used FOT with the most significant changes seen in reactance parameters (Xrs, $Xrs_{insp,}$ Xrs_{exp}, ΔXrs, X_5). All studies assessed respiratory impedance at lower oscillation frequency. In Stevenson et al. IOS assessed resistance and reactance at an oscillation frequency of 5Hz, describing that both X_5 and FEV_1 improved from baseline to follow up, with no change in R_5 (Stevenson et al., 2005). Jetmalani et al. used FOT to measure respiratory impedance at an oscillation frequency of 6 Hz (Jetmalani et al., 2015). This study showed that reactance parameters (but not resistance parameters or FEV_1) changed significantly from onset to recovery in patients with EFL on admission but no changes in reactance, resistance or FEV_1 in those without EFL. These findings and others (Stevenson et al., 2005) suggest that not all COPD patients have EFL during exacerbations. In those that do, EFL is associated with changes in reactance parameters at lower frequency and EFL may identify a subgroup most likely to provide a signal of improvement using FOT. Johnson et al. used FOT at 5Hz oscillation frequency and also reported that FEV_1 and reactance parameters changed significantly while resistance did not (Johnson et al., 2007). Although Jetmalani et al. have used an atypical FOT frequency, there are no marked differences between them as frequencies in the 3 – 10 Hz range appear to demonstrate a good sensitivity to airway calibre

(Farre et al., 1997). Furthermore, several studies have used FOT in this range, and the three included studies reported the same findings of FOT. Reactance parameters in all FOT studies (but not in those without EFL at baseline (Jetmalani et al., 2015)) showed improvements during the recovery from exacerbation. Reactance is frequency-dependent (changes as oscillation frequency changes) due to the heterogeneity across tissue viscoelasticity, airway tree, airway wall shunt, and time constant (King et al., 2019). At lower oscillation frequency, reactance becomes more negative as the mechanical characteristics of the lung and chest wall dominate, which reflects greater elastance (or stiffness) of the oscillation mechanics in accordance with the impedance equation. Furthermore, frequency dependence may be affected by the presence of heterogeneous ventilation resulting from airway diseases (King et al., 2019), and at any given frequency, effective reactance decreases as heterogeneity increases. The reason for the improvement of reactance described in the included studies is unclear but it may be due to the reduction in hyperinflation after bronchodilators, increasing lung compliance over tidal breathing range. Although several studies have indicated that resistance at lower frequency (especially R_5) is also sensitive to change after bronchodilators (Borrill et al., 2008; Borrill et al., 2005), R_5 represents the total airway resistance and does not exclusively assess small airways. FOT may be of use during exacerbations of COPD but assessing resistance at different oscillation frequencies (up to 20Hz) might provide more information as, although resistance at higher oscillation frequencies does not change after bronchodilator therapies (Borrill et al., 2008), it can be used to calculate the difference between R_5 and R_{20} (R_{5-20}). R_{5-20} is used to determine the contribution of peripheral airways which might give an insight about small airway function. However, the anatomical location of the transition between the distal and proximal airways has not been identified (Goldman, Saadeh and Ross, 2005; King et al., 2019). Therefore, future studies should aim to include

both R_5 and R_{20}, so R_{5-20} can be calculated. Impedance measurements often differ when measured by different devices, making comparison between studies difficult, therefore future work should consider if a gold standard technique can be identified, to allow inter-study learning (Dandurand et al., 2019).

Three out of four studies that included MMEF described an improvement in readings over the course of an exacerbation despite differences in the treatments being given and the place of care. Despite the need to correct MMEF for lung volumes (to increase reproducibility) studies did not report if this adjustment had been made. Sahn et al. evaluated two different doses of amoxicillin and described improvements in both MMEF and FEV_1 during the treatment period (Sahn, Baird and Sahn, 1978). However, the treatment groups were combined into one reported outcome, suggesting a high risk of reporting bias. Yetkin et al. also did not indicate whether MMEF was adjusted for lung volumes but both MMEF and FEV_1 improved over the course of an exacerbation (Yetkin and Gunen, 2008). Komlev et al. described an improvement in MMEF in patients when reported results as a whole (Komlev et al., 2007). However, when they did a post hoc analysis the improvements were seen in patients who had increase in FEV_1 by >15% after 14 days of SGS treatment (group 1) but not in group 2, where no improvement in FEV_1 was seen.

Only one study did not report an improvement in MMEF (Parker et al., 2005), although an improvement in FEV_1 was described. Potential reasons for this might include that their study was the smallest among those including MMEF (with 20 patients and three patients who withdrew from the study). Secondly, they included older and more severe patients than the other studies, where significant small airways destruction is likely to already have occurred. Lastly, they did not indicate whether MMEF was adjusted for lung volumes and changes in FVC may impact the reproducibility of MMEF.

MMEF has a wide reference range in clinical practice which might limit its interpretation, and results prone to considerable variability (Quanjer et al., 2014b). Furthermore, MMEF is obtained by performing spirometry; a forced manoeuvre that COPD patients may struggle to perform during an exacerbation. Additionally, established COPD is associated with severely lowered MMEF (approximately 17% predicted in one study (Stockley et al., 2017a)) perhaps limiting its ability to identify change.

Two studies reported airway resistance by body plethysmography. Parker et al. reported that sRaw showed significant % changes during the treatment period (with no change in MMEF) but did not demonstrate the method of obtaining sRaw (Parker et al., 2005). Komlev et al. reported Raw differently (assessing Raw in two phases; expiration and inspiration) (Komlev et al., 2007). Their study showed that R_{ex} changed significantly at day 14 of treatment while R_{in} did not change. Furthermore, when looking at the analysis of the two groups, R_{ex} changed significantly at day 14 of treatment in both groups while R_{in} only changed in group 1 (FEV_1 >15% at day 14 of SGS treatment). However, the method of obtaining Raw was not described. There are limits to the interpretation of these findings. Measures of airway resistance may be influenced by increased resistance of the small or large airways, which may be variable during exacerbation and prone to alteration with breathing effort. Furthermore, inflammation and airflow obstruction in the larger airways may render the small airways less accessible for physiological testing and although airway resistance by body plethysmography may be a valuable tool, the evidence of its sensitivity for small airway changes is still uncertain. Moreover, performing body plethysmography in the acute setting may be challenging as the test cannot be done at the bedside.

6.6.2. Limitations and implication for research and clinical practice

This systematic review was limited by different exacerbation definitions being utilized across included studies and the practical challenges of summarising and synthesising data due to their heterogeneity. Tests of small airways function appear to change during the course of an exacerbation of COPD; hence, more well-structured studies are needed to determine the usefulness of each test. Although most of the included studies showed some changes in small airway tests, it remains unclear which tests of small airways function are the most sensitive to change, which are best tolerated by patients and which are the most practical to deliver. Better designed, larger studies, that compare a number of tests and better characterise the exacerbation and the patient with COPD are needed.

6.7. Conclusion

Exacerbations are common and life-threatening events that may have an impact on health status and lung function. Despite this, diagnostic methods and management approaches have been largely unchanged significantly for over 30 years (Sapey et al., 2019). There is a critical need for sensitive physiological measures to objectively assess and map exacerbations recovery. Small airway dysfunction is a pathophysiological feature of COPD and it may be worsened by the increased inflammation present during exacerbations. Small airway tests may be valuable in recognizing exacerbations and following their recovery or response to treatment (either as a complementary test to FEV_1 or in specific phases of the recovery process), although further evidence is needed to support their use.

7. The utility and acceptability of tests of small airways function during acute exacerbations of COPD: A prospective pilot study

This chapter is a pilot study was planned to assess the feasibility and acceptability of tests of small airways compared to measurements of forced expiratory volume in the first second ($FEV_{1)}$ during an exacerbation of COPD. The protocol for this study was written, and HRA ethical approvals gained (see appendix 7.1.), but the study was paused due to the impact of the COVID-19 pandemic and could not be restarted during the research period for the PhD. This chapter provides a brief introduction and description of the study protocol.

7.1. Brief Introduction

Currently, FEV_1 is used as a surrogate outcome measure to determine the impact of interventions in exacerbations of COPD. Trials using FEV_1 in this setting often require daily spirometry and then weekly or monthly spirometry to assess change from exacerbation. In interventional studies of COPD where FEV_1 is a primary/co-primary endpoint, drop-out rates can be as high as 45% (Decramer et al., 2011) and Patient and Public Involvement work within the Birmingham Respiratory group and South Birmingham Breathe Easy patient forum suggest forced expiratory manoeuvres can be onerous and difficult for patients to complete when they are feeling unwell. Tests of small airways (particularly, forced oscillometry techniques (FOT)) may be a useful and more appropriate tool for monitoring COPD patients during exacerbations (Johnson et al., 2007; Jetmalani et al., 2015) as they can be performed with quiet tidal breathing. However, these tests have not been well investigated in this setting. The published systematic review in chapter 6 suggested that they could be of use, but studies have been small (Alobaidi et al., 2020b). Thus, this indicates that this technique needs further evaluation, particularly in relation to other outcomes of interest in COPD exacerbations such as symptoms and inflammation. Therefore, this pilot study will be conducted to determine whether measuring FOT should be evaluated in a large interventional study as a potential surrogate outcome measure or may have utility as a biomarker of exacerbation severity.

We hypothesise that FOT is feasible and acceptable for patients hospitalised with acute exacerbation of COPD (AECOPD). We also hypothesise that measures of FOT mirrors symptom scores, functional status, FEV_1 and systemic inflammation during exacerbation and the recovery period.

7.2. Aim

To assess the utility and acceptability of FOT during exacerbations of COPD in an observational pilot study.

7.3. Objectives

The primary objective: To determine if measures of FOT are more acceptable and feasible for patients hospitalised with an exacerbation of COPD.

The secondary objectives: To assess if measures of FOT mirror changes in symptom scores, functional status, FEV_1 and systemic inflammation during resolution of an exacerbation of COPD

7.4. Methods

7.4.1. Study design and setting

The design of this study will be prospective, observational pilot study of patients admitted at University Birmingham Hospital (UHB), Queen Elizabeth Hospital Birmingham (QEHB) for an exacerbation of COPD. Patients will initially be seen on the Acute Medical Unit (AMU) or Emergency Department (ED) but will be followed during the course of their admission to other wards where they may be transferred to. The study protocol was evaluated and approved by the East of Scotland Research Ethics Committee (reference no: 21/ES/0101) and will be conducted in accordance with the UK policy framework for Health and Social Care Research, 2018, principles of good clinical practice and Helsinki Declaration.

7.4.2. Study population

Patients will be eligible to take part in the study if they meet the following criteria:

- Are aged between 30 and 85 years
- Have a confirmed diagnosis of COPD (defined FEV_1/FVC <70%)
- Have recognized features of acute exacerbation (breathlessness, increased cough frequency or severity, increased sputum volume and purulence or increased wheeze)
- Potential to be consented to the study within 24 hours of admission to hospital.

Patients will be excluded if they:

- Do not have an exacerbation of COPD (stable COPD)
- Have other chronic lung diseases such as asthma
- Have pneumonia (defined radiologically)
- Have active cardiac disease
- Are unable to perform lung function tests required in the study.
- Have a confirmed COVID-19
- Have respiratory failure required intubation or nasal ventilation.
- Have any contraindication to performing forced lung function manoeuvre.

7.4.3. Study procedures

Eligible participants will be assessed ideally at four time points. As this is a pilot pragmatic study, following the baseline evaluation (visit 1 [this will be within 24 hours of admission]), patients will be followed up at day 3 or 4 (visit 2) and day 5 or 6 (visit 3) of an exacerbation. If possible, patients will be assessed at another follow up visit after discharge (visit 4 [this will be 6 weeks to 6 months after admission]) (see figure 7.1.). Visit 4 could either coincide with a routine care appointment or a research specific visit to hospital. However, data will be collected if and when possible, with missing scheduled events documented with the reasons for this. As this is a pilot study, if a patient declines to provide

any data or complete specific tests at any timepoint, this will not prevent further participation, but will be logged. If a test is described as part of routine care, data will be only collected if the test has been performed as part of routine care. If a patient is discharged prior to a study visit, we will ask permission to collect questionnaire data over the telephone, but would miss out other measurements which would require a face to face visit. The duration of the study will be 12 months.

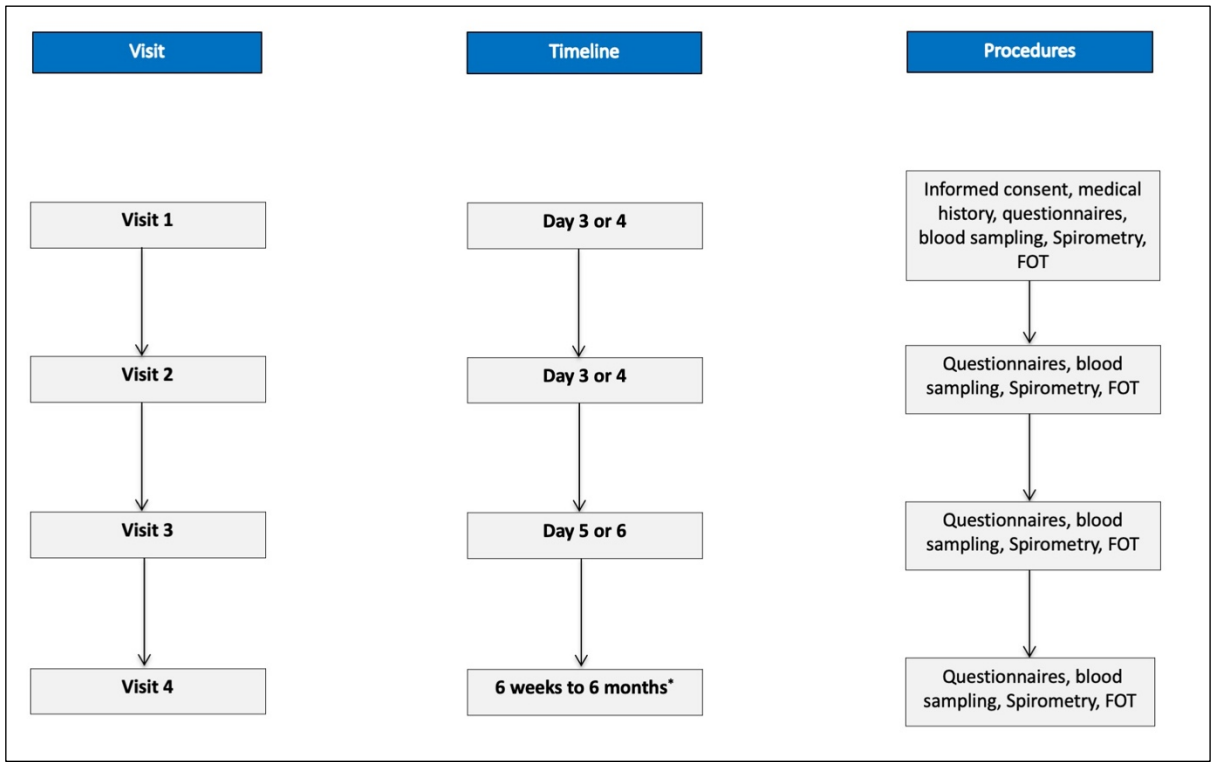

Figure 7.1. Summary of study visit diagram.

Legend: ** This is either during usual care out-patient appointment or as a study visit*

Abbreviations: FOT, forced oscillometry.

7.4.4. Study endpoints/outcomes measurement

7.4.4.1. Primary outcomes

7.4.4.1.1. Acceptability of FOT

Acceptability is defined as 10% or more COPD patients attempting FOT compared to spirometry at the first timepoint.

7.4.4.1.2. Feasibility of FOT

Feasibility is defined as 20% or more of patients providing a valid FOT trace compared to patients providing a valid spirometry trace.

7.4.4.2. Secondary outcomes

7.4.4.2.1. Lung function measurements

All lung function tests will be performed at the patient's bedside using portable devices, and following discharge, in out-patient areas in the QEHB. All tests will be according to standard operating procedures and acceptability criteria. The equipment used will be in accordance with European Respiratory Society (ERS)/ American Thoracic Society (ATS) 2005 criteria, and patients will be tested on the same piece of equipment at each visit to minimize variability. Patients will perform spirometry and FOT across time points (visit 1, visit 2, visit 3 and visit 4). FOT will be performed first and then followed by spirometry.

Spirometry will be performed using Microlab Mark 8 spirometer (CareFusion). Quality control and procedures will be according to the Association for Respiratory Technology & Physiology (ARTP) (Sylvester et al., 2020). Spirometric parameters that will be assessed include, FEV_1, Forced Vital Capacity (FVC), FEV_1/FVC, Maximal mid-Expiratory Flow (MMEF). FEV_1, FVC and FEV_1/FVC will be expressed as either Litres or % predicted, whereas MMEF will be expressed as either L/sec or % predicted.

FOT will be performed using the tremFlo C-100 Oscillometry system (Thorasys Thoracic Medical Systems Inc, Montreal). Quality control and procedures will be in accordance with the ERS technical standards for respiratory oscillometry (King et al., 2019). The FOT device generates pressure oscillations at the mouth, which are disseminated by the movement of the air column in the airways, resulting in dilatation and return of the elastic characteristics of the lung and the generation of backpressure. The pressure oscillations are applied using a sinusoidal wave (multifrequency pseudorandom noise signal) of frequency of 5 Hz to 37 Hz. Low oscillation frequencies (5Hz) penetrate deep into peripheral airways, reflecting the entire lung, whereas high oscillation frequencies (20 Hz) only hit the large airways.

The oscillometry parameters that will be assessed include resistance at 5 Hz (R_5), resistance at 20 Hz (R_{20}), the difference between resistance at 5 Hz and resistance at 20 Hz (R_{5-20}), reactance at 5 Hz (X_5), Frequency resonant (Fres) and area under the reactance curve (AX). All oscillometry parameters will be expressed as $cmH_2O.s/L$ except for Fres, which will be expressed in Hz.

7.4.4.2.2. Laboratory measurements

A blood test will be taken to measure inflammatory mediators and cells, and cardiac markers at each visit. While all tests are validated for clinical care, some would not be routinely performed during an exacerbation of COPD. Blood tests include, Full blood count (FBC), C-reactive protein (CRP), High sensitivity troponin (hs-cTnT) and Brain natriuretic peptide (Pro-BNP). Full blood count will be evaluated to stratify patients into phenotypes based on the implicated cells and will be performed in visit 1, 2 and 3.

CRP, a valuable inflammatory biomarker COPD exacerbation (Prins et al., 2019; Gallego et al., 2016), will be assessed across the study's time points (visit 1, visit 2, visit 3 and visit 4). High sensitivity troponin T assay (hs-cTnT), a commonly used myocardial infarction (MI) marker, will be performed in the first visit to rule out acute MI. Furthermore, studies reported an increased risk of MI and stroke following COPD exacerbation (Malo de Molina et al., 2018; Donaldson et al., 2010). Therefore, hs-cTnT will also be assessed in visit 3 and 4.

Cardiac failure may have a similar clinical presentation or may occur with acute exacerbation of COPD (Global Initiative for Chronic Obstructive Lung Disease, 2022). Therefore, brain natriuretic peptide (Pro-BNP), a commonly evaluated marker of heart failure, will be assessed in the first visit to rule out heart failure. Studies demonstrated a reduction in Pro-BNP over the course of a treated heart failure event (Radosavljevic-Radovanovic et al., 2016; Latini and Masson, 2013). Thus, Pro-BNP will be followed up in visit 3 and 4.

Sputum will be collected on each mentioned visit for a 4-h period from waking and this will be done if produced spontaneously. Mouth washing procedures will be done to reduce the possibility of contamination from saliva. Collected sputum samples will be split into two aliquots: one for microbiology and one for cell counts.

The first aliquot of sputum samples will be used for quantitative bacterial culture to assess whether bacterial infection present or not. Sputum microbiology is an investigational test to detect the presence of bacterial infections, and it is done by performing a sputum culture. Sputum culture is part of the routine care in COPD exacerbation. Sputum culture will only be performed in the first visit.

The second aliquot of sputum samples will be treated with dithiothreitol and cytospins to prepare for total and differential cell counts of squamous cells, neutrophils and

macrophages. Sputum cell count test is used to evaluate the number of cells present in the sputum. Studies reported that inflammatory cells are increased in the sputum during exacerbation (Bhowmik et al., 2000; Tsoumakidou et al., 2005). Therefore, sputum cells count will be evaluated in the first visit and followed up in visit 3 and 4.

7.4.4.2.3. Symptoms based questionnaires

Patients will be asked to complete validated symptoms-based questionnaires to assess the recovery of symptoms, and these includes COPD assessment test (CAT), EXAcerbation of Chronic obstructive pulmonary disease Tool (EXACT) and Birmingham symptom diary card. CAT is a short questionnaire (8-items) which designed to examine the effect of COPD symptoms on health status. CAT has shown to be a reliable tests of exacerbation severity and monitoring tool of recovery (Mackay et al., 2012). Thus, CAT will be assessed across all study time points (visit 1, visit 2, visit 3 and visit 4).

EXACT is a recently developed and validated tool uses a 14-item daily diary aimed to measure patient-reported symptoms of exacerbation in COPD patients. EXACT has demonstrated to be a valuable measure in assessing the symptoms recovery from exacerbation (Mannino et al., 2018). Therefore, EXACT will be assessed across all study time points (visit 1, visit 2, visit 3 and visit 4). Birmingham Diary card was developed to evaluate the recovery from acute exacerbations of chronic lung disease (including sputum characteristics and symptoms) (Llor, Moragas and Miravitlles, 2012; Woolhouse, Hill and Stockley, 2001). Therefore, this will be assessed across all study time points (visit 1, visit 2, visit 3 and visit 4).

7.4.4.2.4. Other measurements

Clinical information on patients' baseline demographics, smoking history, exacerbation history, use of medications, comorbidities, symptoms of exacerbations, seasonality of exacerbations, and length of hospital stay will be collected. Demographics included age, sex, height, weight, body mass index (BMI), and ethnicity. Smoking history will be categorized as never smoker, ex-smoker, and current smoker. Pack-years will also be assessed (calculated by multiplying the number of packs of cigarette smoked per day by the number of years person smoked). Exacerbation history will be stratified as frequent exacerbation ($\geq$2 exacerbations per year) and infrequent exacerbations (<2 exacerbations per year). Comorbidities will be assessed using Charlson Morbidity Index.

Clinical investigations in COPD exacerbation, and these include chest x-ray (CXR) and electrocardiography (ECG) will also be collected. These will be only assessed in the first visit and only where performed as part of routine care. CXR is performed in all patients as part of standard medical care and used to assist with differential diagnoses to rule out other infectious diseases or conditions. ECG is also used as a differential diagnosis to rule out other cardiac diseases that may mimic exacerbation. Table 7.1. summarize the schedule of visits of the data to be collected.

Table 7.1. Schedule of visits of the data to be collected.					
Data description	**Routine care (RC) or research (R)**	**Visit 1 (within 24 hours)**	**Visit 2 (Day 3 or 4)**	**Visit 3 (Day 5 or 6)**	**Visit 4 (6 weeks to 6 months)**
Consent	R	X	X	X	X
Eligibility criteria	R	X	X	X	X
Demographics[1]	R	X			X
Medical conditions recorded	R	X	X	X	X
Medications recorded	R	X	X	X	X
Exacerbation symptoms recorded	R	X	X	X	X
CXR[2]	RC	X			
ECG[2]	RC	X			
Full blood count[2]	RC	X	X	X	
CRP	RC	X	X	X	X
hs-cTnT	R	X		X	X
ProBNP	R	X		X	X
Sputum microbiology[2,3]	RC	X			
Sputum for cell counts[3]	R	X		X	X
Bedside spirometry	R	X	X	X	X
Bedside FOT	R	X	X	X	X
CAT questionnaire	R	X	X	X	X
EXACT questionnaire	R	X	X	X	X
Birmingham symptoms card	R	X	X	X	X

Abbreviations: CXR= Chest X-Ray, ECG=Electrocardiography, CRP= C-reactive protein, hs-cTnT = high-sensitivity troponin, ProBNP= Pro Brain natriuretic peptide, FOT= Forced oscillometry technique, CAT= COPD assessment tool, EXACT= Exacerbation of COPD Tool.
[1]= Demographic will include: age, height, weight, gender, ethnicity, smoking status, pack-year history, exacerbation frequency, Charlson Comorbidity index.
[2]= will only be done if it is assessed as part of routine.
[3] = if producing sputum spontaneously.

