THE RELEVANCE OF CHRONIC RESPIRATORY SYMPTOMS WITHOUT AIRFLOW OBSTRUCTION: HEALTH-RELATED CHARACTERISTICS AND IMPACT ON PATIENT PROGNOSIS

By

Dr Halima D Mohamed Buni

A thesis submitted to the University of Birmingham for the degree of DOCTOR OF PHILOSOPHY

Supervised by Professor Kar Keung Cheng, Dr Rachel Jordan and Dr Alexandra Enocson

Public Health, Epidemiology and Biostatistics
School of Health and Population Sciences
College of Medical and Dental Sciences
University of Birmingham
2016

Abstract

Individuals reporting chronic respiratory symptoms without airflow obstruction (AFO) were originally classified as "at risk" stage (GOLD Stage 0) of Chronic Obstructive Pulmonary Disease (COPD). However, this stage was removed due to lack of evidence regarding its progression to diagnosed COPD. There remain many such individuals in the population, including some already misdiagnosed with COPD despite not meeting required criteria.

This thesis aims to clarify the uncertainty around the relevance of "GOLD Stage 0". There are three systematic reviews examining the risk of developing COPD amongst GOLD Stage 0 patients, their prognosis and the prognostic factors. The independent effect of respiratory symptoms *versus* AFO on quality of life is examined using data from the Health Survey for England. Baseline data from the Birmingham COPD Cohort Study are used for two cross-sectional analyses, (1) comparing GOLD Stage 0 patients with those recently identified with COPD and (2) examining the characteristics of those "overdiagnosed" with COPD.

GOLD Stage 0 patients showed a similar pattern of poor health outcomes to those diagnosed with COPD. Overdiagnosis of COPD was common, particularly among GOLD Stage 0 patients. Obesity and restrictive disease were potential explanations for some overdiagnosed.

The presence of chronic respiratory symptoms has a negative impact on patients' health, regardless of the presence of diagnosed AFO.

Dedication

This thesis is dedicated to the soul of my lovely grandmother

MRS LILAHOM KHALIL ELGHAZAL

Who was one of the greatest inspirations for me to undertake this PhD.

She taught me how to have strength and to never give up.

I wish that she had seen its completion.

Acknowledgements

I am deeply grateful to my supervisors, Kar Keung Cheng, Rachel Jordan and Alexandra Enocson, for their invaluable support and guidance throughout the course of my PhD, as well as for their unconditional kindness and help during the difficult times that arose at the time of writing this thesis due to the situation in my home country of Libya. Without their encouragement my thesis would never have been completed.

I would also like to thank Raoul Reulen for his mentoring support and Peymane Adab and Jen Marsh for their outstanding expert advice on my work. I also want to thank Nicola Adderley for her hard work as a second reviewer of the three systematic reviews in this thesis, Susan Bayliss and Nancy Graham for their advice on the search strategy for the reviews, and Simon Stevens for his help in ordering many articles for the reviews.

I also want to thank all the staff at the Birmingham Lung Improvement Studies Programme (BLISS), especially Andy Dickens and all of the research assistants and administrative staff for their exceptional support. I am also very grateful to the patients who participated in the cohort study.

I would like to thank all of the administrative staff at the School of Health and Population Sciences, particularly Catherine Taylor and the IT service staff, for their help and support.

I am also very grateful to the Libyan Ministry of Higher Education for funding my PhD and to all of the staff at the Libyan Cultural Attaché in London, especially my supervisor Ismael Kamoka for his invaluable administrative assistance.

My deepest gratitude goes to my family; this thesis would not have been completed without the unconditional support and patience of my dear husband Abdulghani Abuaisha, the aspiration of my lovely children Kanzie and Mohamed, my wonderful mother Oumalhana Mansour who has always been behind my success in life, my lovely father Dau Buni who

assists me throughout hard times - he made my dreams of higher education come true, my sisters Eman and Sarah, and my brothers Alhareth and Hatem for their love and support. Last but not the least; I am very thankful to all of my friends here in the UK, back home and everywhere else for their support.

Author's contribution to data collection

The data for the Birmingham COPD cohort study were collected by a trained research team managed by Dr Alexandra Enocson, of which I was a member. I contributed to patient clinical assessments at GP practices, as well as data entry of baseline and follow-up questionnaires and Case report forms and a laboratory work at the QE hospital (September 2013 to June 2014).

This also required additional training courses including Good Clinical Practice (GCP) training, ARTP-level spirometry training, phlebotomy training at the QE hospital, training on CASCOT software for occupational coding and training on data entry.

