A phenotype analysis of the effect of spinal manipulative therapy and pulmonary rehabilitation in chronic obstructive pulmonary disease.

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A thesis presented in candidature for the degree of Master by Research

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Commenced: 1st January 2014

Submission Date: 29th July 2015

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Abstract

Progressive loss of lung function is a hallmark of Chronic Obstructive Pulmonary Disease (COPD). People with COPD are classified according to the degree of airflow obstruction measured by spirometry. They are categorised into stages: mild, moderate, severe or very severe. As COPD is now considered a heterogeneous disease with many other predictors of mortality, such as exercise capacity and dyspnoea levels providing important therapeutic targets, an additional classification system is required that more accurately addresses these facets of the disease.

This research, including a review of the literature regarding COPD phenotypes, proposes an additional classification system that encompasses the different phenotypes in COPD. A systematic review was performed to comment on the methodological quality of the evidence for including spinal manipulative therapy (SMT) in the management of COPD. The methodology describes an algorithm that classifies the participants of a randomised controlled trial (RCT) into one of four phenotypes. Phenotype group analyses that examined the effect of SMT and exercise on the different phenotypes were performed. The results of the analysis showed that there was a difference between phenotypes in response to intervention, and that different proportions of phenotypes within groups may have influenced the results of the original RCT.

It is concluded that performing a phenotype analysis provides new information about underlying disease process in COPD, particularly in response to SMT and exercise.

Dedication

Dr Roger Engel,

"Success is one percent inspiration, ninety eight perspiration and two percent attention to detail"
Phil Dunphy, Modern Family

Thank you for your tireless effort, inspiration and guidance.

Acknowledgements

Dr Roger Engel. For constant advice and supervision, thank you for your problem solving and inventive ideas. And of course, for the hours given to the construct and development of this thesis.

Dr Ben Brown, thank you for constructive advice, you have been an accessible source of information and ideas. Thank you for supporting me through the kinks and bumps of this thesis, your tireless efforts are appreciated. I also acknowledge your contribution as a reviewer in the systematic review included in this thesis.

Academic staff of the Department of Chiropractic, including Dr Stephney Whillier, Dr Mario Pribicevic, and Associate Professor Subramanyam Velmupad for your constructive comments and advice.

Higher degree research office and Macquarie University for structure, accommodation and help in enabling the completion of this thesis.

Danielle Forbes and Sheridan Beaumont as co-reviewers for the systematic review included in this thesis.

To my family and friends, especially my partner, Hilary, and friend, Suzy Labrie for your constant support.

Statement of originality

This is to certify that to the best of my knowledge, the content of this thesis is my own work. This thesis has not been submitted for any degree or other purposes.

I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

Chloe Wearing 29th July 2015

Publications and presentations

The systematic review on the use of spinal manipulative therapy in the management of chronic obstructive pulmonary disease included in Chapter 3, was presented at the Chiropractic Association of Australia research symposium in Sydney in September 2014.

Contribution to systematic review

The systematic review was completed by five authors; Chloe Wearing was the principal author and contributed 75% to the final product. Dr Roger Engel contributed 10%, Dr Ben Brown contributed 5%, Sheridan Beaumont contributed 5%, and Danielle Forbes contributed 5%.

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ABBREVIATION	MEANING
BODE	Body mass index, obstruction, dyspnoea, exercise capacity
BMI	Body mass index
CB	Chronic bronchitis
COPD	Chronic Obstructive Pulmonary Disease
COPDX	Australia and new Zealand guidelines in the management of chronic obstructive pulmonary disease
CT	Computed tomography
CWR	Chest wall rigidity
DLCO	Diffusing capacity for carbon monoxide
E	Emphysema
EC	Exercise capacity
ECLIPSE	Evaluation of COPD longitudinally to identify predictive end points
EFL	Expiratory Flow limitation
EX	Exercise
FE	Frequent exacerbations
FEV_1	Forced Expiratory Volume in the first second
FRC	Functional residual capacity
FVC	Forced Vital Capacity
6MWT	Six minute walking test
GOLD	Global initiative for chronic obstructive lung disease
GORD	Gastro-oesophageal reflux disease
HAD	Hospital anxiety and depression
HRCT	High resolution computed tomography
HRQOL	Health related quality of life
HVLA	High Velocity low amplitude
IC	Inspiratory Capacity

ICS	Inhaled corticosteroids
ITT	Intention to treat
L	Litre
LABA	Long acting beta-2 adrenergic
LOCF	Last observation carried forward
M	Metre
MA	Mixed asthma-COPD
MCID	Minimal clinically important difference
MESH	Medical subject headings
MMRC	Modified medical research council
MT	Manual Therapy
NNT	Number needed to treat
NO	Nitric oxide
OMT	Osteopathic manipulative therapy
PPM	Potentially pathogenic micro-organisms
PR	Pulmonary Rehabilitation
RCT	Randomised controlled trial
RV	Residual Volume
SGRQ	St Georges respiratory questionnaire
SMT	Spinal manipulative therapy
SNP	Single nucleotide polymorphism
ST	Soft tissue therapy
TLC	Total Lung Capacity
TORCH	Towards a revolution in COPD health
UPLIFT	Understanding potential long-term impacts on function with tiotropium
WHO	World health organisation

Chapter One

Introduction

1.1 Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable disease characterised by progressive airflow limitation that is associated with an enhanced chronic inflammatory response (1). Although common, it is often misdiagnosed and consequently under-reported. By 2020 it is expected that COPD will be the third leading cause of death globally, while in Australia, it is estimated that nearly 14% of the population over 40 years of age are affected by the disease (1, 2).

Lung function is the primary test for diagnosis of COPD, which is measured by spirometry, using forced expiratory volume in the 1st second (FEV_1) and forced vital capacity (FVC). Spirometry detects the degree of airflow limitation and patients are graded according to the severity of the limitation. In Australia, COPD is classified into three stages: mild, moderate and severe as set out in the COPDX guidelines (2). Elsewhere, The Global Initiative for Obstructive Lung Disease (GOLD) guidelines classifies COPD into mild, moderate, severe and very severe stages (1). It is worth noting that despite the similarity in names, the spirometry values for the various stages are different in each guideline.

Lung function is used as the primary measure of severity in COPD, even though it has a poor association with mortality rates compared to other parameters. Other parameters such as dyspnoea levels and Health Related Quality of Life (HRQoL) measures are independent predictors of mortality in moderate to severe COPD, while the severity of dyspnoea is only partially correlated with lung function (3). Inspiratory capacity (IC) is a predictor of exercise tolerance while exercise capacity is a reliable

predictor of morbidity and mortality (3). Aside from dyspnoea, predictors such as HRQoL, IC and exercise capacity are not included in the GOLD or COPDX guidelines, even though they are reliable prognostic indicators of survival, exacerbations and hospitalisations (4).

There is a non-linear relationship between spirometry, HRQoL, dyspnoea measures and the 6 minute walking test (6MWT) (1). Recent research has raised the suggestion that the GOLD and COPDX classification systems may be inadequate as the basis for prescribing treatment as they rely on a single measure *i.e.* spirometry (3, 5-7). An alternative classification system that takes into account other factors and measures, such as body mass index (BMI), airflow obstruction, dyspnoea and exercise capacity is the BODE index (8). The BODE index is a comprehensive approach to the evaluation of COPD and is an effective predictor of hospital admission, exacerbation and survival in COPD (9, 10). Furthermore, the BODE index has been described as more valuable for diagnosing and delivering treatment than FEV_1 as it is capable of describing variations between patients according to underlying disease processes (10-12). A comparison of the characteristics of COPDX, GOLD and BODE are described in Table 1.

Retrospective cluster analyses have identified distinct groups within COPD. For example, in a post hoc cluster analysis of 415 patients, two distinct clusters were identified: the first cluster was characterised by patients with higher values of diffusing capacity of the lung for carbon monoxide (DLCO), FEV_1 and vital capacity (VC) while the second cluster was characterised by patients with lower values for DLCO, FEV_1 and VC but higher values for residual volume (RV), RV/total lung capacity (RV/TLC) and functional residual capacity (FRC) (13). Another study of 322 patients with COPD revealed two groups that were significantly different from each other in outcome measures; the first of these groups were generally younger with low BMI and higher

exacerbation frequency, where the second group were older, in the mild-moderate stage of COPD and had a higher prevalence of comorbidities without exacerbations (7). These studies support the necessity to broaden the classification systems to include characteristics that can differentiate distinct sub- groups or phenotypes.

Table 1. Comparison of staging between the GOLD and COPDX guidelines, and the BODE index (1, 2, 14)

COPD classification systems					
GOLD Stage		**COPDX Stage**		**BODE Stage**	
Mild	Stage 1: FEV_1 > 80 Chronic cough, sputum may be	Mild	FEV_1 60-80 Few symptoms Breathlessness in moderate exercise	0	FEV_1 >65 > 350m 6MWD 0-1 MMRC > 21 BMI
Moderate	Stage 2: FEV_1 < 80 Shortness of breath on exertion Cough, sputum Seeks medical advice	Moderate	FEV_1 40-59 Increase dyspnoea, limits to ADL, Breathlessness on flat Sleep apnoea, pulmonary hypertension	1	FEV_1 50-64 250-349 6MWD 2 MMRC < 21 BMI
Severe	Stage 3: FEV_1 < 50 Shortness of breath Decrease exercise capacity Exacerbations	Severe	FEV_1 <40 Dyspnoea on minimal exertion Decrease ADL Severe Hypoxemia Hypercapnia Polycythaemia	2	FEV_1 36-49 150-249 6MWD 3 MMRC
Very Severe	Stage 4: FEV_1 <30 FEV_1 < 50 + Resp. failure FEV_1 < 50 + Comorbidity Decrease Quality of life Exacerbation		N/A	3	FEV_1 < 35 ≤ 149 6MWD 4 MMRC

FEV_1: Forced expiratory volume in the 1st second; 6MWD: Six minute walking distance; mMRC: modified Medical research council; BMI: Body mass index; ADL: Activities of daily living.

As COPD is a complex disease with a significant level of heterogeneity, it is not surprising that the literature describes a deficiency in the current diagnostic and categorisation processes as they do not include parameters such as BMI, lung hyperinflation, HRQoL and exercise capacity (3, 5, 15, 16). What is required to improve

this process is a clinical phenotype classification system for COPD.

A clinical phenotype is defined as an "observable characteristic or disease attribute that describes differences between patients as they relate to clinically meaningful outcomes e.g. symptoms, exacerbations, response to therapy, rate of disease progression or death" (1, 17). In COPD the most common phenotypes currently reported in the literature are chronic bronchitis, mixed asthma-COPD, emphysema and frequent exacerbations (see Table 2). These are well documented and understood by clinicians and they have the potential to improve clinical decision making and evaluation and treatment of the individual patient. Furthermore, using a phenotype classification system could also improve the accuracy of data extrapolation from longitudinal studies and clinical trials (18).

Table 2. Descriptive characteristics of the four phenotypes as reported in the literature (1, 5, 19-23)

COPD Phenotypes	**Definition**
Chronic Bronchitis	• Chronic cough with productive sputum for at least three months in each of two consecutive years • Higher rate of smoking and exacerbations
Emphysema	• Destruction of the lung parenchyma and loss of lung elasticity • Lower BMI, worse pulmonary function, greater dyspnoea • Hyperinflation, and lower gaseous diffusion tests
Frequent Exacerbations	• Episodic worsening of COPD, with rapid, irrevocable decline in lung function • Two or more exacerbations in the last year • Higher levels of mortality and worse quality of life
Asthma-COPD Overlap	• Airway hyper-responsiveness • Positive bronchodilator response, eosinophilia present in the sputum, a history of asthma, atopy and high IgE levels

Currently the focus of research in COPD is on the development of pharmacological interventions that target bronchodilation, exacerbation and inflammation in an attempt to slow the progressive loss of lung function (24, 25). Non-pharmacological interventions may assist this by targeting the extra-pulmonary elements that contribute to this decline. One such approach is pulmonary rehabilitation

(PR), an intervention that improves HRQoL, activity levels and exercise tolerance and is recommended for patients in all stages of COPD (26). Pulmonary rehabilitation is a multi-disciplinary program that combines exercise with nutritional counselling, psychosocial support and education.

Another non-pharmacological approach aimed at slowing the decline in lung function uses a combination of interventions designed to improve exercise capacity. This approach employs manual therapy (MT), in particular spinal manipulative therapy (SMT), combined with exercise, to reduce chest wall rigidity (CWR). Administering this combination to people with various stages of COPD has been shown to increase FVC (28), decrease residual volume (RV) (28, 29) and improve exercise capacity (6MWT) (27, 29) and dyspnoea levels (27). As exercise capacity is an independent predictor of mortality, any increase should be interpreted as an improvement in prognosis.

Currently, investigating the effect of this combination of interventions on COPD phenotypes has not been studied. A phenotype analysis of outcome measures may improve our understanding about the efficacy of this intervention and whether it is suitable for all types of COPD.

1.1 Aim

To develop a phenotype classification algorithm to improve our understanding of the heterogeneity of COPD and its impact on clinical outcomes following a combination of MT and PR.

1.2 Protocol

To perform a retrospective phenotype analysis on a completed clinical trial (RCT). The participants within the intervention groups must be classified into a phenotype, and these phenotypes will then be compared to each other using the primary outcome measures

FEV_1, FVC and 6MWT. To achieve this the three intervention groups from the RCT: PR only, Soft tissue therapy +PR (ST+PR) and ST+ spinal manipulation (SM) +PR (ST+SM+PR) were retained, and a fourth group added that combines participants in the ST+PR and the ST+SM+PR, this group was called the combined MT intervention group. The participants in the four groups were assigned a phenotype ready for analysis.

1.3 Thesis objectives

- To perform a literature review on the current evidence of COPD phenotypes
- To create an algorithm that can be used to classify participants into COPD phenotypes
- To perform a systematic review of the literature on the use of SMT in the management of COPD
- To apply the phenotype classification algorithm to participants in an RCT
- To perform a retrospective analysis by phenotype of the outcomes from the RCT, and compare these results to the results reported from the RCT

1.4 Research questions

i. What phenotypes of COPD are described in the literature?
ii. What is the methodological quality of the research on SMT and COPD?
iii. Does classifying patients with COPD according to phenotype change the outcomes of a randomised controlled trial?
iv. Does an analysis by phenotype of an RCT reveal trends in the data about the effect of MT and PR in COPD?
v. Does analysis by phenotype improve our understanding of the underlying disease mechanisms in COPD?

1.5 Rationale

The two classification systems, COPDX and GOLD are not sufficient to describe the effect of treatment on individuals with COPD. What may be required is a system that groups patients according to disease characteristics that can be used as predictors of treatment outcomes.

Non-pharmacological intervention is an approach that has the potential to impact the loss of lung function in COPD. An analysis by phenotype of the effect of the combination of MT and PR may improve our understanding of COPD and target future research in the field.

1.6 Composition

To the author's knowledge there have been no reports of a phenotype analysis on the effect of MT and PR on COPD. Initially, a literature review on the current evidence of COPD phenotypes and their application in clinical trials was performed. This information was used to create a phenotype classification algorithm which was used in a phenotype analysis of an RCT. This was followed by a systematic review of the literature on the effects of SMT in COPD.

The methodology of the analysis was described in two parts: the methods of an RCT that examined the effect of MT and exercise on moderate to severe COPD; and the methodology of the retrospective phenotype analysis. This included a description of the process of grouping subjects of the RCT into phenotypes and the statistical analyses used to assess the results.

The results section reports the data from the phenotype analysis in three areas: descriptive characteristics of the phenotypes, the response of each phenotype to intervention using the outcome measures FEV_1, FVC and 6MWT, and a comparison of

the performance of the phenotypes to each other, and the results of the RCT to reveal potential trends in the data.

The discussion provided a summary of the phenotype characteristics as reflected in the literature and a discussion of the effect of SMT and PR on COPD phenotypes. Possible explanations and comparison with current hypotheses were discussed followed by limitations of this study and future directions.

1.7 Summary

Phenotype analysis of data from a COPD trial has the potential to inform future research and to improve the efficacy of interventions designed to benefit people with COPD. This research project will create a phenotype classification algorithm and test data from an RCT. The use of the phenotype algorithm on a current, fully powered RCT may have the predictive ability to highlight groups of patients that respond better to treatment.

Chapter Two

Phenotypes in Chronic Obstructive Pulmonary Disease (COPD) and their application in clinical trials: a review of the literature

2.1 Introduction

This chapter answers the first research question i. of this thesis, and consists of a literature review on the current evidence for COPD phenotypes. This information is used to create a phenotype classification algorithm.

COPD is currently classified according to the degree of airflow obstruction. The two most common classification systems in use today are the GOLD and COPDX guidelines. While both guidelines refer to other parameters such as dyspnoea, exercise capacity, HRQoL and BMI neither include assessments of any of these parameters in classifying COPD (1, 2). As these parameters have been shown to have predictive value for morbidity and mortality any diagnostic information they provide would assist in improving treatment outcomes.

The absence of these parameters has led to the call for a new classification system based on sub-groups or phenotypes that takes into account information about the underlying disease processes in an individual (3, 21). A new system has the potential to provide additional information about the efficacy of treatment through retrospective analyses, ongoing longitudinal studies and clinical trials.

Regardless of how COPD is classified, interventions should deliver the best possible outcome for the patient. To achieve this, interventions may need to be targeted at specific sub-groups of patients rather than being uniformly applied to all patients with

COPD. The paucity of research for determining these sub-groups or phenotypes has made it difficult to deliver additional improvements in outcomes.

2.2 Methods

Study design

A review of the literature related to classifying COPD into phenotypes.

Search strategy

The following databases were searched to gather articles for this review: Scopus, Ovid, Medline, ScienceDirect, PubMed and Web of Science. There were no limits to the year of publication for papers included. Only papers published in English were included. Citation lists were also reviewed for relevant papers.

The following key words were used to search for articles on COPD phenotypes:

1. COPD, chronic obstructive airways disease COAD, chronic obstructive lung disease GOLD, Chronic respiratory disease, respiratory disease, chronic bronchitis, frequent exacerbation, acute exacerbation, exacerbation, emphysema, asthma, asthma-COPD, airway obstruction, airway limitation, phenotype, subtypes, subgroups.

Study inclusion criteria

Participants: Adult studies with COPD at any stage of severity using GOLD, COPDX or BODE index.