7.4.5. Statistical analysis

In previous study of exacerbation of COPD, a sample size of 35 was sufficient provide 80% power to detect changes in X_5, FEV_1 and IC (Johnson et al., 2007). Studies of FOT have included between 22 and 37 subjects (Johnson et al., 2007; Jetmalani et al., 2015; Stevenson et al., 2005). If a similar increase in X_5 will be seen in our population, a sample size of 45 patients would provide 90% power to detect a difference between recovery and exacerbation. Considering the frail condition of study participants that may result in some dropouts, we pragmatically aimed to recruit 75 participants for this study, with 50 completing visit 3 of the study. Statistical analysis will be done using IBM SPSS software. The normality of the data was assessed using Shapiro-Wilk's tests. Mean and standard deviation (SD) will be reported

for normally distributed data, whereas median and interquartile range will be reported for non-normally distributed data. Continuous data will be analysed with simple descriptive statistics, including parametric/non-parametric tests (T-tests, Mann-Whitney Tests, one way ANOVA, Kruskal-wallis H tests, Pearson's and Spearman's correlations). Within and between-group differences will be assessed using test for repeated measurements. Statistical significance will be set as $p<0.05$. A correction for the p value will be made using Bonferroni technique for multiple comparison (Bonferroni, 1936).

7.5. Discussion

This is a pilot observational study aimed to determine the feasibility and acceptability of FOT compared to spirometry (particularly FEV_1) during acute exacerbation of COPD. In COPD, FEV_1 has traditionally been used as a primary measure for diagnosing airflow obstruction (AO) severity and a method for monitoring disease progression. Furthermore, FEV_1 is frequently used for research purposes during COPD exacerbations to assess treatment effectiveness or monitor recovery. However, FEV_1 is obtained from spirometry (a forced respiratory manoeuvre), which requires patients to exert effort that can be arduous, especially during exacerbation. FOT has been demonstrated to be helpful in stable COPD, and its indices have been shown to be related to AO severity (Anderson and Lipworth, 2012; Ohishi et al., 2011; Tanaka, Fujii and Kitada, 2011). FOT involves passive, quiet breathing instead of forced breathing, and patients might find this more acceptable. This highlights that FOT seems to be more appropriate than spirometry in mapping and monitoring the recovery from exacerbation in COPD. In this study, we expect to obtain additional insight into the practicality of FOT as a monitoring tool in the acute setting and whether it can be included into clinical practice. Moreover, we sought to determine whether changes in FOT indices

were related to changes in health status, spirometric indices, or systemic inflammation. This, in turn, will establish whether FOT could be used in a large interventional study as a potential surrogate outcome measure or serve as a biomarker for the severity of the disease.

In the systematic review chapter, FOT studies demonstrated that reactance indices improved but not resistance indices during exacerbations (Johnson et al., 2007; Stevenson et al., 2005; Jetmalani et al., 2015). These studies demonstrated that FOT reactance indices appeared to mirror changes in symptoms and FEV_1. In a recent study, Alqahtani et al. assessed FOT in 82 patients with AECOPD, demonstrated that FOT reactance indices seemed to mirror changes in inflammation during the recovery period (Alqahtani et al., 2021). Therefore, FOT indices, in particular reactance, may be a useful tool to monitor exacerbations. However, previous studies did not thoroughly assess FOT as not all FOT indices were reported, including AX, Fres and importantly, R_{5-20} (a surrogate measure of the resistance in the small airways).

This study is different from previous studies in four facets. Firstly, we will comprehensively investigate the tests' potential utility by including all FOT indices (i.e. AX, Fres and R_{5-20}) as previous studies have only reported resistance for lower oscillation frequencies (5-6 Hz) (Johnson et al., 2007; Stevenson et al., 2005; Jetmalani et al., 2015; Alqahtani et al., 2021). Secondly, studies have not examined whether patients were more likely to complete tidal breathing assessment as opposed to forced manoeuvre, although Alqahtani et al. reported that FOT seems to be feasible and acceptable, but this was based on patients' preference and not an assessment of whether a patient was able to complete a test or not (Alqahtani et al., 2021). The present study will assess feasibility differently by comparing FOT trace to spirometry trace, defining feasibility as 20% or more of patients providing valid FOT trace compared to providing valid spirometry trace. Regarding acceptability, we will

determine this as 10% or more patients attempting FOT compared to spirometry at the first timepoint. Thirdly, previous studies did not include validated tools to evaluate exacerbation symptoms, such as EXACT. This study will include the EXACT tool providing a more detailed evaluation of exacerbation symptoms and their changes during recovery. Fourthly, previous FOT studies did not evaluate changes in inflammation, except the study by Alqahtani et al., which only assessed systematic inflammation (Alqahtani et al., 2021). The pilot study will collect and analyse blood samples (to evaluate inflammatory and cardiac markers) and sputum samples, which will provide insight into phenotyping exacerbations. Therefore, we expect this pilot study to provide a comprehensive assessment of FOT's utility in COPD exacerbation in relation to other outcomes.

As stated earlier, AECOPD is associated with significantly worse health outcomes (Hartl et al., 2016), highlighting the need for strategies and tools to help reduce its risks. Evidence suggests that exacerbations differ in their aetiology, inflammation presence, and response to treatment. FOT could help in better monitoring these acute episodes, possibly providing a better characterization of the condition. Importantly, FOT might may allow a better understanding of which patients do not recover from an exacerbation, allowing preventive strategies to be implemented. Thus, poor clinical outcomes such as mortality and readmission could be avoided. Moreover, pharmacological treatments for COPD exacerbation have remained unchanged over the past three decades, possibly due to the reliance on FEV_1 in most clinical trials. In this acute setting, FOT measures could be useful in interventional studies as surrogate outcome measures, which may help evaluate the effectiveness of novel putative therapies. Therefore, we believe FOT may add value to exacerbation management.

8. General Discussion and Conclusion

8.1. Discussion

The overall aim of the thesis was to evaluate the prevalence of small airway dysfunction (SAD) in Chronic Obstructive Pulmonary Disease (COPD) and assess whether the physiological measures of small airways are helpful to guide and help manage COPD either in the stable state or during acute exacerbations of COPD (AECOPD). To achieve this, we initially conducted two cross-sectional analyses of lung function of ever-smokers (chapter 2) and never-smokers (chapter 3) to evaluate the prevalence of SAD in COPD and determine whether SAD alone represents a subgroup of patients at risk for developing COPD, which could be referred to as "pre-COPD". We further conducted a systematic review of the literature to determine the evidence of using the small airway tests in bronchodilator responsiveness (BDR) assessment and whether these can be integrated into routine BDR testing (chapter 4). We then analysed the lung function data to determine the utility of small airways tests in BDR assessment (chapter 5). We further conducted a systematic review of the literature (chapter 6) to study the evidence for using small airways tests during acute COPD exacerbations (AECOPD). Finally, we planned to conduct a pilot study to determine whether small airway tests are feasible and acceptable for patients with acute exacerbations of COPD, but the study was paused due to the impact of the COVID-19 pandemic and could not be restarted during the research period for the PhD.

Overall, this body of work provides the following important findings:

- SAD was detected in nearly all patients with airflow obstruction (AO).
- SAD was detected in some patients with symptoms suggestive of COPD without AO, which was associated with lower lung function indices than those without SAD.
- Tests of small airways demonstrated BDR changes greater than FEV_1.

- BDR in tests of small airways was common in COPD patients, detected in all patients with BDR in FEV_1 and found in some patients without BDR in FEV_1.
- Tests of small airways demonstrated changes during the recovery from AECOPD, usually at higher changes or earlier than changes in FEV_1.

This section aims to summarize and discuss these findings, including their implications for clinical practice and research.

8.1.1. Small airway dysfunction in COPD and pre-COPD

Chapter 2 and 3 studied SAD and AO in smokers with and suspected to have COPD and never smokers with symptoms compatible with COPD. The main results were that SAD is common in COPD, SAD was ubiquitous in those with AO, and even those without AO, SAD was associated with lower lung function measurements. Of note, the presence of SAD was not associated with age or sex or smoking history.

It is well recognized that impairments in the small airways and the lung parenchyma are responsible for AO in COPD (Global Initiative for Chronic Obstructive Lung Disease, 2022). However, there is increasing evidence that small airways are affected early in the disease process, as SAD seems to occur before AO (Hogg, McDonough and Suzuki, 2013; Stockley et al., 2017b) and emphysema in COPD (Hogg, McDonough and Suzuki, 2013), highlighting the crucial role of these airways in the disease's pathological process. Studies have demonstrated that SAD could manifest as abnormalities in physiological tests, including maximal mid-expiratory flow (MMEF) (Stockley et al., 2017b; Kwon et al., 2020), forced oscillometry (FOT) indices (Crisafulli et al., 2017) and inert gas washout indices (Gennimata et al., 2010). Consequently, these tests have been proposed as measures of small airways function. Physiological studies have demonstrated that SAD is prevalent in COPD (Stockley et al., 2017b; Piorunek et al., 2017; Crisafulli et al., 2017) and that SAD can be

physiologically detected in patients suspected of having COPD in the absence of AO (Stockley et al., 2017b; Kwon et al., 2020; Pisi et al., 2021). However, most of these studies have generally included only a small number of patients with or at risk of developing COPD, have used different measurements to detect SAD or different normal ranges to detect abnormalities.

It is still unclear which test of small airways better detects abnormalities, but of the proposed tests, MMEF has demonstrated to be of value in several studies (Stockley et al., 2017b; Kwon et al., 2020; Mirsadraee, Boskabady and Attaran, 2013; Tsushima et al., 2006). It has been shown that MMEF is a useful marker of SAD (Stockley et al., 2017b), and, importantly, appears to be able to identify those at risk of developing COPD (Kwon et al., 2020). In fact, a low MMEF percent predicted in the absence of AO was linked with poorer health status and a faster FEV_1 decline (Stockley et al., 2017b). The availability of MMEF in routine spirometry gives it an advantage over much more complicated and expensive technology. Different methodologies were used in previous studies to define SAD assessed by MMEF, but none have been tested for their comparative predictive ability, accuracy, sensitivity or specificity in identifying COPD, except in the longitudinal study by Kwon et al. In their study, Kwon and colleagues demonstrated that their proposed cut-off for MMEF z-score (- 0.845) significantly predicted COPD development (Kwon et al., 2020). In this study, patients with low MMEF z-scores had a higher COPD incidence rate (41.8% (38/91) vs 7.4% (16/216); $p<0.001$) compared with patients with a normal MMEF z-score. Given that SAD appeared to precede AO (Stockley et al., 2017b) and the fact that loss of >70% of small airways has to occur before COPD becomes detectable by FEV_1/FVC (Hogg, McDonough and Suzuki, 2013), MMEF z-score < -0.845 likely reflect impairments in the small airways

(Kwon et al., 2020). Therefore, in the cross-sectional studies (chapters 2 and 3), we used the MMEF z-score <-0.845 as a criterion to define abnormalities indicating SAD.

The cross-sectional studies (chapters 2 and 3) have physiologically confirmed that SAD is a key feature in patients with AO, seen in nearly all patients, which indicates that physiological assessment of small airways' function could aid COPD management. We have also identified a significantly reduced MMEF in patients with AO, indicating substantial damage to small airways before developing an established AO. Of note, SAD worsened stepwise as the severity of AO increased, similar to the pattern seen in the pathological study by Hogg and colleagues (Hogg et al., 2004) and physiological studies using R_{5-20} as a measure of SAD (Crisafulli et al., 2017; Piorunek et al., 2017). The current results show that there is a relationship between the degree of AO and the severity of SAD. Since AO, once established, cannot yet be fully mitigated, targeting SAD before the development of AO or in those with mild AO may help prevent the severest manifestations of disease. However, this concept will need to be evaluated in randomised controlled trials.

Early detection of the pathophysiological traits of COPD is essential as it may help identify those most at risk of developing established COPD. This could identify a group of patients who may be at a stage called "pre-COPD". "Pre-COPD" is a new term proposed to define patients without spirometrically-defined COPD but have respiratory symptoms and risk factors of COPD and may be or may not at risk of developing COPD (Han et al., 2020). Hence, finding a physiological measure that detects abnormalities that the conventional spirometric measures cannot detect could be of value in this early phase of the disease. In the cross-sectional SAD studies, 51% of symptomatic patients without AO had SAD, which was associated with lower lung function readings (despite being within normal range) than those without SAD and AO. Given that the patients across groups were approximately the same

age, this signifies that those with SAD alone have lung physiology that declines quicker than those without SAD, suggesting that their lung physiology may be indicative of an earlier lung injury and may be at increased risk of COPD. Therefore, these patients probably represent a phenotypic group that warrants careful monitoring.

The data presented within this work supports the concept that patients without AO but with SAD (defined by MMEF z-score <- 0.845) should be considered a phenotypic group that likely reflects "pre-COPD". Modern spirometry also includes MMEF, and it is reasonable to consider it when defining "normality". It can be argued that MMEF is a highly variable measure, which might affect interpretation, but using the z-score might help in minimising this issue. When patients have symptoms suggestive of COPD without an AO but an MMEF z-score < - 0.845, prevention and treatment strategies could be discussed, including smoking cessation and decreasing exposure to environmental pollution and potentially treatment strategies targeting the small airways (such as extra-fine inhalers) may also benefit this group. These strategies, in turn, may decrease disease progression, improve patients' overall health status and more importantly, prevent the development of COPD.

In both cross-sectional studies, the SAD measure (MMEF z-score) was strongly related to measures of AO (FEV_1 and FEV_1/FVC). In the study of ever-smokers (chapter 2), the relationship was preserved even after accounting for smoking history, suggesting that it was independent of cigarette load. Moreover, the logistic regression of all patients in the cohort showed that SAD was associated with lower FEV_1 and FEV_1/FVC but not the smoking exposure history nor age. We postulate that the cohort included patients who may be mechanistically different (such as the presence of dysanapsis) or that other factors (such as epigenetic phenomena, including exacerbations) may play a role. However, this will only be confirmed in longitudinal comprehensive physiological studies incorporating a thorough

medical history. In the study of never-smokers (chapter 3), age was not different between study groups, signifying that age is unlikely to explain differences in lung function between groups. The difference in lung function may be the result of other factors, but comprehensive patient histories were not available in the study of never-smokers. Therefore, a comprehensive study with detailed patient history is needed to determine the factors contributing to SAD alone in never-smokers and whether they differ from those with AO and those with normal lung function.

8.1.2. The utility of small airways tests in the BDR assessment

The utility of small airway tests in BDR assessment is evaluated in this thesis in two studies. Initially, chapter 4 included a systematic review to determine the evidence for the use of SA tests in assessing BDR in COPD. Overall, studies were small, few in number and often biased, but there was evidence of BDR in SA tests, often with a greater degree of change than seen in FEV_1, suggesting potential utility in the assessment of COPD. Further, chapter 5 studied BDR in MMEF, a commonly reported measure of small airways, in COPD patients. The main results were that BDR in the small airways was common in COPD patients, was observed in all patients with BDR in FEV_1, and was identified in some patients without BDR in FEV_1.

The assessment of BDR using FEV_1 can be seen in some COPD patients (Albert et al., 2012; Tan et al., 2012; Tashkin et al., 2008), but to date this has not been used to successfully predict outcomes or identify clinical phenotypes. Moreover, it is increasingly recognised that other physiological measures of COPD can show significant improvements in the absence of BDR of FEV_1 (O'Donnell, Revill and Webb, 2001; Schermer et al., 2007), illustrating the limitations of relying solely on a single physiological measure to identify treatment response. Potentially, additional physiological measurements could be of use in detecting a treatment

response not objectively seen with currently recommended physiological tests. As demonstrated earlier, small airway (SA) plays a vital role in COPD pathophysiology. Therefore, assessing the SA before and after bronchodilators may identify a subgroup of COPD patients who might benefit from inhaled therapies, or represent a group of patients with a different clinical course. A number of studies have shown that different physiological tests can show a BDR in COPD, including tests of SA (Borrill et al., 2005; Park et al., 2019). However, it was unclear which tests of SA were frequently utilized and of what quality these previous studies were. Given that there were no previous systematic reviews of the use of SA tests in BDR assessment, a systematic review was conducted to comprehensively evaluate their utility in determining BDR in COPD patients.

The systematic review in chapter 4 described that SA had been assessed as part of the BDR assessment in COPD, but MMEF and FOT were the only reported measures of SA used in thesis tests. The included studies demonstrated that tests of SA are associated with greater BDR changes than FEV_1 (Borrill et al., 2005; Park et al., 2019), suggesting that these tests may be useful for BDR assessment. However, the evaluated studies were relatively small and included a limited number of participants, which limited conclusions about their use in COPD.

To explore this further, more studies are needed specifically to determine whether they add utility as a supplementary measure to FEV_1. As stated earlier, several physiological measures have been proposed to assess the small airways (McNulty and Usmani, 2014; Stockley et al., 2017a). However, it remains unclear which test is most sensitive in detecting SA and there is no consensus about a recognized threshold for a BDR in measures of SA or agreed thresholds which represent a clinically meaningful change.

For chapter 5, spirometry data were used to assess BDR, and MMEF was chosen for the test of SA, as this is routinely collected and has been demonstrated to be a useful marker of SAD (Stockley et al., 2017b), predicting COPD (Kwon et al., 2020).

In the BDR study (chapter 5), we found BDR in the SA is common in COPD, identified in roughly half of the patients in the cohort. This physiological change in the SA measure is probably attributable to an improved SA patency. This was evident in all patients with BDR in FEV_1, but also was present in some without BDR in FEV_1.

Previous studies have not evaluated SA measures to establish whether BDR in the SA can identify BDR that is not captured by FEV_1. In this thesis, we demonstrate that some COPD patients can display a BDR in SA without BDR in FEV_1, although their BDR in SA was smaller (both in absolute and percent predicted terms) than those with both a BDR in SA and FEV_1. It is unclear whether this represents a group of patients with distinctive pathophysiology, prognosis, or who might benefit from different therapeutic approaches. Potentially inhaled treatments, particularly those designed to achieve peripheral deposition, could be of benefit even in the absence of a BDR in FEV_1. Therefore, tests of SA have the potential to supplement FEV_1 in assessing BDR.

However, before recommending the addition of tests of SA to BDR, further research is needed. First, it remains unclear whether treatment causes symptoms improve in patients with BDR in the SA alone. Therefore, further research is needed to establish whether the BDR in the SA alone is associated with clinical benefits which patients can feels. Second, data collected to date cannot determine if the BDR in SA alone represents a distinct clinical phenotype in COPD (with a different pathological process, prognosis or response to treatment). Thus, an in-depth longitudinal study is needed to determine whether BDR in the SA reflects a clinical phenotype and whether it is associated with a better prognosis.

The BDR study utilized MMEF as a proof of concept to demonstrate post-bronchodilator (BD) improvement in the SA. However, there are limitations with this measure. Firstly, the MMEF changes were associated with a higher variance post-BD than the FEV_1, similar to previous study (Borrill et al., 2005). This highlight that interpreting what is a clinically meaningful change and incorporating this into BDR assessments may be difficult. However, in the BDR study, the BDR in MMEF was defined by criteria proposed by others (Levine et al., 2016; Shim, 1989), which was seen in all patients with BDR in FEV_1. This implies that patients with BDR in MMEF alone likely exhibit a real physiological change post-BD. However, it is unclear why those with BDR in MMEF alone are different (in terms of BDR changes) from those with BDR in both MMEF and FEV_1. Despite this, our findings suggest that patients with a BDR in the MMEF alone may benefit from treatments that target small airways, although a longitudinal study is needed to confirm these benefits. Secondly, studies recommend adjusting the MMEF for lung volume when assessing treatment responses (Cockcroft and Berscheid, 1980; Sherter, Connolly and Schilder, 1978). This was proposed because MMEF has failed to demonstrate significant changes in the presence of changes to FVC. In the BDR study, the percent change of MMEF in group 2 was more than 30%, indicating that the adjustment for lung volume is unlikely to be necessary and does not affect the finding that MMEF identified a group of patients with a BDR likely representing an improvement in patency in the SA.

While extensive work is necessary before tests of the SA can be incorporated into clinical practice, these tests' role in BDR assessment should be considered further in COPD research. An important contribution is related to assessing the benefit of treatment targeting small airways. With the advent of extra-fine particle inhalers, a measure that evaluates the improvement in the SA could be utilized as objective outcome measures determining the

efficacy of these treatments, especially when coupled with symptomatic responses to BDR. Another contribution relates to the identification of treatable traits in COPD. The presence of BDR in the SA alone in some patients suggests that these patients may have different disease mechanisms and perhaps benefit from a specific treatment strategy, such as inhalers with extra-fine particles. However, randomized clinical trials should be conducted to evaluate this. If this is true, this will allow treatment using treatable traits, leading to improvements in patient outcomes in COPD.

8.1.3. The utility of small airways tests in acute exacerbation of COPD

In the systematic review of the use of SA tests to assess COPD exacerbations, only a few studies were identified for review, with overall quality being fair to poor, and they were heterogeneous. The main findings were that tests of SA improved correspondingly with FEV_1 during recovery from exacerbation. Of note, tests of SA demonstrated changes that preceded changes in FEV_1 from the onset of exacerbation.

AECOPD are prevalent in COPD and associated with negative outcomes, including significant mortality and morbidity (Hartl et al., 2016). Currently, guidelines emphasize the importance of treating exacerbations immediately and minimizing future risks (Global Initiative for Chronic Obstructive Lung Disease, 2022; National Institute for Health and Care Excellence, 2019; Khan et al., 2014). However, the current criterion for diagnosing exacerbation is based on subjective assessment of symptoms that vary from day to day (Global Initiative for Chronic Obstructive Lung Disease, 2022), rendering it challenging to detect acute changes at the beginning and end of the exacerbation. Moreover, for more than three decades, there has been no progress in therapeutic strategies for AECOPD. This could be due to the dependence on less sensitive objective markers such as FEV_1 in research studies.

While sputum volume and purulence objectively help guide management of AECOPD (particularly those caused by bacterial infection) (Stockley et al., 2000), there are no objective tools that can measure a change in symptoms such as dyspnoea. This indicates that objective tools that could recognise exacerbations or map recovery, especially when dyspnoea is the only or main symptom, are warranted. Here, small airway tests might provide more sensitive and specific assessments during exacerbations. Studies have demonstrated that these tests may better detect physiological changes during exacerbation than FEV_1 (Jetmalani et al., 2015; Johnson et al., 2007). Given that there has been no thorough evaluation of the utility of small airways tests in COPD exacerbation, a systematic review was necessary to present a definitive evaluation of their utility.

The systematic review in chapter 6 reported that studies were heterogeneous by the different tests used and study designs, limiting a definitive conclusion about small airways tests and their use in the acute setting. However, the review demonstrated that the changes in small airways tests, including FOT and MMEF, were usually at a higher magnitude or occurred before a change in FEV_1 was recorded. This indicates that tests of small airways could provide early indications of change following the diagnosis and treatment of an exacerbation. Therefore, these measures could be important in this acute setting, either as a complementary test to FEV_1 or in specific stages of the recovery period. However, the review revealed that three questions need to be answered before confirming their utility in this setting. It was unclear which test was the most sensitive, which tests patients could tolerate when acutely unwell and which test was the most practical to deliver at the bedside. These questions would require more extensive studies comparing several tests to be answered. Of the identified tests, FOT seems to be the most practical in this setting as it can be performed

during tidal breathing and can be measured at the patient's bedside. Therefore, in the pilot study (chapter 7), we selected FOT as a test of small airways.