Table of Contents

1 INTRODUCTION 1
1.1 Chronic Obstructive Pulmonary Disease (COPD) 1
1.2 The Burden of COPD in the UK 1
1.2.1 Epidemiological Burden 1
1.2.2 Economic Burden 2
1.3 Risk Factors 3
1.4 Symptoms of COPD 4
1.4.1 Cough and sputum 4
1.4.2 Dyspnoea 4
1.4.3 Wheeze 4
1.4.4 Systematic symptoms 5
1.5 Diagnosis of COPD 5
1.6 Management of COPD 6
1.6.1 Smoking cessation 6
1.6.2 Pharmacotherapy 6
1.6.3 Pulmonary rehabilitation 6
1.6.4 Immunisation 7
1.6.5 Self-management and rescue packs 7
1.7 Overdiagnosis of COPD 8
1.7.1 Primary care practitioners related factors 9
1.7.2 COPD and asthma overlap 10
1.7.3 Patient related factors 11
1.8 Chronic respiratory symptoms but normal lung function: COPD GOLD Stage 0 11
1.8.1 COPD GOLD Stage 0: areas of controversy 13
1.8.2 Natural history of COPD GOLD Stage 0 13
1.9 Rationale for studying GOLD Stage 0 14
1.9.1 Insufficient evidence 14
1.9.2 Uncertainty about the predictive value of GOLD Stage 0 on the risk of developing COPD 15
1.9.3 Uncertainty about the prognostic value of GOLD Stage 0 on longer term outcomes 15

1.10 Thesis aim and objectives 15
1.10.1 Aim 15
1.10.2 Objectives 16
1.11 Definition of GOLD Stage 0 16
1.12 Thesis Structure 17
1.13 Contribution to research and clinical practice 17
2 GOLD STAGE 0 AND THE RISK OF DEVELOPING COPD: A SYSTEMATIC REVIEW 18
2.1 Abstract 18
2.2 Introduction 19
2.3 Methods 19
2.3.1 Protocol and registration 19
2.3.2 Inclusion criteria 20
2.3.3 Search strategy 21
2.3.4 Study selection 22
2.3.5 Data extraction 22
2.3.6 Methodological quality assessment 22
2.3.7 Data synthesis process 22
2.4 Results 23
2.4.1 Study selection 23
2.4.2 The study characteristics 25
2.4.3 Methodological quality of the included studies 34
2.4.4 Main findings 37
2.5 Discussion 41
2.5.1 Summary of evidence 41
2.5.2 Limitations 41
2.5.3 Implication for research and clinical practise 42
2.5.4 Conclusion 42
3 PROGNOSIS AND PROGNOSTIC FACTORS OF GOLD STAGE 0: SYSTEMATIC REVIEWS 43
3.1 Abstract 43
3.2 Introduction 44
3.3 Methods 45

3.3.1 Inclusion criteria 46
3.4 Results 47
3.4.1 Study selection 47
3.5 Review (2): What is the prognosis of patients with chronic respiratory symptoms but normal lung function compared to confirmed COPD patients? 49
3.5.1 Results 49
3.5.2 Discussion 64
3.6 Review (3): What are the main factors that can affect the prognosis of patients with chronic respiratory symptoms but normal lung function? 67
3.6.1 Results 67
3.6.2 Discussion 72
4 CHRONIC RESPIRATORY SYMPTOMS *VERSUS* AIRFLOW OBSTRUCTION: THE EFFECT ON PATIENT'S QUALITY OF LIFE—THE HEALTH SURVEY FOR ENGLAND (2010) 75
4.1 Abstract 75
4.2 Introduction 76
4.3 Methods 77
4.3.1 Study design 77
4.3.2 Study setting 77
4.3.3 Study Population 78
4.3.4 Definitions 79
4.3.5 Statistical Analysis 81
4.4 Results 82
4.4.1 Study sample 82
4.4.2 Description of patient characteristics 83
4.4.3 The independent effect of symptoms and airflow obstruction on HRQoL 87
4.4.4 The effect of individual symptoms on self-assessed general health 90
4.5 Discussion 91
4.5.1 Main Findings 91
4.5.2 Comparison with the Existing Evidence 92
4.5.3 Strengths and Limitations 92
4.5.4 Implications for research and clinical practise 93
4.5.5 Conclusion 93