Interventions: Studies including information about the epidemiology, incidence, diagnosis, management and treatment with pharmacological or non-pharmacological intervention including complementary and alternative therapies, cluster and sample analyses, retrospective studies and trials studying intervention on COPD subtypes

Outcome measures: Pulmonary function (FVC, FEV_1), six minute walking test (6MWT), the modified medical research council dyspnoea scale (mMRC), quality of life questionnaires, systemic biomarkers and/or radiography.

Study design: Both primary and secondary designs were included.

Study selection and screening

Studies were selected based on the inclusion/exclusion criteria, full text and published in English. Articles were used for discussion of COPD phenotypes and their use in clinical trials.

2.3 Results

Study selection

Following a search of the databases using MeSH terms, 4893 articles were found with an additional 46 articles obtained from reference lists. After deletion of duplicates and application of the inclusion/exclusion criteria 158 relevant articles remained. Due to the heterogeneity of the studies, quality appraisal and meta-analysis could not be performed, however an assessment of bias could be performed and is available in Appendix 1 in the table of results.

Study characteristics

Of the 40 articles that remained after the eligibility criteria were applied, there were 20 review articles, 2 randomised controlled trials, 3 cluster analysis, 1 meta-analysis, 11 cross sectional studies and 3 cohort studies. Figure 1 is a flow diagram outlining study selection.

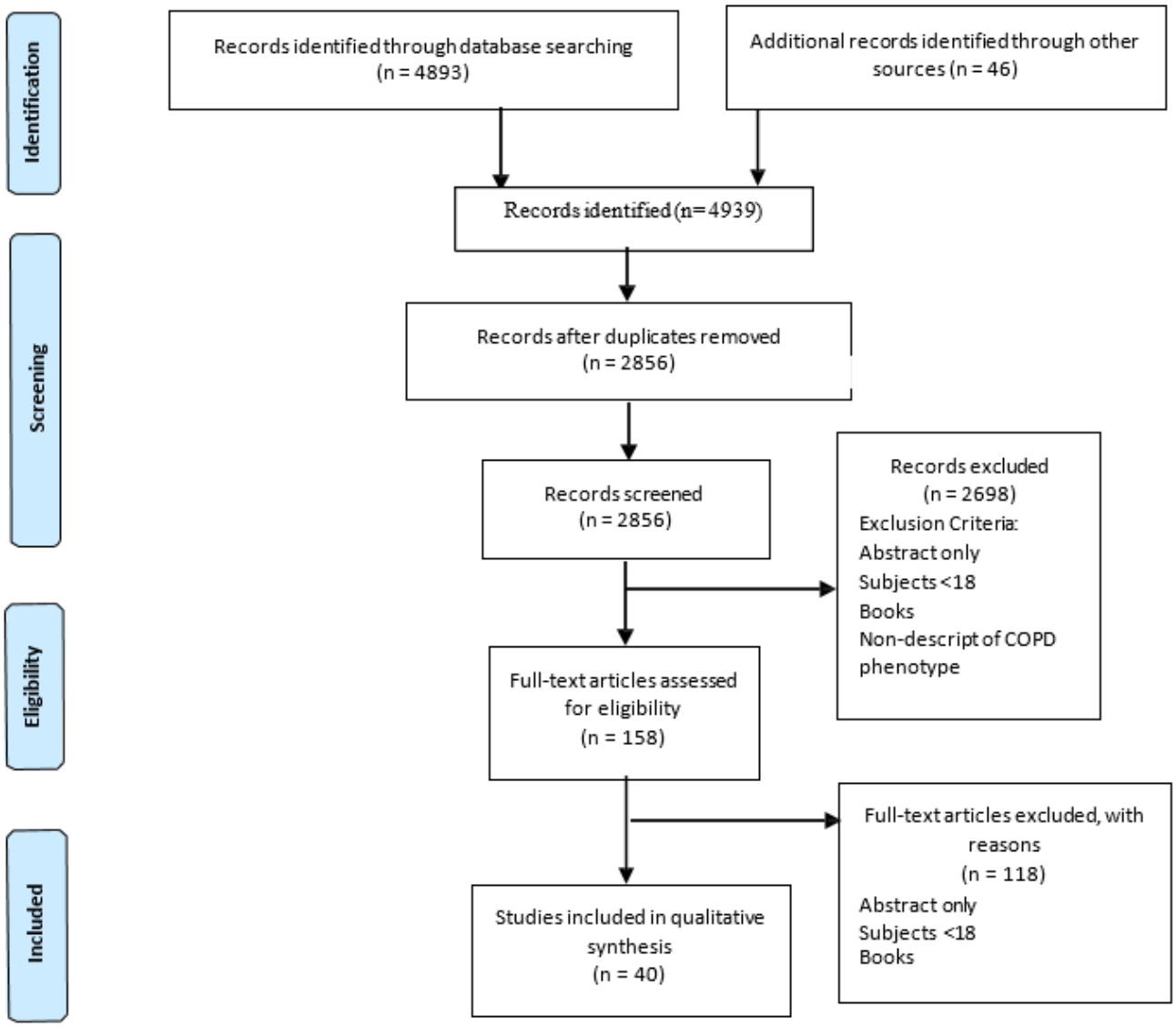

Figure. 1. Flow diagram of study selection for review of COPD phenotypes (30)

2.4 Discussion

Four phenotypes of COPD can be described from the literature using descriptive data, cluster analysis and clinical trial results, they are: chronic bronchitis, mixed asthma-COPD, emphysema and frequent exacerbations.

Chronic Bronchitis

Chronic bronchitis (CB) is defined as a chronic cough with productive sputum for

at least three months in each of two consecutive years (1). CB has been associated with exacerbations and described as a modulator of their severity and frequency (5). An exacerbation is defined as an "episode of worsening symptoms associated with a decline in lung function that persists beyond the actual exacerbation, to a worsening of quality of life and an increase in mortality" (6). There are suggestions that the presence of CB may simply increase the likelihood of frequent exacerbations and should not, in itself, be considered as a separate sub-group (5).

However, a study by Kim *et al* in 2011 reviewed 1,061 patients from the COPDgene study (31) and found that 27.3% had CB (22).This finding is worth noting as the majority of the participants in the trial were young, with a high pack per year smoking history and a higher reported incidence of exacerbations (22). While initially appearing to support the claim that CB acts as a modulator of exacerbations in COPD, the reported rate is high and CB can be considered a sub-group rather than a modulator.

Clinically, CB is associated with mucous hyper-secretion that is the result of goblet cell hyperplasia. These secretions increase airflow obstruction and predispose a person to infection, cigarette exposure increases the process of hyper-secretion (22). This finding is supported by two studies: a French study that reported an association between active smoking and respiratory symptoms that were consistent with the presence of CB, and this combination increased the risk of developing COPD later in life (32); and a Japanese study that reported a high incidence of airflow limitation (47.2 %; n=197) in people with CB (33).

Mixed Asthma-COPD

Asthma is episodic in nature, a symptom that is used to distinguish the condition from COPD. Asthma is usually associated with a history that originates from a young age, with deficits in lung function that are reversible. Asthma itself has been

recognised as having phenotypes based on inflammatory markers (20). For example, asthmatics with airway eosinophilia experience a decrease in symptoms when treated with anti- inflammatory therapy whereas patients with non-eosinophilic asthma do not (5, 34).

Reports of asthma and COPD occurring together appear in the literature (5, 20, 21, 35). As differentiating the two can be difficult clinically, the presence of both has been referred to as 'Asthma-COPD overlap' or 'mixed asthma-COPD'. The combination is usually associated with some degree of broncho-reversibility which often results in patients with this type of respiratory dysfunction being excluded from many COPD trials (6).

Asthma and COPD are the two most common forms of respiratory disease worldwide with chronic airflow limitation a common feature in both (5, 20). Miravitlles *et al* described the mixed asthma-COPD phenotype as "airflow obstruction that is not completely reversible, accompanied by symptoms or signs of increased obstruction reversibility (5)." He described two main presentations: the smoker with asthma who responds less to corticosteroid therapy and has a high airway neutrophilia; and the non- specific bronchial hyper-reactive patient who wheezes and has higher plasma IgE concentrations (5). This is in keeping with Carolan *et al* who described the Asthma-COPD phenotype as having a positive bronchodilator response, eosinophilia present in the sputum, a history of asthma, atopy and high IgE levels (20).

Airway hyper-responsiveness has been recognised as exclusive to this phenotype and linked to eosinophilia in the airways (23). Dima *et al* compared a group of stable asthmatics with people diagnosed with COPD. He attempted to identify inflammatory biomarkers that could be used to distinguish the two groups concluding that there were no such biomarkers. He did, however identify that inflammatory markers were closely

related to smoking status and the presence of symptoms such as bronchial hyper-reactivity, sputum production and broncho-reversibility (35).

Izqueirdo *et al* reported 12.1% of patients with COPD presented as the mixed asthma-COPD phenotype and that they responded well to a combination of long-acting Beta-2 adrenergic (LABA) and inhaled corticosteroid (ICS) therapy (21). This is in line with a consensus document by Soler-Cataluna and colleagues that recommended similar treatment, and even an adjustment in ICS dosage according to symptoms and/or presence of eosinophilia in sputum (36).

Due to the high incidence of both asthma and COPD and the inability to clearly differentiate between the two there appears to be enough evidence to support the mixed-COPD phenotype as a sub-group in COPD.

Emphysema

Emphysema involves destruction of the lung parenchyma with associated loss in lung elasticity. These changes contribute to a structural component of chronic airflow obstruction resulting in decreased gas transfer which can be diagnosed using spirometry, diffusing capacity for carbon monoxide (DLCO) and/or high resolution computed tomography (HRCT) (1, 5).

Patients with emphysema have lower BMI, worse pulmonary function, lower fat-free index, poorer quality of life, higher rates and severity of dyspnoea, decreased exercise capacity, hyperinflation and lower gaseous diffusion. Dyspnoea and exercise capacity have been shown to be independent predictors of mortality in moderate to severe COPD, while hyperinflation and impaired gas exchange are indicators of mortality and exacerbations, regardless of COPD severity (3, 5, 21, 37)

Emphysema represents a large proportion of patients with COPD. In a cross

sectional study of 331 patients diagnosed with COPD using HRCT emphysema was present in 43.2% of the cases (21). Emphysema is recognised as an important disease process in COPD, due to this and distinct characteristics of emphysema described in the literature, emphysema can be regarded as a phenotype of COPD that requires a specialised approach.

Frequent exacerbations

Regardless of the degree of loss of lung function there are a group of patients that present with episodic worsening of the disease. These episodes are referred to as exacerbations and are accompanied by a rapid decline in lung function and a worsening of quality of life that persists after the exacerbation has ended. The onset of an exacerbation is independent of lung function and is a marker of disease progression (6, 19).

Exacerbations are important as they highlight a time when the course of the disease changes and when new medications may be required. Exacerbations represent a major burden of disease accounting for approximately 60% of hospital services related to COPD (5). People who experience frequent exacerbations may initially present as one of the three phenotypes referred to previously in this section i.e. chronic bronchitis, mixed asthma- COPD or emphysema (21). There is support in the literature for recognising frequent exacerbations as a distinct sub-group with a presentation that reflects CB and two or more exacerbations per year. To be classified, a person must have already experienced an exacerbation with at least 4-6 weeks before a relapse. A history of gastro-oesophageal reflux disease (GORD) and the presence of CB increase the likelihood of an exacerbation (19, 22).

Bronchial infection, inflammation and bronchiectasis are underlying predispositions for acute infection and increased inflammation that may give rise to

an exacerbation. This is due to potentially pathogenic micro-organisms that exist in the airways and colonise parts of the lung in the right conditions (5). Burge and Wedzicha reported that these patients had increased inflammatory biomarkers such as interleukin-6 (IL-6) and interleukin-8 (IL-8) as well as an increase in bacterial colonisation. They reported that the increase in airway inflammation contributed to an accelerated decline in lung function (38).

Frequent exacerbations can occur at every stage of COPD. Noujiem *et al* reported that 22% of patients with GOLD Stage 2, 33% with GOLD Stage 3 and nearly half of the patients with GOLD Stage 4 had a history of exacerbations (19). It is therefore reasonable to conclude that a considerable proportion of people with COPD experience exacerbations, and that these exacerbations are associated with a unique set of characteristics that require individualised treatment.

Phenotypes in Clinical Trials

Central to clinical research in COPD is an attempt to discover effective interventions capable of slowing disease progression in people diagnosed with the disease. Recently, there has been an interest in examining the efficacy of interventions that target specific sub-groups and/or characteristics. This has involved classifying COPD in to sub- groups or phenotypes. Where previous interventions may have targeted a single measure such as lung function as the primary outcome, COPD is now considered a heterogeneous disease with sub-groups that have been shown to produce different clinical responses to the same intervention (5) (See Table 2).

The World Health Organization (WHO) states that therapy for COPD should aim to '.... prevent disease progression, relieve symptoms, improve exercise tolerance, improve health status, prevent and treat complications, prevent and treat exacerbations,

and reduce mortality" (39). To do this effectively in a heterogeneous population, evaluation of an individual's symptoms and characteristics is required as they may vary from one patient to the next.

A cross sectional study titled the 'Evaluation of COPD Longitudinally to Identify Predictive End points' (ECLIPSE) described clinical, functional and radiological characteristics of 2,164 patients with COPD and compared them with 337 smoking and 245 non-smoking controls (40). The study reported that, as the disease progressed and airflow limitation became more severe, there was an increase in exacerbations and emphysema, a decrease in BMI, airflow reversibility and distance walked (40). This trend occurred across all stages of the disease (GOLD) with the researchers concluding that comorbidities and their incidence were independent of airflow limitation (40). The ECLIPSE study describes the heterogeneity of COPD broadly. This is in line with an analysis performed by Pistolesi *et al* on 415 patients with COPD (41). They classified these patients into two groups using clinical, functional and radiological data. The first group showed emphysema on HRCT and an array of physical signs such as a non-productive cough, pursed lip breathing, chest inspiratory in-drawing and high intensity sounds on chest percussion (41). The second group presented with a more productive cough, less or no areas of emphysema on HRCT and increased chronic lung inflammation and adventitious breath sounds. They considered the second group as presenting in line with a bronchial phenotype and proposed that each group would respond differently to treatment, reasoning that, because of the differences in radiographic appearance the cause of the expiratory flow limitation was different in each group (41).

Additionally, a cross sectional study by Garcia-Aymerich *et al* analysed 342 patients hospitalised due to a COPD exacerbation and uncovered patterns in their

respiratory histories to suggest the presence of three sub-types (42). Subtype 1 showed a worse respiratory status and lower exercise capacity; Subtype 2 showed a milder respiratory status but with a substantial level of emphysema without bronchial wall thickening; and Subtype 3 exhibited a mild respiratory status but with a higher burden of comorbidity and higher levels of inflammatory biomarkers (42). Although seeking to validate subtypes other than the four phenotypes mentioned above, this study recognised three additional subtypes under the general diagnosis of COPD each with specific characteristics that could be used to target therapeutic intervention. Notwithstanding, these findings were consistent with the conclusions from the ECLIPSE study (41).

The authors of these studies expressed concern about the heterogeneous nature of COPD and the effect this could have on management of the disease in the future. They expressed concern that COPD should be considered under subgroups both in the clinic and in research, so that effective therapy can be delivered (40-42).

Retrospective analyses of clinical trials have revealed that these subgroups influence the outcomes of studies. For example, the 'Towards a Revolution in COPD Health' (TORCH) study evaluated 6,200 subjects and compared the effect of fluticasone, salmeterol and the combination of these compared to placebo over a period of three years (43). The combination group showed a reduction in mortality compared to placebo, however, this finding was not significant (43). The study excluded patients with a positive bronchodilator test which may have influenced the results as mixed asthma-COPD patients who returned a positive result for bronchodilation were excluded from the trial. These patients may have responded well to corticosteroid treatment, and therefore their exclusion may have altered the results of the study. In contrast, the 'Understanding Potential Long-term Impacts on function with Tiotropium' (UPLIFT) study, a randomised controlled trial, studied the effect of tiotropium bromide

on 5,993 subjects over 4 years (44). This study included subjects with a positive bronchodilator response, and they reported a significant improvement in the progression of the disease over 4 years in the group that received therapy (44). Aside from using different pharmaceutical interventions the finding may have been attributable to characteristics of the patients included in the study.

Studies targeting exacerbations also provide data supporting the concept of using phenotypes in clinical research for COPD. Exacerbations often result in hospitalisation and higher rates of re-admission. Health related quality of life (HRQoL) and daily physical activity also decline as lung function falls (45, 46). This has led to the development of targeted pharmaceutical interventions that account for these differences (47, 48). For example, Rennard *et al* performed a post- hoc pooled analysis on two randomised controlled trials that investigated the effectiveness of Roflumilast (a phosphodiesterase 4 inhibitor) in COPD (47). They found that the group that received Roflumilast had a significant decrease in exacerbations and improvements in chronic bronchitis symptoms, cough and sputum. This was in line with results from a meta-analysis of antibiotic therapy for acute exacerbation in COPD (48). The study concluded that in the presence of at least two of the following symptoms - increased dyspnoea, increased sputum or purulent sputum, a short term (5 days) course of antibiotics was effective in treating the acute exacerbation (48). Instead of applying the intervention to the entire COPD cohort they targeted a subgroup that would benefit the most.

These studies highlight how selective intervention can improve outcomes in certain COPD phenotypes. Grouping patients according to phenotype could lead to more individualised treatment in the future (6). Information from this chapter is provided in Table 3.

Table 3. Descriptive characteristics of the four COPD phenotypes as they appear in the literature.