In previous FOT studies, it has been demonstrated that changes in FOT reactance but not resistance reflected changes in symptoms and FEV_1 (Johnson et al., 2007; Stevenson et al., 2005; Jetmalani et al., 2015; Alqahtani et al., 2021). In the study by Alqahtani et al., inflammation biomarkers (such as CRP, WBC, and neutrophils) mirrored EFL index changes, but not resistance (Alqahtani et al., 2021). In these studies, it appears that FOT parameters, particularly reactance, may be valuable for monitoring exacerbations (Johnson et al., 2007; Stevenson et al., 2005; Jetmalani et al., 2015; Alqahtani et al., 2021). In their study, Alqahtani et al. concluded that FOT was feasible and acceptable. However, this was determined by patient preferences alone and did not assess whether the patient could complete the test. Therefore, as well as asking patients what they prefer, it would be important to compare the number of completed measurements and the quality of the physiology recordings taken. In the proposed pilot study, the feasibility of FOT was to be determined based on the percentage of patients who provides a valid FOT trace compared to spirometry trace, the acceptability was to be determined based on the percentage of patients who complete FOT compared with spirometry, and patient preference was to be assessed. Moreover, studies did not report other FOT parameters, including AX, Fres and importantly, R_{5-20} (a surrogate measure of the resistance in the small airways). The pilot study was to comprehensively assess all FOT indices and examine whether their changes were related to changes in other outcomes, such as FEV_1, symptoms, inflammation, providing a better insight into the utility of FOT in AECOPD.

The pilot study was not completed due to the COVID-19 pandemic. From the systematic review and previous studies of FOT, it is likely that FOT will contribute to the

field of COPD in two ways. First, considering that exacerbations differ in their causes (Bafadhel et al., 2011), the presence of inflammation (Bafadhel et al., 2011), and treatment response (Seemungal et al., 2000a), FOT might be useful in diagnosing these acute episodes and tracking their recovery. In fact, FOT might identify those who do not recover from an exacerbation and possibly assist in identifying risk factors for non-recovered exacerbations. Identifying these factors could allow prevention strategies to be implemented, perhaps preventing worse clinical outcomes such as mortality. Second, COPD exacerbation treatments have remained the same for decades, which could be due to the reliance on measures (i.e. FEV_1) obtained from the onerous forced respiratory manoeuvre. FOT does not require extra effort from patients as performed during tidal breathing. Therefore, in this acute setting, FOT indices may be useful as surrogate outcome measures in interventional studies, which may help evaluate the efficacy of novel putative treatments for COPD exacerbations. For these reasons, we believe that FOT may add value to exacerbation management.

8.2. Strengths and limitations of the thesis

The strength of this thesis lies in conducting the first systematic reviews of the use of small airway tests in BDR assessment (chapter 4) and during AECOPD (chapter 6) using standardised methodology. Another strength is the use of large lung function data routinely collected in a large tertiary hospital (chapter 2). However, there are some limitations. Firstly, Studies in chapters 2, 3 and 5 are limited by the retrospective nature of their research, which is based on routinely collected data. Since there was no data on symptoms in these studies, it is unclear if symptoms differ between groups in studies in chapters 2 and 3 or if BDR improvements in the analysis in chapter 5 are related to symptoms improvements. Secondly, the studies in chapters 2 and 3 were cross-sectional, but longitudinal study using similar

abnormality cut-off for MMEF z-score showed that these were predictive of COPD. Thirdly, we used a pragmatic approach due to the lack of a recognised threshold for BDR of SA. Fourthly, over 90% of the participants in chapters 2, 3 and 5 were of White ethnicity. Hence, the findings might not be generalizable to other ethnic backgrounds. Another limitation is the small sample size among those with SAD alone in never-smokers, which may explain the non-significance of differences in demographic data and some lung function parameters between this group and others.

8.3. Future work suggestions

8.3.1. SAD in COPD and pre-COPD

- **What other risk factors could account for the presence of SAD with and without AO in ever-smoking participants?**

Since smoking exposure history alone does not account for the physiological differences between patients with SAD alone and patients with SAD and AO, other factors may be responsible for such differences. Because of the retrospective nature of studies in chapters 2 and 3, comprehensive medical histories of these patients explaining their potential susceptibility were not available. Therefore, a prospective study that examines a more detailed patient's history and take biological samples may help to identify whether other risk factors influence the susceptibility to SAD with and without AO and what the biological mechanism of SAD might be.

- **Are there differences in the symptomatology between those with and without SAD and with and without AO?**

In chapters 2 and 3, lung function data were collected from patients with symptoms suggesting COPD. However, we did not have data about symptomatology, so we are not sure if symptoms vary between groups. A prospective study examining the differences in symptoms between patients with SAD and patients with SAD and AO would be more informative in this regard.

- **What are the risk factors for SAD with and with AO in never-smoking participants?**

A comprehensive information about patients' medical history was not included in the analysis of the lung function data in never-smokers, except that they were known not to have AATD. Moreover, the study identified a small number of patients exhibiting SAD alone (only 22 patients) with no statistically significant differences in the available demographics compared to those with AO. Therefore, a larger study of non-AATD never-smoking participants with more detailed patient histories would help identify risk factors for the presence of SAD.

8.3.2. The utility of small airway tests in the BDR assessment in COPD

- **Is the BDR in MMEF alone associated with improvement in patient's symptoms?**

We have demonstrated that BDR in MMEF alone identified a group of patients who may have a physiological improvement that FEV_1 did not capture. As no symptomatology data were available, a prospective study would be necessary to determine the clinical impact of the improvement.

- **What are the predictors for the presence of BDR in MMEF alone?**

Since the study in chapter 5 is retrospective, it only presents routinely collected data, not a complete medical history for these patients. A prospective study involving comprehensive details about the patient's history, longitudinal change and biological sampling will help to determine the risk factors and mechanisms associated with BDR in the MMEF alone.

- **Is BDR in MMEF alone a clinical phenotype associated with a better prognosis?**

Since BDR in MMEF only measured patients at two-time points within the same day in the BDR study, it is unclear if this group of patients reflect a clinical phenotype. A longitudinal study would help to determine whether BDR in MMEF alone reflects a clinical phenotype and whether it contributes to a better or worse prognosis.

- **What is the most accurate threshold for BDR in MMEF?**

In the BDR study, we have chosen a threshold for BDR in MMEF pragmatically based on reported results. It is unclear what is the best threshold to determine BDR in MMEF. Despite this threshold identifying a response that was not captured by FEV1, a prospective study should be conducted to establish the most accurate threshold for BDR in MMEF.

- **What is the best test at detecting BDR in the small airways?**

In the BDR study, we have used MMEF to define BDR in the SA because of its availability, as a pragmatic choice. Other small airways tests might also identify a BDR. Therefore, it would be necessary to evaluate different measures of SA to determine which is the most specific and sensitive test to detect BDR in the SA.

8.3.3. The utility of small airway tests in acute exacerbation of COPD.

- **Is FOT feasible and acceptable to COPD patients during exacerbation of COPD? Do FOT indices mirror changes in symptoms, spirometry, inflammation?**

The COVID-19 pandemic did not allow me to complete the FOT study during my PhD. Due to its potential value in the acute setting, this study should be completed.

8.4. Conclusion

In summary, this thesis highlighted three important findings regarding the role of physiological assessment of small airways in COPD. First, SAD (determined by low MMEF z-score) is ubiquitous in patients with established AO and appears able to detect lung damage in the absence of and potentially before AO appears. This highlights that physiological assessment of small airways' function could be valuable in helping better guide management in patients with established COPD, identifying those without COPD but with SAD and reducing their risk of developing COPD. Second, the BDR in the SA (using MMEF % change) could be of value in COPD, providing insight into a subgroup of patients exhibiting BDR in the SA alone. This suggests these patients may have distinctive treatment characteristics. Nonetheless, it has yet to be determined whether BDR in the SA can predict improvements in patients' outcomes longitudinally or whether the response is associated with improved symptoms, highlighting the need for further investigation. Third, although a comprehensive study is needed to confirm this, previous studies have reported that SA tests (especially FOT) can monitor COPD exacerbation, which in turn may result in better patients' outcomes of COPD exacerbation.

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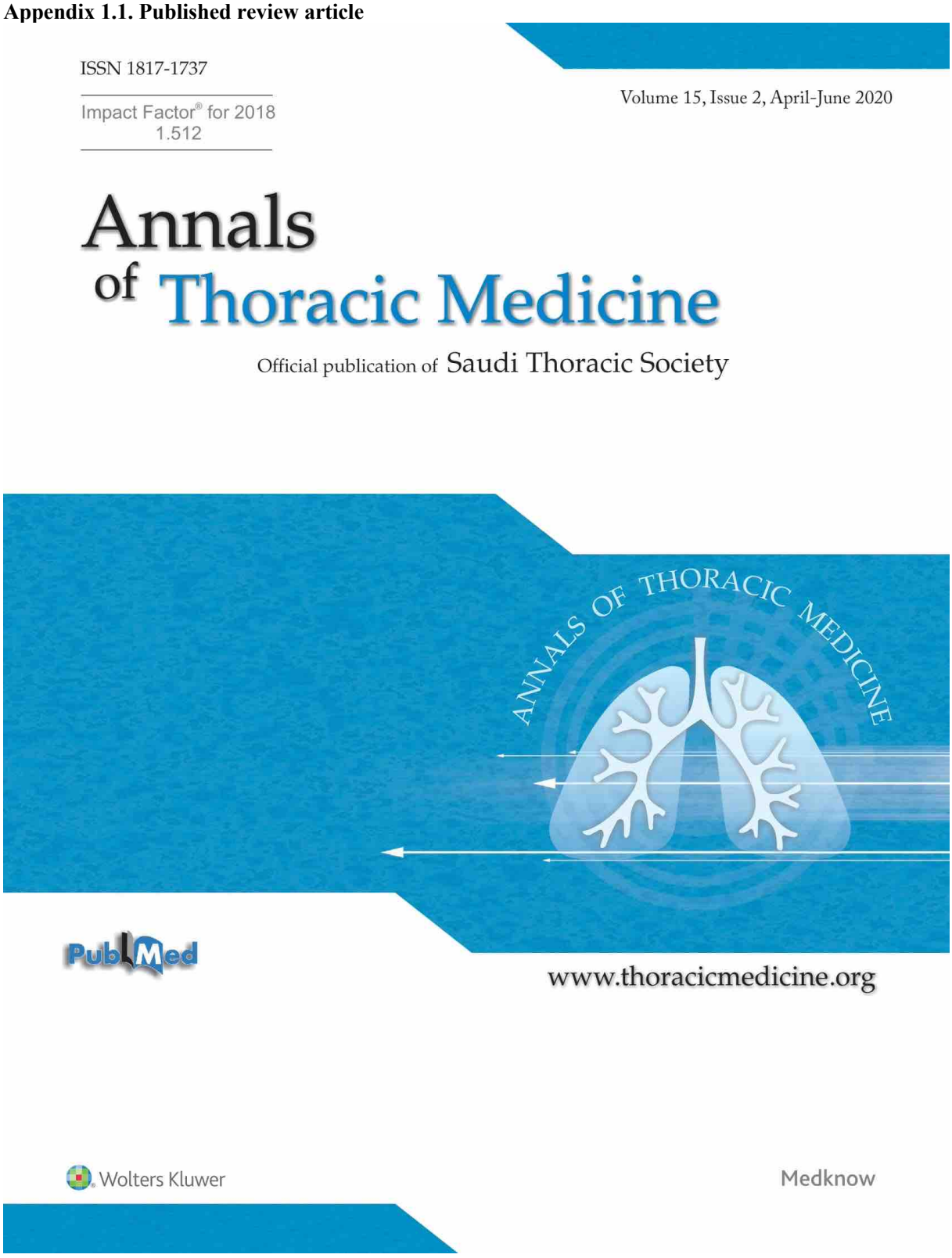
Appendices

Chapter 1

Appendix 1.1. Published review article



Review Article

An overview of exacerbations of chronic obstructive pulmonary disease: Can tests of small airways' function guide diagnosis and management?

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Abstract:

Chronic obstructive pulmonary disease (COPD) is common and debilitating. Most patients with COPD experience intermittent, acute deterioration in symptoms which require additional therapy, termed exacerbations. Exacerbations are prevalent in COPD and are associated with poor clinical outcomes including death, a faster decline in lung health, and a reduced quality of life. Current guidelines highlight the need to treat exacerbations promptly and then mitigate future risk. However, exacerbations are self-reported, difficult to diagnose and are treated with pharmacological therapies which have largely been unchanged over 30 years. Recent research has highlighted how exacerbations vary in their underlying cause, with specific bacteria, viruses, and cell types implicated. This variation offers the opportunity for new targeted therapies, but to develop these new therapies requires sensitive tools to reliably identify the cause, the start, and end of an exacerbation and assess the response to treatment. Currently, COPD is diagnosed and monitored using spirometric measures, principally the forced expiratory volume in 1 s and forced vital capacity, but these tests alone cannot reliably diagnose an exacerbation. Measures of small airways' function appear to be an early marker of COPD, and some studies have suggested that these tests might also provide physiological biomarkers for exacerbations. In this review, we will discuss how exacerbations of COPD are currently defined, stratified, monitored, and treated and review the current literature to determine if tests of small airways' function might improve diagnostic accuracy or the assessment of response to treatment.

Keywords:

Chronic obstructive pulmonary disease, diagnosis, exacerbation, monitoring, small airway dysfunction, small airway tests

Chronic obstructive pulmonary disease (COPD) is characterized by persistent respiratory symptoms and progressive airflow limitation which is believed to be mainly the result of chronic inflammation.[1] Many patients with COPD experience acute events termed exacerbations, which are associated with additional morbidity and increased mortality. Currently, patients self-report exacerbations on the basis of a perceived deterioration in symptoms. In 1987, Anthonisen *et al*. defined these episodes by a deterioration of 3 key symptoms (breathlessness, sputum volume, and sputum purulence).[2] Whereas sputum volume and purulence can be observed, it is difficult to define a change in breathlessness and there are no objective biomarkers which can measure this. Small airways' dysfunction is a feature of COPD both when stable and during exacerbations. In this review, we will discuss how exacerbations of COPD are currently defined, stratified, monitored, and treated and review the

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evidence for whether tests of small airways' function might explain the change in dyspnea and hence improve diagnostic accuracy or response to treatment.

The Importance of Chronic Obstructive Pulmonary Disease

COPD is an important, worldwide public health challenge.[3] It is the fourth leading cause of death globally[4] and is projected to be the third leading cause of death by 2020.[5] Population studies suggest COPD effects 10% of adults in Europe and the USA, but the prevalence is predicted to increase due to the continual exposure to risk factors and a globally aging population.[5] Although COPD is more common in men, recent evidence indicates the prevalence has increased in women, reflecting increases in smoking rates.[3] In the UK, one in eight emergency hospital admissions are for COPD,[3] and COPD is estimated to cost the UK economy ≤1.9 billion each year.[6]

While COPD has become an important public health issue in the Middle Eastern countries, it remains underdiagnosed and underrecognized.[7] Here, the most common risk factors for developing COPD are tobacco smoking, waterpipe smoking ("shisha"), passive smoking, biomass fuel smoke exposure, and pollution.[7] The prevalence of smoking in men and women varies but is high (reported as 20% of men and 1% of women in Iran, 48% of men and 31% of women in Lebanon, 62.0% of men and 21% of women in Syria and 43% of men and 12% of women in Turkey).[8,9] In the Middle East, approximately 25%–45% of COPD patients are never smokers but many are exposed to biomass fuel smoke.[7]

COPD is characterized by persistent respiratory symptoms and airflow limitation.[1,3] A combination of small airways' disease and parenchymal destruction causes the airflow obstruction which defines COPD,[4] but COPD is heterogeneous, encompassing several clinical/pathological conditions including chronic bronchitis, bronchiectasis, and emphysema.[3] COPD can be modified with acute acting therapies but is not curable and is usually slowly progressive.[10] In the ECLIPSE study, the mean rate of decline in forced expiratory volume in the 1 s (FEV_1) was 33 ml/year, but there was substantial variability across participants and the rate of progression only exceeded the normal age-related decline in a proportion of patients.[11]

In Saudi Arabia, the diagnosis and management of COPD patients follow the Saudi Initiative for Chronic Airway Diseases (SICAD).[8] Although the SICAD panel is adapted from the Global Initiative for Chronic Obstructive Lung Disease (GOLD), there are some differences. In the SICAD panel, COPD is classified into three groups based on symptoms and the risk of future exacerbations, in comparison to four groups in GOLD.[4,8] Symptoms are assessed using the COPD Assessment Tool (CAT), and risk of exacerbation is assessed by the number of exacerbations in both the SICAD panel and GOLD. In SICAD, Class I is the same as GOLD Group A where Class II is equivalent to GOLD Group B, and Class III reflects both GOLD Groups C and D. The SICAD classifications of COPD are presented in Table 1.

Exacerbation of Chronic Obstructive Pulmonary Disease: Definitions, Severity, and Importance

In many patients with COPD, periods of disease stability are punctuated with acute episodes of increased symptoms, termed exacerbations. Approximately 75% of COPD patients experienced at least one exacerbation per year,[12] with the frequent exacerbation phenotype being defined by two or more episodes per year.[13] Exacerbations are associated with substantial mortality and morbidity, a reduction in the quality of life and lung function.[14] Exacerbations are also associated with significant healthcare utilization and cost.[15]

Despite the significant cost of exacerbations, their pharmacological treatments (corticosteroids, short-acting bronchodilators (SABD) with or without antibiotics) have changed little over 30 years. This is in stark contrast to other acute deteriorations of chronic disease, where treatment advancements have revolutionized outcomes.

GOLD[4] defines exacerbation severity by the treatment or level of care needed by the patient. Mild exacerbations require an increase in SABD alone. Moderate exacerbations are treated with SABD plus oral corticosteroids with or without antibiotics. Severe exacerbations require hospitalization or an emergency room visit. There are limitations to this definition. First, exacerbations are defined by symptoms. COPD is a heterogeneous condition, and patients describe variability in their daily burden of symptoms, making acute changes sometimes difficult to identify both at onset and conclusion.[4] The symptom-based definition does not provide any insight into pathology or treatment requirements apart from sputum purulence, which has been associated with bacterial infection and a clinical improvement when treated with antibiotics.[16] Second, patients with COPD suffer from comorbidities; breathlessness and cough can be a manifestation of these other conditions, including cardiac disease, anxiety, deconditioning and pneumonia, as well as COPD. The use of treatment or place of care provision to define severity also has limitations. COPD is more common with increasing age and often co-occurs with frailty. Age, frailty, and multimorbid disease are risk factors for hospital admission, and some patients

Table 1: SICAD Classifications of COPD

SICAD class	Features	Number of exacerbations in the past year.	CAT score	Equivalent to GOLD
Class I	Less symptoms, low risk of exacerbation	0-1	≤ 10	Group A
Class II	More symptoms, low risk of exacerbation	0-1	≥ 10	Group B
Class III	High risk of exacerbation	≥ 2	Any score	Group C and D

may require hospital care due to a low threshold for increased support rather than severity of the respiratory event.[17]

Minimizing the effect of the current exacerbation and preventing the development of future events are major goals of most COPD guidelines.[3,4,8] The current management strategies do not usually stratify patients by potential cause. However, there is increasing evidence that not all exacerbations are the same, both in cause, inflammatory infiltrate, and response to treatment.

Pathogenesis of Chronic Obstructive Pulmonary Disease Exacerbations

Exacerbations of COPD are associated with several potentially causative factors, including environmental changes and infections, which can be bacterial or viral. Studies indicate that 50%–70% of exacerbations are caused by respiratory infections,[18] 10% are caused by environmental-related causes[19] and approximately 30% have no identifiable cause.[20]

Potentially pathogenic bacteria have been identified in approximately 30%–50% of sputum cultures in studies during exacerbations,[21,22] and *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Haemophilus parainfluenzae*, and *Pseudomonas aeruginosa* are the most common isolated.[21,23] Approximately 20%–40% of exacerbations are associated with viruses.[24] Rhinovirus is implicated for the majority of these episodes[25] with a lower percentage associated with parainfluenza and adenoviruses. Of note, exacerbations caused by viral infections are associated with a protracted recovery and a greater effect on healthcare utilization.[26] This probably reflects the limited treatment options for viral infections. Approximately 9% of exacerbations are thought to be caused by environmental pollution,[19] which is an increasing global health concern.

Most studies suggest inflammation is increased during exacerbations,[27] and just as with stable disease, most studies also report an increase in neutrophil counts in the bronchial walls and bronchial secretions during exacerbations.[28,29] Airway inflammation leads to increased airway edema, increased bronchial tone, and increased mucus secretion or plugging,[30] especially of the small airways. These airway changes result in increased airway resistance, worsening expiratory flow limitation (EFL), and ventilation/perfusion mismatch.[30] The deterioration in EFL leads to increased air trapping and hyperinflation (which increases the work of breathing), as well as insufficient time to empty the lungs between the rapid and shallow breathing patterns present during exacerbations.[31]

Studies have focused on dividing exacerbating COPD patients into those with purulent or colored sputum and those without. Although most describe a relationship with bacteria and sputum purulence, with sputum purulence having an 85% sensitivity and specificity for bacterial etiology in one study,[16,32,33] others studies have not.[34] More recently, Bafadhel *et al*.[35] phenotyped COPD exacerbation into four biological groups: 55% of exacerbations were associated with bacteria, 29% with viruses, 28% with significant sputum eosinophilia, and 14% with no inflammation (termed pauci-inflammatory). Of note, these groups did not signify differences in symptom burden or clinical presentation, including sputum purulence, which could not discriminate between causes.

Clinical Tools used to Assess Exacerbation Responses in Trials

Exacerbations of COPD have both short-term clinical impacts and long-term clinical effects. Symptom recovery is variable: half of community-treated exacerbations recover within a week but 14% take up to 35 days, and some patients do not appear to return to baseline.[26] Assessing response to treatment or recovery is crucial both when managing COPD patients, and when evaluating novel putative therapies and symptoms, spirometry and inflammatory changes are the most commonly used methods to assess exacerbation responses.

Patient-reported outcomes validated for exacerbations include the St George's Respiratory Questionnaire (SGRQ), COPD Assessment Test (CAT), and Exacerbation of Chronic Pulmonary Disease Tool (EXACT). The SGRQ can identify exacerbation and recovery;[36] but, this questionnaire is long, complex for patients to complete when acutely unwell, and requires a scoring algorithm to assess response. CAT is shorter, far easier to complete and scored using simple addition,[37] with scores associated with systemic inflammation and decline in FEV_1 at exacerbation.[38] EXACT is still awaiting FDA approval for exacerbations[39] but has been validated for use in this setting.[40] There are also a number of symptom diary cards which have been used in clinical studies.[26,32]

Spirometry has been used in clinical trials during exacerbations, and FEV_1 is commonly the primary outcome for these COPD studies. FEV_1 strongly correlates with recovery[41] but has only a weak association with symptoms.[42] There have been a number of negative studies assessing therapies at COPD exacerbation where FEV_1 was the primary endpoint, including intravenous aminophylline[43] and erdosteine.[44] In spite of the utilization of FEV_1 in clinical trials, FEV_1 has shown to have several limitations. Being a forced, effort-dependent maneuver, patients may struggle during episodes of increased breathlessness and even in the stable state, variability in measurements is common. For example, a study which only accepted measurements following three blows which technically acceptable (that is, they varied by <±5% and by ±01 L)[45] described a mean change of 22 ml (standard deviation 170 ml) in FEV_1 repeated after a 20 min interval in health.[46]

Inspiratory capacity (IC) (the maximum volume inhaled from end-tidal exhalation) is the most common measurement of lung volume and capacity used in clinical trials of exacerbation. IC has a strong association with symptoms, response to treatment, and recovery.[47,48] Although lung volumes can be obtained using spirometry with inert gas analyzers or plethysmography, they are not similar and lung volumes in patients with moderate–severe airflow obstruction can be underestimated by dilution methods.[49] Moreover, lung volumes measured by plethysmography can be overestimated if inaccurately measured.[50]

Several inflammatory markers have been used to assess COPD exacerbations, although not as primary endpoints in clinical trials. Poor clinical outcomes have been related to persistent systemic inflammation[51] with higher levels of serum C-reactive protein present in those with no symptom recovery or those with recurrent exacerbations.[52] Fibrinogen has been proposed as putative biomarker of risk of exacerbations, with higher levels associated with increased admissions.[53] However, inflammatory mediators have limitations in clinical studies (as recently reviewed).[54] First, inflammation is not a feature of all exacerbations (the pauci-inflammatory events) and they are also extremely variable, especially in pulmonary secretions.[55] Without a "baseline" measure, it is difficult to assess whether the changes indicate exacerbation onset or recovery.