4.6 Acknowledgments 94
4.7 Supplementary Tables 95
5 COPD GOLD STAGE 0 AND NEWLY DIAGNOSED COPD PATIENTS: HEALTH-RELATED CHARACTERISTICS AND OUTCOMES−BIRMINGHAM COPD COHORT STUDY 97
5.1 Abstract 97
5.2 Introduction 98
5.3 Methods 99
5.3.1 Study Design 99
5.3.2 Setting 99
5.3.3 Patient included in this analysis 100
5.3.4 Measurements and data collection 100
5.3.5 Study Variable Definitions 101
5.3.6 Diagnostic criteria 104
5.3.7 Statistical analysis 105
5.4 Results 105
5.4.1 Patients recruitment 105
5.4.2 Characteristics of participants and non-participants 107
5.4.3 Comparison of the health-related characteristics between GOLD Stage 0 patients and newly diagnosed COPD patients 107
5.4.4 Comparison of the health outcome measures between GOLD Stage 0 patients and newly diagnosed COPD patients 110
5.5 Discussion 112
5.5.1 Main findings 112
5.5.2 Comparison with the existing evidence 113
5.5.3 Strengths and Limitations 114
5.5.4 Implications for research and clinical practise 115
5.5.5 Conclusion 115
5.6 Supplementary Table 116
6 COPD OVERDIAGNOSIS IN THE UK: THE BIRMINGHAM COPD COHORT STUDY 117
6.1 Abstract 117
6.2 Introduction 118
6.3 Methods and Materials 122

6.3.1 Study design/setting 122
6.3.2 Measurements and data collection 122
6.3.3 Study variables definitions 123
6.3.4 Diagnostic criteria 123
6.3.5 Statistical analyses 124
6.4 Results 125
6.4.1 Patient recruitment 125
6.4.2 Characteristics of participants and non-participants 126
6.4.3 Magnitude of COPD overdiagnosis 127
6.4.4 Comparing the clinical and lung function related characteristics of non-COPD and confirmed COPD groups using the current NICE criteria 129
6.4.5 Comparing the health outcome measures between non-COPD and confirmed COPD using the current NICE definition 133
6.4.6 The implications of applying the LLN criteria 134
6.5 Discussion 137
6.5.1 Main findings and comparison with the existing evidence 137
6.5.2 Strengths and Limitations 140
6.5.3 Implications for research and clinical practise 141
6.5.4 Conclusion 141
7 DISCUSSION AND CONCLUSION 143
7.1 Background and context 143
7.2 Key findings 143
7.2.1 Risk of developing COPD among individuals with GOLD Stage 0 symptoms 143
7.2.2 Prognosis of individuals with GOLD Stage 0 symptoms 144
7.2.3 Health related characteristics of GOLD Stage 0 patients 145
7.2.4 COPD overdiagnosis in the UK primary care setting 146
7.3 Strengths and limitations 147
7.4 Implication for research 148
7.5 Implication for clinical practice 148
7.6 Conclusion 149
8 APPENDIX A: A SYSTEMATIC REVIEW PROTOCOL 150
8.1 Step 1: the Review's Topic 150

8.1.1 Background and Rationale for the Topic 150
8.1.2 Rationale for a systematic review 153
8.1.3 Review aims and Questions 153
8.1.4 Selection Criteria for Considering Studies for this Review 154
8.2 Step 2: Search strategy and identifying relevant literature 156
8.2.1 Selection of Relevant Databases to Search 156
8.2.1.4 Identifying Relevant Studies 160
8.3 Step 3: Data extraction and management 164
8.4 Step 4: Methodological Quality Assessment 164
8.5 Step 5: Data synthesis and analysis 164
8.6 Step 6: Protocol Registration and Plan of Dissemination 165
9 APPENDIX B: LIST OF THE SEARCH TERMS USED IN THE SYSTEMATIC REVIEWS 166
10 APPENDIX C: STRENGTHENING THE REPORTING OF OBSERVATIONAL STUDIES IN EPIDEMIOLOGY CHECKLIST (STROBE) 167
11 APPENDIX D: QUALITY IN PROGNOSIS STUDIES (QUIPS) TOOL 169
12 APPENDIX E: NEWCASTLE-OTTAWA SCALE 171
13 APPENDIX F: METHODOLOGICAL QUALITY OF INDIVIDUAL COHORT STUDIES INCLUDED IN THE SYSTEMATIC REVIEWS 173
14 APPENDIX G: COPD ASSESSMENT TEST (CAT) 179
15 APPENDIX H: EQ-5D (5 LEVEL VERSION) 180
16 APPENDIX I: COPD OVERDIAGNOSIS CONFERENCE ABSTRACT (ORAL PRESENTATION AT SAPC, POD AND THE ERS CONFERENCES) 181
17 List of References 183

List of Tables

Chapter 1

Table 1: MRC Dyspnoea Scale ……....4

Table 2: Other conditions that may present with similar symptoms as COPD ……..…….....9

Table 3: Clinical features differentiating COPD and asthma…….11

Table 4: 2001 GOLD classification of COPD Severity……..12

Chapter 2

Table 5: PECOS components of the review's question……..21

Table 6: Study characteristics and the main findings ……...…….27

Table 7: Risk of bias assessment for the included cross-sectional studies…….....36