Phenotype	History	Diagnostic tests – Primary	Diagnostic tests – Secondary	Biomarkers	Intervention
Chronic Bronchitis	Chronic cough and sputum for 3 months duration in 2 years High BMI No emphysema, asthma Current smokers Younger High BODE scores Exacerbation and comorbidities	Spirometry Sputum hyper secretion Gas trapping Airway wall thickening on radiography No emphysema on CT	High BODE scores High mMRC Dyspnoea Scale High SGRQ score	Goblet cell hyperplasia Bacterial/fungal colonisation	Target Airway remodeling and sputum hyper secretion Antibiotics Mucolytic Anti-inflammatory PR
Mixed asthma-COPD	History of asthma <40yrs Atopy Less frequency of smoking history	Broncho reversibility Spirometry	Sputum Eosinophilia Exhaled NO Poor HRQoL	High IgE Pneumoallergen prick test Exhaled NO	Target Eosinophilia, or neutrophilia ICS LABA + ICS PR
Emphysema	Hyperinflation Dyspnoea Low BMI	DLCO (carbon monoxide transference capacity) HRCT – emphysema	Inspiratory Capacity	Inflammatory biomarker Alpha-1-antitrypsin deficiency (congenital emphysema)	Target Hyperinflation Lung reduction surgery Combination bronchodilators PR
Frequent Exacerbations	At least 2 exacerbations in last 2 years resulting in a worsening of symptoms, a change in the disease progression, or a change in medication Comorbidities	Spirometry Sputum colonisation PPMs bacteria – 55%, Virus – 29%, Eosinophil's – 28% present in airways	Inflammatory markers GORD Chronic Bronchitis Bronchiectasis	Inflammatory biomarker	Target exacerbations LABA ICS Antibiotics as prophylaxis Macrolides

PR: Pulmonary rehabilitation; NO: Nitric oxide; ICS: Inhaled corticosteroids; LABA: Long acting beta agonist; GORD: Gastro oesophageal reflux disease; CT: Computed tomography; BMI: Body Mass Index; mMRC: Modified medical research council; SNP: Single nucleotide polymorphism; DLCO: Carbon monoxide diffusion capacity; PPM: Potentially pathogenic microorganisms; HRQoL: Health related quality of life

Table 4. Phenotype classification algorithm

Phenotype Classification Algorithm		
Chronic Bronchitis	Primary (2points)	Secondary (1point)
	Diagnosis by specialist Chronic cough and sputum production for 3 months duration in 2 years Specialist or GP diagnosis pre/post COPD diagnosis	High pack/year smoking history Comorbidities Goblet cell hyperplasia/mucous wall thickening (CT scan) Mucous/lavage samplings Medication: Mucolytic common, Antibiotics common Exacerbation history
Mixed Asthma – COPD	Diagnosis by specialist History of asthma <40yrs age Broncho-reversibility higher Bronchial hyper-reactivity noted Sputum or blood eosinophilia	History Atopy Low smoke pack/year History of allergy and atopy Exhaled Nitric Oxide Medications: LABA + ICS, ICS, history of asthma medication
Emphysema	Diagnosis by specialist Presence of emphysema on radiology investigation Hyperinflation present	BMI low DLCO
Frequent Exacerbations	Diagnosis or recognition by specialist At least 2 exacerbations in last 2 years Episodes where symptoms became worse	Comorbidities present Presence of GORD Previous history of chronic bronchitis Medications: LABA and ICS, Rofumilast (P4) ,Antibiotics
PR: Pulmonary rehabilitation; NO: Nitric oxide; ICS: Inhaled corticosteroids; LABA: Long acting beta agonist; GORD: Gastro oesophageal reflux disease; CT: Computed tomography; BMI: Body Mass Index; mMRC: Modified medical research council; SNP: Single nucleotide polymorphism; DLCO: Carbon monoxide diffusion capacity; PPM: Potentially pathogenic microorganisms; HRQoL: Health related quality of life		

2.5 Value of using phenotypes in clinical research

The findings from this literature review suggest the presence of four phenotypes in COPD that are based on patient history, diagnostic tests and response to treatment. The phenotypes have been validated by cluster analysis, longitudinal data and clinical trials. Using these phenotypes may improve the efficacy of outcomes in research and lead to improved interventions, table 4 provides a phenotype classification algorithm that can be used in research to assign a COPD phenotype to a participant for analysis. This algorithm and its application is further described in chapter 4 of this thesis. Further research is required to test the validity of this approach and the ability of phenotype classification to improve treatment outcomes.

2.6 Limitations

Limitations include the lack of a standardised phenotype classification system, and using phenotypes as a basis for intervention in clinical trials or practice remains cumbersome. The overlap between phenotypes may confound results as not all participants fit a single sub-group (6).

2.7 Conclusion

In any population of people with COPD at least four dominant phenotypes have been identified: chronic bronchitis, mixed asthma-COPD, emphysema and frequent exacerbations. Chronic bronchitis is associated with a higher incidence of smoking and mucous hyper-secretion that affects airflow limitation. Asthma-COPD overlap is associated with airflow obstruction that has a degree of broncho-reversibility and airway hyper- reactivity. Emphysema is associated with higher levels of dyspnoea, lower BMI and lower exercise capacity and the presence of hyperinflation. Frequent exacerbations are two or more episodes of a sudden worsening of disease status in the previous 12 months. Of the four phenotypes chronic bronchitis and frequent exacerbations are the most alike, however, frequent exacerbations produce a higher burden on healthcare services and have a higher rate of mortality. This review supports the use of phenotypes in clinical research in order to improve the outcomes from therapeutic intervention, and further research is required to validate and standardise a phenotype classification system. Longitudinal studies are required to achieve this within different COPD populations.

Chapter Three

The use of spinal manipulative therapy in the management of chronic obstructive pulmonary disease; a systematic review

3.1 Introduction

This chapter is a systematic review of the literature that evaluates the methodological quality of the evidence for spinal manipulative therapy (SMT) in the management of COPD. This answers the second research question ii.

Extra-pulmonary aspects of COPD such as skeletal muscle dysfunction, co-morbidities and depression have been recognised as having a significant impact on the severity of COPD in individuals (49). It is estimated that 18-36% of people with COPD experience skeletal muscle dysfunction at a level that affects predictors of mortality such as exercise capacity (EC) and dyspnoea levels (50). EC refers to the amount of exercise that can be performed before the onset of leg fatigue or exercise-limiting dyspnoea (3). A low level of EC is also associated with a poorer quality of life and higher hospitalisation rates (51). Dyspnoea describes breathlessness on exertion. It can limit exercise performance and is a predictor of survival in COPD.

While pharmaceutical interventions can slow the progression of COPD, there are currently no interventions that can halt the loss of lung function (24, 25). Non-pharmacological interventions such as pulmonary rehabilitation (PR) are designed to preserve as much lung function as possible over time. A recent systematic review and meta- analysis describes PR as a well-developed, multi-disciplinary approach that includes exercise performance, nutritional counselling and psychological support (7). Whilst PR does deliver a range of benefits it has little effect on lung function (52, 53).

Another intervention with the potential of addressing changes in respiratory mechanics associated with COPD is manual therapy (MT). This intervention includes a range of techniques including soft tissue massage and joint mobilisation/manipulation. A recent systematic review on the use of MT for COPD reported a high incidence of musculoskeletal pain in patients with COPD (45%) (54). While using MT to increase thoracic mobility was considered a reasonable approach, an adequate explanation of the link between the respiratory and musculoskeletal systems in COPD is still required (54).

Spinal manipulative therapy (SMT) is a recognised form of MT. SMT employs a high velocity low amplitude (HVLA) force to move a joint. This technique is used by osteopaths, chiropractors and qualified physical therapists to decrease pain and increase range of motion in a joint (55-58).

As SMT is a specific form of joint manipulation and differs from other forms of MT, this systematic review evaluates the methodological quality of the evidence for SMT as an intervention in COPD. A search of the literature returned 5291 articles. After application of eligibility criteria 6 articles were used in this review, see figure 2. A Cochrane review data collection form was used to extract data and risk of bias and the results were synthesised into tables

The aim of this systematic review is to evaluate the effect of SMT on outcome measures in COPD such as dyspnoea levels, exercise capacity and pulmonary function.

3.2 Methodology

Study design

A systematic review of the literature.

Study eligibility criteria

To be eligible for the review, a study must include participants over 18 years of age with a diagnosis of COPD. MT intervention had to involve some form of joint mobilisation or manipulation such as SMT that was administered either as a stand-alone intervention or in conjunction with other therapies such as pharmacological intervention, exercise, massage, and/or stretching. A control or comparator was not a pre-requisite and trials were not excluded on this basis.

Trials had to include at least one measure of lung function taken by spirometry. This included: forced vital capacity (FVC), forced expiratory volume in the 1st second (FEV_1), residual volume (RV) and/or total lung capacity (TLC). Trials could include any measure of chest wall movement, dyspnoea, exercise capacity, quality of life or patient reported outcomes.

All quantitative study designs were accepted for review including case studies, observational studies and randomised controlled trials.

Search

MESH terms (see Table 5) were entered into the following databases: Medline/Ovid, ScienceDirect, Pubmed, Web of Science and Scopus. There was no limit on date of publication and full texts were required. Citations and reference lists were also used to search for articles.

Table 5: Medical subject headings for SMT and COPD.

MeSH (Search terms)	Chronic Obstructive Pulmonary Disease, Chronic Respiratory Disease, Respiratory disease, Dyspnoea, Chronic Asthma, Chronic Bronchitis, Emphysema, Manual Therapy, Manipulative Therapy, Physical Therapy, Chiropractic, Osteopathy, Physiotherapy, Spinal manipulative therapy, and/or exercise/pulmonary rehabilitation

Study selection

Studies were reviewed and excluded according to the eligibility criteria in Table 6. All articles that met the eligibility criteria were sent to an external reviewer not involved in data collection. Any discrepancies in application of the eligibility criteria were discussed with the lead reviewer (CW).

Table 6: Eligibility criteria for research papers on SMT and COPD.

Inclusion Criteria
• Peer Reviewed journal articles • Randomised controlled trials, case control, cross over, case series, case studies, clinical trials, pilot trials, preliminary trials (Primary research) • Articles in English • Full text available • Respiratory disease measured with spirometry • Participants Age >18 • Manipulation or manipulative manual therapy (High Velocity, Low Amplitude (HVLA)) only, or in conjunction with other therapies (medications, exercise etc.) • Intervention on respiratory disease
Exclusion Criteria
• Books, Reference views, Systematic reviews, Literature reviews (secondary research) • Participants <18yrs • Manual therapy that isn't spinal manipulation (massage only, exercise only, tens etc.) • Lung cancer, other cancers affecting the lung/airways

Data collection

Using an adapted Cochrane Review Group standardised data collection form (59), three reviewer's independently extrapolated data from the included trials. This included information on study design, intervention/s, randomisation and concealment, participant characteristics, methodologies, statistical analyses, outcome measures and results. The data was tabulated and any discrepancies were resolved by discussion at a focus group meeting of all three reviewers (CW, SB and DF).

Risk of bias in individual studies

All elements from the Cochrane Risk of Bias Table (60) were applied to every included trial. Each element was assessed as being either 'present', 'not present' or 'unclear'.

Synthesis of results

Due to the heterogeneous nature of the included trials meta-analysis of the results was not appropriate.

3.3 Results

Study Selection

A search of the literature returned 5,297 articles with an additional 4 articles recovered from reference lists. After application of the eligibility criteria 5, 291 were rejected as they were duplicates, SMT was not an intervention, COPD not diagnosed, and/or full text was unavailable. Six articles were retained for review. Of these; 3 were randomised controlled trials (RCTs) (27, 29, 61), 1 was a pre-post observational study (62), 1 was a case series (63) and 1 was a single case study (64). Two of the RCTs were preliminary or pilot trials (27, 29). The PRISMA flow diagram for article

selection is presented in Figure 2.

Participant Characteristics

Results of the data extraction form are found in Table 8. The sample sizes from the included trials ranged from 1 to 33. Inclusion/exclusion criteria were adequately reported in studies except the single case study and the pre-post study (62, 64). Two RCTs by Engel *et al* (27, 61) attempted to match participants at baseline for age, gender and lung function. However only one managed to match for age (61) and another could not match for gender (27). Trials by Engel *et al* and Dougherty *et al* (61, 63) included an analysis of adverse events and an assessment of osteoporosis. The age of the participants ranged from 40 to 90 years however, Howell *et al* (62) did not report age. Gender favoured males in all studies. All three RCTs excluded participants if they could not complete a 6 minute walking test (6MWT).

Intervention and control groups

Intervention varied across studies. Two studies Howell *et al* (62) and Zanotti *et al*

(29) did not report details about the intervention other than to refer to it as 'spinal manipulation' or 'Osteopathic Manipulative Therapy (OMT)'. One study by Dougherty *et al* (63) described in detail the type of HVLA manipulation used including instrument assisted manipulation. The single case study (64) reported therapy that varied in type and frequency over time. The two RCTs by Engel *et al* (27, 61) reported using a standardised manual therapy protocol (MTP) that included soft tissue therapy and thoracic spinal manipulation. All three RCTs included a control group of either sham manipulation or exercise only. The quasi-experimental studies did not use a comparator.

Outcome Measures

All outcome measures and reported results are shown in Table 9. All trials included spirometry as a primary outcome measure. The study by Howell *et al* (62) and Zanotti *et al*

(29) also included RV and TLC as outcome measures. The three RCTs and the case series included a 6MWT to evaluate exercise capacity and standardised quality of life questionnaires such as the St George's Respiratory Questionnaire, the Hospital Anxiety and Depression scale and an assessment of dyspnoea (the Borg scale) (27, 29, 61, 63). The single case study by Masarsky *et al* (64) reported patient subjective comments about fatigue and breathlessness.

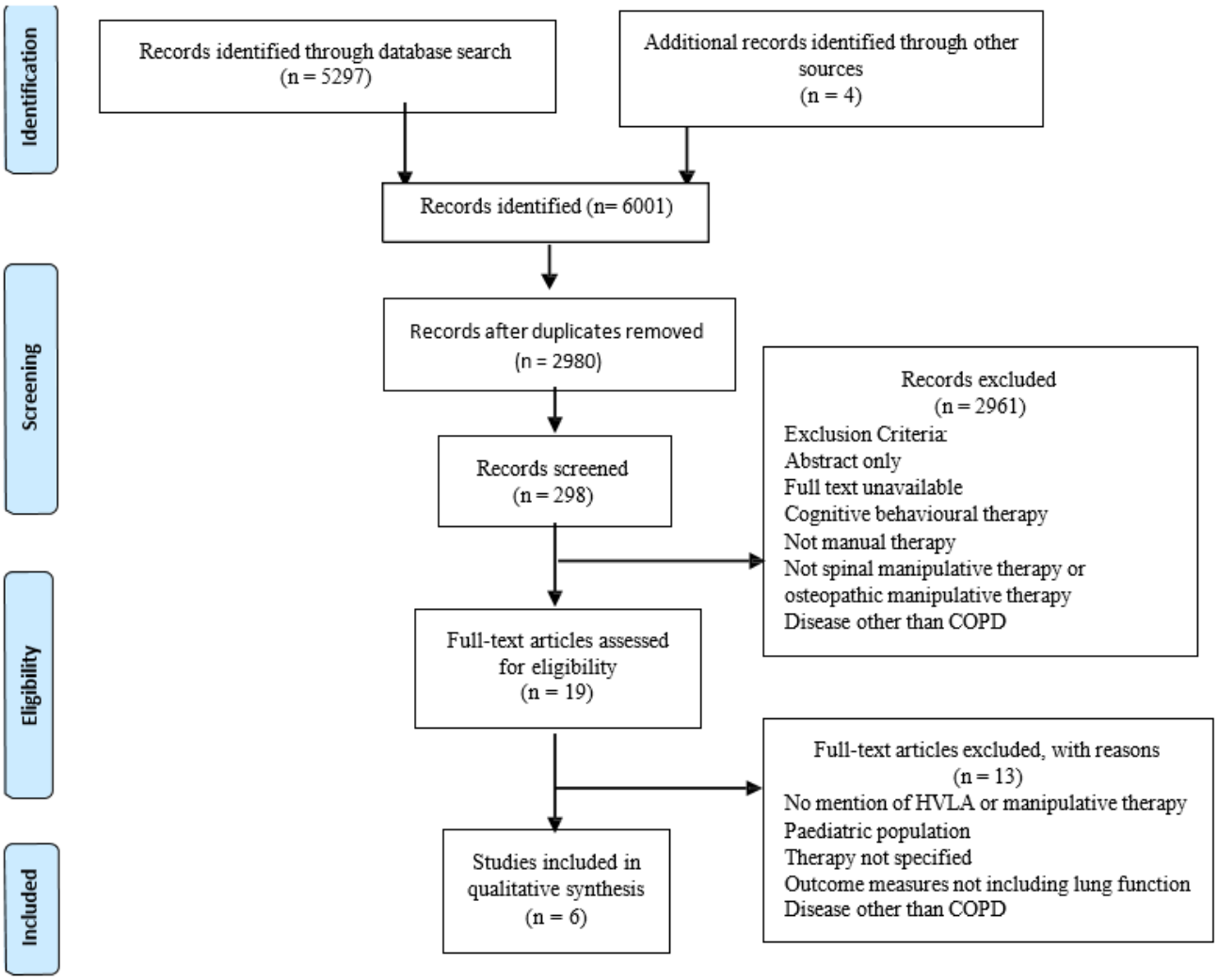

Figure. 2. PRISMA flow diagram of study selection for review of manual therapy and COPD (30) HVLA: High velocity low amplitude

Risk of Bias

As recorded in Table 7, the three RCTs had a low risk of bias (27, 29, 61). The non- randomised trials had a high risk of bias primarily associated with methodology. There was some level of performance bias in all trials including the RCTs.

Table 7: Risk of bias in studies.

Risk of Bias Table							
Author/Date/ Country	**Selection Bias**	**Performance Bias**	**Detection Bias**	**Attrition Bias**	**Reporting Bias**	**Level of Bias**	**Score**
Howell *et al*., 1975 USA	Present	Present	Unclear	Present	Unclear	High	3
Engel *et al*., 2014 Australia	Not present	Present	Not present	Not present	Not present	Low	2
Dougherty *et al*., 2011 USA	Present	Present	Present	Present	Not present	High	4
Zanotti *et al*., 2012, Italy	Not present	Present	Not present	Not present	Unclear	Low	1
Masarsky and Weber., 1988, USA	Present	Present	Present	Present	Present	High	5
Engel *et al*., 2013, Australia	Not present	Present	Not present	Not present	Not present	Low	1

Reported Results of Studies

The study by Zanotti *et al* (29) and Howell *et al* (62) reported a significant decrease in RV and an increase in TLC. The two trials by Engel *et al* (27, 61) reported significant increases in FVC in the groups receiving MT. The single case study, Masarsky *et al* (64) also reported significant increases in FVC and FEV_1 but only in the short term. The three RCTs reported significant increases in distance walked in the groups receiving MT. Engel *et al* (27) reported an improvement in dyspnoea scores. There was little change reported in quality of life across all trials (27, 61). Only the trials by Dougherty *et al* (63) and Engel *et al* (27) recorded adverse events reporting a small number of minor adverse events following SMT intervention.