The limitations of the current tools to identify exacerbations or map recovery/response, especially when dyspnea is the only or main symptom have generated interest in other physiological tests which might provide more sensitive and specific measures, most notably tests of small airways' function.

Small Airways' Dysfunction in Chronic Obstructive Pulmonary Disease

Although COPD is defined by airflow obstruction, there is evidence that small airways' disease (defined as airways of <2 mm diameter) might be the earliest pathological manifestation.[56,57] Studies by Hogg *et al*. reported a significant loss of small airways preceding the development of airflow obstruction or emphysema in COPD patients.[57] These findings were supported by a study of small airways' function in patients with Alpha 1 Anti-trypsin Deficiency (AATD)-related COPD.[56] In this study tests of small airways dysfunction (SAD) preceded conventional spirometric evidence of COPD and all with spirometric evidence of COPD had evidence of severe small airways' dysfunction (only 17.5% of the predicted value), despite the airflow obstruction being only mild (65% of the predicted FEV_1 value). Other studies have shown that a reduction in small airways' diameter was present in resected lungs of smokers with airflow obstruction[58] and progressive increments in SAD in COPD correlated with health status.[59] There are a number of different tests which can be used to assess small airways' function in COPD, including physiological and imaging studies, as described below.

Measuring Small Airways' Dysfunction

Expiratory flows

Flow measurements obtained from the expiratory curve include maximal expiratory flow at 75% of forced vital capacity (FVC), at 50% of FVC, and at 25% of FVC, and mid-maximal expiratory flow (MMEF). MMEF is one of the most commonly studied measures of small airway function, obtained by performing forced spirometry. It is reliant on the FVC, and thus may be affected by changes in FVC and consequently has a wide normal range in clinical practice, which limits interpretation.[60] Nevertheless, a study by Tsushima *et al*.[61] showed a lower percentage predicted MMEF in GOLD stage 0 COPD (symptomatic patients with a normal FEV_1/FVC) than healthy controls. More recently, Stockley *et al*.[56] assessed MMEF, FEV_1, FEV_1/FVC ratio, health status, and computed tomography (CT) in AATD COPD patients and suggested MMEF may be a valuable tool in identifying early disease.

Inert gas washout

Inert gases (especially Nitrogen) washout has a number of clinical applications and can be used to assess different lung volumes as well as ventilation heterogeneity. There are two types of nitrogen washout tests: single breath nitrogen washout (SBNW) and multiple breath nitrogen washout (MBNW).

Single breath nitrogen washout

SBNW involves breathing in 100% oxygen from residual volume (RV) to total lung capacity and then breathing out slowly to RV.[62] Nitrogen concentration during the second expiratory phase can be divided into four stages, reflecting anatomical dead space (Phase I), the bronchial tree (Phase II), alveoli (Phase III), and airway closure (Phase IV). Closing volume (CV) is the volume of gas exhaled when small airway closure starts.[63] Validated reference ranges for SBNW parameters are available in clinical practice[64] and in obstructive lung disease, CV is increased because of the earlier closure of the airways.[65] Abnormal CV results have been described in 44% of male and 36% female smokers, whereas FEV_1 appeared abnormal in only 12% of these participants.[66] A new method of performing single breath inert gas washout has been established recently,[67] using the differential distribution of two inhaled tracer gases (helium and sulfur hexafluoride) and evaluating tidal Stage III slope.[68] Although it is considered as a sensitive measure in assessing small airways' dysfunction in moderate to severe COPD,[69] further evaluation will be needed before it can be used clinically.

Multiple breath nitrogen washout

MBNW is another nitrogen washout method, performed by breathing 100% oxygen during tidal breathing. The lung clearance index (LCI) is obtained and used to evaluate the heterogeneity of ventilation. LCI rises with the severity of airflow obstruction[70] and is one of the first tests to decrease in children with cystic fibrosis, supporting its value in recognizing early anatomical change.[71] Recently, a study has also demonstrated that LCI may be useful as an indicator of early disease in AATD before spirometry becomes abnormal.[72] Moreover, MBNW allows the identification of variation of ventilation heterogeneity between the conducting airways (S_{cond}) and the small airways in the acinar region (S_{acin}). Recent study by Liu *et al*. has found that both S_{cond} and S_{acin} are higher in patients with established COPD.[73]

Airway resistance by body plethysmography

Assessments of airway function can be obtained by directly measuring airway resistance (Raw). Raw is measured using body plethysmography and relates driving pressure to airflow during tidal breathing.[74] During nonvolitional tidal breathing, specific Raw (sRaw) can be measured. sRaw is obtained from the specific resistance loop using a line of best fit (sReff), the line linking the maximum variance in shift volume (sRtot), or infrequently, the line connecting expiratory flow between ± 0.5 and − 0.5 L/s (sR0.5). In healthy subjects, sRaw loop is linear, and these three parameters are approximately the same whereas, in airflow obstruction, hysteresis of the sRaw loop is common and results in notable differences between sReff, sRtot and sR0.5. Recently, a study in COPD suggested that sReff and sRtot identify small airway dysfunction and relate to symptoms of dyspnea.[75] Specific airway conductance (sGaw) is the reciprocal of sRaw, and it is often recognized as a stronger measure than Raw or sRaw because of its linear relationship with lung volumes.[76] Although a study has described significant decrease in Raw and sGaw in AATD patients with airflow obstruction,[77] studies in COPD are small and sRaw does not appear to rise substantially until moderate airflow limitation is established.[78]

Oscillometry techniques

Forced oscillation technique (FOT) and impulse oscillometry (IOS) are used to assess the respiratory impedance (resistance and reactance) in the respiratory tract noninvasively during tidal ventilation using different frequencies (between 5 and 35 Hz). They use oscillating pressure differences to identify the mechanical characteristics of the lung. At high frequencies, oscillations relate to central airways while at low frequencies, oscillations enter into peripheral lung, reflecting small airways.

FOT assesses the respiratory impedance by applying sinusoidal pressure differences through a mouthpiece. FOT may be sensitive to early small airway changes in smokers[79,80] and may be valuable in monitoring COPD patients.[81] Other studies have shown that FOT might help to distinguish between COPD and asthma[82,83] and may be more sensitive than spirometry following bronchodilator therapy[84] or bronchoprovocation tests.[85] FOT may also be a valuable tool for evaluating COPD patients during acute exacerbation.[86,87] Recently, there have been significant advancement in FOT technology, and recent FOT devices are able to evaluate EFL and separate inspiratory/expiratory resistance and reactance.

IOS is a later version of FOT, and several parameters are reported when IOS is performed. R5-R20 (the difference in the measurement of resistance at high and low frequencies) has been used as an outcome measure to identify peripheral resistance.[88] Reactance at 5 Hz (X5) is used to evaluate the structural characteristics of the lung parenchyma in the periphery and correlates with measures of spirometry.[89] Recently, studies have suggested that IOS can identify small airway dysfunction in COPD[90-92] and might be more sensitive than spirometry to early changes.[89,93]

Computed tomography

CT scans of the lungs assess the presence and the distribution of emphysema, both visually, but more sensitively using density data from the images. Lung density, evaluated at full inspiration, decreases with

Table 2: Test of small airways function during exacerbation of COPD

Test	Advantages	Disadvantages
Mid-Maximal Expiratory Flow	1. can be done at bedside 2. Widely accessible 3. Provide assessment of small airway dysfunction.	1. Very effort dependent 2. May be hard to do during exacerbation. 3. Poor reproducibility if not adjusted for lung volume
Single breath washout	1. Provide assessment of ventilation heterogeneity 2. Quick to perform 3. Requires only tidal breathing if double trace gases method is used. 4. Can be done at bedside.	1. Classical method is effort dependent 2. Double tracer gas method not fully justified
Multiple breath washout	1. Provides assessment of ventilation in the acinar and small conducting airway. 2. Effort independent 3. can be done at bedside	1. Time consuming 2. It may have variabilities
Plethysmography	1. Effort independent. 2. Quick technique to perform.	1. Method can be technically demanding when obtaining TGV 2. Not particular to small airway function 3. Cannot be done at bedside.
Oscillation techniques	1. Quick to perform. 2. Effort independent. 3. Specific to small airway function 4. Clinically validated. 5. Can be done at bedside.	1. Specialized equipment
CT	1. Provides direct evaluation of the presence of disease 2. Gold standard for detecting and phenotyping emphysema	1. High exposure to radiation 2. Costly 3. cannot be done at bedside 4. Achieving consistent RV is difficult

Abbreviations: TGV, thoracic gas volume, RV, residual volume

the amount of emphysema and is a highly sensitive measure of emphysema progression.[94] CT images are also increasingly being used to assess the presence of small airways' disease, by studying excess gas trapping at full expiration. Here, gas trapping is assumed to be a consequence of the loss or early closure of the small airways. Parametric response mapping (PRM) analyzes inspiratory and expiratory CT data, potentially identifying gas trapping caused by small airway disease alone through subtraction of defined emphysema. Although there are studies that have utilized CT techniques (specifically PRM) to assess small airways,[94,95] they still need to be fully validated to determine their clinical utility.

The Rationale for and Practicality of Measuring Small Airways' Tests During Exacerbations of Chronic Obstructive Pulmonary Disease

The effect of exacerbation on small airways is likely to be amplified and therefore measuring small airways' function during exacerbations may of interest in identifying both the duration of the episode and the response to treatment. However, there are potential caveats to its use. Although comprehensive testing has not been completed in COPD, all AATD patients with mild spirometric evidence of COPD had significant small airways' dysfunction.[56] If this were true of non-AATD COPD, small airways' function would be greatly impaired even in the stable state and potentially only milder COPD may provide a detectable signal during an exacerbation.

As previously stated, the assessment of small airways' function can be carried out using a number of tests, but whether these tests are clinically useful or could be delivered during exacerbations of COPD has yet to be fully explored. To be clinically useful, tests should provide a pretreatment measure which identifies the start, end, and response to treatment of an exacerbation, is practical by the bedside and acceptable to patients. A summary of advantages and disadvantages of each test is presented in Table 2.

In general, studies utilizing small airway tests in COPD exacerbation have been limited, both in the number of studies carried out and the number of patients recruited. Furthermore, the majority of these studies have been conducted during hospitalized exacerbations. Although two studies have included moderate exacerbation in their studies, most of the others have not specified the severity of exacerbation. In general, all studies did not specify the COPD severity of patients being examined; however, by assessing at the baseline FEV_1, most studies have assessed the small airways in moderate to severe COPD.

FOT and spirometry were used in an observational study to compare changes in COPD patients hospitalized with an exacerbation and demonstrated that inspiratory resistance was associated with a significant improvement in symptoms.[87] IC and reactance by FOT have been shown to relate to exacerbation recovery.[86] Tests of small airways have also been used in several interventional studies including identifying a significant decrease in airway resistance by plethysmography after 14 days of treatment with systematic corticosteroid[96] and identifying a significant improvement in MMEF (referred to as FEF 25–75 by the authors) at 10 and 30 days following treatment with erdosteine.[44] Another study compared treatment delivered via vibrating mesh nebulizer and small volume jet nebulizer using spirometry, body plethysmography, and IOS, demonstrating an improvement in spirometry, lung volume, and airway impedance with recovery.[97] Although studies using tests of small airways' dysfunction to assess exacerbation are small, there is consistent evidence that these tests offer the ability to map recovery (especially in milder disease).

The Evidence Gap: What Research is Needed to Decide if Tests of Small Airways Should be Incorporated Into Clinical Studies and Usual Clinical Practice?

Currently, the studies exploring small airways' tests during exacerbations of COPD are limited both in number and the number of patients studied. They have utilized different tests of small airways and different definitions of an exacerbation of COPD. While this review highlights the limitations in the current evidence for the use of small airways, a formal systematic review would provide a definitive assessment of the current tests of small airways used, the bias contained within published studies and any comparison between them. If any of the tests of small airways' function appeared sensitive to changes during exacerbation, a pilot study to see if test delivery is feasible and acceptable by the patient during exacerbation of COPD in the acute setting would be of great value. This might inform larger studies to determine if tests of small airways could be validated as outcome measures in exacerbations, and which tests might be the most informative, especially in episodes where dyspnea is the sole symptom.

Conclusion

COPD is characterized by airflow limitation that is caused by a combination of small airways' disease and parenchymal destruction.[4] Many COPD patients experience exacerbations, associated with poor health outcomes[4] that are commonly caused by viral and bacterial infections.[35] In clinical practice, recovery is assessed using unstructured symptoms reporting, but in clinical trials, more robust and reproducible measures are needed. Here, exacerbation response is commonly assessed using spirometry (especially FEV_1), symptom-based questionnaires, and sometimes an assessment of inflammation. There are limitations with these tools and therefore significant interest in developing and testing other methodologies for use in this area. Small airways' dysfunction is thought to be one of the earliest physiological changes in COPD, and tests of small airways' function have been used in experimental studies of both stable disease and during exacerbations. Thus, hypothetically tests of small airways' function may form a tool to assess exacerbations, especially in milder disease. Small airways' dysfunction can be assessed using MMEF, inert gas washout, airway resistance (by body plethysmography, FOT and IOS), and CT, but each has potential advantages and disadvantages. Some studies have used small airways' tests to evaluate COPD patients during an exacerbation and have suggested that these are sensitive measures to assess response, but studies have been few. This small body of evidence now needs to be built upon to robustly test whether tests of small airways' function can improve the diagnosis and management of COPD exacerbations. This includes assessing which tests of small airways are the most acceptable to patients, practical to deliver and have utility within clinical trials or as a tool to help improve clinical outcomes. Currently, there is insufficient evidence to support the use of small airways' tests to clinically guide the diagnosis and management of exacerbations of COPD; however, early studies suggest they have promise to improve patient care, and further research is clearly warranted.

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Conflicts of interest

There are no conflicts of interest.

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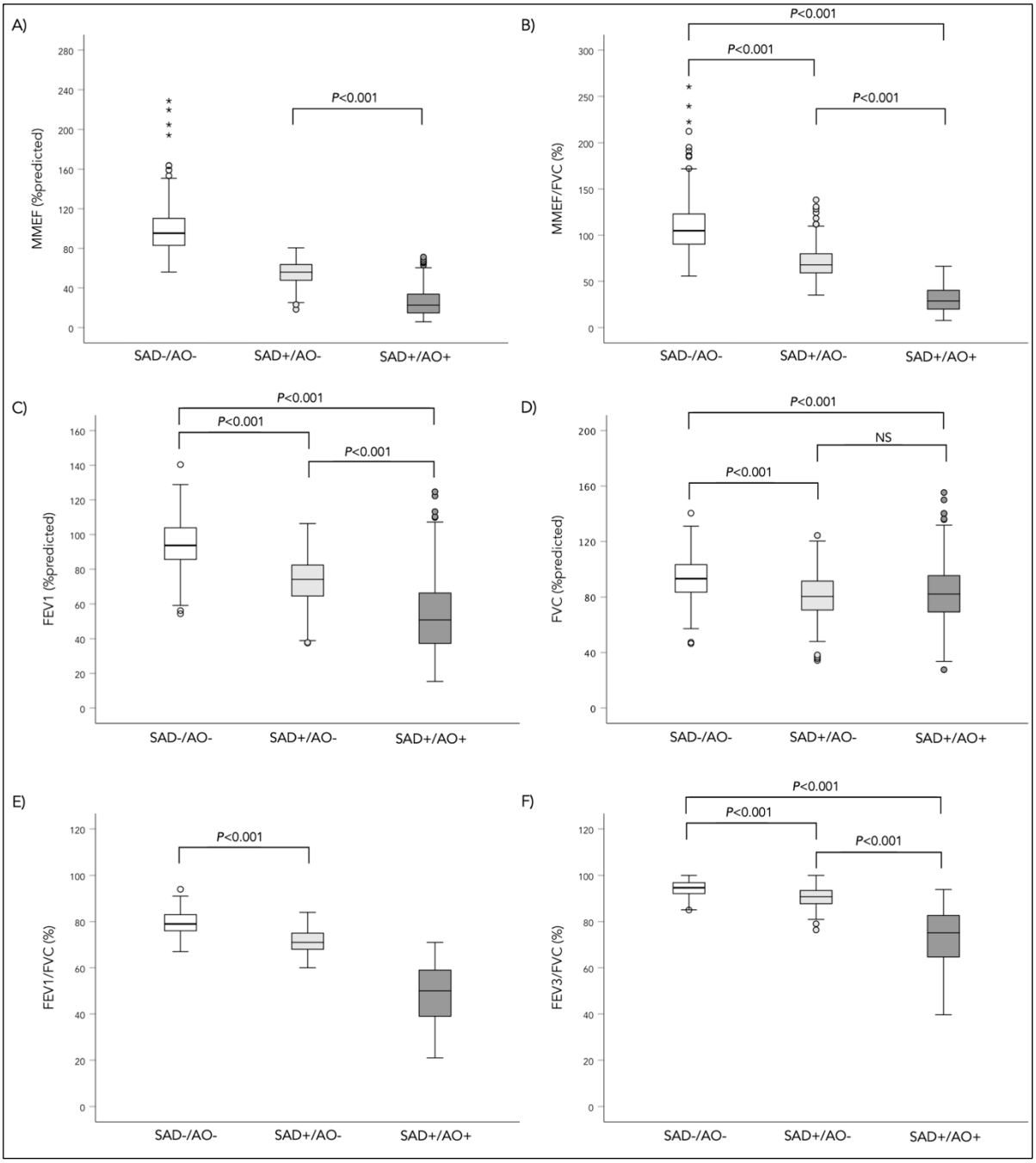
Chapter 2

Appendix 2.1. List of medications used in the included participants

Variable	Total n= 1458	SAD-/AO- *n = 316*	SAD+/AO- *n = 335*	SAD+/AO+ *n = 806*
SABA	891 (61.1)	128 (40.5)	186 (55.7)*	576 (71.4)*†
SAMA	51 (3.5)	2 (0.6)	10 (3)	39 (4.8)*
SABA/SAMA	1 (0.1)	0 (0)	0 (0)	1 (0.1)
ICS	85 (5.8)	17 (5.4)	22 (6.6)	45 (5.6)
LABA	24 (1.6)	1 (0.3)	3 (0.9)	20 (2.5)*
ICS/LABA	405 (27.8)	33 (10.4)	70 (21)*	302 (37.4)*†
LAMA	353 (24.2)	20 (6.3)	47 (14.1)*	286 (35.4)*†
LABA/LAMA	36 (2.5)	2 (0.6)	9 (2.7)	25 (3.1)
ICS/LABA/LAMA	7 (0.5)	0 (0)	0 (0)	7 (0.9)
Systematic CS	55 (3.8)	2 (0.6)†‡	15 (4.5)	38 (4.7)
Antibiotic	28 (1.9)	1 (0.3)	8 (2.4)	19 (2.4)
Montelukast	25 (1.7)	3 (0.9)	4 (1.2)	18 (2.2)
CV Medications	687 (47.1)	183 (57.9)†‡	160 (47.9)	343 (42.5)
GI Medications	381 (26.1)	97 (30.7)	96 (28.7)	187 (23.2)*
Domiciliary Oxygen	19 (1.3)	2 (0.6)	5 (1.5)	12 (1.5)
Mucolytic	101 (6.9)	3 (0.9)	14 (4.2)*	88 (10.9)*†
Theophylline	15 (1.0)	0 (0)	1 (0.3)	14 (1.7)

Legend: Data is presented in n (%).*Significantly different from SAD-/AO-; †Significantly different from SAD+/AO-; ‡Significantly different from SAD+/AO+. Significance level was set at $P<0.05$

Abbreviations: SAD, small airway dysfunction; AO, airflow obstruction; SABA, short-acting beta-2 agonist; SAMA, short-acting muscarinic antagonist; ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist; CS, corticosteroid; CV, Cardiovascular; GI, gastrointestinal



Appendix 2.2. **Distribution of %predicted or ratio of spirometric measures across study groups**.

Legend: A box plot demonstrating the distribution of the % predicted or ratio of spirometric measures across study groups. The plot shows median, interquartile range, minimum and maximum. A) The distribution of MMEF % predicted across groups. B) The distribution of MMEF/FVC ratio across groups. C) The distribution of FEV_1 % predicted across groups. D) The distribution of FVC % predicted across groups. E) The distribution of FEV_1/FVC ratio across groups. F) The distribution of FEV_3/FVC ratio across groups. For groups' comparisons, Kruskal-Wallis H test was performed, and for statistically significant test, a post-hoc Dunn's test

was applied. The presented *P* values were adjusted using the Bonferroni method to account for multiple comparisons. For figures A and E, statistical test was only done for differences between groups where a definition did cause the variable to differ, and the reported p-values are for the Mann-Whitney U test. For figures B, C, D and F, the presented p-values are for post-hoc Dunn's test, and the Kruskal Wallis tests p-values for all figures were <0.001.

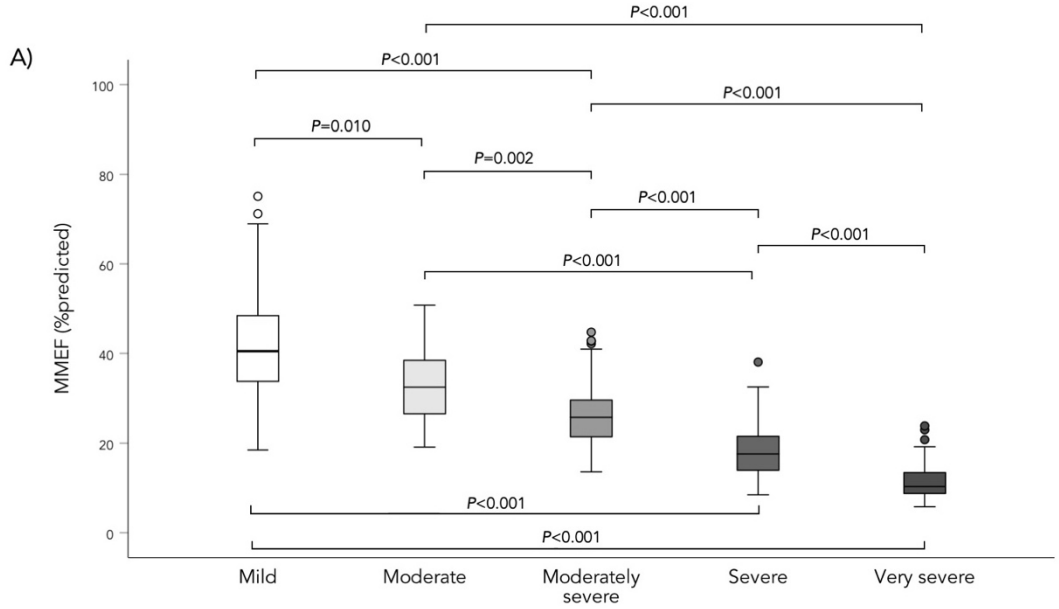
Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; MMEF, maximal mid-expiratory flow; FEV_3, forced expiratory volume in the first 3 seconds; AO, airflow obstruction; SAD, small airway dysfunction; NS, not significant.