Chapter 3

Table 8: PECOS components for reviews 2 and 3……...….....47

Table 9: Study characteristics and the main findings (Review 2)……..….....51

Table 10: Risk of bias assessment for the included cross-sectional studies in review 2……...59

Table 11: Study characteristics and the main findings (Review 3)…….....68

Chapter 4

Table 12: Univariable socio-demographics and clinical characteristics by groups of "Exposure" compared to the normal population……..…….....85

Table 13: Self-reported respiratory symptoms by lung function…….…….....86

Table 14: Univariable measures of HRQoL by groups of "Exposure" compared to the normal population…….....87

Table 15: The adjusted difference in general health between "Exposure" groups compared to the normal population …….…….88

Table 16: The adjusted difference in psychosocial wellbeing between "Exposure" groups compared to the normal population……..……...89

Table 17: The adjusted difference in the EQ-5D domains between "Exposure" groups compared to the normal population …...…….…….....90

Table 18: The adjusted individual effect of respiratory symptoms on general health……..……..91

Table 19: Summary of the available evidence on the chapter's topic……...……..…...95

Chapter 5

Table 20: Spirometry contraindications ……..……..……....105

Table 21: Univariable characteristics of participants and non- participants…….....107

Table 22: The adjusted socio-demographic characteristics of the study population……108

Table 23: The adjusted difference in respiratory symptoms, BMI and comorbidities by patients group…….....109

Table 24: Univariable post-bronchodilator reversibility by patients group……..110

Table 25: The adjusted difference in HRQoL by patients group…….....110

Table 26: The adjusted difference in self-reported exacerbation events by patients group…….....111

Table 27: The adjusted difference in self-reported healthcare utilisation by patients group…….....112

Table 28: The adjusted difference in exercise capacity by patients group……..…112

Table 29: Summary of the available evidence on the chapter's topic…….....116

Chapter 6

Table 30: Summary of available evidence on COPD overdiagnosis……..…….…….....120

Table 31: Univariable characteristics of participants and non-participants……..127

Table 32: Prescribed respiratory medications by lung function group using the current NICE criteria…….....128

Table 33: The adjusted socio-demographic characteristics by lung function group using the current NICE criteria……..…….....130

Table 34: The adjusted difference in respiratory symptoms, BMI and comorbidities by lung function group using the current NICE criteria.....131

Table 35: Univariable spirometry findings by lung function group using the current NICE criteria…….....132

Table 36: Adjusted clinical factors associated with COPD overdiagnosis based on the current NICE criteria …..…..133

Table 37: The adjusted difference in health outcome measures by lung function group using the current NICE criteria….....134

Table 38: The adjusted difference in clinical and spirometry-related characteristics by lung function group using the LLN criteria…….…….....135

Appendix A

Table 39: 2001 GOLD classification of COPD severity…….....151

Table 40: PECOS components of the review questions……..…….....156

Table 41: Questions components and search terms……..…….....159

Table 42: Piloting some studies against the selection criteria……..…….....161

Appendix B

Table 43: Search terms for systematic reviews 1, 2 and 3……....166

Appendix F

Table 44: Risk of bias assessment for the included cohort studies (systematic review 1)……...173

Table 45: Risk of bias assessment for the included cohort studies (systematic review 2)…..……..175

Table 46: Risk of bias assessment for the included cohort studies (systematic review 3)…….....177

List of Figures

Chapter 2

Figure 1: PRISMA flow diagram of study selection……..24

Figure 2: Overall risk of bias of the included cohort studies…….35

Chapter 3

Figure 3: PRISMA flow diagram of study selection……..48

Figure 4: Risk of bias for overall included cohort studies (Review 2)…….....58

Figure 5: Risk of bias for overall included cohort studies (Review 3)…….....70

Chapter 4

Figure 6: Flow diagram of patient selection procedure…….…….....83

Chapter 5

Figure 7: Flow diagram of patient recruitment procedure …….…….....106

Chapter 6

Figure 8: Flow diagram of patient recruitment procedure ……..…....126

Figure 9: Rate of COPD overdiagnosis based on three different definitions…….....128

List of Abbreviations

COPD	Chronic obstructive pulmonary disease
AFO	Airflow obstruction
GOLD	Global Initiative of Obstructive Lung Disease
QOF	Quality Outcome Framework
CB	Chronic bronchitis
MRC	Medical Research Council
NICE	National Institute for Health and Care Excellence
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
ERS	European Respiratory Society
ATS	American Thoracic Society
LLN	Lower Limit of Normal
SABA	Short-acting beta agonists
SAMA	Short-acting antimuscarinic antagonists
LABA	Long-acting beta agonists
LAMA	Long-acting antimuscarinic antagonists
ICS	Inhaled corticosteroids
GPs	General Practioners
PFT	Pulmonary function test
CMH	Chronic mucous hypersecretion
HRQoL	Health related quality of life
HSE	Health Survey for England
BD	Bronchodilator
HR	Hazard ratio
PF	Prognostic factor
BMI	Body mass index
GHQ12	12-item general health questionnaire