Table 8: Outcome measures used and results reported in studies

Author/Date/Country	Study Design and Intervention	Outcome Measures	Results	Comments
Howell *et al.*, 1975 USA	Pre-post, OMT	RV, FVC FEV_1, arterial gases. Disease severity score	Progressive decline in severity score 10.7 Average decrease:PCO_2 p = 0.005, O_2 saturation p = 0.05, TLC p=0.001, RV p = 0.05	Disease severity score
Engel *et al.*, 2014 Australia	RCT, MTP and/or Ex	FEV_1, FVC blood pressure, SGRQ, HAD, 6MWT	FVC at 24 weeks (P=0.04) ST+SM+PR group compared to PR only. Significant increase in FVC at 24 weeks (P=0.03) Difference between groups for distance walked (6MWT) at 16 (P=0.01) and 24 weeks (P=0.03) No differences between groups for the SGRQ or HAD	
Dougherty *et al.*, 2011 USA	Case Series, SM, IASM	FVC, FEV1	No clinically significant change in FEV1 at 2 or 4 weeks.	
Zanotti *et al.*, 2012, Italy	RCT, OMT	VC, FVC, FEV1, RV, 6MWT Modified Borg scale.	PR and OMT gain in 6MWD (p = 0.01). PR and OMT (p = 0.05) reduction in RV which decreased of about 11%.	
Masarsky and Weber., 1988, USA	Case Study, Chiropractic techniques including MT	FEV1, FVC, dyspnoea, fatigue	FVC is greater in phase I compared to baseline (6 months) P<0.005 FVC is greater in phase II compared to baseline (3 months) P<0.005 Mean of subjective coughing scores during phase II < baseline in phase II (3 months): statistically sig, p<0.005 All others not statistically significant	Most outcome measures compared to baseline and Phase 1,2,3
Engel *et al.*, 2013, Australia	RCT, MTP and/or Ex	FEV_1, FVC, 6MWT	FVC increased ST + SM +EX (4weeks) P =.0001 Distance increased ST + MT +EX and ST +MT compared with ST P=.0001 Dyspnoea improved ST + MT +EX and ST + MT compared to ST P.0001	Adverse events reported small number of minor events

RCT: Randomised controlled trial; MTP: Manual therapy protocol; OMT: Osteopathic manipulative therapy; Ex: Exercise; RV: Residual volume; FVC: Forced vital capacity; 6MWD: Six minute walking distance; TLC: Total lung capacity; SGRQ: St George respiratory questionnaire; PR: Pulmonary rehabilitation; FEV_1: Forced expiratory volume in the 1st second; SM: Spinal manipulation; IASM: Instrument assisted spinal manipulation; VC: Vital capacity; HAD: Hospital anxiety and depression questionnaire; 6MWT: Six minute walking test; MT: Manual therapy.

Zanotti *et al.*, 2012, Italy	Osteopathic manipulative treatment effectiveness in severe chronic obstructive pulmonary disease: A pilot study	RCT, Pilot	Exclusion: acute exacerbation, neurological disease or joint disease Inclusion: stable COPD, GOLD stage III (severe)	N = 20 Gender = 5 female Age = 60 yr. Stage III (severe)	PR - 1 session on cyclette and 1 on cycle ergometer for 5 days/week for 4 weeks OMT 1 x week for 4 weeks	GROUP 1 PR plus sham OMT GROUP 2 OMT + PR
Masarsky and Weber., 1988, USA	Chiropractic management of chronic obstructive pulmonary disease	Case Study	No Inclusion/exclusion	N = 1 Gender = male Age = 53	Two baseline phases 2 weeks duration: no treatment Two treatment phases 3-4 months duration: mixed treatment with SMT	No Comparator
Engel *et al.*, 2013, Australia	Short Term Effects of a Course of Manual Therapy & Exercise in People with Moderate COPD: A Preliminary Trial	RCT, Preliminary	Exclusion: inability to walk unassisted, Contraindicated to SMT Inclusion: Aged 40 – 65 years, moderate stage COPD	N = 15, 14/15 completed Gender = M:60% F:40% Age = 56.1 years moderate COPD Groups matched for age	PR twice per week for 4 weeks Manual Therapy Protocol Exercise: Walking on a flat surface for 6 minutes	3 groups: ST ST + MT ST + MT + Ex

ST: Soft tissue therapy; PR: Pulmonary rehabilitation; RCT: Randomised controlled trial; N: Number; COPD: Chronic obstructive pulmonary disease; SM: Spinal manipulation; NR: Not reported; OMT: Osteopathic manipulative therapy; Yr.: Years; Ex: Exercise; GOLD: Global initiative for chronic lung disease.

Table 9: Outcome measures used and results reported in studies

Author/Date/Country	Study Design and Intervention	Outcome Measures	Results	Comments
Howell *et al.*, 1975 USA	Pre-post, OMT	RV, FVC FEV_1, arterial gases. Disease severity score	Progressive decline in severity score 10.7 Average decrease: PCO_2 p = 0.005, O_2 saturation p = 0.05, TLC p=0.001, RV p =0.05	Disease severity score
Engel *et al.*, 2014 Australia	RCT, MTP and/or Ex	FEV_1, FVC blood pressure, SGRQ, HAD, 6MWT	FVC at 24 weeks (P=0.04) ST+SM+PR group compared to PR only. Significant increase in FVC at 24 weeks (P=0.03) Difference between groups for distance walked (6MWT) at 16 (P=0.01) and 24 weeks (P=0.03) No differences between groups for the SGRQ or HAD	
Dougherty *et al.*, 2011 USA	Case Series, SM, IASM	FVC, FEV1	No clinically significant change in FEV1 at 2 or 4 weeks.	
Zanotti *et al.*, 2012, Italy	RCT, OMT	VC, FVC, FEV1, RV, 6MWT Modified Borg scale.	PR and OMT gain in 6MWD (p = 0.01). PR and OMT (p = 0.05) reduction in RV which decreased of about 11%.	
Masarsky and Weber., 1988, USA	Case Study, Chiropractic techniques including MT	FEV1, FVC, dyspnoea, fatigue	FVC is greater in phase I compared to baseline (6 months) P<0.005 FVC is greater in phase II compared to baseline (3 months) P<0.005 Mean of subjective coughing scores during phase II < baseline in phase II (3 months): statistically sig, p<0.005 All others not statistically significant	Most outcome measures compared to baseline and Phase 1,2,3
Engel *et al.*, 2013, Australia	RCT, MTP and/or Ex	FEV_1, FVC, 6MWT	FVC increased ST + SM +EX (4weeks) P =.0001 Distance increased ST + MT +EX and ST +MT compared with ST P=.0001 Dyspnoea improved ST + MT +EX and ST + MT compared to ST P.0001	Adverse events reported small number of minor events

RCT: Randomised controlled trial; MTP: Manual therapy protocol; OMT: Osteopathic manipulative therapy; Ex: Exercise; RV: Residual volume; FVC: Forced vital capacity; 6MWD: Six minute walking distance; TLC: Total lung capacity; SGRQ: St George respiratory questionnaire; PR: Pulmonary rehabilitation; FEV_1: Forced expiratory volume in the 1st second; SM: Spinal manipulation; IASM: Instrument assisted spinal manipulation; VC: Vital capacity; HAD: Hospital anxiety and depression questionnaire; 6MWT: Six minute walking test; MT: Manual therapy.

Discussion

This is the first systematic review to evaluate the effect of SMT on outcome measures in COPD. Findings include an improvement in lung function (FEV_1 and FVC), a decrease in RV and an improvement in breathlessness and dyspnoea following SMT intervention. Exercise capacity as measured by the 6MWT also showed an increase, as is highlighted by the Zanotti *et al* (29) trial which reported an increase in distance walked in the PR only group of approximately 17 metres while the addition of SMT resulted in a further improvement of approximately 75 metres.

While performance bias was present across all trials this may have been the result of difficulty blinding manual therapists to MT intervention regardless of whether it is a sham or not.

The rate of adverse events reported by Engel *et al* (61) were at levels similar to reports from other SMT trials (63). These studies reported a small number of mild adverse events consisting of muscle soreness up to 2 days post treatment. These findings suggest that using SMT for patients with COPD appears to be relatively safe. The two studies that used a pre-determined manual therapy protocol (MTP) which combined soft tissue therapy and manipulation of the thoracic spine reported a similar rate of adverse events, leading to the conclusion that this MTP is safe across all stages of COPD (27, 61).

Zanotti *et al* (29) and Engel *et al* (61) suggest that the reduction of RV and the increase in FEV_1 and FVC may delay the onset of exercise limiting dyspnoea (27, 29, 61). This could explain the reported improvements in exercise capacity as delaying the onset of exercise limiting dyspnoea would permit more exercise to be performed. SMT may increase chest wall flexibility, which appears to improve the ability of the

respiratory system to accommodate the increase in the ventilatory demands of exercise, which leads to an extension of exercise performance.

In light of the methodological limitations, the findings of this systematic review suggest that SMT may have the potential to benefit COPD, in particular lung function and exercise capacity. This is significant when considering the evidence that PR has little effect on lung function (29, 53). The improvements in exercise capacity may be a by-product of a decrease in thoracic compliance (an increase in chest wall flexibility), and any improvement in exercise capacity should be considered significant, as exercise capacity is a predictor of mortality in COPD. This review supports the suggestion that including SMT as an adjunct to current management strategies carries with it a potential to alter the prognosis of the disease.

The findings of this review contrast those of Heneghan *et al* who could not recommend further research in the area was warranted (54). However, as previously mentioned, the current review included SMT in combination with other modalities. It is likely that this difference accounts for the contrast in findings between the two reviews. It is therefore recommended that a large RCT designed to investigate the combination of SMT and other modalities in particular, exercise be performed. This RCT should assess exercise capacity and chest wall flexibility as secondary outcome measures and use a standardised protocol for MT intervention.

There were a number of methodological limitations associated with the trials included in this review. The limitations include: small sample sizes (N = 1 to 33), variation in participant characteristics, performance bias (referred to previously) and the possibility that the cohorts may not be representative of the general population of people with COPD.

Chapter Four

Methodology

4.1 Introduction

This chapter outlines the methodology chosen to perform a retrospective phenotype analysis on data from an RCT investigating the effect of MT and PR in COPD. This methodology was designed to address research questions iii, iv, v and the following research objectives:

- To apply the phenotype classification algorithm to participants in an RCT
- To compare a retrospective analysis by phenotype of the outcomes from the RCT to the results reported in the RCT

Data for this study was collected from a randomised controlled trial (RCT) conducted in an Australian public hospital in 2011 (61). This RCT was designed to study the effect of including manual therapy (MT) in a pulmonary rehabilitation (PR) program for people with chronic obstructive pulmonary disease (COPD). A retrospective analysis was performed on the data from this trial to evaluate the effect of the interventions on the four COPD phenotypes identified in Chapter 2 *i.e.* chronic bronchitis, mixed asthma- COPD, emphysema and frequent exacerbations.

The background describes previous reports on the use of MT for COPD and the rationale behind performing a retrospective phenotype analysis on data from a completed RCT.

This chapter is divided into two parts: Part 1 describes the RCT including study design, protocol, statistical methods and ethical considerations; Part 2 describes the retrospective phenotype analysis and includes study characteristics, design, protocol and statistical methods.

4.2 background

Reports of using MT as an adjunct intervention for COPD consist of a range of MT techniques including massage (65), muscle and joint mobilisation (66) and spinal manipulative therapy (29, 62, 63). Although results are mixed, other studies that include the use of SMT and exercise together, have reported promising results for lung function, dyspnoea levels and exercise capacity (see Chapter 3) (29, 62, 63).

Currently there are no reports in the literature on the effect of MT on COPD by phenotype. As COPD is a heterogeneous disease it may not be sufficient to classify people into stages of severity using only spirometry. Incorporating other signs and symptoms into a classification system has led to patients being grouped according to phenotypes (3, 5, 21). Although there is a degree of overlap between groups in some patients this approach has the potential to improve treatment outcomes by focusing on functional aspects of the disease, thereby improving the accuracy and efficacy of an intervention. These functional aspects include dyspnoea levels, hyperinflation, exercise capacity, BMI and bronchial hyper-reactivity. Using the phenotype classification system described in Chapter 2, a retrospective analysis was performed on an RCT that investigated the effect of MT and PR on COPD (61).

4.3.1 Part 1: Randomised controlled trial

4.3.2 Design:

A randomised controlled trial (RCT) is used to study an intervention by comparing its effect to a control or non-intervention group (67). This design limits the number of variables that can confound the results. RCTs are also designed to minimise bias by blinding the participants and/or researchers.

4.3.3 Protocol

The title of the RCT was:

The effect of combining manual therapy with a pulmonary rehabilitation exercise program for chronic obstructive pulmonary disease (COPD): a randomised controlled pilot trial.

The trial was conducted at Sutherland Hospital, a public teaching hospital located in Sydney.

4.3.4 Research aim

To measure the medium term effect of pulmonary rehabilitation with and without manual therapy for people with COPD.

4.3.5 Hypothesis

That adding manual therapy to a pulmonary rehabilitation program improves lung function over the medium term in people with COPD.

4.3.6 Ethical considerations

The study was approved by the Human Ethics committees of Macquarie University (HE23MAR2007-D05054) and the South Eastern Sydney and Illawarra Area Health Service (07/41) and registered with the Australian New Zealand Clinical Trials Registry (ACTRN:012607000388415). The trial was funded by Macquarie University's Higher Degree Research Fund.

4.3.7 Method

Sample size

33 participants with COPD were randomly allocated to three intervention groups;

- Intervention Group 1 – PR only (n=15)
- Intervention Group 2 – Soft Tissue (ST) and PR (n=9)
- Intervention Group 3 – ST, Spinal Manipulation (SM) and PR (n=9)

Recruitment

Participants were recruited by referral from their respiratory specialist to the pulmonary rehabilitation unit at Sutherland Hospital.

Randomisation

Participants selected an opaque envelope with one of the three group numbers inside. Each participant was then assigned to a group according to that number.

Participant Characteristics

The eligibility criteria for the RCT is outlined in Table

10. Table 10: Inclusion/exclusion criteria for the RCT.

Eligibility criteria	
Inclusion Criteria	**Exclusion Criteria**
• Age 50-70 • Diagnosis of COPD • Non-smoking (for preceding 12 months) • Able to complete a 6 minute walking test (6MWT) unassisted	• Contra-indicated to thoracic spinal manipulation • Bone density T score > -2.5 and Z score > -1 • Inability to understand English • Current pregnancy • People aged <50 and >70 • People with an intellectual and/or mental impairment

Diagnostic criteria

According to both the GOLD and COPDX guidelines a diagnosis of COPD is suspected if there is breathlessness, chronic cough and sputum and/or a history of exposure to smoking or other noxious stimuli (1, 2). Spirometry is used to ascertain the level of airflow limitation and a diagnosis of COPD is confirmed if the ratio FEV_1/FVC is below

1.7 and FEV_1 is below 80% predicted.

In addition to spirometry, other diagnostic tests and assessments may be

performed when assessing a patient with COPD. They include: dyspnoea levels (Borg scale), exercise capacity (6 minute walking test: 6MWT or shuttle test), blood perfusion tests (measurement of oxygen saturation in the blood) and high resolution computed tomography or chest x- rays (2).

Health related quality of life (HRQoL) measures such as the St George's Respiratory Questionnaire (SGRQ) and the Hospital Anxiety and Depression (HAD) scale were also used in the RCT. The RCT used the GOLD diagnostic criteria (table 1).

Intervention

The manual therapy protocol (MTP) used in this RCT has been described previously (27, 68). It consisted of a combination of soft tissue therapy (ST) and thoracic spinal manipulation (SM). Two SMs were administered in each intervention session. The first was applied at the level of the upper/middle thoracic spine while the second was applied at the level of the middle/lower thoracic spine. Both manipulations were administered as non- specific, multi-joint (group) manipulations, which reduced the total number of SMs required to cover the thoracic spine and corresponding rib cage. A single MT session (ST plus SM) lasted approximately 20 minutes and was administered immediately prior to exercise.

The PR program lasted 24 weeks and delivered in two phases: intervention and non- intervention. The intervention phase was made up of two 8-week stages: the first was the 'Introductory' stage where participants were 'trained' in the exercise program; and the second was the 'Maintenance' stage where participants continued to exercise at the level they had reached at the end of the 'Introductory' stage. The non-intervention phase followed the maintenance stage and consisted of an 8-week period of no intervention. Participants were directed to exercise at their own discretion during this phase. A summary of the stages and interventions is set out in Table 11.

There were four assessment points during the 24 week trial period:

- Week 0: Baseline
- Week 4: Midpoint of introductory stage – start of MT intervention
- Week 8: End of introductory stage
- Week 16: End of maintenance stage
- Week 24: End of non-intervention phase, end of trial

Table 11: Schedule of interventions in the RCT.

	Intervention			Non-Intervention
	Introductory		Maintenance	
Interventions	Week 0 Baseline	Week 8	Week 16	Week 24 End of trial
Medical history	✓			
Inclusion / Exclusion criteria	✓			
Screening for contraindications to SMT	✓			
Informed Consent	✓			
Physical examination (BMI, BP)	✓	✓	✓	✓
Spirometry	✓	✓	✓	✓
6 minute walking test	✓	✓	✓	✓
Quality of Life questionnaires	✓	✓	✓	✓
Exercise		✓	✓	Own discretion
Manual Therapy (Group 2 and 3 only)		✓	✓	
Adverse Event Assessment		✓	✓	✓
BMI: Body mass index; BP: Blood pressure.				

Outcome Measures

The primary outcome measure in this trial was lung function (FEV_1 and FVC); the secondary outcome measures were exercise capacity (6MWT) and health related quality of life (SGRQ and HAD).

Participant flow through the RCT

Figure 3 shows the flow of participants through the RCT.