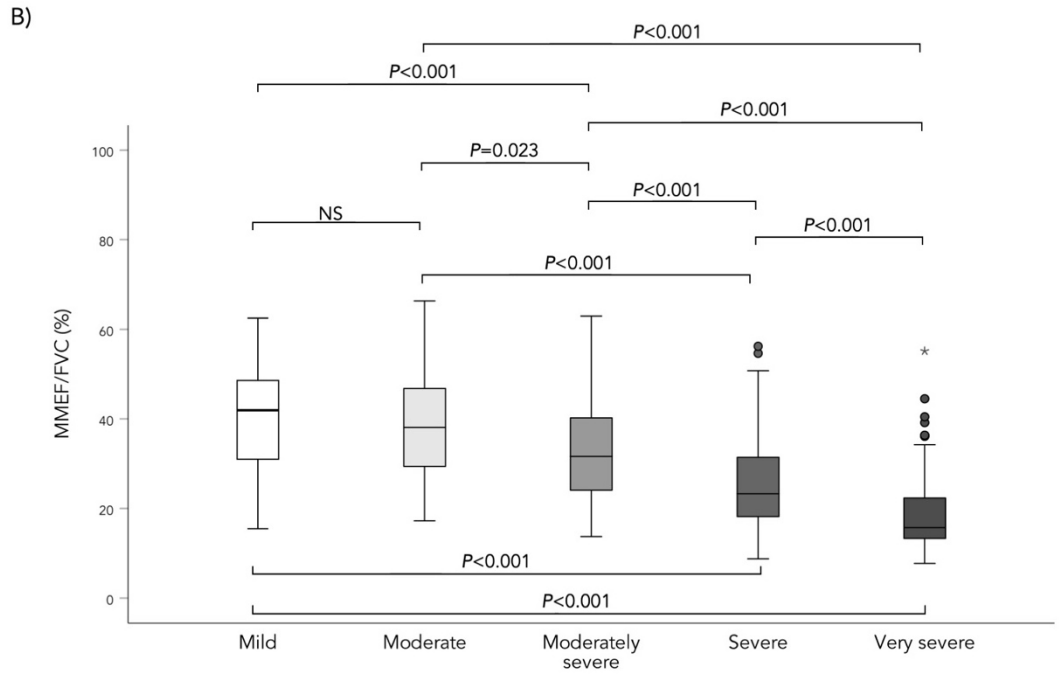
Appendix 2.3. List of medications across airflow obstruction severity.

Variable	Mild *n = 178*	Moderate *n = 111*	Moderately severe *n = 120*	Severe *n = 263*	Very severe *n = 135*
Medications (n, %)					
SABA	103 (57.9)	77 (69.4)	83 (69.2)	197 (74.9)*	116 (85.9)*†‡
SAMA	5 (2.8)	4 (3.6)	7 (5.8)	15 (5.7)	8 (5.9)
SABA/SAMA	0 (0)	0 (0)	0 (0)	1 (0.4)	0 (0)
ICS	10 (5.6)	5 (4.5)	6 (5)	17 (6.5)	8 (5.9)
LABA	4 (2.2)	2 (1.8)	2 (1.7)	9 (3.4)	3 (2.2)
ICS/LABA	43 (24.2)	29 (26.1)	41 (34.2)	112 (42.6)*†	77 (57)*†‡
LAMA	40 (22.5)	40 (36)	29 (24.2)	114 (43.3)	63 (46.7)*‡
LABA/LAMA	3 (1.7)	4 (3.6)	1 (0.8)	12 (4.6)	5 (3.7)
ICS/LABA/LAMA	1 (0.6)	1 (0.9)	1 (0.8)	1 (0.4)	3 (2.2)
Systematic CS	6 (3.4)	4 (3.6)	6 (5)	14 (5.3)	8 (5.9)
Mucolytic	10 (5.6)	8 (7.2)	8 (6.7)	36 (13.7)	26 (19.3)*‡
Antibiotic	1 (0.6)	2 (1.8)	3 (2.5)	7 (2.7)	6 (4.4)
Montelukast	1 (0.6)	0 (0)	2 (1.7)	9 (3.4)	6 (4.4)
CV Medications	89 (50)	44 (39.6)	60 (50)	109 (41.4)	41 (30.4)*‡
GI Medications	44 (24.7)	36 (32.4)	30 (25)	56 (21.3)	22 (16.3)†
Domiciliary Oxygen	0 (0)	4 (3.6)	1 (0.8)	4 (1.5)	3 (2.2)
Theophylline	0 (0)	1 (0.9)	1 (0.8)	7 (2.7)	5 (3.7)

Legend: Data is presented in n (%). *Significantly different from mild; †Significantly different from moderate; ‡Significantly different from moderately severe; §Significantly different from severe. Significance level was set at $p<0.05$.

Abbreviations: SABA, short-acting beta-2 agonist; SAMA, short-acting muscarinic antagonist; ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist; CS, corticosteroid; CV, Cardiovascular; GI, gastrointestinal





Appendix 2.4. **Distribution of measures of SAD across FEV_1 z-score severity**.

Legend: A box plot demonstrating the distribution of measures of SAD across airflow obstruction severity. The plot shows median, interquartile range, minimum and maximum. A) The distribution of MMEF % predicted across severity. B) The distribution of MMEF/FVC ratio across severity. Airflow obstruction severity was assessed using FEV_1 z-score. For groups' comparisons, Kruskal-Wallis H tests was performed, and for statistically significant test, a post-hoc Dunn's test was applied. The presented *P* values were adjusted using the

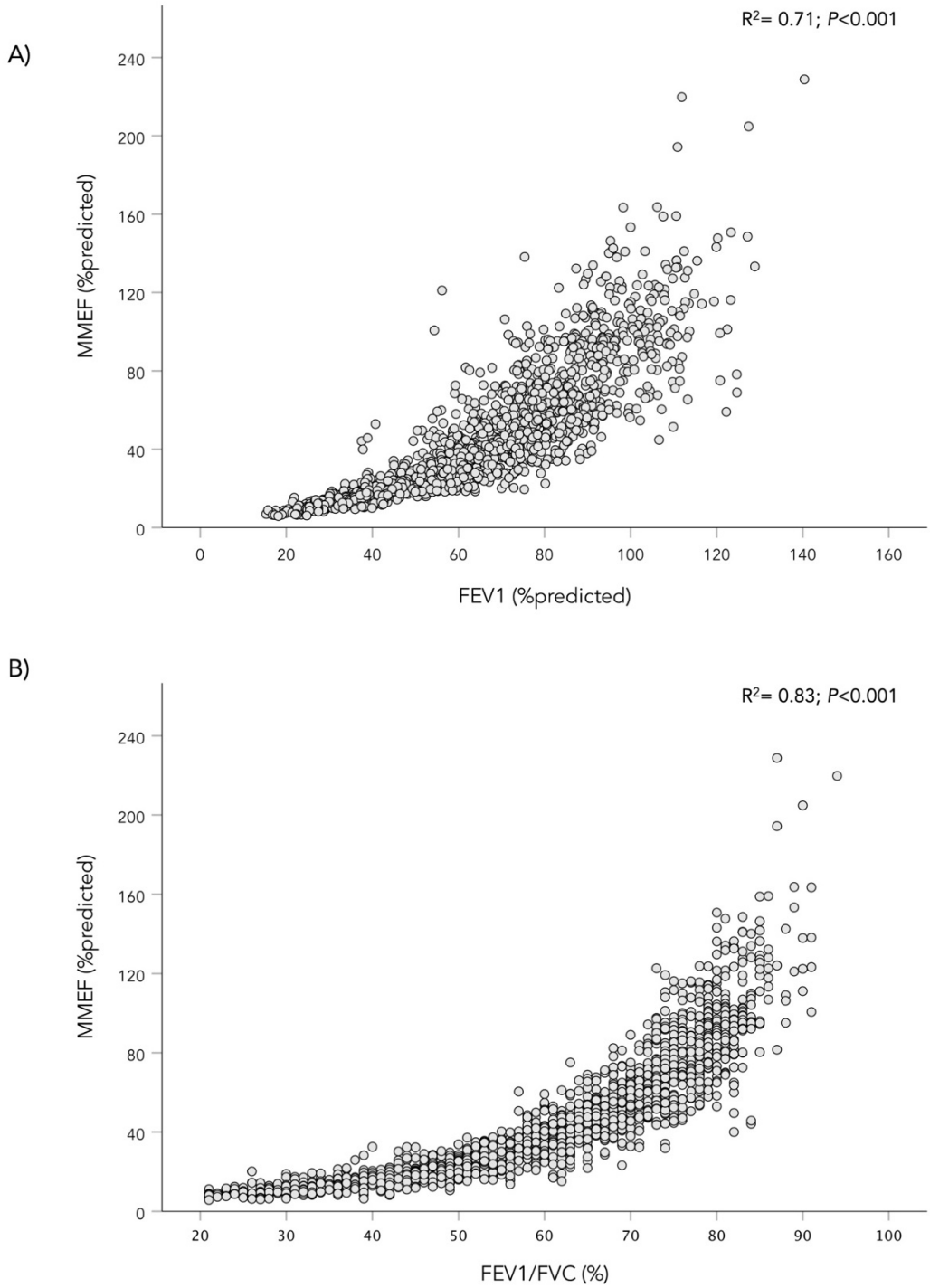
Bonferroni method to account for multiple comparisons. The p-values for Kruskal-Wallis H tests for both figures were <0.001.

Abbreviations: MMEF, maximal mid-expiratory flow; FVC, forced vital capacity; NS, not significant.

Appendix 2.5. The relationship of MMEF and MMEF/FVC with spirometric measures (n=1458)

Spirometric measures	**MMEF % predicted**		**MMEF/FVC**	
	r^2	*P value*	r^2	*P value*
FEV_1 (% predicted)	0.71	<0.001	0.47	<0.001
FVC (% predicted)	0.13	<0.001	0.006	<0.001
FEV_1/FVC (%)	0.83	<0.001	0.92	<0.001
FEV_3/FVC (%)	0.70	<0.001	0.82	<0.001

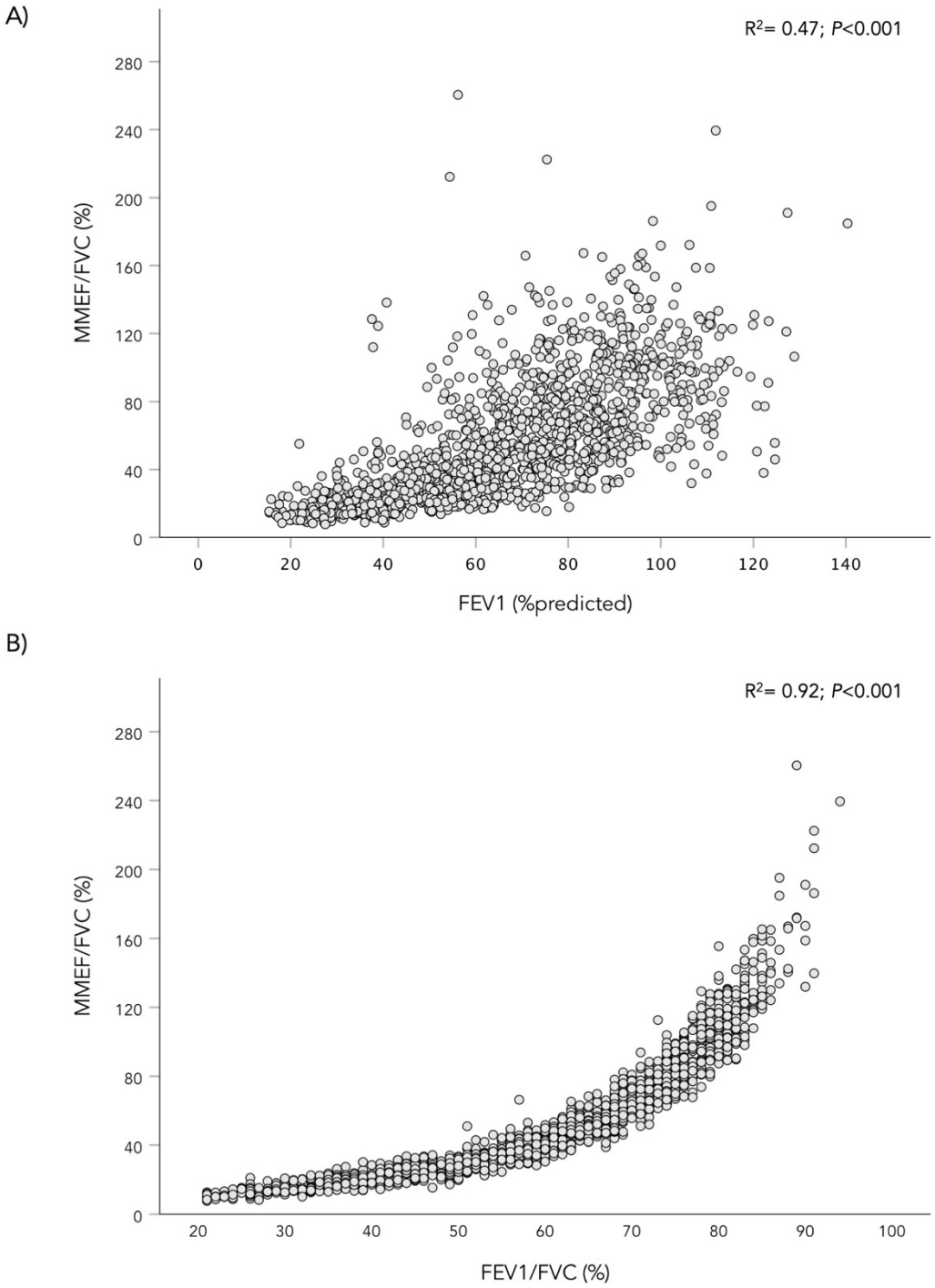
Legend: This tables presents the relationship of MMEF % predicted and MMEF/FVC with other spirometric measures. The relationship was assessed using curvilinear regression analysis, with coefficient of determination (r^2) reported.
Abbreviations: MMEF, maximal mid-expiratory flow; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; FEV_3, forced expiratory volume in three seconds.



Appendix 2.6. FEV_1 % predicted and FEV_1/FVC plotted against MMEF % predicted.

Legend: A) A scatter plot showing the relationship between MMEF % predicted and FEV_1 % predicted. B) A scatter plot showing the relationship between MMEF % predicted and FEV_1/FVC %. The coefficient of determination (r^2) for the curvilinear regression is shown in the figure along with its *P* value.

Abbreviations: MMEF, maximal mid-expiratory flow; FEV_1, forced expired volume in the first second; FVC, forced vital capacity.

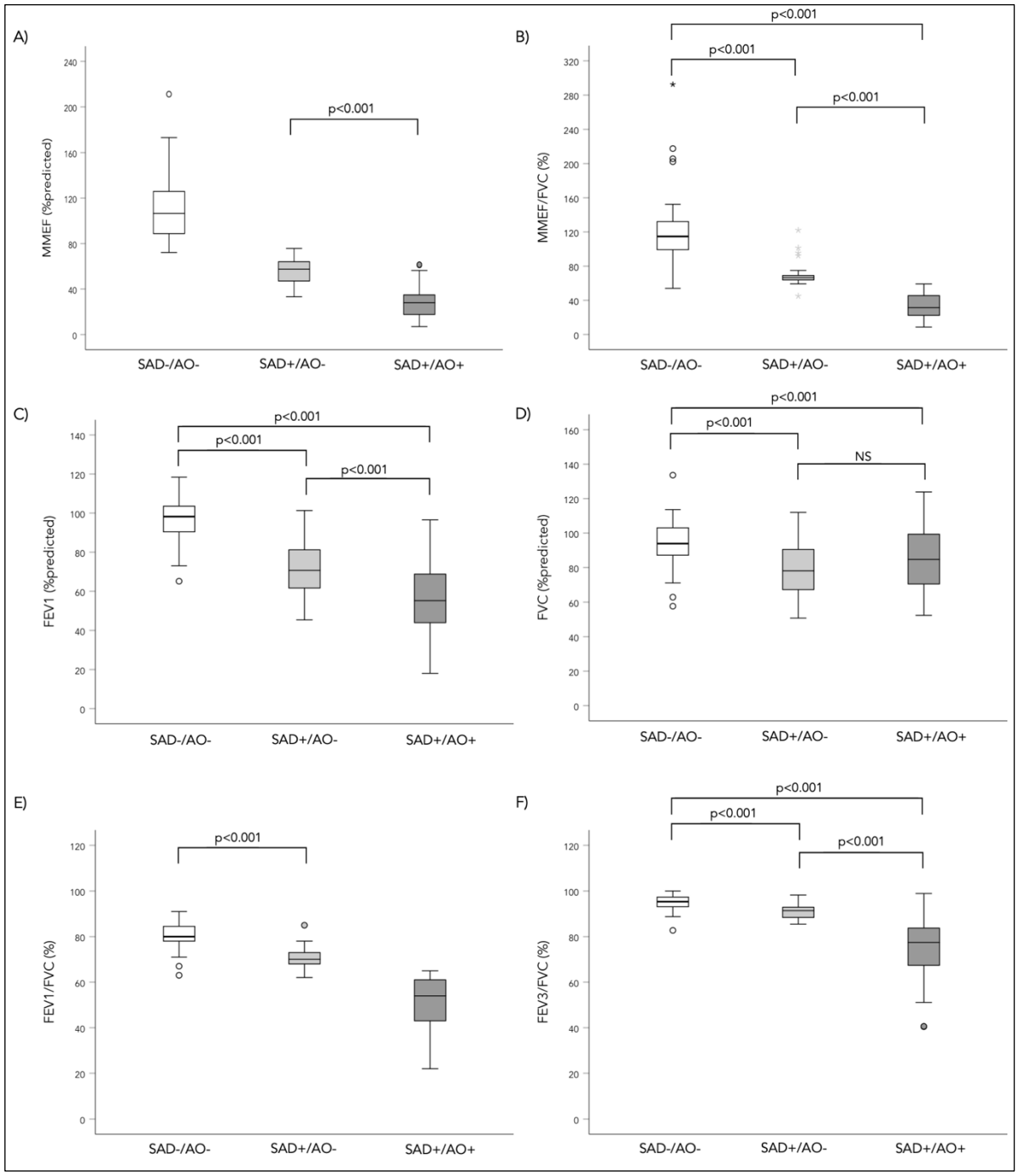


Appendix 2.7. FEV_1 % predicted and FEV_1/FVC plotted against MMEF/FVC.

Legend: A) A scatter plot showing the relationship between MMEF/FVC and FEV_1 % predicted. B) A scatter plot showing the relationship between MMEF/FVC and FEV_1/FVC. The coefficient of determination (r^2) for the curvilinear regression is shown in the figure along with its *P* value.

Abbreviations: MMEF, maximal mid-expiratory flow; FEV_1, forced expired volume in the first second; FVC, forced vital capacity.

Chapter 3



Appendix 3.1. **Distribution of spirometric measures %predicted across study groups**.

Legend: A) The distribution of MMEF % predicted across groups. B) The distribution of MMEF/FVC ratio across groups. C) The distribution of FEV_1 % predicted across groups. D) The distribution of FVC % predicted across groups. E) The distribution of FEV_1/FVC ratio across groups. F) The distribution of FEV_3/FVC ratio across groups. For figures A and E, statistical test was only done for differences between groups where a

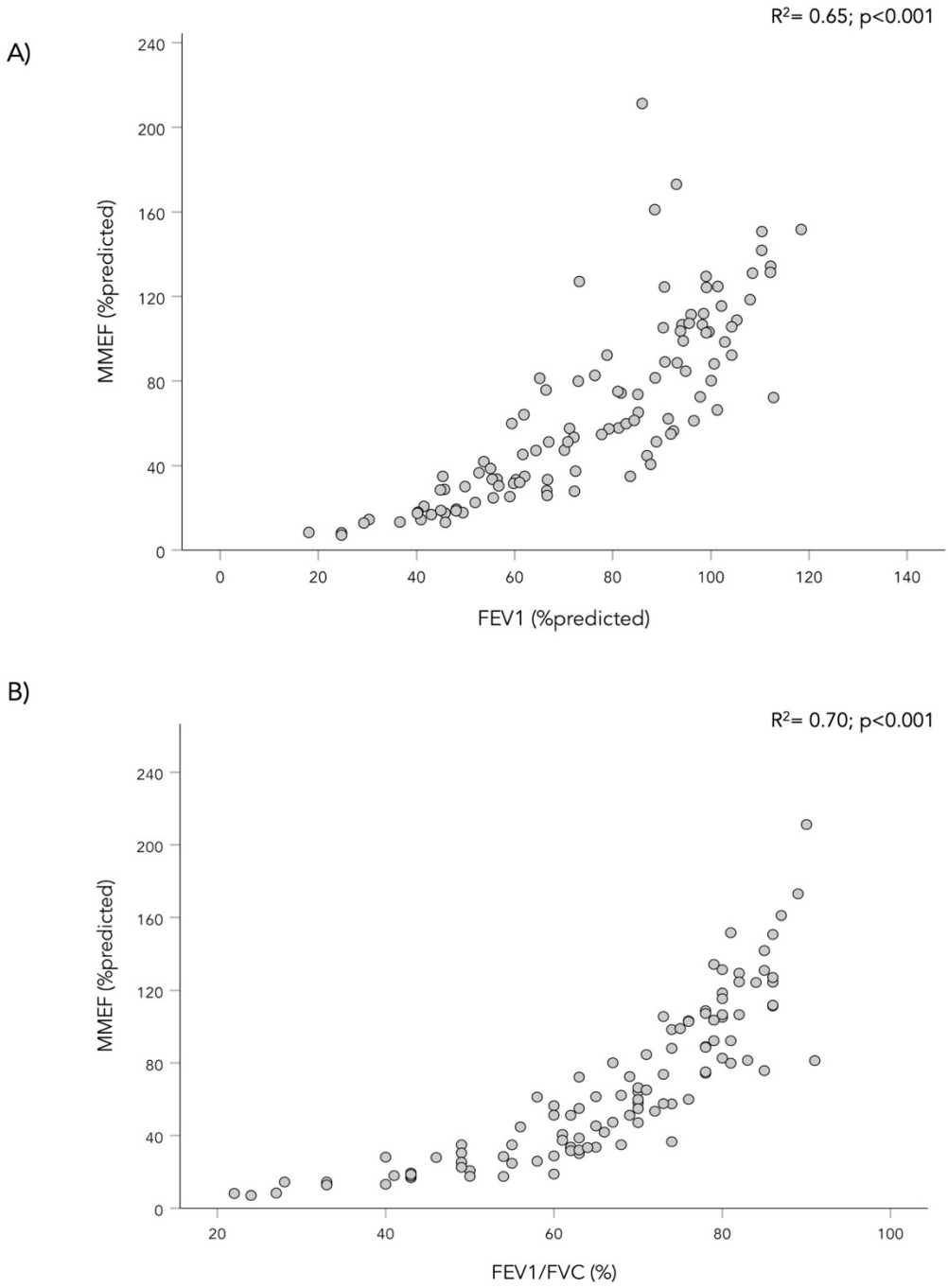
definition did cause the variable to differ, and the reported p-values are for the Mann-Whitney U test. For figures B, C, D and F, the presented p-values are for post-hoc Dunn's test, and the Kruskal Wallis tests p-values for all figures were <0.001.

Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; MMEF, maximal mid-expiratory flow; FEV_3, forced expiratory volume in 3 seconds SAD, small airway dysfunction, AO, airflow obstruction.