WHO	World Health Organisation
CVDs	Cardiovascular diseases
VAS	Visual analogue scale
SE	Standard error
ORs	Odds ratios
CI	Confidence interval
CAT	COPD assessment test
A & E	Accidents and emergency department
GLI	Global Lung Initiative
SD	Standard deviation
IQR	Interquartile range

1 INTRODUCTION

1.1 Chronic Obstructive Pulmonary Disease (COPD)

COPD is a complex heterogeneous disease (1, 2) consisting of a number of chronic respiratory disorders that progress gradually into airflow obstruction (3, 4). It is usually associated with chronic respiratory symptoms such as cough, sputum production, dyspnoea, and wheeze (5). The most widely used definition of COPD is that of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) committee, which defines COPD as *'a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients'*(6, 7).

1.2 The Burden of COPD in the UK

COPD is a major public health concern (8) and an important cause of morbidity and mortality worldwide (9-11). As a result of the demographic, environmental and socioeconomic changes over the last decades, the prevalence of COPD is markedly increasing (12), with the global burden of COPD predicted to escalate in the coming decades (12, 13). However in its early stages, COPD usually remains unrecognised or misdiagnosed (12, 14).

1.2.1 Epidemiological Burden

1.2.1.1 Prevalence

According to the Quality Outcome Framework (QOF) statistical bulletin, the prevalence of diagnosed COPD in 2012/2013 was 1.74% of the UK population and increased to 1.78% in

2013/2014 with an estimation of approximately 1.5 million people diagnosed with COPD (15). However, the estimated number of people actually affected by COPD in the UK is three million (16), with about half remaining undiagnosed (7).

1.2.1.2 Mortality

Ascertainment of the COPD mortality rate is challenging; many patients with COPD die because of COPD-related causes, with their deaths certified as caused by these complications rather than COPD itself (7, 13). In 1990, the Global Burden of Disease Study ranked COPD as the sixth cause of death and it is predicted to become the third by the year 2020 (6, 13). In the UK, around 30,000 deaths each year are attributed to COPD (3, 7, 16).

1.2.1.3 Morbidity

Morbidity measures commonly include physician visits, emergency department visits and hospital admissions (6); however, COPD coexists with other tobacco-smoking-related diseases, such as cardiovascular diseases and lung cancer, with these comorbidities making COPD morbidity measures much more complicated (7). In the UK, there are approximately 1.4 million COPD consultations within general practice each year—a figure four times greater than the number of angina consultations (7).

1.2.2 Economic Burden

COPD is a costly disease (7). Its direct cost to the UK healthcare system has been estimated at between £810 million and £930 million each year (7) with an annual average of £2,108 per patient (16). Moreover, the indirect costs of COPD are considerable due to its influence on annual productivity, which has been estimated at 24 million lost working days per year (7, 17, 18), with a cost of more than £3.8 billion to employers and the UK economy (17).

1.3 Risk Factors

Whilst cigarette smoking is known to be the main risk factor for COPD (6, 19), there are other factors which must be also considered (20), as epidemiological studies have consistently shown the development of COPD amongst non-smokers (6, 21). Other risk factors include occupational exposure (22), outdoor pollution (23), indoor pollution such as exposure to passive smoking (24) and biomass smoke (25), and some rare genetic syndromes such as alpha-1 antitrypsin deficiency (21).

The presence of asthma and bronchial hypersensitivity are also found to be risk factors for COPD (21), although the evidence is not definitive (6). According to the "Dutch hypothesis", bronchial hyper responsiveness, a distinctive feature of asthma, leads to the development of COPD (26). Results from previous studies have shown an overlap of up to 30% between patients who have a clinical diagnosis of COPD and asthma (26). Furthermore, airways hyper responsiveness has been found to be an independent risk factor for the accelerated decline in FEV_1 (27) particularly among smokers (28). However, this hypothesis remains controversial due to lack of consistent supporting evidence (28, 29).

Moreover, COPD results from a complex gene-environment interaction (6). Importantly, gender could affect a person's smoking behaviour or exposure to occupational or environmental factors (6, 19), and low socioeconomic status is associated with many factors that increase the risk of developing COPD (26) such as crowding, poor nutritional status and higher smoking rates (26). Low socioeconomic status might also influence a child's birth weight, which could, in turn, affect lung growth and predisposition to develop COPD (30, 31). Furthermore, aging has the potential to result in a longer lifetime exposure to COPD risk factors (6).