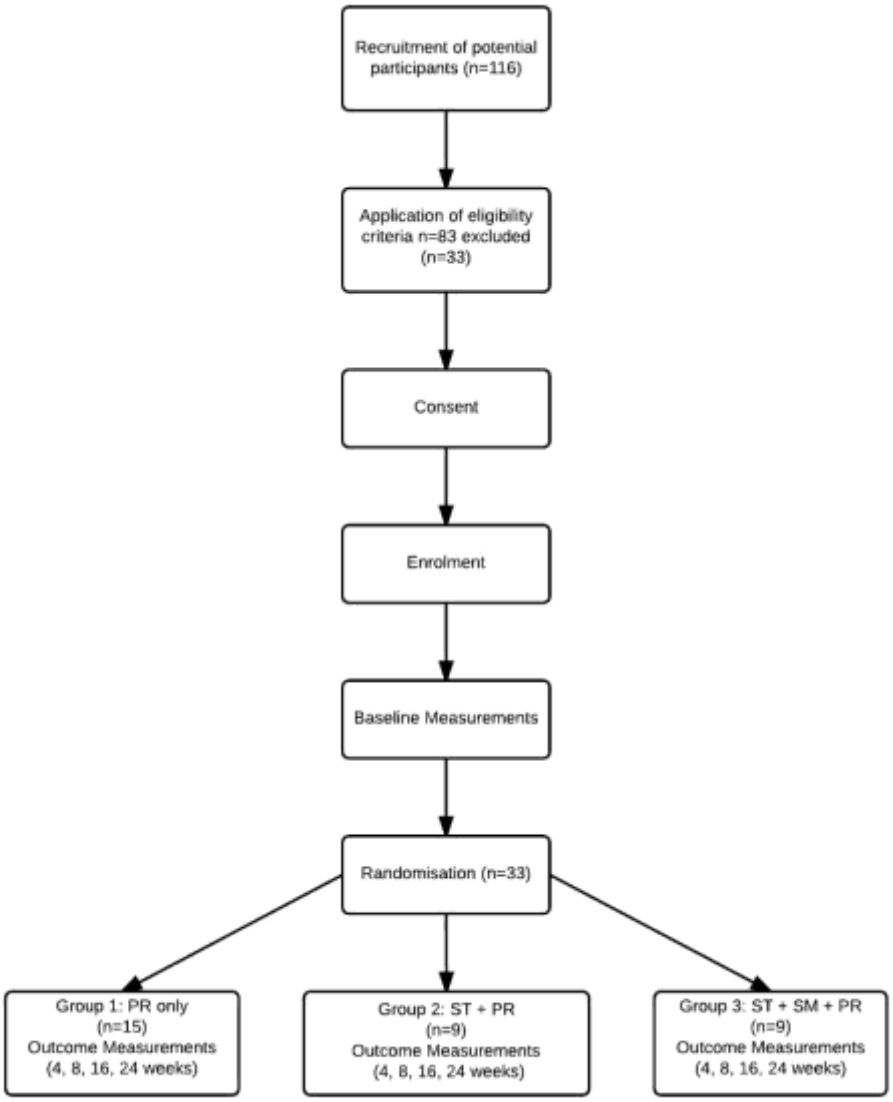

Figure 3. Flow of participants through the RCT.

Statistical analysis for RCT

Data was reported as group means with standard deviations and confidence intervals (95%) calculated for each group. Analysis was performed as an ANCOVA for difference between groups with baseline as a covariate and standard errors calculated using a non- parametric bootstrap to allow for the different error variances for each group. A p value (< 0.05) was set for statistical significance. For outcomes found to be statistically significant, the proportion of participants with a change greater than the minimum clinically important difference (MCID) was calculated. A Bonferroni correction for between-group comparisons was made to correct for multiple comparisons between the three groups with adjusted P values. The number needed to treat (NNT) was calculated using Bender's method for confidence intervals. Missing data was accounted for by using an intention-to- treat (ITT) analysis with data from subjects lost to follow-up imputed using the last observation carried forward (LOCF) method.

4.4.1 Part 2: Retrospective phenotype analysis

4.4.2 Design

The decision to use a retrospective study design on data from an existing RCT was made for pragmatic reasons. The analysis was performed without the need for interaction between researchers and participants, negating the potential for any observational bias of the data. The weakness of a retrospective analysis includes a lack of external validity where the sample size may not be large enough to represent the population (69). The strength of a retrospective analysis is that it allows for the benefit of hindsight when generating new hypotheses. In this instance, a retrospective analysis of results from the RCT is an opportunity to test a hypothesis about using a phenotype classification system. The aim of this approach was an attempt to reveal new information from existing data that could lead

to an improvement in the efficacy of interventions that target subgroups of patients with COPD.

4.4.3 Hypothesis

Through analysis and comparison of the four COPD phenotypes in response to MT and PR, for the outcome measures: FEV_1, FVC, and 6MWT, additional descriptive information can be extrapolated and there is a difference in response to intervention between the phenotypes.

4.4.4 Methods

Study design

A retrospective analysis was conducted on data from an RCT that was designed to investigate the effect of including MT in a PR program for people with COPD.

Sample size

The RCT has been described in section 4.3.1. For the phenotype analysis, the three RCT intervention groups were retained and a fourth group created consisting of the combined results from the two manual therapy groups in the RCT *i.e.* the ST+PR and ST+SM+PR groups. This fourth group was labelled the Combined MT Intervention group and was created to increase the sample size and distribution of phenotypes within a group that included spinal manipulation. Participants in each of the four groups were then classified into one of four phenotypes: chronic bronchitis (CB), mixed asthma-COPD (MA), emphysema (E) and frequent exacerbations (FE). Figure 4 describes the flow of participants through the phenotype classification analysis.

Phenotype Classification

Medical records of 33 participants were reviewed using the criteria listed in Table

12. These included elements such as exacerbation history, mucous production, infections, medications taken, exercise capacity and history of asthma. While this information was available in the medical history of participants enrolled in the RCT, most of these elements were not considered when classifying a patient based on disease. Table 4 in chapter 2 describes the information used to classify participants in to one of the four phenotypes for this analysis.

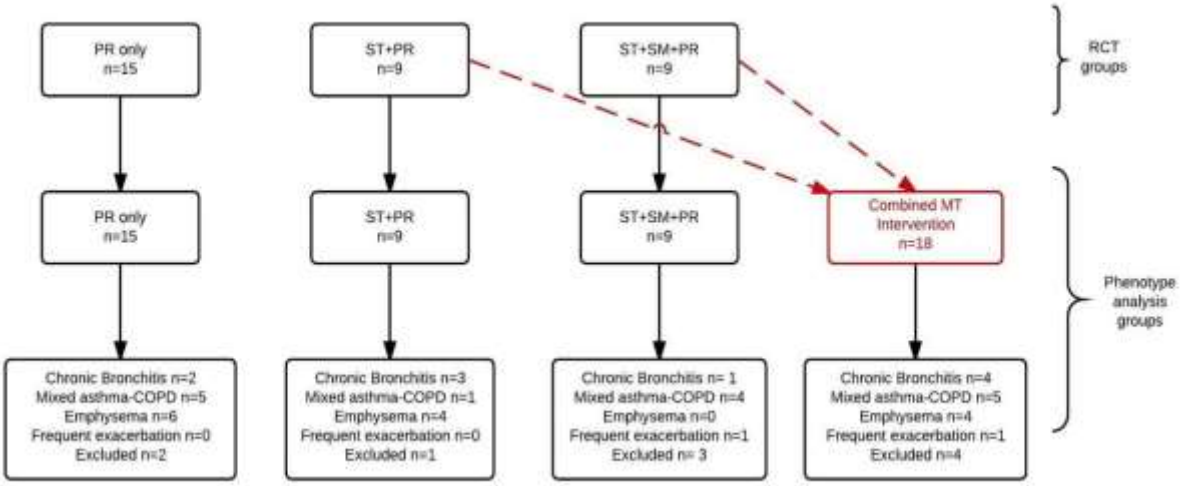

Figure 4. Flow of participants from the intervention groups of the RCT to the phenotype analysis.
Note that Group 2 and group 3 of the RCT were combined to form group 4; The Combined MT Intervention group for the phenotype analysis.

Phenotype classification used a tally algorithm system based on the information listed in Table 4 in chapter 2. Each phenotype had a series of primary and secondary diagnostic criteria. The presence of a primary criterion attracted a score of 2 points while the presence of a secondary criterion attracted a score of 1 point. The phenotype with the highest score was assigned to the participant. A minimum score of 2 was required for a participant to be classified into a phenotype. If the participant had a score for more than one phenotype, either the highest score was the assigned phenotype or the participant was

assigned as an overlap phenotype e.g. CB + E, and was not used in the analysis.

The score for each participant was tallied by a single researcher (CW). Once phenotype classification had been completed the statistical and trend analyses were performed using these phenotypes.

Table 12: Questions to aid phenotype classification

Phenotype History Questions
• Current or ex-smoker, never smoked, unreported.
• Episode of an acute exacerbation (where COPD symptoms became worse, hospitalised? Needed new medications?) How Many/often?
• Presence of mucous? Daily/often? Colour?
• History of asthma?
• Presence of allergies (dermatitis, psoriasis, chronic itchy skin, dandruff)? Skin and/or respiratory?
• Other medical conditions/co-morbidities? Diabetes, cardiovascular etc.?
• Medication list?
• Ongoing or frequent antibiotic use?
• Presence of Gastro-oesophageal reflux disease? (GORD/GERD)
• Presence of Chronic bronchitis, bronchitis, bronchiectasis?

Statistical Analysis for Phenotypes

The methods used for the statistical analyses of the primary and secondary outcomes in the RCT were reported in section 4.2.1. For the retrospective phenotype analysis, descriptive statistics were employed to illustrate the proportions of individual phenotypes in each intervention group of the RCT and to describe other findings such as average BMI and smoking history.

The means for each of the primary outcome measures such as FEV_1, FVC and 6MWT at baseline, 16 and 24 weeks were calculated for each phenotype. This was done within each of the RCT's intervention groups as well as the combined MT intervention group. A student's t-test was performed on the means comparing each phenotype (E v CB, M v CB etc.). The mean difference from baseline to weeks 16 and 24 were then calculated for each phenotype for the following outcome measures: FVC, FEV_1, and 6MWT. The mean differences were then compared to the mean differences of each intervention group from the RCT. A student's t-test was performed on the mean differences comparing the phenotype data to the full RCT data within each intervention group. The t-tests were used to calculate the significance of the differences between phenotypes for response to interventions and also to compare the performance of the phenotypes against the findings in the RCT. Not only do these methods allow for testing the classification algorithm but they also provide data on how phenotypes respond to the intervention.

4.5 Summary

Improving outcomes from pulmonary rehabilitation have the potential to help ease the increasing burden of disease that is currently associated with COPD. This analysis is designed to provide more accurate information about how participants respond to intervention. If successful it will provide support for considering the introduction of phenotype classification in to pulmonary rehabilitation where treatment could be targeted to specific sub-groups.

This is the first report of a phenotype analysis on participants from a trial investigating MT and PR in COPD. It has the potential to generate new hypotheses that could see phenotype analyses performed on larger cohorts in this field of research.

Chapter Five

Results

5.1 Introduction

The purpose of this chapter is to present the findings of a retrospective phenotype analysis of an RCT designed to investigate the effect of MT and PR on COPD. This chapter addresses the research questions iii, iv, v and will provide the results from this analysis plus a comparison of them with the results of the RCT. Details of the process of applying the phenotype classification algorithm to participants in the RCT was reported in Chapter 4 and the process of this is also presented in this chapter.

The results of the phenotype analysis are presented in three parts:

1. Descriptive characteristics of the four phenotypes and the proportion of each phenotype in the intervention groups;
2. The response of each phenotype to intervention using a student's t-test on outcome measures; and
3. The response of each phenotype to intervention is compared with the results from the RCT using tables and graphs to identify potential trends.

The chapter concludes with a summary of results.

5.2 Summary of results from the RCT

116 participants were assessed for eligibility with 83 excluded due to age outside the nominated range, contra-indicated to spinal manipulation, not having COPD, currently smoking and the presence of osteoporosis. The remaining 33 volunteers were randomly allocated to 3 groups: pulmonary rehabilitation only (PR) (n=15); soft tissue therapy (ST) plus PR (ST+PR) (n=9); and ST plus spinal manipulation (SM) plus PR

(ST+SM+PR) (n=9). The groups were similar at baseline except for gender and anxiety. The mean age was 65.5 ± 4 years. Table 13 shows an intention-to-treat (ITT) analysis of the change in outcome measures for each group from baseline to 16 and 24 weeks. The main findings from the RCT were an increase in FVC for the ST+SM+PR group compared to PR only at 24 weeks (0.40, p=0.04) and a difference between groups in the 6MWT at 16 and 24 weeks (p=0.01, p=0.03 respectively). There were no changes in quality of life measures in any of the groups.

5.3 Deviations from original study

The current study was designed to compare outcomes within intervention groups by phenotype. Due to the small sample size of the RCT, the range of statistical analyses was limited and only t-tests could be performed on the outcome measures. Trend and descriptive analyses of results was used to show differences between phenotypes. This was done in an attempt to generate new hypotheses that could be used in a larger clinical trial currently underway (n=200).

Table 13: Change in outcome measures and 95% CI compared to baseline by intervention group at 16 and 24 weeks (Intention-to-Treat). BP: Blood pressure; FEV_1: Forced expiratory volume in 1st second

	Group					
	PR		ST + PR		ST + SM + PR	
	Week of assessment					
Outcome measure	16	24	16	24	16	24
Systolic BP	-3.6 (-13.5,6.3)	-7.1 (-17.3,3.0)	-10.6 (-19.6,-1.5)	-6.9 (-15.8,2.1)	-8.3 (-20.5,3.8)	-10.1(-25.6,5.4)
Diastolic BP	-3.5 (-12.6,5.6)	-4.7 (-13.3,4.0)	-7.7 (-17.1,1.8)	-8.1 (-17.8,1.5)	-4.7 (-13.5,4.2)	-8.0 (-19.6,3.6)
+FEV_1 (litres)	-0.042 (-0.113,0.029)	-0.077 (-0.164,0.011)	-0.021 (-0.115,0.072)	-0.089 (-0.175,-0.003)	-0.020 (-0.136,0.096)	-0.020 (-0.144,0.104)
+FVC (litres)	0.10 (-0.14,0.35)	0.10 (-0.14,0.34)	0.45 (0.13,0.77)	0.32 (-0.05,0.68)	0.37 (0.22,0.53)	* 0.53 (0.26,0.81)
SGRQ	-4.6 (-9.8,0.5)	-8.1 (-14.6,-1.6)	-0.7 (-7.2,5.8)	1.0 (-3.5,5.5)	-3.3 (-16.3,9.7)	-4.3 (-19.9,11.3)
HAD Anxiety	-0.1 (-1.5,1.3)	-0.9 (-2.8,1.1)	-0.3 (-2.4,1.8)	-0.8 (-3.7,2.2)	0.5 (-0.7,2.0)	0.2 (-1.3,1.7)
HAD Depression	-0.9 (-1.7,-0.2)	-1.3 (-2.1,-0.4)	-1.3 (-3.8,1.1)	-0.8 (-2.7,1.2)	-1.9 (-4.2,2.2)	-0.7 (-4.4,3.1)
+6 MWT (meters)	22.7 (-6.1,51.4)	12.1 (-18.0,42.2)	5.8 (-25.1,36.7)	-16.4 (-55.1,22.2)	51.7 (29.8,73.6)	35.0 (-1.5,71.5)

FVC: Forced vital capacity; SGRQ: St George's respiratory questionnaire; HAD: Hospital anxiety and depression scale; 6MWT: 6 minute walking test * indicates values that reached significance (p=<0.05). Outcome measures used in the phenotype analysis are marked with a +

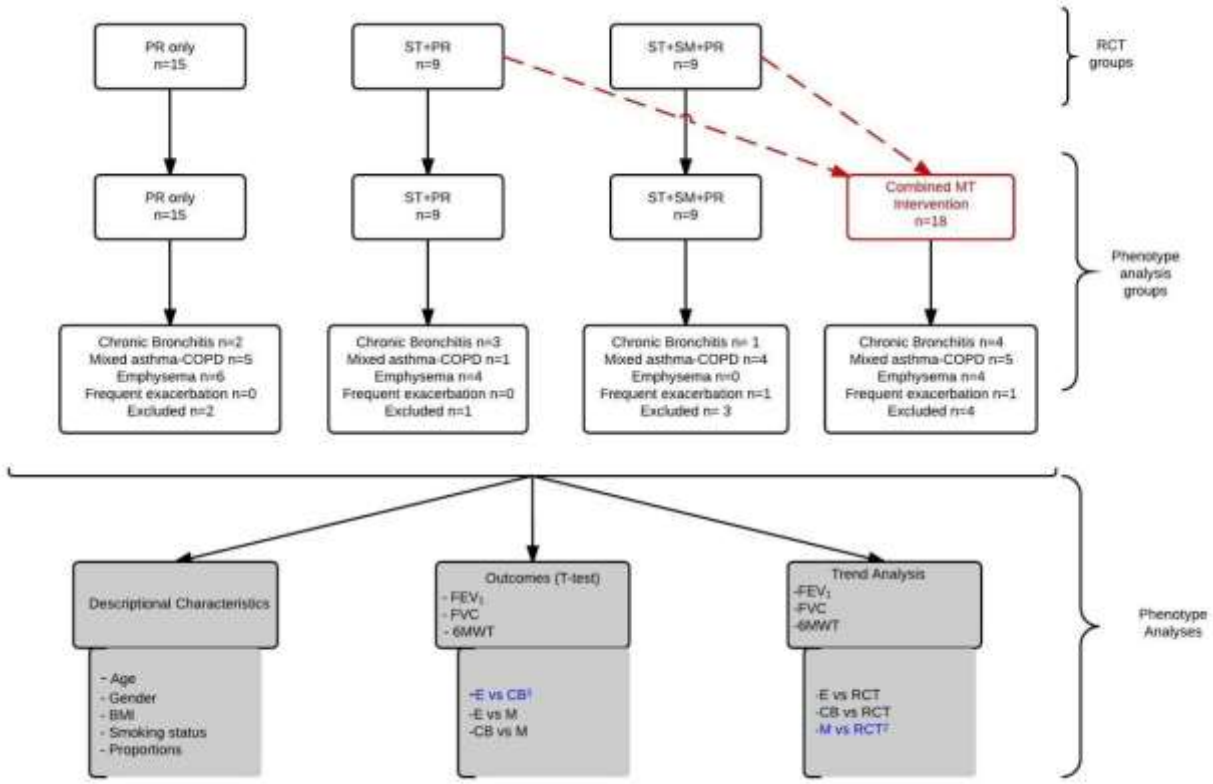

Figure 5. Flow of participants through the phenotype analysis.
Note that the ST+PR and the ST+SM+PR were merged to create the combined MT intervention group.
1 denotes the finding of a difference between scores of emphysema and chronic bronchitis at week 24 for FVC
2 denotes the difference between the mixed asthma-COPD phenotype and the RCT results for the PR only group at week 16 for the 6MWT.
PR: Pulmonary Rehabilitation; ST+PR: Soft tissue and PR; ST+SM+PR: ST and Spinal Manipulation and PR; E: Emphysema; CB: Chronic bronchitis; M: Mixed asthma-COPD.