Appendix 3.2. The relationship of MMEF and MMEF/FVC with spirometric measures (n=109)

Spirometric measures	**MMEF % predicted**		**MMEF/FVC**	
	r^2	*p*	r^2	*p*
FEV_1 (% predicted)	0.65	<0.001	0.38	<0.001
FVC (% predicted)	0.07	0.005	0.0001	0.925
FEV_1/FVC (%)	0.70	<0.001	0.72	<0.001
FEV_3/FVC (%)	0.54	<0.001	0.56	<0.001

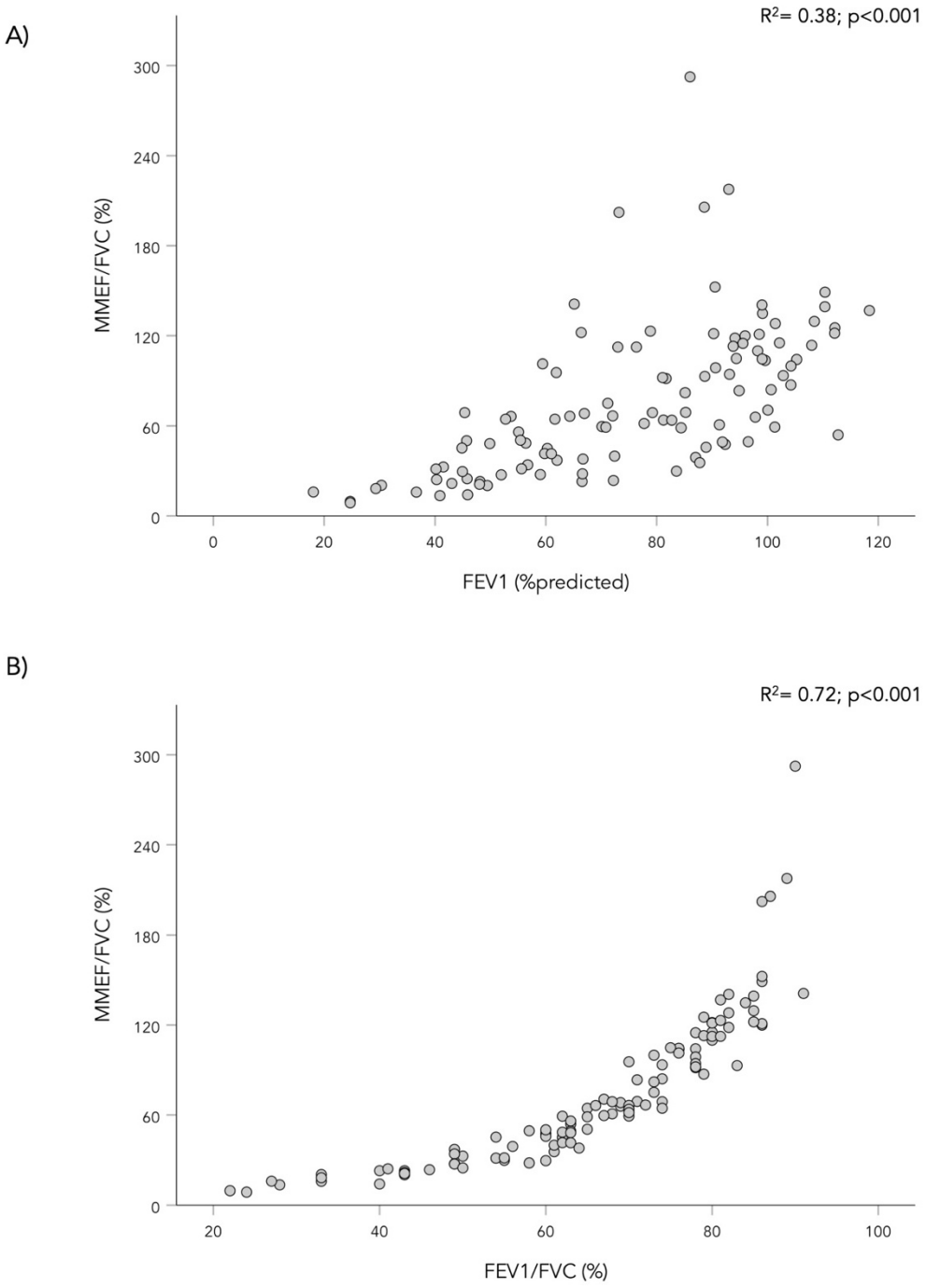
Legend: This tables presents the relationship of MMEF % predicted and MMEF/FVC with other spirometric measures. The relationship was assessed using curvilinear regression analysis, with coefficient of determination (r^2) reported.
Abbreviations: MMEF, maximal mid-expiratory flow; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; FEV_3, forced expiratory volume in three seconds.



Appendix 3.3. FEV_1 % predicted and FEV_1/FVC plotted against MMEF % predicted.

Legend: A) A scatter plot showing the relationship between MMEF % predicted and FEV_1 % predicted. B) A scatter plot showing the relationship between MMEF % predicted and FEV_1/FVC %. The coefficient of determination (r^2) for the curvilinear regression is shown in the figure along with its p value.

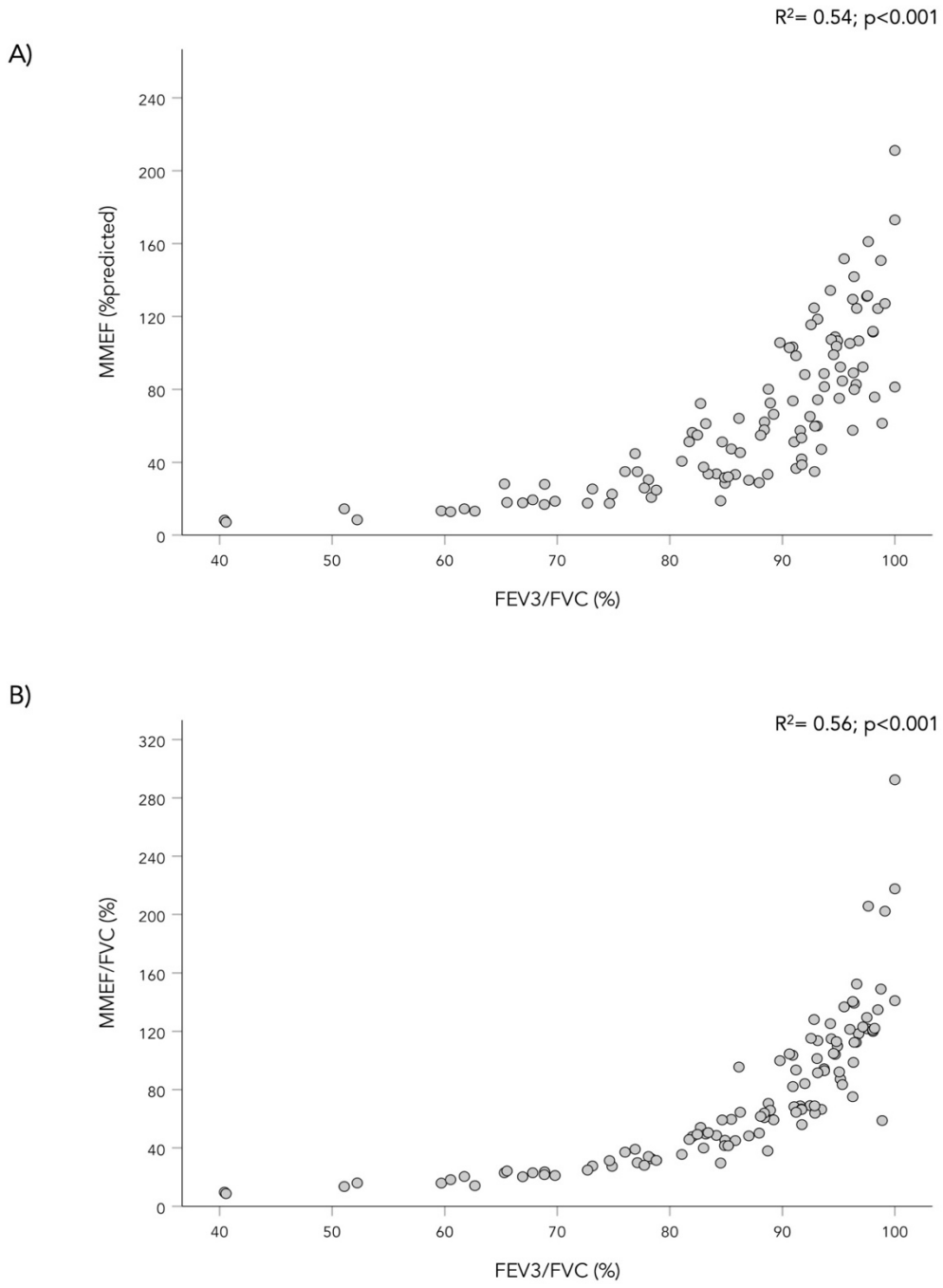
Abbreviations: MMEF, maximal mid-expiratory flow; FEV_1, forced expired volume in the first second; FVC, forced vital capacity.



Appendix 3.4. FEV_1 % predicted and FEV_1/FVC plotted against MMEF/FVC.

Legend: A) A scatter plot showing the relationship between MMEF % predicted and FEV_1 % predicted. B) A scatter plot showing the relationship between MMEF % predicted and FEV_1/FVC %. The coefficient of determination (r^2) for the curvilinear regression is shown in the figure along with its p value.

Abbreviations: MMEF, maximal mid-expiratory flow; FEV_1, forced expired volume in the first second; FVC, forced vital capacity.



Appendix 3.5. FEV_3/FVC plotted against MMEF % predicted and MMEF/FVC.

Legend: A) A scatter plot showing the relationship between MMEF % predicted and FEV_1 % predicted. B) A scatter plot showing the relationship between MMEF % predicted and FEV_1/FVC %. The coefficient of determination (r^2) for the curvilinear regression is shown in the figure along with its p value.

Abbreviations: MMEF, maximal mid-expiratory flow; FEV_1, forced expired volume in the first second; FVC, forced vital capacity.

Chapter 4

Appendix 4.1. Published congress abstract
Small airways response to bronchodilator in asthma and COPD: a systematic review
M Almeshari, NY Alobaidi, E Sapey, OS Usmani

Abstract
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.

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Appendix 4.2. Published systematic review

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Open Access Full Text Article 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.

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.

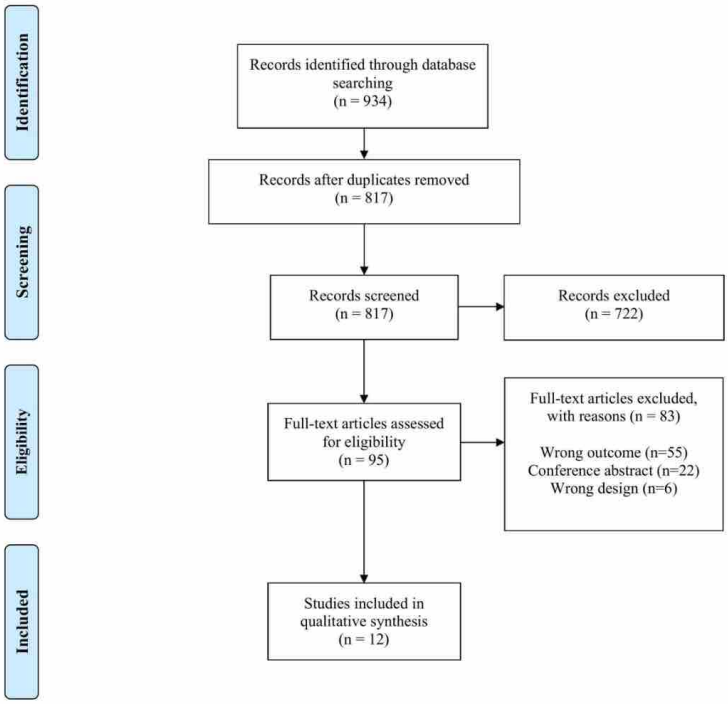

Figure 1 PRISMA flow chart showing the studies identification process from EMBASE and Medline databases.
Notes: Adapted from: Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097.[62] Creative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

(*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 FEV1 is reported. Change in SAF and FEV1 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

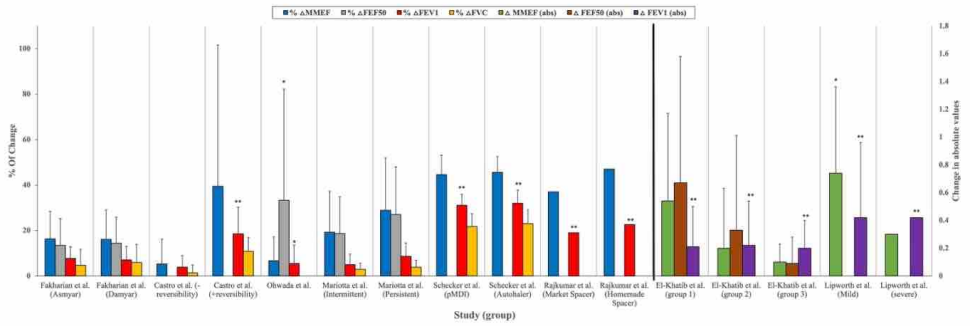

Figure 2 The average percentage change and absolute change in MMEF, FEF_{50}, FEV_1 and FVC across asthma studies.
Notes: Left vertical axis is % of change in MMEF, FEF_{50}, FEV_1 and FVC in asthmatic patients. Right Vertical axis is absolute change in MMEF, FEF_{50}, FEV_1. Data presented are means ± 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

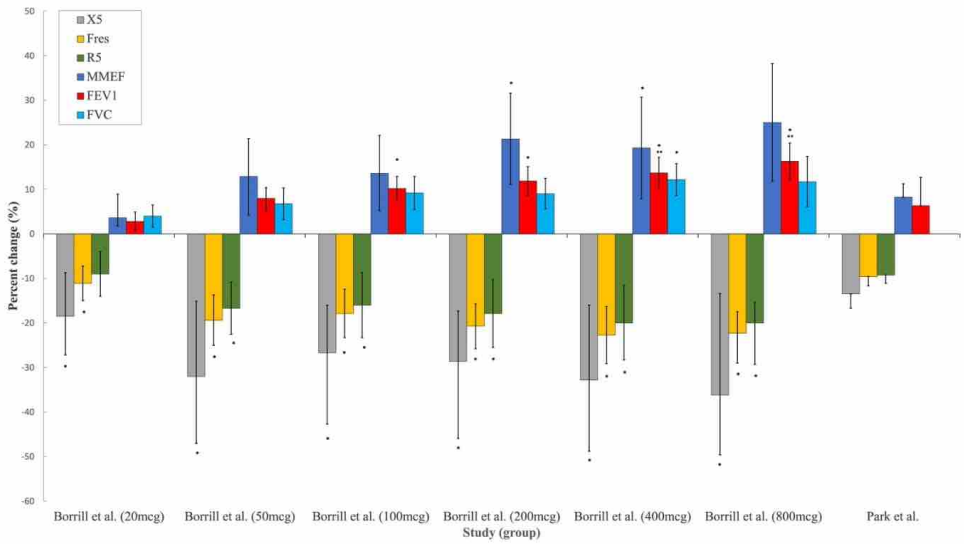

Figure 3 The % of change in spirometry indices (MMEF, FEV_1, and FVC) and in oscillometry indices (X5, Fres, and R5) in COPD patients.
Notes: Vertical axis is % of change in spirometry indices and oscillometry indices across different doses of salbutamol Borrill et al.[26] Data presented in the figure 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

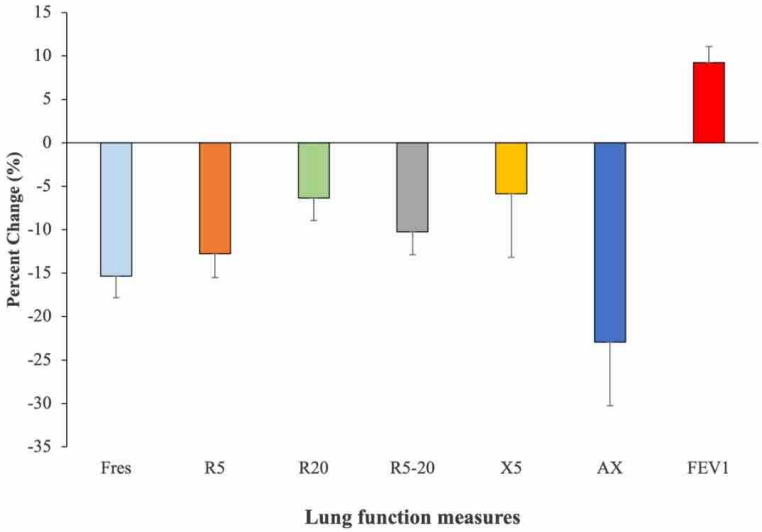

Figure 4 The percentage change of IOS parameters and FEV_1 in Asthmatic patients following BDR.
Notes: Vertical axis is % of change in oscillometry parameters in comparison to FEV_1 in asthmatic patients. Data is adapted from Park et al.[45] Data presented in the figure are the mean % change (± standard 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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Appendix 4.3. Search Strategy

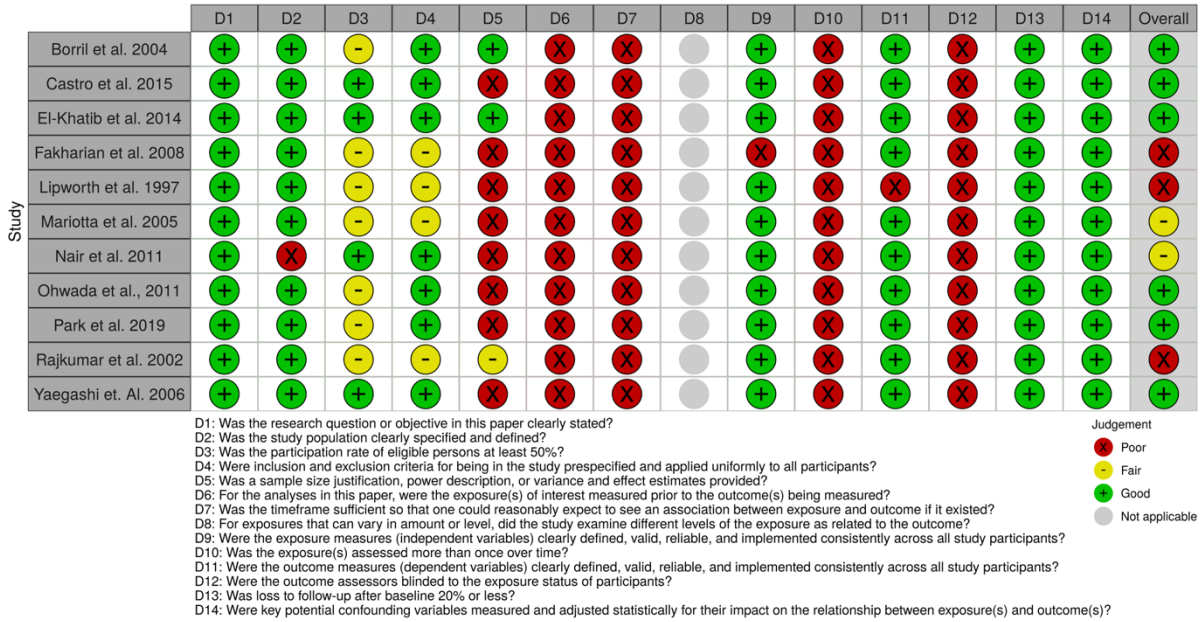
MEDLINE:

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

Appendix 4.4. Quality Assessment Graph



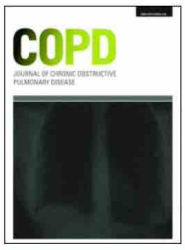
Chapter 6

Appendix 6.1. Published congress abstract

A systematic review of the use of physiological tests assessing the acute response to treatment during exacerbations of COPD

Nowaf Alobaidi, Mohammed Almeshari, James Stockley, Elizabeth Sapey, Ross Edgar
European Respiratory Journal 2020 56: 156; DOI: 10.1183/13993003.congress-2020.156
Abstract
Introduction: Currently there is a lack of sensitive and specific tools which can objectively identify exacerbations and assess their progress or treatment response. FEV1 is often reported as a study outcome, but this forced manoeuvre has significant limitations. Studies have suggested that small airways measures might provide physiological biomarkers during exacerbations.
Aims and Objectives: to assess which physiological tests of small airways function have been used in the acute setting during exacerbations of COPD and the evidence to support their use.
Methods: Following PRISMA guidelines, a systematic review was conducted using several databases for relevant published studies of >10 participants which compared at least one small airway test with FEV1 at both exacerbation and a follow-up measurement up to and including two months after exacerbation onset to assess response to treatment.
Results: From 1436 screened articles, seven studies were found to be eligible for inclusion. There was heterogeneity in which tests of small airways were used. Four different measures were reported (Impulse oscillometry (IOS), Maximal mid-expiratory flow (MMEF), Forced oscillation technique (FOT) and airway resistance (Raw) by body plethysmography). Studies were small (including 20 to 87 subjects). Six articles reported improvements in small airway measurements during the recovery from exacerbation which correlated with FEV1.
Conclusion: There is some evidence to support the use of small airway tests in exacerbations of COPD; however, studies have been small with different tests being utilized. Further pilot studies to determine the usefulness of each test may be of interest

Appendix 6.2. Published systematic review



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A Systematic Review of the Use of Physiological Tests Assessing the Acute Response to Treatment During Exacerbations of COPD (with a Focus on Small Airway Function)

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ABSTRACT

Exacerbations are prevalent in Chronic Obstructive Pulmonary Disease (COPD) patients and associated with poor clinical outcomes. Currently, there is a lack of sensitive and specific tools that can objectively identify exacerbations and assess their progress or treatment response. FEV_1 is often reported as a study outcome, but it has significant limitations. Studies have suggested that small airways measures might provide physiological biomarkers during exacerbations. Therefore, this study was done to assess which physiological tests of small airways function have been used in the acute setting during exacerbations of COPD and the evidence to support their use. An electronic databases search was conducted in April 2019. A standard systematic review methodology was used. Eligible studies were those of $\geq$10 participants that compared at least one small airway test with FEV_1 to assess response to treatment with baseline and a follow-up measurement $\leq$2 months after. Analyses were narrative. Of 1436 screened studies, seven studies were eligible. There was heterogeneity in which tests of small airways were used and three different small airways measures were reported. Studies were small (including 20 to 87 subjects). Six articles reported improvements in small airway measurements during the recovery from exacerbation which correlated with FEV_1. Included studies varied in their timing and duration of the assessment. There is some evidence to support the use of small airway tests in acute exacerbations of COPD. However, studies have been small with different tests being utilized. Further studies to determine the usefulness of each test may be of interest.

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KEYWORDS
COPD; exacerbation; monitoring; small airways' tests; small airway dysfunction; Lung function

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory lung disease that is progressive [1] and characterized by persistent respiratory symptoms and progressive airflow limitation [2]. The combination of parenchymal destruction and small airways dysfunction (with small airways defined as those with an internal diameter of <2mm) lead to airflow limitation [2]. There has been increasing interest in the involvement of small airways in the pathophysiology of COPD since Hogg et al. described small airway resistance in this condition [3]. Pathological studies have shown that smokers with established airflow limitation had a generalized reduction in the diameter of the small airways [4] and, pathophysiologically, the small airways appear to be the major contributor to airflow limitation in COPD [5,6]. Furthermore, studies have shown that small airway disease may precede the onset of emphysema and airflow obstruction [6–8].

Many patients with COPD undergo exacerbations, which are associated with substantial mortality and morbidity [9]. Global Initiative for Chronic Obstructive Lung Disease (GOLD) [2] defines an exacerbation as "an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication". Exacerbations are associated with a reduction in quality of life and lung function, and substantial healthcare cost and utilization [10]. Recently, the United Kingdom national COPD audit data identified difficulties in diagnosing exacerbations and poor care during exacerbations as significant, unfulfilled health needs [11]. Methods of diagnosing COPD exacerbations and assessing the response to treatment currently rely on self-reported symptoms in clinical practice and spirometry in research studies. Commonly, the forced expiratory volume in the first second (FEV_1) has been the primary physiological outcome measure for clinical trials during exacerbation. However, this forced respiratory maneuver is variable (even during

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stable COPD) [12] and insensitive to change over time [13], making it a poor biomarker for exacerbations. For example, bronchodilators have been shown to decrease hyperinflation, lessen the work of breathing and improve symptoms in the absence of a significant spirometric response [14].

Tests of small airway function might provide more sensitive and specific measures during exacerbations but there are a number of physiological measurements that have been proposed as measures of small airways function and a number of different devices available for each measurement [15–17]. The reported measurements include (but are not limited to) Mid-Maximal Expiratory Flow (MMEF which is also referred to as the forced expiratory flow between 25% and 75% of the forced vital capacity (FVC) ($FEF_{25-75\%}$)), nitrogen washout tests, Forced oscillation technique (FOT) and airway resistance (Raw) obtained by body plethysmography.

While there remain some debate about the specificity of certain tests to evaluate small airways function [18], studies suggest that tests of small airways may be better able to identify physiological responses to treatment compared with conventional spirometric measures [19]. However, it is unclear whether such tests would be clinically valuable during an exacerbation of COPD as there are no previous comprehensive reviews of the evidence in this area. The aim of this review was to summarize the findings of studies comparing a measure of small airways function to FEV_1 during exacerbations of COPD to inform whether these tests could be incorporated as a primary outcome for further studies within this population. FEV_1 was chosen pragmatically as a comparator as it remains the most commonly reported physiological test in exacerbations of COPD, despite the potential limitations of this measure, as discussed above.