1.4 Symptoms of COPD

1.4.1 Cough and sputum

Cough is usually the first symptom of COPD (18), starting intermittently before progressing to become persistent, with variable sputum production (3). The presence of chronic cough with regular sputum production for three months or more over two consecutive years has been the epidemiological definition of chronic bronchitis (CB) (18). However, this pattern of sputum production is not always seen in COPD, which usually has variable patterns (7, 18)

1.4.2 Dyspnoea

Shortness of breath is the most disabling symptom of COPD (3). It is usually the primary symptom that drives patients to seek medical advice (3, 18). The impact of breathlessness on patients is usually graded using the Medical Research Council (MRC) dyspnoea scale (Table 1). This scale can be used to assist with treatment plans and also as a prognostic indicator (3).

Table 1: MRC Dyspnoea Scale (3)

Grade	Degree of breathlessness related to activities
1	Not troubled by breathlessness except on strenuous exercise
2	Short of breath when walking or hurrying up a slight hill
3	Walks slower than contemporaries on level ground because of breathlessness, or has to stop for breath when walking at own pace
4	Stops for breath after walking about 100 metres or after a few minutes on level ground
5	Too breathless to leave the house, or breathless when dressing or undressing

1.4.3 Wheeze

Chest wheezing and tightness are non-specific and variable symptoms in COPD (6); the presence of these symptoms does not confirm the diagnosis of COPD and their absence does not exclude it (18).

1.4.4 Systematic symptoms

In many patients, COPD may present with systematic manifestations (32). These may include cardiovascular compromise, malnutrition and weight loss, muscle wasting, anaemia, osteoporosis, and clinical depression (33-35).

1.5 Diagnosis of COPD

The diagnosis of COPD in the UK primary care setting follows the guidelines of the National Institute for Health and Care Excellence (NICE) (16). NICE recommends that a clinical diagnosis of COPD should be suspected in patients over 35-40 years of age, complaining of chronic cough with sputum and dyspnoea (7) and with a positive clinical history of exposure to COPD risk factors (7). However, spirometry is required to confirm the diagnosis (7). Currently, there is no international consensus on the best spirometric criteria for a clinical diagnosis of COPD (36); the presence of post-bronchodilator ratio of forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) of <0.70 (FEV_1/FVC<0.70) confirms COPD diagnosis according to the GOLD committee/current NICE guidelines (6, 7). Whilst a former criteria in the UK is that of the British Thoracic Society/NICE (2004) which requires a combination of the FEV_1/FVC fixed ratio of less than 0.7 with a low FEV_1 value of less than 80% of predicted (equivalent to COPD GOLD Stage 2) (36). However, the use of fixed ratio is recognised as potentially overestimating the prevalence of COPD amongst the elderly (37), because it does not account for normal age-related airflow limitation (38, 39) and may overestimate the effect of age by 50% (40). Therefore, the European Respiratory Society (ERS) and the American Thoracic Society (ATS) have adopted the Lower Limit of Normal (LLN) criteria to diagnose COPD (41), which categorises lung values below the 5^{th} percentile of the healthy non-smoking reference population as ‘abnormal’ following adjustment for age, sex, height and ethnicity (41, 42).

1.6 Management of COPD

NICE guidelines have developed comprehensive management plans for patients with COPD (7). The following are some of the main components for managing stable COPD:

1.6.1 Smoking cessation

Smoking cessation is the most effective intervention in patients diagnosed with COPD (7). Evidence has shown that, stopping smoking in COPD patients slows the rate of FEV_1 decline (43, 44) and improves patients' symptoms (45), leading to slower disease progression rate and better survival (7). In the UK, smoking cessation services are widely accessible and have shown effective improvement in short term smoking cessation rates (53% in four weeks and 15% in one year) (46).

1.6.2 Pharmacotherapy

COPD is usually treated with inhaled medications (7) including, short-acting beta agonists (SABA) and short-acting antimuscarinic antagonists (SAMA) for treating breathlessness and exercise restriction (7). Long-acting beta agonists (LABA) and long-acting antimuscarinic antagonists (LAMA) for treating severe stable COPD (16). Whilst inhaled corticosteroids (ICS) and combination inhalers are usually recommended by NICE for treating exacerbations or persistent breathlessness (7). Furthermore, COPD patients with exacerbations may also be prescribed oral antibiotics and corticosteroids (7). Long term oxygen therapy is recommended by NICE for patients with severe COPD as it has been shown to improve their survival (7, 47).

1.6.3 Pulmonary rehabilitation

Pulmonary rehabilitation is *'a multidisciplinary programme of care for patients with chronic respiratory impairment that is individually tailored and designed to optimise each patient's*

physical and social performance and autonomy' (7). It becomes an increasingly effective management option of patients with moderate to severe COPD (usually with MRC dyspnoea scale grade three or higher) (7). Rehabilitation aims mainly to help patients to better cope with their disease (7). It has been shown to reduce patients' breathlessness and fatigue (48), improves their psychological function (48) and quality of life (49) and reduce the hospital admissions and mortality risk following acute exacerbations (49).