5.4 Participant Characteristics

Figure 5 shows the flow of participants through the phenotype classification algorithm and the types of analysis performed on the phenotypes, 33 participants were included in the RCT however 6 were excluded from the phenotype analysis due to the inability to assign a phenotype.

A summary of participant characteristics from the RCT and the

number and proportion of each phenotype in each of the four groups of the phenotype analysis are set out in Table 14. The majority of participants in the study were female. The ST+PR group varied the most compared to the others in smoking history and BMI.

The proportion of each COPD phenotype varied within each group with not all phenotypes represented in each group (see Figure 6). The PR group (Group 1) had emphysema, chronic bronchitis and mixed asthma-COPD participants whereas the ST+SM+PR group (Group 3) had no participants with emphysema.

Table 14: Participant characteristics of RCT and sample size of each group, and the breakdown of phenotypes proportions present in each group. Note that ST+PR and ST+SM+PR have been merged to form group 4 – combined intervention group

Participant Characteristics				
	PR	ST+PR	ST+SM+PR	Combined MT intervention (group 2 and 3 combined)
Gender (% female)	92.30%	62.50%	50%	57.14%
Mean age	64.54 ± 3.99	67.25 ± 3.58	63.66 ± 4.5	65.71 ± 4.25
Mean BMI	26 ± 5.38	30.52 ± 5.54	28.72 ±3.8	29.75 ±4.79
Smoking history (% yes)	61.54%	100%	66.67%	85.71%
Phenotype	N=13	N=8	N=6	N=14
E	6	4	0	4
CB	2	3	1	4
M	5	1	4	5
FE	0	0	1	1
E: Emphysema; CB: Chronic bronchitis; M: Mixed asthma-COPD; FE: Frequent exacerbation; ST: Soft tissue therapy; PR: Pulmonary rehabilitation; SM: Spinal manipulation; MT: Manual therapy; BMI: Body mass index.				

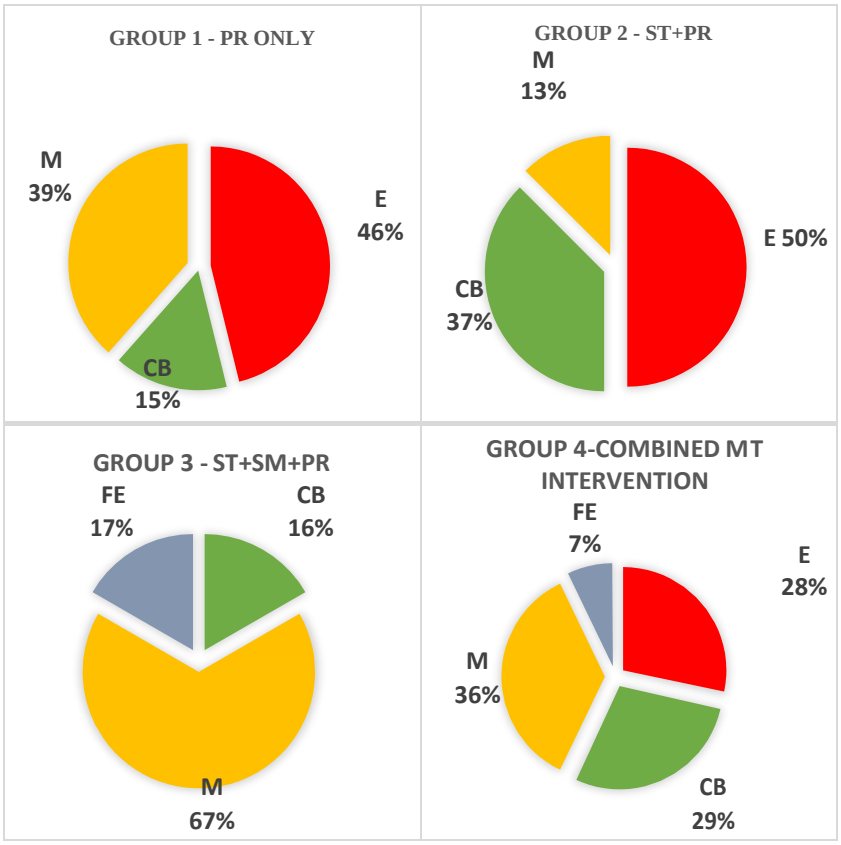

Figure 6: Proportions of phenotypes present in each of the groups of the RCT. E: Emphysema; CB: Chronic bronchitis; M: Mixed asthma-COPD; FE: Frequent exacerbations.

5.5 Retrospective Phenotype analysis results

5.5.1 Phenotype Classification System

As participants in the RCT had been referred by their respiratory specialist, most had a previous diagnosis of a secondary disease to COPD. If they did not have a previous diagnosis their medical records were searched for signs and symptoms that would indicate the appropriate phenotype that should be assigned. The results of this scoring system are reported in Table 15. The phenotype with the highest number of points was the designated phenotype for that participant.

Table 15: Results of phenotype classification algorithm, by tally system.

GROUP 1- PR only						GROUP 2 – ST+PR						GROUP 3 – ST+SM+PR					
Subject	E	CB	M	FE	Phen	Subject	E	CB	M	FE	Phen	Subject	E	CB	M	FE	Phen
102	4	0	0	0	E	228	3	1	0	0	E	327	0	3	1	0	CB
104	4	1	0	0	E	211	4	2	0	0	E	323	0	2	0	3	FE
108	3	2	0	0	E	205	4	0	0	0	E	326	0	2	4	0	M
110	2	0	0	0	E	203	3	2	0	0	E	314	0	0	2	0	M
117	2	1	0	0	E	201	0	3	2	0	CB	301	0	0	4	0	M
112	4	2	0	0	E	221	0	4	0	0	CB	329	0	1	4	0	M
130	1	4	0	0	CB	225	0	5	1	0	CB						
109	0	4	2	0	CB	229	0	2	4	0	M						
113	0	0	3	0	CB												
119	0	2	4	0	M												
120	0	0	2	0	M												
124	0	1	4	0	M												
132	0	0	4	0	M												

E: Emphysema; CB: Chronic bronchitis; M: Mixed asthma-COPD; FE: Frequent exacerbations; Phen: Phenotype; PR: Pulmonary Rehabilitation; ST+PR: Soft tissue and PR; ST+SM+PR: ST and Spinal Manipulation and PR

5.5.2 Phenotype Response to Intervention (outcome of Student's T-test)

A student's t-test was applied to the means of the outcome measures FVC, FEV_1 and 6MWT for each of the phenotype groups within each of the four intervention groups. There was a difference between chronic bronchitis and emphysema for FVC in the combined MT intervention group (ST+PR plus ST+SM+PR) at 24 weeks (p=0.03). There was also a difference at 16 weeks in the mixed asthma-COPD group for 6MWT within the PR only intervention group compared to the RCT results (p=0.04). There were no other differences between means for phenotype outcomes at any of the time points.

5.5.3 Results of phenotype analysis

The potential trends of performance over time for FEV_1, FVC and the 6MWT was calculated for each phenotype and compared to the trends in the RCT.

Analysis results for FEV_1

Mean differences at 16 and 24 weeks for each phenotype were compared to the RCT, see table 16 and figure 7. For FEV_1 the emphysema phenotype differed to the RCT data in the PR only group at 16 weeks showing an increase in FEV_1 where the RCT reported a decrease, the difference between scores was 0.06L. The mixed Asthma-COPD group differed to the RCT data PR only group at 24 weeks, showing an increase in FEV_1 where the RCT reported a decrease, the difference between scores was 0.16L. In the ST+PR group, the emphysema phenotype followed the same trend as the RCT but showed a greater decrease in FEV_1, the difference was 0.06L. In the ST+SM+PR group, the mixed asthma- COPD phenotype showed an increase in FEV_1 compared to the RCT data at week 24, the difference between scores was 0.10L. The chronic bronchitis phenotype followed the results of RCT in direction and in magnitude.

Analysis results for FVC

There was a difference between phenotype groups compared to the RCT results for FVC, see Table 17 and Figure 8. In the PR only group emphysema and chronic bronchitis showed a decline in FVC where the RCT results and the mixed asthma-COPD group reported an increase. In the ST+PR group the largest difference was between chronic bronchitis and emphysema at week 16 where the difference was 0.39L. And at week 24 where the difference was 0.41L, in both cases emphysema showed the largest increase in FVC. Even though this difference was significant, the scores followed the trend of the RCT.

Table 16: Mean differences between baseline (week 0) and week 16, and week 24 for FEV_1. Each group is presented with the RCT data and phenotype data. Shaded columns represent the difference between the phenotype score compared to the RCT score. Data for frequent exacerbation phenotype does not appear as there were limited or no data present.

FEV_1 Difference between phenotypes and RCT results. Scores compared to baseline at 16 and 24 weeks																								
	PR only							ST+PR						ST+SM+PR						Combined MT Intervention					
	RCT	CB	Diff	M	Diff	E	Diff	RCT	CB	Diff	M	E	Diff	RCT	CB	M	Diff	E	RCT	CB	Diff	M	Diff	E	Diff
16	-0.04	0	**0.04**	-0.02	**0.02**	0.10	**0.06**	-0.02	-0.02	0	NA	-0.08	0.06	-0.02	NA	.003	-0.02	NA	-0.04	-0.02	0.02	-0.02	0.02	-0.08	0.04
24	-0.08	-0.08	**0**	0.08	**0.16**	0.15	**0.07**	-0.09	-0.13	0.04	NA	-0.15	0.06	-0.02	NA	-0.12	0.1	NA	-0.12	-0.13	0.01	-0.12	0	-0.15	0.03

E: Emphysema; CB: Chronic bronchitis; M: Mixed asthma-COPD; FE: Frequent exacerbations; Phen: Phenotype; PR: Pulmonary Rehabilitation; ST+PR: Soft tissue and PR; ST+SM+PR: ST and Spinal Manipulation and PR; Diff: Difference. All units in litres

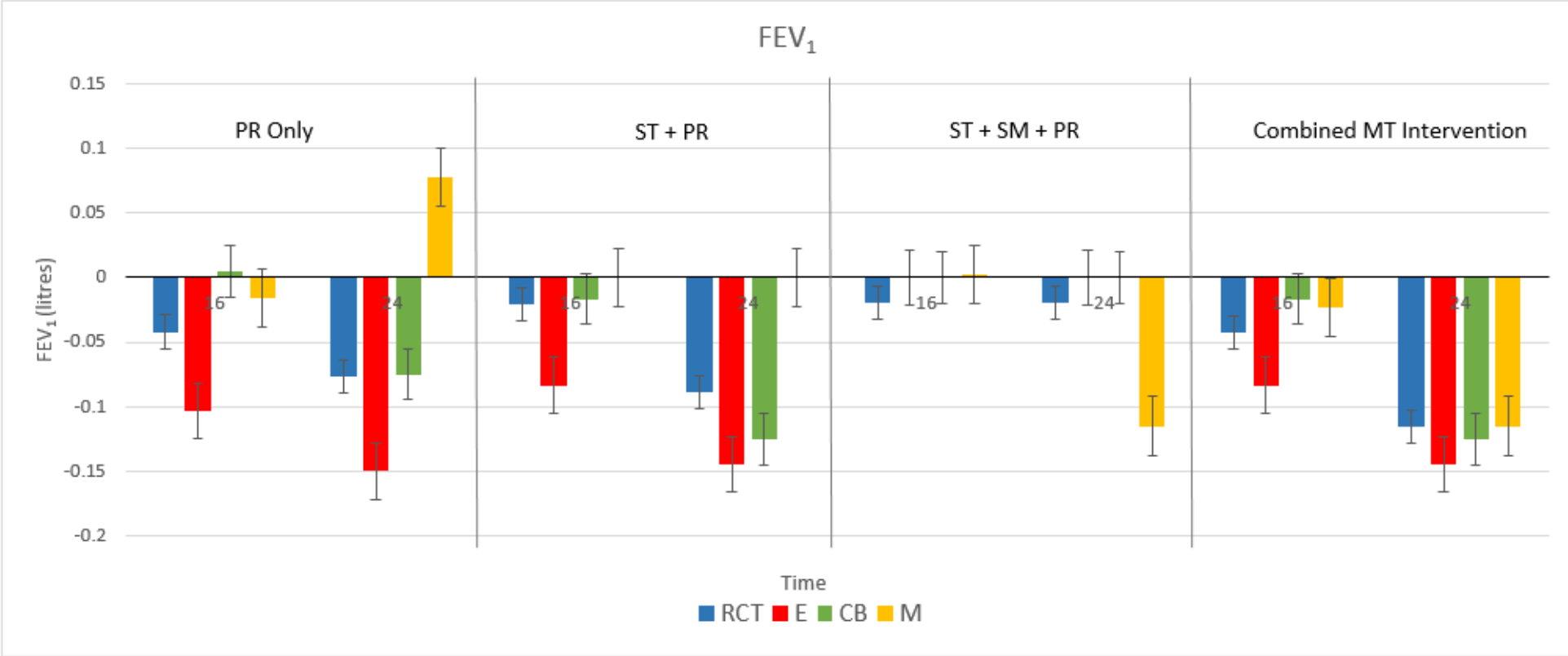

Figure 7: Comparison of the RCT data to each phenotype of each group, scores are the mean differences of week 0-16 and week 0-24 for FEV_1

Table 17: Mean differences between baseline (week 0) and week 16, and week 24 for FVC. Each group is presented with the RCT data and phenotype data. Shaded columns represent the difference between the phenotype score compared to the RCT score. Data for frequent exacerbation phenotype does not appear as there were limited or no data present

FVC Difference between phenotypes and RCT results. Scores compared to baseline at 16 and 24 weeks																								
	PR only							ST+PR						ST+SM+PR					Combined MT Intervention					
	RCT	CB	Diff	MA	Diff	E	Diff	RCT	CB	Diff	MA	E	Diff	RCT	CB	MA	Diff	E	RCT	CB	Diff	MA	Diff	E	Diff
16	0.10	-0.01	**0.11**	0.31	**0.21**	0.01	**0.09**	0.45	0.36	0.09	NA	0.75	0.30	0.37	NA	0.21	0.16	NA	0.46	0.36	0.10	0.31	0.15	0.75	0.29
24	0.10	-0.10	**0.20**	0.28	**0.06**	-0.01	**0.11**	0.32	0.15	0.17	NA	0.56	0.24	0.52	NA	0.51	0.01	NA	0.38	0.15	0.18	0.45	0.07	0.56	0.28

E: Emphysema; CB: Chronic bronchitis; M: Mixed asthma-COPD; FE: Frequent exacerbations; Phen: Phenotype; PR: Pulmonary Rehabilitation; ST+PR: Soft tissue and PR; ST+SM+PR: ST and Spinal Manipulation and PR; Diff: Difference. All units in litres

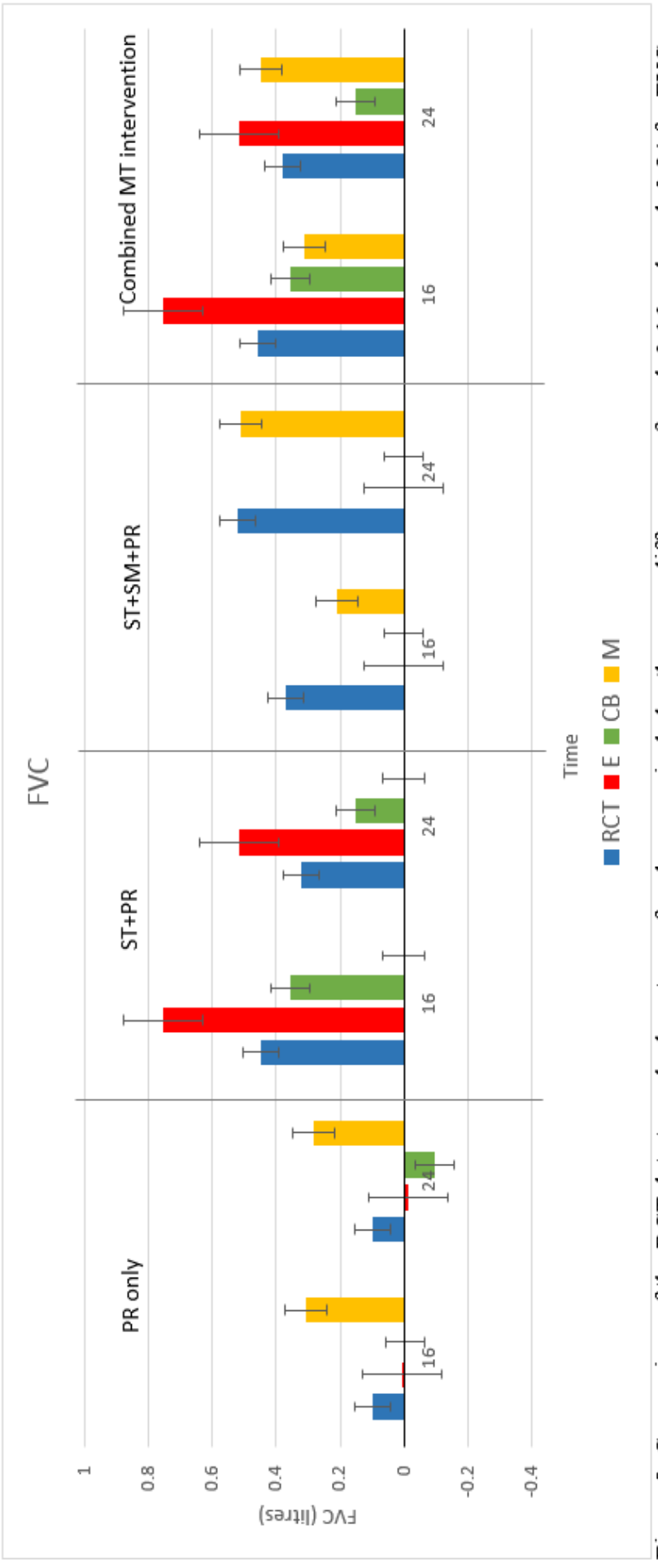

Figure 8: Comparison of the RCT data to each phenotype of each group, includes the mean differences of week 0-16 and week 0-24 for FVC

Analysis results for 6MWT

Mean differences at 16 and 24 weeks for each phenotype were compared to the RCT for 6MWT, see table 18 and figure 9. In the PR only group, the emphysema group reported a decline in distance walked where the RCT reported an increase, with the difference between scores being 18.93m (metres). In the PR only group, the mixed asthma-COPD phenotype showed a greater increase than the RCT reported, with the difference being 67.53m at 16 weeks and 57.63m at 24 weeks. In the ST+PR group, chronic bronchitis phenotype showed a decrease in distance where the RCT reported a slight increase, with the difference being 7.8m. In the ST+SM+PR group at 16 weeks, the mixed asthma-COPD phenotype showed a decrease in distance walked where the RCT reported an increase, the difference between scores was 49m. In the combined MT intervention group at 16 weeks, the emphysema and chronic bronchitis groups showed an increase in distance where the RCT reported a decrease.