Methods and design

Protocol and registration

The systematic review protocol was prepared following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [20] and registered on PROSPERO (registration number: CRD42019131939).

Eligibility criteria

Study design

Randomized controlled trials (RCT), non-randomized interventional studies, observational studies, case series and uncontrolled studies of $\geq$10 that compared at least one small airway test with FEV_1 at both exacerbation onset (this was clinician-defined exacerbation) and a follow-up measurement up to and including two months after exacerbation onset.

Type of participants

Adult patients older than 18 years with a clinical diagnosis of COPD during exacerbation with no limitation on either COPD or exacerbation severity were included. Studies of COPD patients not experiencing an exacerbation (therefore, stable) were excluded. Studies of patients with a primary diagnosis of other lung diseases, including asthma, were also excluded.

Intervention and comparator

Studies were included if they contained at least one of the following commonly used tests of small airways in comparison to FEV_1: FOT, MMEF, Raw by body plethysmography and nitrogen washout tests.

Objective

The objective of this study was to assess treatment response using small airway tests in comparison to FEV_1 during exacerbation of COPD.

Outcome

Tests of small airways which included but (were not limited to) FOT, MMEF, Raw by body plethysmography, and nitrogen washout tests.

Search strategy

A comprehensive search was conducted using MEDLINE (*via* Ovid), EMBASE (*via* Ovid), CINAHL, and the Cochrane Central Register of Controlled Trials (CENTRAL). Different search strategies were used for each database (shown in the online supplement). ClinicalTrials.gov was used to search for completed and ongoing clinical trials. Where possible, articles not in English were translated. References lists of peer-reviewed published articles was also manually searched for additional references. Search results were downloaded to Rayyan [21] and duplicates were removed.

Study selection

Two authors independently screened studies to assess eligibility for inclusion in the study according to the pre-specified inclusion and exclusion criteria (NYA and MA). Disagreements were resolved through the third reviewer (RGE). Full-text studies were screened and reviewed by two independent reviewers using the pre-specified inclusion and exclusion criteria (NYA and MA). Disagreement was resolved through discussion with a third reviewer (RGE) and reasons for exclusion recorded. Study selection was done through Rayyan [21]. The selection process was reported using the PRISMA flow diagram (see Figure 1).

Data extraction

For each included study, data were extracted using customized electronic data extraction form, which was piloted by two reviewers (NYA and MA) before the data extraction phase. Data extraction was completed by one reviewer (NYA) and checked for accuracy by a second reviewer (MA). Corresponding authors were contacted if data were ambiguous or missing.

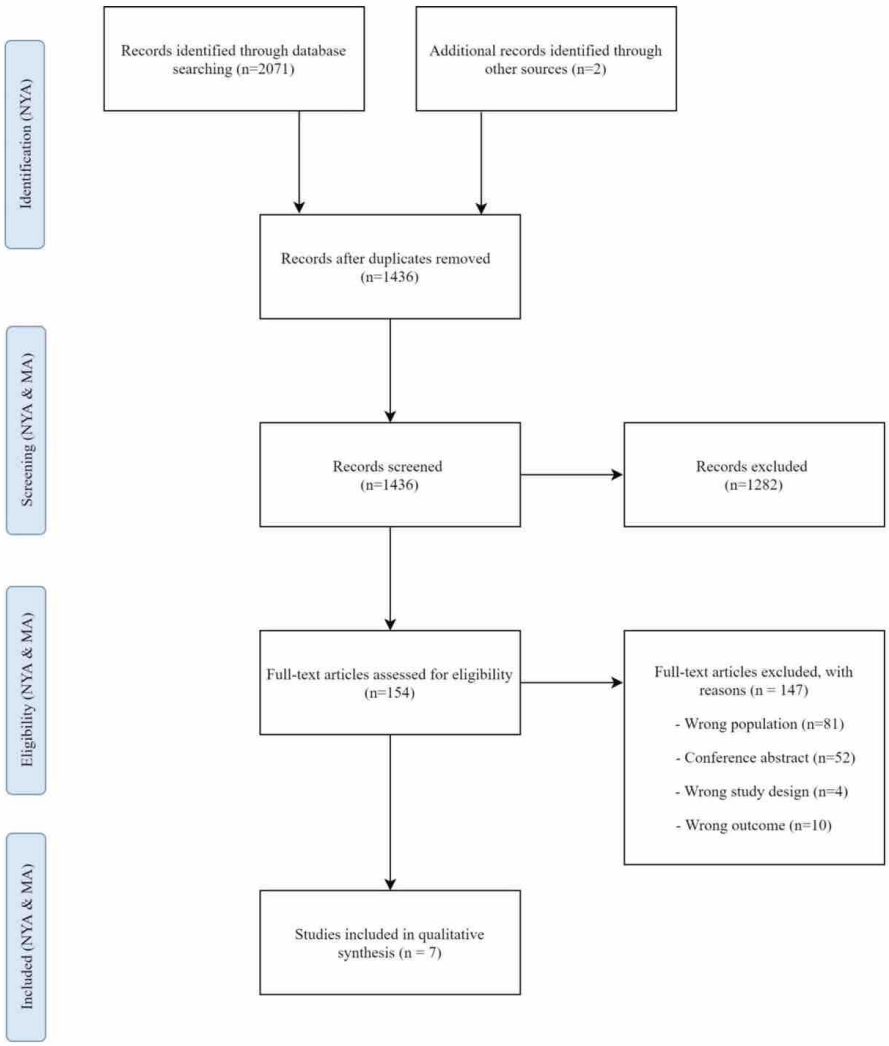

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram [16].

Risk of bias and quality assessment

Risk of bias was assessed using two quality assessment tools. RCTs were evaluated with the revised Cochrane tool for assessing the risk of bias in RCT [22], with the risk of bias classified as high, some concern or low for each study. Non-randomized studies were assessed using NIH Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group [23], with the quality classified as good, fair or poor. Two reviewers independently checked each selected article (NYA and MA). Disagreement was resolved through discussion.

Data synthesis

Outcomes of the included studies were compared and a narrative analysis was performed. Due to the high degree of heterogeneity (with different tests of small airways, different definitions of exacerbations used and different outcome measures), a meta-analysis of included studies was not possible.

Results

Of 1436 citations (excluding duplicates), 154 relevant studies met inclusion criteria. Thirteen were non-English articles

Table 1. Definition of exacerbation in the included studies:.

Author	Definition of exacerbation
Stevenson et al. [25]	An increase in at least two major symptoms: dyspnea, sputum purulence, or increased sputum volume, sufficient to require hospitalization.
Sahn et al. [26]	Not explained
Yetkin et al. [28]	Episodes of worsening breathlessness and/or wheezing, often accompanied by greater volume or purulence of sputum and increased cough
Parker et al. [25]	According to the criteria adopted by the Canadian Thoracic Society, "a sustained worsening of dyspnea, cough or sputum production leading to an increase in the use of maintenance medication and/or supplementation with additional medications"
Komlev et al. [24]	an increase in cough, an increase in the amount of sputum and a change in its character, an increase in shortness of breath and a decrease in exercise tolerance, moderate signs of intoxication syndrome that requires therapy.
Jetmalani et al. [29]	GOLD definition "an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication"
Johnson et al. [26]	Increased breathlessness for at least 24 h with at least two criteria of increased cough frequency or severity, increased sputum volume or purulence or increased wheeze.

Notes: This table demonstrates how exacerbations were defined among included studies. Each row provides the definition of exacerbations used in the stated study. Although they have defined exacerbations differently, most of the studies' definitions met current international guidelines of exacerbation.

(four German, two Russian, two Chinese, one Korean, one Polish, one Bulgarian and one French) but were included for full text screening. After the full-text screening, seven articles were eligible to be included in the review and 147 were excluded with exclusion reasons documented. Of the seven articles included, only one was not in English and was written in Russian [24] (See Figure 1).

Of the included studies, six studies were non-randomized [24–29], and one was RCT [30]. Five studies were hospitalized exacerbations [24,26–29], one included both hospitalized and community exacerbations [25], and one included community exacerbations only [30]. Different definitions of exacerbation were used in most studies and they are reported in (Table 1). The duration of included studies ranged from 5 to 60 days, with a median time of 14 days (Interquartile Range (IQR) 8 to 42). The sample size across all studies ranged between 20 to 87 participants, with a median size of 29 participants (IQR 22.5 to 52.5). The characteristics and the main findings of the seven included studies are detailed in the online supplement.

Of the seven included articles three studies used FOT [26,27,29], four studies used MMEF [24,25,28,30] and two studies used Raw by body plethysmography [24,25]. Using small airways tests and FEV_1, treatment response was assessed in all of the included studies. However, included studies varied in how they reported response to treatment. Some studies reported pre- and post-measure [24,27–30] while, in the others, pre-measure and the changes in the outcome measured were reported [25,26].

Quality assessment of included studies

All non-randomized studies had clearly stated their objective, research question and eligibility criteria. However, three of the studies did not justify the sample size of the study [24,28,29], although two had the highest number of participants among the included studies [24,28]. Participants of the included studies were representative of the general population of interest in all of the studies. Four of the studies had a number of visits where measurements were taken [25–27,30]. One study was felt to be of good quality [26], two of fair quality [24,28] and three of poor quality [25,27,29] (as shown in Table 2). The risk of bias of the only included RCT [30] was found to be high (as shown in Table 3).

Forced oscillation technique (FOT)

FOT was used to assess treatment response in COPD exacerbation in three observational studies. Impulse oscillometry (Jaeger MasterScreen (IOS)), which is a later version of FOT, was used in one study. Stevenson et al. [27] used IOS and FEV_1 to assess treatment response during exacerbation in a longitudinal study. Here, after the baseline assessment (day 1 of the exacerbation), IOS and FEV_1 were repeated at day 2, day 3, discharge day and day 42. The median length of hospital stay was 7 days (range 3-10 days). The authors only reported R5 (total respiratory resistance) and X5 (total respiratory reactance), with both reported as mean ± standard deviation (SD). R5 did not show any improvement during the treatment period. X5 showed an average improvement of 26% from baseline (-0.42 ± 0.03 kPa/L/s) to discharge day (-0.31 ± 0.03 kPa/L/s; $p < 0.001$) and a 33% improvement from baseline to day 42 (-0.28 ± 0.04 kPa/L/s; $p < 0.01$). FEV_1 also improved during the treatment period from a mean of 1.03 ± 0.08 L at baseline to 1.08 ± 0.08 L ($p < 0.05$) at day 2 with no changes at day 3. At discharge, FEV_1 increased to 1.12 ± 0.09 L ($p < 0.05$) (an average of 8% improvement) but this did not meet the accepted Minimal Clinically Important Difference ((MCID) of at least 100 ml) for FEV_1 [31]. The 100 ml MCID was not observed until day 42 (1.26 ± 0.10 L; $p < 0.01$), where there was an average 22% improvement from baseline.

Jetmalani et al. [29] who used an in-house-built FOT device at 6 Hz, assessed if expiratory flow limitation ((EFL) representing a physiological condition in which expiratory flow cannot rise by increasing respiratory effort [32]) related to symptoms during hospitalized exacerbations of COPD.

Table 2. NIH quality assessment tool of included non-randomized studies.

NIH Quality assessment	Yetkin et al. [23]	Jetmalani et al. [29]	Parker et al. [25]	Johnson et al. [26]	Stevenson et al. [25]	Komlev et al. [24]
Was the study question or objective clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes
Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	Yes	Yes	Yes	Yes	Yes
Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	Yes	Yes	Yes	Yes	Yes
Were all eligible participants that met the prespecified entry criteria enrolled?	CD	CD	CD	CD	CD	CD
Was the sample size sufficiently large to provide confidence in the findings?	Yes	CD	No	Yes	No	Yes
Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	Yes	Yes	Yes	Yes	Yes
Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes
Were the people assessing the outcomes blinded to the participants' exposures/interventions?	NA	NA	NA	NA	NA	NA
Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	CD	No/NA	Yes/CD	Yes/Yes	Yes/Yes	CD
Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	Yes	Yes	Yes	Yes	Yes
Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	Yes	Yes	CD	Yes	Yes	CD
If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	CD	CD	CD	CD	CD	CD
Overall Quality rating	**Fair Quality**	**Poor Quality**	**Poor Quality**	**Good Quality**	**Poor Quality**	**Fair Quality**

Notes: Quality assessment was done using NIH tool. Each question was assessed by two reviewers separately (NYA. and MA), and overall rating was blindly determined. Results were then discussed, and Conflicts in questions and overall rating resolved through discussion. The overall quality rating for included studies is the agreed rating between reviewers.
Abbreviations: CD = Cannot determine, NA = Not applicable.

The authors categorized patients into two groups: those with EFL at admission and those with no EFL at admission. They performed assessments on admission and prior to discharge, with mean length of stay being 5 days (±1 SD). All FOT results were reported as mean ± SD. Resistance parameters (Rrs (total respiratory resistance), Rrs_{insp} (resistance during inspiration), Rrs_{exp} (resistance during expiration)) did not change in either group. Reactance parameters improved in the EFL group prior to discharge. Although Xrs_{insp} (reactance during inspiration) showed improvement (increasing from -3.73 ± 0.97 $cmH_2O{\cdot}s{\cdot}L^{-1}$ to -2.90 ± 0.87 $cmH_2O{\cdot}s{\cdot}L^{-1}$, $p = 0.01$), Xrs (total respiratory resistance), Xrs_{exp} (reactance during expiration), ΔXrs (expiratory flow limitation index, which is used to measure EFL (Xrs_{insp} - Xrs_{exp})) demonstrated the most pronounced improvement (Xrs increased from -7.37 ± 2.27 $cmH_2O{\cdot}s{\cdot}L^{-1}$ to -4.41 ± 1.92 $cmH_2O{\cdot}s{\cdot}L^{-1}$ ($p = 0.008$), Xrs_{exp} from -8.70 ± 3.19 $cmH_2O{\cdot}s{\cdot}L^{-1}$ to -5.12 ± 2.33 $cmH_2O{\cdot}s{\cdot}L^{-1}$ ($p = 0.008$), and ΔXrs from 4.97 ± 2.64 $cmH_2O{\cdot}s{\cdot}L^{-1}$ to 2.21 ± 1.51 $cmH_2O{\cdot}s{\cdot}L^{-1}$ ($p = 0.008$)). FEV_1 did not change in either group.

Johnson et al. [26] used FOT (with an oscillation frequency of 5 Hz) and FEV_1 to assess treatment response across three visits (<48 h of admission, after one week and after 6 weeks). All results are reported as mean and standard error of mean [8]. No significant changes were seen in resistance parameters (Rrs, Rrs_{insp}, Rrs_{exp}) across timepoints. Following one week of admission, mean Xrs_{insp} increased by 13% (4.5 SEM) ($p < 0.05$); Xrs by 27.9% (7 SEM) and Xrs_{exp} 31.5% (7.8 SEM) ($p < 0.001$ for both). After 6 weeks, Xrs_{insp} increased by 27.4% (6.7 SEM) ($p < 0.001$), Xrs by 35.2% (8.9 SEM) and Xrs_{exp} by 37.1% (10.0 SEM) ($p < 0.005$ for both). FL% (flow limitation percentage, which represents the proportion of breaths for which ΔXrs indicated the flow limitation) improved at visit two (decreasing by 19.2 ± 6.1%, $p < 0.005$) and decreasing by 19.5 ± 7%, ($p < 0.05$) at visit 3.

Table 3. Risk of bias assessment of the included RCT.

Study ID	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
Sahn et al. [26]	High	High	High	Some concerns	Some concerns	**High risk of bias**

Notes: Risk of bias was evaluated using Revised Cochrane tool for RCT. The tool assesses risk of bias on several domains: Randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported results. The risk of bias was evaluated as recommended: high risk, some concerns, or low risk. Each domain was assessed by two reviewers independently (NYA and MA). Conflict in domains and overall risk of bias were resolved through discussion.

FEV_1 also improved, meeting the MCID criterion at visit two (improvement of $0.153\,L \pm 0.046$ ($6.4 \pm 1.7\%$; $p < 0.005$)) and three ($0.274\,L \pm 0.064$ ($11.4 \pm 2.3\%$; $p < 0.001$)). When expressed as a percentage changes, reactance parameters improved more than FEV_1.

MMEF

MMEF was used in four studies. Sahn et al. [30] (who included only male patients in their RCT) used MMEF and FEV_1 to assess the response to high (1000 mg three times a day (TID)) or standard (500 mg TID) dose amoxicillin during an episode of acute bronchitis in patients with COPD (reflecting the terminology of exacerbations at that time). However, they reported the results as only one mean and SD irrespective of the different doses of antibiotic being given. MMEF and FEV_1 (pre and post-bronchodilator) were collected at day 0, day 2 and day 7 with MMEF changing throughout the treatment period ($p < 0.05$). At day 2, pre-bronchodilator MMEF increased from 1.25 ± 0.26 L/s to 1.46 ± 0.28 L/s ($p < 0.05$) but there was no difference in pre-bronchodilator MMEF when day 7 (1.39 ± 0.29 L/s) was compared to baseline. Post bronchodilator MMEF improved only at day 7, where it rose from 1.35 ± 0.28 L/s to 1.67 ± 0.32 L/s ($p < 0.05$) (an average 24% increase). FEV_1 also improved during the treatment period, meeting the MCID criterion. Pre-bronchodilator FEV_1 increased from 1.65 ± 0.22 L to 1.82 ± 0.22 L at day 2 and to 1.81 ± 0.23 L at day 7 ($p < 0.05$). Post-bronchodilator FEV_1 rose from 1.80 ± 0.23 L to 1.94 ± 0.22 L ($p < 0.05$) at day 2 and to 1.98 ± 0.23 L ($p < 0.05$) at day 7 (an average 10% increase).

MMEF was also used in two observational studies. Yetkin et al. [28] used MMEF (termed FEF_{25-75} in their study (L/s and %)) and FEV_1 to assess treatment response during an exacerbation, collecting readings on admission day and discharge day (mean length of stay 9 days ± 2). All results were reported as mean and SD. MMEF and FEV_1 changed at discharge ($p < 0.05$): MMEF increased from 0.43 ± 0.14 L/s to 0.52 ± 0.14 L/s ($p < 0.05$) (an average 20% increase) and FEV_1 increased from 1.14 ± 0.29 L to 1.22 ± 0.32 L, (p-value <0.05) (an average 7% increase), which FEV_1 did not meet the MCID.

Parker et al. [25] assessed both Inspiratory Capacity (IC) and MMEF in comparison to FEV_1 to evaluate the severity and recovery of acute exacerbations of COPD in a longitudinal study with multiple visits (admission day, day 7, day 14, day 30 and day 60). All results were reported as mean and SEM. MMEF did not show any change throughout the treatment period. In contrast, FEV_1 improved during the recovery period of the exacerbation although changes above the MCID criterion were only seen from day 14 (FEV_1 increased by 0.12 ± 0.06 L at day 14, 0.13 ± 0.06 L at day 30 ($p < 0.05$) and by 0.24 ± 0.06 L at day 60 ($p < 0.01$))

In an interventional study, Komlev et al. [24] also used MMEF and FEV_1, assessing the effect of systemic glucocorticoid steroids (SGS) during acute exacerbations of COPD from admission to day 14 of treatment. All results were reported as mean and SD. In their study, MMEF demonstrated improvements at day 14 (rose from $15.7 \pm 7.0\%$ to $21.5 \pm 14\%$, $p < 0.05$; an average improvement of 37%). FEV_1 also demonstrated improvements (increased from $41.1 \pm 14\%$ to $50.1 \pm 16\%$, $p < 0.05$; an average 22% increase). They also separated patients into two groups: group 1 (>15% change in FEV_1 at day 14 of SGS) and group 2 (<15% changes in FEV_1 at day 14 of SGS). At day 14, group 1 demonstrated improvements in MMEF and FEV_1 ($p < 0.05$) with no change in group 2. In group 1, MMEF increased from $12.4 \pm 7.0\%$ predicted to $28.8 \pm 18.0\%$ predicted at day 14 of SGS treatment ($p < 0.05$), and FEV_1 increased from $34.2 \pm 11.0\%$ to $60.5 \pm 14.0\%$. Although it could not be determined whether the improvement in FEV_1 met MCID criteria as actual values were not given, a 25% change represents a clinically relevant change.

Raw by body plethysmography

Raw obtained by body plethysmography was used to assess treatment response in two studies. Parker et al. [25] reported MMEF, FEV_1 and specific airway resistance (sRaw) in their observational study at admission, day 7, day 14, day 30 and day 60 (as described previously). All results were reported as mean and SEM. Although sRaw decreased at day 7 and day 30, it only demonstrated significant improvement at day 14 and day 60 ($p < 0.05$). Compared to the baseline assessment, sRaw changed by $133 \pm 57\%$ and $128 \pm 51\%$ at day 14 and 60, respectively ($p < 0.05$) with FEV_1 improving most at day 60 ($p < 0.01$).

As described previously, Komlev et al. [24] assessed airway resistance during inspiration [18] and expiration (R_{ex}) at admission day and day 14 of SGS. All results were reported as mean and SD. R_{ex} showed significant improvement (decreasing from 1.05 ± 0.66 kPa/L/s to 0.76 ± 0.5 kPa/L/s; $p < 0.05$), while R_{in} did not. When separated into the two groups, R_{in} did not change at day 14 in either group. In contrast, R_{ex} decreased both in group 1 (from 1.02 ± 0.5 kPa/L/s to 0.57 ± 0.4 kPa/L/s; $p < 0.05$) and group 2 (from 1.06 ± 0.7 kPa/L/s to 0.84 ± 0.5 kPa/L/s; $p < 0.05$), with FEV_1 improving only in group 1 ($p < 0.05$).

Discussion

This is the first systematic review evaluating the use of physiological tests of small airway function during exacerbations of COPD. The aim of this review was to assess whether there was sufficient evidence to incorporate measures of small airways function as a primary outcome for studies of COPD exacerbations. In summary, the small number of studies, low participant numbers, study heterogeneity and general mixed quality of the studies limits any conclusions about the utility of these tests during exacerbations. However, in most studies, there were early signals of small airways measurement change following the diagnosis and treatment of an exacerbation. This was reported (albeit not consistently) for FOT, MMEF and sRaw, often at an increased magnitude or prior to an FEV_1 change. This suggests further studies are warranted to determine if these physiological tests provide information about the early recovery phase of exacerbations. However, more information is needed to determine population reference ranges, which test should be used in which setting and which devices provide comparable results.

Exacerbations are common and serious events and are associated with reductions in quality of life, health status and lung function [10]. Diagnostic tools and treatment approaches have not changed significantly for over 30 years [33] but there is great interest in testing new therapies to prevent or treat exacerbations and finding more sensitive and specific tools to diagnose exacerbations and map their recovery. It is increasingly recognized that small airways dysfunction and damage is an early feature of COPD [6,8] and these processes may also be implicated in exacerbations [34,35]. Exacerbations are usually associated with an increase in airway inflammation, impacting on small airways through airway narrowing, mucus hypersecretion and sometimes plugging [34,35]. In light of this, small airways tests have been proposed as potential tools that could be used in studies of COPD [36].

In general, published studies of tests of small airways function during exacerbations were small and heterogeneous, using different small airway tests and different definitions of an exacerbation. The methodological quality of these studies was variable and mainly of fair to poor quality. There was only one study of good quality [26], with two of fair quality [24,28], three of poor quality [25,27,29] and one trial rated as having a high risk of bias [30]. Small airways tests along with FEV_1 demonstrated improvement following the recovery from exacerbation in the majority of the included studies but different studies reported improvements at different time points, even with the same test.