1.6.4 Immunisation

According to the National policy, annual influenza vaccination should be provided to all patients with COPD regardless of the disease severity (7). Available evidence has shown that influenza vaccine significantly reduces the frequency of exacerbations among COPD patients (50) and significantly reduces COPD-related hospital admission rates (51).

Pneumococcal vaccine is also recommended for all COPD patients (7), as Streptococcus pneumoniae is a common bacterial pathogen causing COPD exacerbation (52). However, evidence is inconclusive from previous randomised controlled trials regarding the effectiveness of Pneumococcal immunisation on reducing exacerbations, hospitalisation and mortality in COPD patients (53).

1.6.5 Self-management and rescue packs

Self-management can be described as *'a set of skilled behaviours and refers to the various tasks that a person carries out for management of their condition'* (54). Although there is no consensus on the most effective method and the main components of self-management plans in COPD (7, 55), self-management interventions among COPD patients have been found to be associated with improved health related quality of life (HRQoL) and dyspnoea scores (56) and with reduced hospital admission rates (56, 57).

The primary aim of self-management in COPD is to prevent exacerbations (55) by assisting patients to acquire the skills to respond to the early signs of exacerbations by starting or adjusting their medications (7, 58). Therefore, patients at risk of exacerbations should be provided with self-management plans and given a course of steroids and antibiotic (COPD Rescue Pack) to keep at home enabling them to respond earlier to the symptoms of exacerbation (7). However, the appropriate use of these medications must be monitored and patients must be advised to contact a healthcare professional if they do not improve (7).

1.7 Overdiagnosis of COPD

The problems of overdiagnosis and underdiagnosis of chronic diseases (including COPD) coexist in many healthcare settings in the developing and developed world (59), which pose challenges in daily practice with subsequent inappropriate patient management (36). However, a correct diagnosis of COPD is essential because of its specific therapeutic and prognostic consequences on diagnosed patients (60). The inappropriate use of COPD medications to treat patients who do not have the disease may not only result in under-management of the true underlying aetiology that caused the patient's symptoms (61) but also exposes patients to potentially harmful adverse effects of these medications (62, 63). For instance, ICS have been associated with an increased risk of pneumonia (64, 65) and LABAs may cause adverse cardiovascular effects (61, 66). Furthermore, COPD is associated with higher healthcare costs (61) and provision of COPD management to patients who do not have the disease is an inefficient use of healthcare resources with unnecessary expenditure (60, 62, 67, 68). There are number of reasons why COPD may be overdiagnosed in primary care:

1.7.1 Primary care practitioners related factors

1.7.1.1 Spirometry underuse

Lack of spirometry confirmation, especially when General Practitioners (GPs) rely upon the nonspecific clinical respiratory symptoms and smoking history for COPD diagnosis (69), increases the risk of misdiagnosis of COPD, asthma or other comorbidities (Table 2) (68). All of which have different physiological mechanisms and thus different management strategies (68, 70). Some studies in the UK have found that approximately one third of practices had no spirometry available (71, 72) and in many practices that owned spirometry, nurses lacked adequate training and support to perform spirometry and interpret the results (71-73).

Table 2: Other conditions that may present with similar symptoms as COPD (7)

Common: • Asthma • Bronchiectasis • Congestive cardiac failure • Bronchial carcinoma	Uncommon: • Obliterative bronchiolitis • Broncho pulmonary dysplasia

1.7.1.2 Pre-bronchodilator spirometry for COPD diagnosis

Relying upon pre-bronchodilator spirometry may lead to an overestimation of COPD prevalence (72) due to its higher rate of false positive diagnosis (74). Therefore, the GOLD and the current NICE (2010) guidelines specify the relevance of post-bronchodilator spirometry in diagnosing COPD (6, 7, 72). However, the previous NICE (2004) guidelines did not specify pre- or post-bronchodilator spirometry for COPD diagnosis (7). Despite guidelines, a recent internet-based survey in 12 countries including the UK, found that 22% of primary care practitioners and 15% of respiratory specialists reported the use of pre-bronchodilator spirometry only in diagnosing COPD (75).

1.7.1.3 Lack of awareness and implementation of COPD guidelines

Standard guidelines sometimes are not well implemented by many GPs in diagnosing and managing COPD (72, 76). Moreover, some studies have found that, in primary care, inhaled corticosteroids are commonly prescribed in patients with respiratory symptoms but who have not had a proper diagnosis or indication for this treatment (77, 78).