5.6 Summary

This chapter compares the results of an RCT designed to investigate the effects of MT and PR in COPD with a phenotype analysis of the same results. The results of t-tests performed on these results at baseline, 16 and 24 weeks for FEV_1, FVC and 6MWT are described along with the results of an analysis comparing the phenotype performance with the results of the RCT. In summary, chronic bronchitis and mixed asthma-COPD phenotypes responded better to both MT and PR than emphysema. Mixed asthma-COPD also differed from the results of the RCT for 6MWT showing a greater improvement in the PR only group.

Table 18: Mean differences between baseline (week 0) and week 16, and week 24 for 6MWT. Each group is presented with the RCT data and phenotype data. Shaded columns represent the difference between the phenotype score compared to the RCT score. Data for frequent exacerbation phenotype does not appear as there were limited or no data present

6MWT Difference between phenotypes and RCT results for outcome measures. Scores compared to baseline at 16 and 24 weeks																								
	PR only							ST+PR						ST+SM+PR					Combined MT Intervention					
	RCT	CB	Diff	MA	Diff	E	Diff	RCT	CB	**Diff**	MA	E	**Diff**	RCT	CB	MA	**Diff**	E	RCT	CB	**Diff**	MA	**Diff**	E	**Diff**
16	22.7	22.5	**0.02**	68.2	**45.5**	0.67	**22.03**	5.8	-2.5	**8.3**	NA	4	**1.8**	51.7	NA	49.75	**0.25**	NA	-8	13.33	**21.33**	-11	**3**	4	**12**
24	12.1	15.5	**3.4**	50.8	**38.7**	-6.83	**18.93**	-16.4	-7.5	**8.9**	NA	-56.5	**40.1**	35	NA	-14	**49**	NA	-23	-7.5	**15.5**	-14	**9**	-56.5	**33.5**

E: Emphysema; CB: Chronic bronchitis; M: Mixed asthma-COPD; FE: Frequent exacerbations; Phen: Phenotype; PR: Pulmonary Rehabilitation; ST+PR: Soft tissue and PR; ST+SM+PR: ST and Spinal Manipulation and PR; Diff: Difference; All units in metres

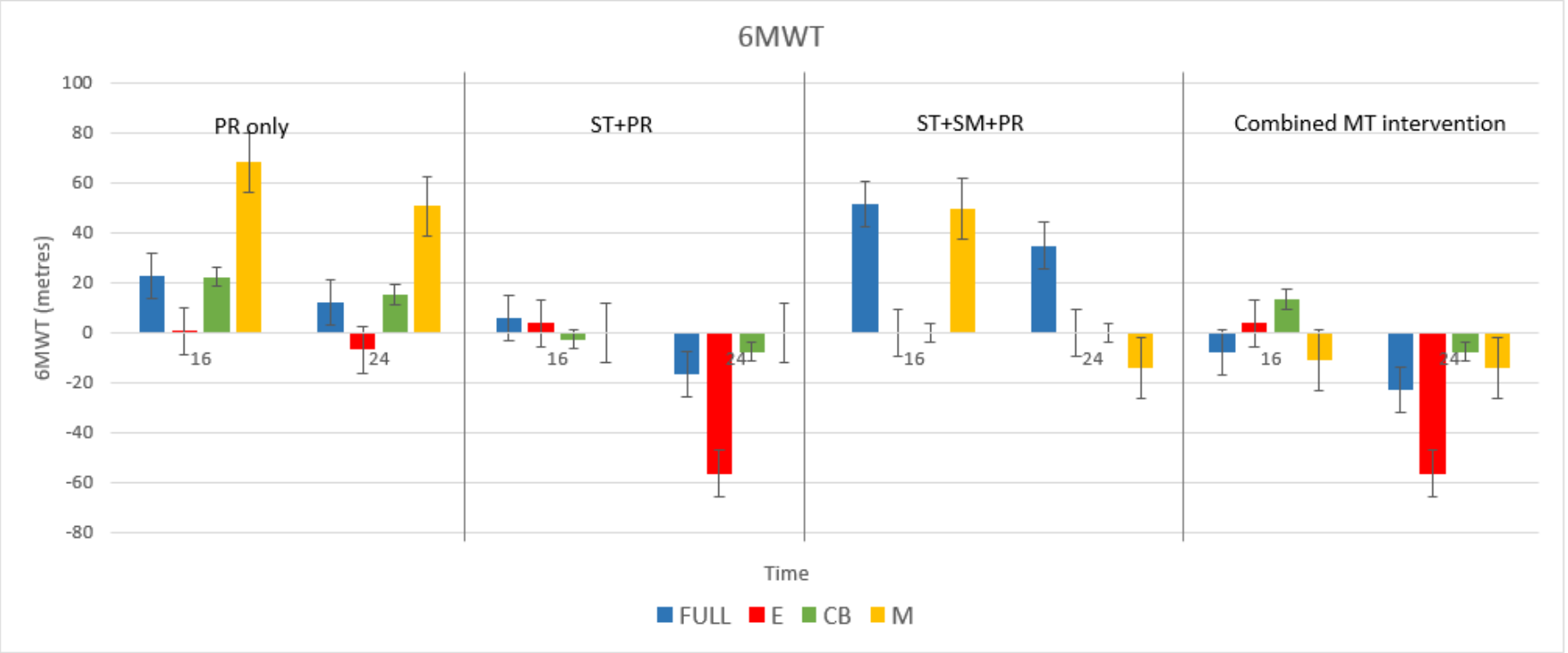

Figure 9: Comparison of mean differences of the RCT data and by each phenotype of each group, includes the mean differences of week 0-16 and week 0-24 for 6MWT.

Chapter Six

Discussion and Conclusion

6.1 Introduction

This chapter explores the results of a phenotype analysis on data from an RCT designed to investigate the effect of including MT in a PR program for COPD to answer the research questions iii, iv and v. The discussion of the results begins with a summary of the key findings followed by the possible mechanism of action of MT and PR in COPD. The process of categorising participants into phenotypes and the trend analyses of the performance of the COPD phenotypes are evaluated and compared to the current literature in the field.

The research hypothesis is then examined and evaluated in light of these results. The generalisability of the results are discussed along with limitations of the study. Recommendations for future research, and the importance and implications of this study concludes the chapter.

6.2 Discussion of Results

6.2.1 Summary of key findings

In the phenotype analysis there was a difference in FVC between chronic bronchitis and emphysema in the combined MT intervention group at 24 weeks. For the 6MWT the mixed asthma-COPD phenotype was different to the RCT results in the PR only group at 16 weeks.

The phenotype analysis showed that the emphysema phenotype displayed similar trends to the RCT results, but with generally lower scores for FEV_1, FVC and 6MWT. Results for the chronic bronchitis and mixed asthma-COPD groups were similar to the RCT data across all intervention groups for each of the outcome measures. Although both

groups responded better than emphysema, the response was different for each. While chronic bronchitis reported an improvement in both lung function and 6MWT, mixed asthma-COPD reported greater improvements for these, particularly in the 6MWT.

6.2.2 Gender and BMI

Historically, the prevalence of COPD is higher in men than women. This is partially due to exposure to noxious inhalants through occupation and smoking rates in men, particularly in the developed world (70). However, in Australia, the number of women diagnosed with COPD has been increasing (71). This may be due to an increase in smoking among women, but also the introduction of women to previously male dominated occupations. While it is clear that both men and women can develop COPD, the gender distinction is less clear now that both are exposed to similar levels of risk factors. Notwithstanding, the pathophysiological process of COPD may be different between sexes. The literature shows that some effects of noxious inhalants on the lung may be gene and/or hormone mediated (70, 72). A matched case series on gender differences in reporting the outcomes of the BODE index, found that men have a higher impact on the BODE score through FEV_1 and 6MWT, while women have a higher impact through mMRC (dyspnoea score) and BMI (73). The authors concluded that if diagnosis and treatment for COPD relied heavily on FEV_1 levels then the burden of disease in women may be underestimated. Cohen *et al* showed that while there were morphological differences in the airways between women and men, there was no difference between gender for spirometry values and airway hyper-responsiveness. Interestingly their study revealed that men may experience symptoms due to the structure and change in airway dimensions such as air trapping, while women were more likely to have airway inflammation that caused airway obstruction (74). Aryel *et al* reported higher levels of airway hyper-responsiveness, a common sign

of asthma, in women (70). Other research reports that more women are diagnosed with asthma by their physician, are less likely to receive a preliminary diagnosis of COPD, and therefore less likely to receive diagnostic tests such as spirometry, which represents a gender bias among physicians (75).

In COPD research, BMI is used to indicate nutritional status of the patient. It is included as part of the BODE index and is an independent predictor of mortality (11, 76). BMI has been found to be lower in the COPD population compared to non-COPD with BMI decreasing as COPD becomes more severe (77). Low BMI has been associated with the emphysema phenotype, while high BMI has been associated with chronic bronchitis (22). The results of the phenotype analysis are partially in line with this as participants with emphysema had a lower BMI than participants with chronic bronchitis. However, the mixed asthma-COPD phenotype had the highest BMI in this study.

6.2.3 Mechanism of action of MT and PR in COPD

Pulmonary Rehabilitation

Prior to the 1960s exercise was considered a risk for patients with COPD and they were advised to avoid activity that brought on dyspnoea (78). In 1963, Petty developed a rehabilitative exercise program that improved exercise tolerance (78). This led to the development of a multidimensional approach, called pulmonary rehabilitation that targeted smoking cessation, symptom management and exercise capacity. A minimum of 4 weeks participation is required before effective improvements in HRQoL, dyspnoea, fatigue, and exercise tolerance are achieved (52, 79). A recent systematic review advised that no further research is required to investigate the efficacy of PR, but that further research should be directed to improving and refining the program (79), as there is no clinically significant improvement in lung function, and the short term benefits (3 months) seem to wear off once PR is discontinued.

Manual Therapy

The term 'manual therapy' is used to describe a range of techniques including muscle stretching (80), massage (81), spinal manipulative therapy (SMT) (27, 63), osteopathic manipulative therapy (OMT) (28) and chest physiotherapy (82). Combining MT and other therapies, like acupuncture, to PR have been reported in the literature (53). Combination therapy appears to allow participants with COPD to exercise for longer and with more intensity, thereby enhancing the benefits of PR (83). Zanotti *et al* used OMT in conjunction with exercise and found that this group improved in the 6MWT by 72.5 ± 7.5 metres, compared with exercise only group that improved by 23.7 ±9.7 metres (29). The use of OMT and SMT with PR has not only shown an improvement in exercise capacity but also in lung function (FEV_1, FVC) (27, 29, 61, 62). These findings were reported in the systematic review in Chapter 3.

Mechanism of Action of MT

Spinal manipulative therapy (SMT) involves the application of a high velocity low amplitude (HVLA) force targeted at spinal joints and the surrounding tissues, such asjoint capsules, ligaments and muscles. This type of manipulation is used by osteopaths, chiropractors and manipulative physiotherapists, to increase joint range of motion, and decrease pain (55, 57, 58).

In COPD extra-pulmonary elements indirectly affect lung function and exercise capacity. These include skeletal muscle dysfunction and quadriceps muscle fatigue. In the case of skeletal muscle dysfunction, the mechanical and biochemical properties of respiratory muscles undergo change which affects the endurance and contractibility of the muscles (1, 84). As a consequence, movements in the joints of the chest wall become restricted and the chest wall loses flexibility. Coupled with hyperinflation the chest wall

becomes rigid and increases thoracic compliance which negatively affects breathing mechanics (85). . Over time, these changes become chronic as they adapt to increasing airflow limitation.

Changes also occur in the diaphragm. These include shortening of the muscle with a decrease in the number of sarcomeres and a switch to Type 1 muscle fibres. This adaptive process alters the geometrical shape of the chest wall, especially when accompanied by hyperinflation (86, 87). The changing shape of the chest wall plus the increase in contractile demand on the inspiratory muscles has an effect on the intercostal and accessory respiratory muscles. These mechanical adaptive processes combined with the biochemical effects of COPD such as oxidative stress, hypoxia, low nutritional status, systemic inflammation, and activation of muscle enzymes increase the fatigue-ability of these muscles and are associated with an increase in dyspnoea and exercise limitation (86, 87). This combination leads to muscle failure where ventilatory demands cannot be met.

Engel and Velmupad proposed the concept of a 'reserve' respiratory function of the paraspinal and large extensor muscles of the trunk which contract to increase extension of the spine during laboured breathing (85). Extension of the spinal structures allows for recoil of the ribs during respiration. Where the diaphragm has shortened and the respiratory muscles function at non-optimal lengths, the 'reserve' structures also become shortened. Due to this, the muscles cannot accommodate ventilatory demands, especially when those demands increase during exercise (85). The suggestion is that HVLA manipulation improves the flexibility of the reserve structures and leads to an improvement in thoracic compliance, which then delays the onset of dyspnoea, allowing the person to exercise for longer (85). This may explain the improvements in exercise capacity and lung function in the RCT. Other authors have explained the improvement

in exercise capacity in functional terms as the result of a decrease in residual volume (29). Figure 10 shows the proposed mechanism of action of SMT in COPD.

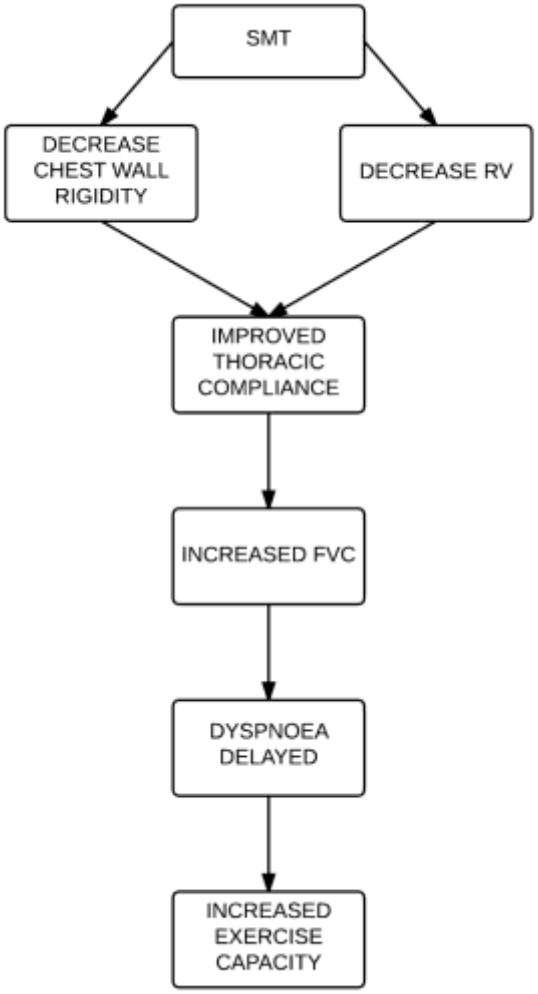

Figure 10. Proposed mechanism of action of SMT in COPD

6.2.4 Phenotype classification

A review of the literature revealed the lack of a standardised phenotype classification system that could be used in clinical trials or longitudinal studies. Where phenotypes were investigated, different systems were used to categorise them. De Oca *et al* discussed the difficulty of phenotype classification in a study that investigated the

prevalence of chronic bronchitis (the PLATINO study) (88). They used the definition 'the presence of phlegm on most days, at least 3 months per year for > 2 years', and also included 'cough and phlegm on most days, at least 3 months per year for > 2 years' in a separate analysis (88). Their results reported a smaller prevalence of chronic bronchitis compared to similar studies, a finding they explained may have been due to the definition used to identify the disease. Kim *et al* used a similar definition to detect participants with chronic bronchitis in the COPDgene study. This study reported a higher prevalence of chronic bronchitis but did not adjust for the presence of emphysema. It is clear that some participants had both chronic bronchitis and emphysema and this may have raised the prevalence of chronic bronchitis in their study (22). Izquierdo-Alonso *et al* included more descriptive and diagnostic criteria in their categorisation method when investigating the prevalence of emphysema, chronic bronchitis and COPD-asthma (21). This allowed for the classification of either chronic bronchitis or COPD-asthma without emphysema providing a clearer distinction between the phenotypes. In COPD, using disease definitions when performing a phenotype analysis is not specific enough to explore the underlying disease mechanism, characteristics or response to treatment. The classification algorithm described in Chapters 2 and 4 included history, presentation, diagnostic tests and medication history. The tally system also allowed for grouping participants who overlap phenotypes *i.e.* chronic bronchitis + emphysema.

In this study some of the participants in the chronic bronchitis groups were originally diagnosed with bronchiectasis in their medical records. As bronchiectasis and chronic bronchitis have similar presentations they both met the criteria to be classified as chronic bronchitis phenotype in this study. Despite the similarities between chronic bronchitis and bronchiectasis such as chronic cough, dyspnoea, mucous secretions

and chest discomfort, bronchiectasis has a more acute onset and is associated with severe airflow obstruction, especially in the elderly (89-91). Furthermore, bronchiectasis and COPD can co-exist, particularly in the moderate to severe stages. Martinez-Garcia *et al* performed High Resolution Computed Tomography (HRCT) on 92 participants with COPD and found that 57.6% had bronchiectasis (90). They also reported that bronchiectasis was associated with low FEV_1 scores (<50%), the presence of potentially pathogenic micro-organism (PPM) and hospital admission for acute exacerbation in the previous year (90). It is unclear whether bronchiectasis is a modulator of exacerbation frequency in COPD, as it certainly increases the likelihood of infection, or whether it should be recognised as a separate COPD phenotype.