Despite these important limitations, there were suggestions of an earlier signal of change from exacerbation onset in the tests of small airways compared to FEV_1. For example, for FOT: while Stevenson et al. [27] reported a difference in FEV_1 across all time points, there was only an average improvement of 8% in FEV_1 at discharge in contrast to an average improvement of 26% in X5 (with average length of stay 7 days). Johnson et al. [26] reported improvements in FEV_1 as well as FOT, with FOT having a greater percentage change than FEV_1. Jetmalani et al. [29] did not find a difference in FEV_1 at discharge (day 5) despite describing difference in measures of FOT. For MMEF, Sahn et al. [30] described an average increase of 24% in MMEF but only a 10% increase in FEV_1 at day 7 post-exacerbation. Komlev et al. [24] reported a greater percentage increase in MMEF than FEV_1 at day 14 post-exacerbation and improvements in R_{ex}. Yetkin et al. [28] described a 20% increase in MMEF but only a 7% increase in FEV_1 between admission and hospital discharge (with an average admission length of 9 days). Parker et al. [35] described no significant change in MMEF or FEV_1 within the first two weeks following exacerbation onset but significant improvements in FEV_1 and sRaw after day 14. When interpreting these data, the variance of results should be carefully considered alongside the average percentage change, but these results support some small airways signal during exacerbations for at least some COPD patients.

Although tests of small airway and FEV_1 seems to mirror each other in terms of physiological improvement, (especially in the later recovery phases of an exacerbation), obtaining FEV_1 measurement can be challenging (as spirometry is a maximal forced maneuver) [2] compared to some small airways' tests (for example, IOS, FOT) where patients perform tidal breathing. Furthermore, patients during exacerbation may be too unwell to perform spirometry. Potentially, FOT may be a more acceptable test to perform at the bedside but, unfortunately, the included studies did not report completeness of data at each testing time for each test. Therefore, it is unclear if patients were more likely to complete tidal breathing assessments as opposed to forced maneuvers.

Three studies used FOT with the most significant changes were seen in reactance parameters (Xrs, Xrs_{insp}, Xrs_{exp}, ΔXrs, X5). All studies assessed respiratory impedance at a lower oscillation frequency. In Stevenson et al. IOS assessed resistance and reactance at an oscillation frequency of 5 Hz, describing that both X5 and FEV_1 improved from baseline to follow up, with no change in R5 [27]. Jetmalani et al. [29] used FOT to measure respiratory impedance at an oscillation frequency of 6 Hz. This study showed that reactance parameters (but not resistance parameters or FEV_1) changed significantly from onset to recovery in patients with EFL on admission but no changes in reactance, resistance or FEV_1 in those without EFL. These findings and others [27] suggest that not all COPD patients have EFL during exacerbations. In those that do, EFL is associated with changes in reactance parameters at lower frequency and EFL may identify a sub group most likely to provide a signal of improvement using FOT. Johnson et al. [26] used FOT at 5 Hz oscillation frequency and also reported that FEV_1 and reactance parameters changed significantly while resistance did not. Although Jetmalani et al. have used an atypical FOT frequency, there are no marked differences between them as frequencies in the $3-10$ Hz range, with all appearing to demonstrate a good sensitivity to airway caliber [37]. Furthermore, several studies have used FOT in this range, and the three included studies reported the same findings of

FOT. Reactance parameters in all FOT studies (but not in those without EFL at baseline [29]) showed improvements during the recovery from exacerbation. Reactance is frequency-dependent (changes as oscillation frequency changes) due to the heterogeneity across tissue viscoelasticity, airway tree, airway wall shunt, and time constant [18]. At a lower oscillation frequency, reactance becomes more negative as the mechanical characteristics of the lung and chest wall dominate, which reflects greater elastance (or stiffness) of the oscillation mechanics in accordance with the impedance equation. Furthermore, frequency dependence may be affected by the presence of heterogeneous ventilation resulting from airway diseases [18], and at any given frequency, effective reactance decreases as heterogeneity increases. The reason for the improvement of reactance described in the included studies is unclear but it may be due to the reduction in hyperinflation after bronchodilators, increasing lung compliance over tidal breathing range. Although several studies have indicated that resistance at lower frequency (especially R5) is also sensitive to change after bronchodilators [19,38], R5 represents the total airway resistance and does not exclusively assess small airways. FOT may be of use during exacerbations of COPD but assessing resistance at different oscillation frequencies (up to 20 Hz) might provide more information as, although resistance at higher oscillation frequencies does not changes after bronchodilator therapies [38], it can be used to calculate the difference between R5 and R20 (R5-20). R5-20 is used to determine the contribution of peripheral airways which might give an insight about small airway function. However, the anatomical location of the transition between the distal and proximal airways has not been identified [18,39]. Therefore, future studies should aim to include both R5 and R20, so R5-20 can be calculated. Impedance measurements often differ when measured by different devices, making comparison between studies difficult, therefore future work should consider if a gold standard technique can be identified, to allow inter-study learning [40].

Three out of four studies that included MMEF described an improvement in readings over the course of an exacerbation despite differences in the treatments being given and the place of care. Despite the need to correct MMEF for lung volumes (to increase reproducibility) studies did not report if this adjustment had been made. Sahn et al. [30] evaluated two different doses of amoxicillin and described improvements in both MMEF and FEV_1 during the treatment period. However, the treatment groups were combined into one reported outcome, suggesting a high risk of reporting bias. Yetkin et al. [28] also did not indicate whether MMEF was adjusted for lung volumes but both MMEF and FEV_1 improved over the course of an exacerbation. Komlev et al. [24] described an improvement in MMEF in patients when reported results as a whole. However, when they did a post hoc analysis the improvements were seen in patients who had increase in FEV_1 by >15% after 14 days of SGS treatment (group 1) but not in group 2, where no improvement in FEV_1 was seen.

Only one study did not report an improvement in MMEF [25], although an improvement in FEV_1 was described. Potential reasons for this might include that their study was the smallest among those including MMEF (with 20 patients and three patients who withdrew from the study). Secondly, they included older and more severe patients than the other studies, where significant small airways destruction is likely to already have occurred. Lastly, they did not indicate whether MMEF was adjusted for lung volumes and changes in FVC may impact the reproducibility of MMEF.

MMEF has a wide reference range in clinical practice which might limit its interpretation, and results prone to considerable variability [41]. Furthermore, MMEF is obtained by performing spirometry; a forced maneuver that COPD patients may struggle to perform during an exacerbation. Additionally, established COPD is associated with severely lowered MMEF (approximately 17% predicted in one study [17]) perhaps limiting its ability to identify change.

Two studies reported airway resistance by body plethysmography. Parker et al. [25] reported that sRaw showed significant % changes during the treatment period (with no change in MMEF) but did not demonstrate the method of obtaining sRaw. Komlev et al. [24] reported Raw differently (assessing Raw in two phases; expiration and inspiration). Their study showed that R_{ex} changed significantly at day 14 of treatment while R_{in} did not change. Furthermore, when looking at the analysis of the two groups, R_{ex} changed significantly at day 14 of treatment in both groups while R_{in} only changed in group 1 (FEV_1 >15% at day 14 of SGS treatment). However, the method of obtaining Raw was not described. There are limits to the interpretation of these findings. Measures of airway resistance may be influenced by increased resistance of the small or large airways, which may be variable during exacerbation and prone to alteration with breathing effort. Furthermore, inflammation and airflow obstruction in the larger airways may render the small airways less accessible for physiological testing and although airway resistance by body plethysmography may be a valuable tool, the evidence of its sensitivity for small airway changes is still uncertain. Moreover, performing body plethysmography in the acute setting may be challenging as the test cannot be done at the bedside.

Limitations and implication for research and clinical practice

This systematic review was limited by different exacerbation definitions being utilized across included studies and the practical challenges of summarizing and synthesizing data due to their heterogeneity. Tests of small airways function appear to change during the course of an exacerbation of COPD; hence, more well-structured studies are needed to determine the usefulness of each test. Although most of the included studies showed some changes in small airway tests, it remains unclear which tests of small airways function are the most sensitive to change, which are best tolerated by patients and which are the most practical to deliver. Better designed, larger studies that compare a number of tests and

better characterize the exacerbation and the patient with COPD are needed.

Conclusion

Exacerbations are common and life-threatening events that may have an impact on health status and lung function. Despite this, diagnostic methods and management approaches have been largely unchanged significantly for over 30 years [33]. There is a critical need for sensitive physiological measures to objectively assess and map exacerbations recovery. Small airway dysfunction is a pathophysiological feature of COPD and it may be worsened by the increased inflammation present during exacerbations. Small airway tests may be valuable in recognizing exacerbations and following their recovery or response to treatment (either as a complimentary test to FEV_1 or in specific phases of the recovery process), although further evidence is needed to support their use.

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Authors contributions

NYA and ES designed the study. NYA performed the initial search and data extraction. NYA, RGE and MA assessed the eligibility of the included studies. NYA and MA performed the quality assessment for the included studies. NYA wrote the initial manuscript. RGE, ES and JS revised the manuscript. All authors read and approved the final version of the manuscript.

Declaration of interest

The authors report no conflict of interest.

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Appendix 6.3. Search Strategy

Medline search strategy
1. **Chronic Obstructive Pulmonary Disease.ti,ab**
2. **Chronic Obstructive Airway Disease.ti,ab**
3. **Chronic Obstructive Lung Disease.ti,ab**
4. **COPD.ti,ab**
5. **Small Airway disease.ti,ab**
6. **Chronic Lung diseases.ti,ab**
7. **Emphysema.ti,ab**
8. **exp chronic obstructive pulmonary disease/**
9. **exp Emphysema/**
10. **Exacerbation.ti,ab**
11. **AECOPD.ti,ab**
12. **exp disease exacerbation/**
13. **exp disease progression/**
14. **exp acute disease/**
15. **OR/1-14**
16. **Lung* adj3 function*.ti,ab**
17. **PFT.ti,ab**
18. **Pulmonary* adj3 function* adj3 test*.ti,ab**
19. **Respiratory* adj3 function* adj3 test*.ti,ab**
20. **Spirometry.ti,ab**
21. **Spirometric.ti,ab**
22. **Force* adj3 expire* adj3 volume.ti,ab**
23. **FVC.ti,ab**
24. **FEV1.ti,ab**
25. **exp forced expiratory volume/**
26. **Exp Forced Vital Capacity/**
27. **Exp Spirometry/**
28. **Exp Pulmonary Function Test/**
29. **Exp respiratory function test/**
30. **Exp Vital capacity/**
31. **Exp peak expiratory flow rate/**
32. **Exp residual volume/**
33. **OR/16-32 (256,212 on 08/04/2019)**
34. **Impulse* adj3 oscillometry*.ti,ab**
35. **IOS.ti,ab**
36. **MMEF.ti,ab**
37. **forced expiratory flow.ti,ab**
38. **FEF 25 - 75.ti,ab**
39. **FEF25-75.ti,ab**
40. ***Single* adj3 breath* adj3 nitrogen* adj3 test*.ti,ab***
41. ***Multiple* adj3 breath* adj3 nitrogen* adj3 test*.ti,ab***
42. **Nitrogen* washout*.ti,ab**
43. **Plethysmograph*.ti,ab**
44. **Force* adj3 oscillation* technique*.ti,ab**
45. **FOT.ti,ab**
46. **Exp maximal midexpiratory flow/**

47. Exp oscillometry/
48. FEF25-75%.ti,ab
49. **OR/34-48**
50. Treatment.ti,ab
51. treatment response.ti,ab
52. treatment effect.ti,ab
53. reversibility.ti,ab
54. responsiveness.ti,ab
55. Exp treatment outcome/
56. Exp treatment effect/
57. Exp physiologic monitoring/
58. Monitoring of outcome.ti,ab
59. Physiologic monitoring.ti,ab
60. **OR/ 50-59**
61. **And/14,32,46,54**

Embase search strategy
1. Chronic Obstructive Pulmonary Disease.ti,ab
2. Chronic Obstructive Airway Disease.ti,ab
3. Chronic Obstructive Lung Disease.ti,ab
4. COPD.ti,ab
5. Small Airway disease.ti,ab
6. Chronic Lung diseases.ti,ab
7. Emphysema.ti,ab
8. exp chronic obstructive pulmonary disease/
9. exp Emphysema/
10. Exacerbation.ti,ab
11. AECOPD.ti,ab
12. exp disease exacerbation/
13. exp disease progression/
14. exp acute disease/
15. OR/1-14
16. Lung* adj3 function*.ti,ab
17. PFT.ti,ab
18. Pulmonary* adj3 function* adj3 test*.ti,ab
19. Respiratory* adj3 function* adj3 test*.ti,ab
20. Spirometry.ti,ab
21. Spirometric.ti,ab
22. Force* adj3 expire* adj3 volume.ti,ab
23. FVC.ti,ab
24. FEV1.ti,ab
25. exp forced expiratory volume/
26. Exp Forced Vital Capacity/
27. Exp Spirometry/
28. Exp Pulmonary Function Test/
29. Exp respiratory function test/
30. Exp Vital capacity/
31. Exp peak expiratory flow rate/

32. Exp residual volume/
33. **OR/16-32**
34. Impulse* adj3 oscillometry*.ti,ab
35. IOS.ti,ab
36. MMEF.ti,ab
37. forced expiratory flow.ti,ab
38. FEF 25 - 75.ti,ab
39. FEF25-75.ti,ab
40. *Single* adj3 breath* adj3 nitrogen* adj3 test*.ti,ab*
41. *Multiple* adj3 breath* adj3 nitrogen* adj3 test*.ti,ab*
42. Nitrogen* washout*.ti,ab
43. Plethysmograph*.ti,ab
44. Force* adj3 oscillation* technique*.ti,ab
45. FOT.ti,ab
46. Exp maximal midexpiratory flow/
47. Exp oscillometry/
48. FEF25-75%.ti,ab
49. **OR/34-48**
50. Treatment.ti,ab
51. treatment response.ti,ab
52. treatment effect.ti,ab
53. reversibility.ti,ab
54. responsiveness.ti,ab
55. Exp treatment outcome/
56. Exp treatment effect/
57. Exp physiologic monitoring/
58. Monitoring of outcome.ti,ab
59. Physiologic monitoring.ti,ab
60. **OR/ 50-59**
61. **And/14,32,46,54**

CINAHL search strategy
1. TI “chronic obstructive pulmonary disease” OR AB “chronic obstructive pulmonary disease”
2. TI “chronic obstructive lung disease” OR AB “chronic obstructive lung disease”
3. TI “chronic obstructive Airway disease” OR AB “chronic obstructive Airway disease”
4. TI COPD OR AB COPD
5. TI "small airway disease" OR AB "small airway disease"
6. TI "chronic lung disease" OR AB "chronic lung disease"
7. TI emphysema OR AB emphysema
8. TI exacerbation OR AB exacerbation
9. TI acute exacerbation OR AB acute exacerbation
10. TI "COPD exacerbation" OR AB "COPD exacerbation"
11. TI AECOPD OR AB AECOPD
12. (MH “chronic obstructive pulmonary disease+”)
13. (MH “chronic Lung disease+”)
14. (MH “emphysema+”)
15. (MH “disease exacerbation+”)
16. (MH “disease progression+”)

17. (MH “acute disease+”)
18. **S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17**
19. TI Lung* N3 function* OR AB Lung* N3 function*
20. TI PFT OR AB PFT
21. TI Pulmonary* N3 function* N3 test* OR AB Pulmonary* N3 function* N3 test*
22. TI respiratory* N3 function* N3 test* OR AB respiratory* N3 function* N3 test*
23. TI spirometry OR AB spirometry
24. TI spirometric OR AB spirometric
25. TI Force* N3 expire* N3 volume* OR AB Force* N3 expire* N3 volume*
26. TI FVC OR AB FVC
27. TI FEV1 OR AB FEV1
28. (MH “Forced expiratory volume+”)
29. (MH “Forced Vital Capacity+”)
30. (MH “Spirometry+”)
31. (MH “Respiratory Function Test+”)
32. (MH “Pulmonary Function Test+”)
33. (MH “Vital Capacity”)
34. (MH “peak expiratory flow rate+”)
35. (MH “residual volume+”)
36. **S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35**
37. TI Impulse* N3 oscillometry* OR AB Impulse* N3 oscillometry*
38. TI IOS OR AB IOS
39. TI MMEF OR AB MMEF
40. TI FEF 25 - 75 OR AB 25 - 75
41. TI FEF25-75% OR AB FEF25-75%
42. TI FEF25-75 OR AB FEF25-75
43. TI Force* n3 expiratory* n3 flow* OR AB Force* n3 expiratory* n3 flow*
44. TI Single* N3 breath* N3 nitrogen* N3 test* OR AB Single* N3 breath* N3 nitrogen* N3 test*
45. TI multiple* N3 breath* N3 nitrogen* N3 test* OR AB multiple* N3 breath* N3 nitrogen* N3 test*
46. TI nitrogen* washout* OR AB nitrogen* washout*
47. TI Plethysmograph* OR AB Plethysmograph*
48. TI Force* N3 oscillation* N3 technique* OR AB Force* N3 oscillation* N3 technique*
49. TI FOT OR AB FOT
50. (MH “maximal midexpiratory flow+”)
51. **S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50**
52. TI treatment OR AB treatment
53. TI reversibility OR AB reversibility
54. TI responsiveness OR AB responsiveness
55. TI treatment* n3 response* OR AB treatment* n3 response*
56. TI treatment* n3 effect* OR AB treatment* n3 effect*
57. (MH “treatment effect +”)
58. (MH “treatment outcome+”)
59. TI monitoring* n3 outcome* OR AB monitoring* n3 outcome*
60. TI physiologic* n3 monitoring* OR AB physiologic* n3 monitoring*

61. (MH "physiologic monitoring +")
62. **S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 (694,556 on 08/04/2019)**
63. **S16 AND S34 AND S49 AND S57**

Cochrane search strategy
1. "Chronic Obstructive Pulmonary Disease"
2. Chronic Obstructive Pulmonary Disease
3. "Chronic Obstructive Airway Disease"
4. "Chronic Obstructive lung Disease"
5. Chronic Obstructive lung Disease
6. COPD
7. "chronic lung disease"
8. chronic lung disease
9. Emphysema
10. AECOPD
11. Exacerbation
12. Acute exacerbation
13. acute exacerbation of chronic obstructive pulmonary disease
14. acute disease
15. MeSH descriptor: [Pulmonary Disease, Chronic Obstructive] explode all trees
16. MeSH descriptor: [Emphysema] explode all trees
17. MeSH descriptor: [Acute Disease] explode all trees
18. MeSH descriptor: [Disease Progression] explode all trees
19. **#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 or #14 or #15 or #16 or #17 or #18**
20. Lung* NEAR/3 Function*
21. PFT
22. respiratory* NEAR/3 Function* NEAR/3 Test*
23. spirometry
24. spirometric
25. Force* NEAR/3 expire* NEAR/3 volume*
26. FVC
27. FEV1
28. MeSH descriptor: [Forced Expiratory Volume] explode all trees
29. MeSH descriptor: [Spirometry] explode all trees
30. MeSH descriptor: [Respiratory Function Tests] explode all trees
31. MeSH descriptor: [Vital Capacity] explode all trees
32. MeSH descriptor: [Peak Expiratory Flow Rate] explode all trees
33. MeSH descriptor: [Residual Volume] explode all trees
34. **#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. Impulse* NEAR/3 oscillometry*
36. IOS
37. MMEF
38. FEF
39. Force* near/3 expiratory* near/3 flow
40. Force* NEAR/3 oscillation* NEAR/3 technique*
41. MMEF

42. FOT
43. nitrogen* washout*
44. single* near/3 breath* near/3 nitrogen* near/3 washout*
45. multiple* near/3 breath* near/3 nitrogen* near/3 washout*
46. Plethysmograph
47. MeSH descriptor: [Maximal Midexpiratory Flow Rate] explode all trees
48. MeSH descriptor: [Oscillometry] explode all trees
49. **#35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48**
50. Treatment
51. Treatment response
52. Treatment effect
53. responsiveness
54. reversibility
55. monitoring of outcome
56. physiologic monitoring
57. MeSH descriptor: [Treatment Outcome] explode all trees
58. MeSH descriptor: [Monitoring, Physiologic] explode all trees
59. **#38 or #39 or #40 or #41 or #42 or #43**
60. **#12 and #27 and #37 and #44**

Chapter 7
Appendix 7.1. HRA ethical approval.

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Professor Elizabeth Sapey
Consultant in Acute and Respiratory Medicine
University Hospitals Birmingham NHS Foundation Trust
Centre for Translational Inflammation Research, Queen Elizabeth Hospital
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Edgbaston, Birmingham
B15 2TT

Email: approvals@hra.nhs.uk
HCRW.approvals@wales.nhs.uk

13 December 2021

Dear Professor Sapey

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Prospective observational pilot study to assess the utility and acceptability of tests of small airways function during acute exacerbations of COPD (AECOPD).**
IRAS project ID:	**295812**
Protocol number:	**RG_21-033**
REC reference:	**21/ES/0101**
Sponsor	**University of Birmingham**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The standard conditions document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **295812**. Please quote this on all correspondence.

Yours sincerely,

Kathryn Murray
Approvals Specialist

Email: approvals@hra.nhs.uk

Copy to: *Dr Birgit Whitman, University of Birmingham*

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
Covering letter on headed paper [Letter for ethical review]		23 August 2021
Covering letter on headed paper [Letter for ethical review]	1.0	25 November 2021
Covering letter on headed paper [Letter for ethical review]		08 December 2021
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Professional Indemnity]		01 August 2021
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Public and Products Liabiltiy]		01 August 2021
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Employer's Liability]		01 August 2021
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Clinical Trials]		01 August 2021
GP/consultant information sheets or letters [GP Notification letter]	1.0	08 March 2021
IRAS Application Form [IRAS_Form_03092021]		03 September 2021
IRAS Application Form XML file [IRAS_Form_03092021]		03 September 2021
IRAS Checklist XML [Checklist_25112021]		25 November 2021
Letter from funder [Letters for three years separately. They are merged in one file. The date of the documents is the date of the recent letter received.]		24 February 2021
Letter from sponsor [Sponsor Letters]		
Letters of invitation to participant [Invitation letter]	1.0	08 March 2021
Organisation Information Document	1.0	12 December 2021
Participant consent form [Consent form (highlighted changes)]	2.0	25 November 2021
Participant information sheet (PIS) [PIS (highlighted changes)]	3.0	25 November 2021
Research protocol or project proposal [Research Protocol (highlighted changes)]	4	08 December 2021
Schedule of Events or SoECAT [SoECAT form]	1.19	20 September 2021
Summary CV for Chief Investigator (CI) [CV Sapey]		01 March 2021
Summary CV for student [CV for the student]		01 March 2021
Summary CV for supervisor (student research) [E Sapey CV]		01 March 2021
Validated questionnaire [CAT Questionnaire]		
Validated questionnaire [EAXT Questionnaire]	1.1	
Validated questionnaire [Symptoms Diary Cards]		

IRAS project ID	295812

Information to support study set up

The below provides all parties with information to support the arranging and confirming of capacity and capability with participating NHS organisations in England and Wales. This is intended to be an accurate reflection of the study at the time of issue of this letter.

Types of participating NHS organisation	Expectations related to confirmation of capacity and capability	Agreement to be used	Funding arrangements	Oversight expectations	HR Good Practice Resource Pack expectations
All sites will perform the same research activities therefore there is only one site type.	Research activities should not commence at participating NHS organisations in England or Wales prior to their formal confirmation of capacity and capability to deliver the study.	An Organisation Information Document has been submitted and the sponsor is not requesting and does not expect any other site agreement to be used.	Please note that the SoECAT submitted for this study has not been authorised by an AcoRD Expert. HRA or HCRW sign off is for versioning only. This sign off does not constitute authorisation of the content of the SoECAT or confirmation that the cost attribution is appropriate.	A Principal Investigator should be appointed at study sites of this type	No Honorary Research Contracts, Letters of Access or pre-engagement checks are expected for local staff employed by the participating NHS organisations. Where arrangements are not already in place, research/network staff (or similar) undertaking any of the research activities listed in the IRAS form (except for administration of questionnaires or surveys), would be expected to obtain an honorary research contract from one NHS organisation (if university employed), followed by Letters of Access for subsequent organisations. This would be on the basis of a Research Passport (if university employed) or an NHS to NHS confirmation of pre-engagement checks letter (if NHS employed). These should confirm enhanced DBS checks, including appropriate barred list checks, and occupational health clearance. For research team members only administering questionnaires or surveys, a Letter of Access based on standard DBS checks and occupational health clearance would be appropriate.

Other information to aid study set-up and delivery

This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales in study set-up.
The applicant has indicated that they do not intend to apply for inclusion on the NIHR CRN Portfolio.