6.2.5 Phenotype performance in RCT

Emphysema

Participants with emphysema performed poorer in response to MT and PR intervention. This phenotype followed the trend of the RCT but with lower scores for FEV_1, FVC and 6MWT. An exception to this was for FVC in the ST+PR intervention group where participants with emphysema showed an increase at 16 and 24 weeks.

The finding that participants with emphysema performed poorer for lung function and exercise capacity is supported by the literature, as the incidence of emphysema increases with severity of COPD (5, 21, 92). This finding could be explained by the relationship between lung structure and function. Diaz *et al* compared COPD participants with and without dyspnoea and found that dyspnoeic participants were more likely to have emphysema on CT scan. They also had expiratory flow limitation (EFL), dynamic hyperinflation (DH), the lowest values for DLCO/Alveolar volume, and the lowest values for arterial oxygen saturation (51). These findings support the concept

that structural damage of the lung parenchyma in emphysema is associated with poorer performance compared to other phenotypes.

The reported increase in FVC in the ST+PR group runs contrary to this concept and may be due to the direct effect of ST on the respiratory muscles and thoracic compliance (85).

Diaz and colleagues reported an association between lung parenchymal destruction and poor performance in the 6MWT on two occasions (51, 93). In their 2010 study, they reported that the degree of emphysema was independently correlated with the level of exercise capacity (93). As emphysema is associated with dyspnoea at rest and during exercise, and with dynamic hyperinflation, it is not surprising that participants with emphysema responded poorly to MT and PR. The loss of elastic recoil of the lungs together with airway collapse would perpetuate chest wall rigidity.

Unfortunately there were no participants with emphysema in the ST+SM+PR group of the RCT, so the response to SM cannot be investigated. The analysis of the emphysema phenotype to intervention in the RCT raises the following research questions: Does a decrease in chest wall rigidity account for changes in lung function following the application of MT? How do participants with emphysema respond to a combination of SMT and exercise? SMT has been shown to improve exercise capacity in participants with COPD, however, the benefits of including it as an intervention for patients with emphysema remain unclear.

Chronic bronchitis

The response of participants with chronic bronchitis closely matched the outcomes of the RCT. The exception was for FEV_1 in the PR only group at 16 weeks where chronic bronchitis showed an improvement compared to the other phenotypes and the RCT results. There was also a difference in FVC between emphysema and chronic bronchitis at 24 weeks in the combined MT intervention group, where chronic bronchitis participants showed an improvement in FVC compared to emphysema. This finding means that either chronic bronchitis responded better than emphysema to manual therapy with respect to lung function (FVC), or that chronic bronchitis and emphysema initially responded equally well (no difference at 16 weeks) with only chronic bronchitis maintaining the improvement. The number of chronic bronchitis participants in the ST+SM+PR group was too low to comment on the effect in this group.

There was also a difference for chronic bronchitis in the ST+PR and combined MT intervention groups for the 6MWT at 16 weeks. As there was no change in the PR only group, this indicates that participants with chronic bronchitis responded better to manual therapy than emphysema.

In contrast to emphysema, chronic bronchitis is a disease of the large airways involving goblet cell hyperplasia and mucous hyper-secretion. Mucous hyper-secretion has progressed from that associated with smoking, to purulent sputum that causes obstruction of the airways (94). Neutrophilia may be present along with an array of potentially pathogenic micro-organisms, with neutrophilia itself associated with the production of mucous (94, 95). Airflow obstruction is the result of the formation of mucous plugs that are difficult to clear, along with remodeling of the bronchial walls caused by chronic inflammation. These processes create an advantageous environment that harbours m i c r o -

organisms which can trigger an exacerbation. Longitudinal studies investigating the incidence of chronic bronchitis within a COPD population found that chronic bronchitis was associated with current smokers, dyspnoea, lower values of lung function, and exacerbations (22, 88, 96).

In chronic bronchitis the relationship between lung structure and function relates more to the large airways rather than lung parenchyma as seen in emphysema. The trend in this phenotype analysis showed that chronic bronchitis responds more favourably to MT and PR than emphysema. This may be due to the nature of the EFL which is more amenable to the effects of MT on the chest wall.

The current management of chronic bronchitis targets mucous clearing in the airways through broncho-pulmonary hygiene techniques that include chest percussion and postural drainage. While results of this approach are mixed, there have been reports of improvements in lung function following postural drainage and chest percussion (97, 98). A systematic review performed by Jones *et al* reported that although there was an improvement in pulmonary clearance of sputum there was little effect on pulmonary function. They concluded that the efficacy of these techniques was inconclusive (99). Interestingly, the MT techniques used in the RCT for this study were directed at CWR and not sputum clearance.

The results of this phenotype analysis raise the following research questions: Does MT and exercise improve sputum clearance in chronic bronchitis? Do participants with chronic bronchitis experience a different effect from MT and PR than participants with emphysema?

Mixed Asthma-COPD

The ST+SM+PR group in the RCT consisted mostly of participants with the mixed asthma-COPD phenotype, so it was not surprising that this phenotype followed the results of the RCT which showed an improvement in lung function and exercise capacity. Participants of this phenotype performed differently to chronic bronchitis and emphysema for FVC, FEV_1 and 6MWT.

Due to the predominance of this phenotype in the ST+SM+PR group, and the seemingly favourable response of the phenotype to PR, it is difficult to ascertain whether participants respond more favourably to MT only or the combination of MT and PR.

The finding that the mixed asthma-COPD phenotype responded differently to an intervention when compared to other phenotypes is not an unexpected finding in COPD research. The presence of broncho-reversibility in this phenotype is responsible for the enhanced response to inhaled corticosteroids compared to other phenotypes (44). This difference in treatment response has led some researchers to develop clinical guidelines that classify patients with asthma and COPD into a distinct phenotype (36, 100). Soler-Cataluna *et al*, in a consensus document on the COPD-asthma overlap, described diagnostic criteria for mixed asthma-COPD that included a positive bronchodilator test with an increase in FEV_1 > 15%, eosinophilia in the sputum and a history of asthma (36). These authors reported that neutrophilia in the airways was associated with a decrease in FEV_1 reversibility and that this presentation is common in asthmatics that also smoke (36). The nature of the airflow obstruction in mixed asthma-COPD is comparable to that of chronic bronchitis in that there are variable amounts of inflammation in the airways, the inflammation is chronic and it can vary biochemically in smokers. Airway remodeling also contributes to obstruction, as does incomplete growth of lungs in patients who have had

asthma from childhood (100). A population based study performed by Miravitlles *et al* examined physical activity of people with mixed asthma-COPD and found that these participants were more likely to be women, have a higher BMI, experience more dyspnoea, have lower daily activity levels and worse quality of life scores for the St Georges Respiratory Questionnaire (SGRQ) (101). The findings of this phenotype analysis support the view that the mixed asthma-COPD phenotype responds well to PR, which has been shown to improve daily activity levels and health related quality of life (HRQoL) (52, 53, 102, 103).

The findings for the mixed asthma-COPD phenotype raise the following research questions: What are the effects of PR and MT on HRQoL in mixed asthma-COPD? Does MT and PR have a greater effect on the mixed asthma-COPD compared to emphysema?

6.3 Do the results support the research hypothesis?

The hypothesis for this thesis was:

- Through analysis and comparison of the four COPD phenotypes in response to MT and PR, for the outcome measures: FEV_1, FVC, and 6MWT, additional descriptive information can be extrapolated and there is a difference in response to intervention between the phenotypes.

The descriptive comparison alone does not provide the statistical power to completely support the hypothesis. It is accepted that additional descriptive information can be attained from a phenotype analysis, and that this information allows for comment on the trends and differences between phenotypes in response to MT and PR.

6.4 Do the results achieve the aims of this research project?

The aim of this research project was:

- To improve our understanding of the heterogeneity of COPD and its relevance to clinical outcomes following MT and PR intervention

The classification system described in Chapter 2 established a process of classifying patients with COPD into phenotypes. It achieved this by using factors such as history, presentation, diagnostic tests and the medication history of a patient. Although the statistical power of the analysis was low, the research project improves our understanding of the heterogeneity of COPD and how this is reflected through phenotype categorisation.

6.5 Limitations

There are a number of limitations associated with this study. The types of analyses that could be run were restricted due to the small sample size of the RCT, the analyses used could not account for some variables and as such the conclusions of this thesis are moreover qualitative and hypothesis-generating. This also limited the generalisability of the results.

While phenotypes were assigned to participants, the results may have been affected by COPD severity which ranged from moderate to severe in the RCT.

There were unequal proportions of each phenotype in the intervention groups in the RCT. This restricted the comparison of phenotypes across groups. The combined MT intervention group was created to address this issue and allow for evaluation of phenotype responses to MT.

The statistical analyses used in the RCT and the retrospective analysis were different. Where the RCT used ANCOVA and ITT analyses, the phenotype analyses

were performed on raw data using the student's t-test. In addition to this the RCT reported missing data through an ITT analysis which may have also affected the phenotype analysis.

6.6 Generalisability

External validity of a study pertains to the ability of the study to be replicated and the results to cross over from the study population to the general population. The external validity of this study is low due to the small sample size of the RCT.

There was a bias in gender distribution in this study toward female participants. As the burden of COPD affects women and men differently, this finding may impact the generalisability of the results. The study sample was drawn from a clinical population referred to PR by a respiratory specialist and it is possible that the presence of comorbid conditions may have influenced referral by the physician. Therefore, the population in this research project may not fully reflect the general COPD population. Further studies with larger cohorts are required to retest the classification system and explore the results of a phenotype analysis.

6.7 Future directions

Following a discussion of the results of the phenotype analysis there are a number of recommendations for future research in the field of COPD phenotype analysis of clinical interventions. Firstly, as COPD phenotypes appear to respond differently to the same intervention, it is recommended that participants be randomised according to phenotype or other disease mechanisms like the presence of broncho-reversibility. Secondly, further research is required on the effect of SMT on emphysema and chronic bronchitis. And thirdly, measures of chest wall rigidity and sputum clearance be included in trials using MT intervention to ascertain the effect on these underlying disease factors.

As this study included a limited number of frequent exacerbation phenotype, it may be necessary to include this COPD phenotype in a separate analysis.

6.8 Conclusion

This research was conducted with the aim of furthering our understanding of COPD heterogeneity, and to explore the performance of COPD phenotypes in response to MT intervention. The thesis was designed to answer the following research questions;

iii. Does classifying patients with COPD according to phenotype change the outcomes of a randomised controlled trial?

iv. Does an analysis by phenotype of an RCT reveal trends in the data about the effect of MT and PR in COPD?

v. Does analysis by phenotype improve our understanding of the underlying disease mechanisms in COPD?

While the RCT results reported improvements in FVC following MT and PR intervention at 24 weeks, the phenotype analysis revealed that most of the participants in this group were classified in the mixed asthma-COPD phenotype. As the response to MT intervention was not uniform across phenotypes it is possible that the representation of phenotypes within the intervention groups affected the results of the RCT. Therefore, classifying patients by phenotypes has the potential to provide additional information and change the outcomes of an RCT.

The results of this phenotype analysis provide preliminary information on trends in a COPD population and should be repeated in a larger clinical trial before its full value can be adequately assessed.

In light of the results of this analysis it is hypothesised that the difference in response to intervention may be due to the relationship between lung structure

and function, which varies between phenotypes. This variation affects the magnitude of response to intervention and reflects the underlying disease mechanism of each phenotype.

While the impact of MT and PR on thoracic compliance and chest wall rigidity may be similar, the response to MT appears to differ between phenotypes. This supports the view that subgrouping COPD patients is important as these subgroups respond differently to the same intervention. Phenotype analysis should therefore be included in future research to facilitate improvements in outcomes following intervention.

It is clear from this research that the current classification systems that stage the severity of COPD using a single measure do not adequately evaluate all factors of COPD. Classification of participants into phenotypes has demonstrated the heterogeneity of COPD and provided information to propose that phenotypes respond differently to MT and PR.

This study provides a preliminary phenotype analysis of participants in an RCT and provides information about how phenotypes of COPD respond to MT and PR. This study serves as a platform for future research and provides a phenotype classification algorithm for this purpose.

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Appendix

Appendix 1 Summary of articles used in chapter 2 titled Phenotypes in Chronic Obstructive Pulmonary Disease (COPD) and their application in clinical trials: a review of the literature

Summary of included articles							
Author/Date	Title	Study Design	Selection Bias	Performance Bias	Attrition Bias	Detection Bias	Reporting Bias
Garcia-aymerich et al, 2009	Phenotypic heterogeneity of COPD	Expert opinion/ review article	N/A	N/A	N/A	N/A	N/A
Cataluna et al, 2007	Prognostic factors of EPOC	Review article	N/A	N/A	N/A	N/A	N/A
Miravitlles et al, 2012	Clinical phenotypes of COPD: Identification, definition and implications for guidelines	Review article	N/A	N/A	N/A	N/A	N/A
Almagro et al, 2013	COPD. Are the times changing?	Review article	N/A	N/A	N/A	N/A	N/A
Burgel et al, 2010	Clinical COPD phenotypes: a novel approach using principal component and cluster analysis	Post hoc cluster analysis	Not present	N/A	Not present	Not present	Not present
Ong et al, 2005	A multidimensional grading system (BODE index) as predictor for hospitalisation for COPD	Retrospective cohort analysis	Not present	N/A	Not present	Not present	Not present
Sin et al, 2006	Mortality in COPD: role of comorbidities	Review article	N/A	N/A	N/A	N/A	N/A
Celli, 2010	Predictors of mortality in COPD	Review article	N/A	N/A	N/A	N/A	N/A
Celli et al, 2004	The body mass index, air flow obstruction, dyspnea and exercise capacity index in COPD	Longitudinal, observational cohort study	Not present	N/A	Not present	Not present	Not present

Paoletti et al, 2009	Explorative data analysis techniques and unsupervised clustering methods to support clinical assessment of COPD phenotypes	Observational, cluster analysis	Not present	N/A	Not present	Not present	Not present
Papaioannou et al, 2009	Global assessment of the COPD patient. Time to look beyond FEV1?	Review article	N/A	N/A	N/A	N/A	N/A
Burgel et al, 2012	Clinical COPD phenotypes identified by cluster analysis: validation with mortality	Longitudinal follow up	Not present	N/A	Present	N/A	Not present
Bourbeau et al, 2014	Phenotyping of COPD: challenges and next steps	Review article	N/A	N/A	N/A	N/A	N/A
Noujiem et al, 2013	COPD updates: what's new in pathophysiology and management?	Review article	N/A	N/A	N/A	N/A	N/A
Carolan et al, 2013	Clinical phenotypes of COPD and asthma: recent advances	Review article	N/A	N/A	N/A	N/A	N/A
Izquierdo-alonso et al, 2013	Prevalence and characteristics of three clinical phenotypes of COPD	Cross sectional, observational	Not present	N/A	Not present	Not present	Not present
Kim et al, 2011	The chronic bronchitic phenotype of COPD; An analysis of the COPDGene study	Cross sectional	Not present	N/A	Not present	Not present	Unclear
Lacoste et al, 1993	Eosinophilic and neutrophilic inflammation in asthma, chronic bronchitis and COPD	Cross sectional	Unclear	N/A	Not present	Not present	Not present
Ferre et al, 2012	Chronic bronchitis in the general population: Influence of age, gender	Cross sectional	Not present	N/A	Not present	Not present	Not present

	and socioeconomic conditions						
Chibana et al, 2010	Prevalence of airflow limitation in patients diagnosed and treated for symptoms of chronic bronchitis by general practitioners in Tochigi Prefecture, Japan	Cross sectional	Not present	N/A	Not present	Not present	Unclear
Siva et al, 2007	Eosinophilic airway inflammation and exacerbations of COPD: a randomised controlled trial	Randomised controlled trial	Not present	Present	Not present	Not present	Not present
Dima et al, 2010	Pulmonary function tests, sputum induction and bronchial provocation tests: diagnostic tools in the challenge of distinguishing asthma and COPD phenotypes in clinical practice	Cross sectional	Not present	N/A	Unclear	Not present	Not present
Soler-cataluna et al, 2012	Consensus document on the overlap phenotype COPD-asthma in COPD	Expert opinion	N/A	N/A	N/A	N/A	N/A
Rennard et al, 2011	Reduction of exacerbations by the PDE4 inhibitor roflumilast-the importance of defining different subsets of patients with COPD	Post hoc pooled cluster analysis	Not present	Not present	Not present	Not present	Not present
Papaioannou et al, 2010	Systemic airway inflammation and the presence of emphysema in patients with COPD	Cross sectional	Unclear	N/A	Unclear	Not present	Not present

Burge and Wedzicha, 2003	COPD exacerbations: definitions and classifications	Review article	N/A	N/A	N/A	N/A	N/A
Agusti et al, 2010	Characterisation of COPD heterogeneity in the ECLIPSE cohort	Longitudinal cross sectional	Not present	N/A	Not present	Not present	Unclear
Pistolesi et al, 2008	Identification of a predominant COPD phenotype in clinical practice	Prospective cross sectional study	Not present	N/A	Not present	Not present	Not present
Garcia-Aymerich et al, 2011	Identification and prospective validation of clinically relevant COPD subtypes	Prospective analysis and cross sectional	Not present	N/A	Not present	Not present	Not present
Celli et al, 2008	Effect of pharmacotherapy of the rate of decline of lung function in COPD: results of the TORCH study	Post hoc analysis	Not present	Not present	Not present	Not present	Not present
Decramer et al, 2004	Clinical trial design considerations in assessing long-term functional impacts of tiotropium in COPD: the UPLIFT trial	Review article	N/A	N/A	N/A	N/A	N/A
Seemungal and Wedzicha, 2003	Management of exacerbations of COPD	Review article	N/A	N/A	N/A	N/A	N/A
Decramer et al, 2008	Targeting the COPD exacerbation	Review article	N/A	N/A	N/A	N/A	N/A
El Moussaoui, 2008	Short-course antibiotic treatment in acute exacerbations of chronic bronchitis and COPD: a meta-analysis of double-blind studies	Meta-analysis	N/A	N/A	N/A	N/A	N/A