1.7.2 COPD and asthma overlap

One of the important differential diagnoses of COPD is asthma and both conditions often coexist (7). However, it is important to differentiate between both conditions to ensure correct treatment and the best possible outcome for the patient (76). Although there is similarity between COPD and asthma symptoms (78, 79) and both conditions are associated with inflammation and reduced pulmonary airflow, they have different underlying mechanisms and different medical history and clinical presentation (80, 81) (Table 3). Therefore, in most cases both conditions can be differentiated based on a proper history and clinical assessment (76). Furthermore, reversibility testing is beneficial in differentiating COPD and asthma in cases where there may be doubt (72). However, neither GOLD nor NICE guidelines recommends reversibility testing for diagnosis of COPD but recommends a differentiation between asthma and COPD based on clinical features (6, 7, 72), unless a diagnostic uncertainty remains, where only a significant reversibility of FEV_1 of more than 400 ml confirms asthma diagnosis (7). However, the misclassification of asthma and COPD in primary care settings remains common (69, 80, 82, 83).

Table 3: Clinical features differentiating COPD and asthma (7, 76)

Diagnostic features	COPD	Asthma
Symptoms under age 35	Rare	Often
Smoker or ex-smoker	Nearly all	Possibly
Allergic hypersensitivity	Rarely a factor	Usually
Chronic productive cough	Common	Uncommon and non-productive
Breathlessness	Persistent and progressive	Variable and intermittent
Nocturnal symptoms	Uncommon except in severe stages	Common
Cause of exacerbations	Bacterial/viral respiratory infection	Allergens, exercise or cold air
Response to bronchodilators	Variable, PFT does not normalize but may show some improvement	Quick response and PFT may significantly improve, e.g. FEV1 may improve 400ml

PFT: pulmonary function test

1.7.3 Patient related factors

Patients' clinical factors such as age, sex, smoking, obesity and nasal obstruction secondary to allergic rhinitis and hay fever may lead to a clinical presentation with chronic respiratory symptoms and increase the possibility of over diagnosing those patients with COPD (60). Furthermore, patients with other chronic disease such as congestive heart failure (6), may present with similar respiratory symptoms of COPD (Table 2). Restrictive lung disease is another differential diagnosis of COPD (84) and it has different aetiological factors including, congestive heart failure, diabetes mellitus, obesity, muscular weakness and interstitial lung disease (85). However, evidence about patient related clinical factors associated with COPD overdiagnosis is limited.

1.8 Chronic respiratory symptoms but normal lung function: COPD GOLD Stage 0

The GOLD guidelines for COPD were first published in 2001 (86) and aimed to provide a standard global framework for COPD prevention and management (12, 86, 87). Five stages of

COPD severity were originally classified according to post-bronchodilator spirometric lung function measurements (Table 4). Many components of the original GOLD guidelines and staging system are controversial (86), particularly COPD GOLD Stage 0 (12), which has been defined by '*the presence of chronic respiratory symptoms, such as cough and sputum production, but with preserved normal lung function (FEV_1/FVC >70%)*' (86, 88). Patients at this stage were considered as being 'at risk' of developing COPD in the future (19, 89) and the main idea behind the inclusion of this stage was to allow for early intervention, prior to progression to Stage 1 or even more advanced stages of diagnosed COPD (90). However, due to lack of supporting evidence regarding this progression from GOLD Stage 0 to COPD Stages 1+, GOLD Stage 0 has been excluded from the GOLD staging scheme since 2006 (91). However, the significance of the public health message that chronic respiratory symptoms are abnormal and their underlying causes must be identified remains unchanged (91).

Table 4: 2001 GOLD classification of COPD Severity (88, 92)

	Characteristics	
	Post-bronchodilator spirometry	**Chronic respiratory symptoms**
GOLD Stage 0 (At risk)	Normal spirometry ($FEV_1/FVC > 0.70$)	+
GOLD Stage I (Mild COPD)	$FEV_1/FVC < 0.70$ $FEV_1 \geq 80\%$ predicted	±
GOLD Stage II (Moderate COPD)	$FEV_1/FVC < 0.70$ $FEV_1 < 80\%$ but $\geq 50\%$ predicted	±
GOLD Stage III (Severe COPD)	$FEV_1/FVC < 0.70$ $FEV_1 < 50\%$ but $\geq 30\%$ predicted	±
GOLD Stage IV (Very Severe COPD)	$FEV_1 \leq 30\%$ predicted or $FEV_1 <$ 50% predicted plus chronic respiratory failure[1]	±

FEV_1: forced expiratory volume in one second. FVC: forced vital capacity

[1]Respiratory failure is defined as 'arterial partial pressure of oxygen (PaO2) less than 8.0 kPa (60 mm Hg) with or without arterial partial pressure of CO2 (PaCO2) greater than 6.7 kPa (50 mm Hg) while breathing air at sea level'

1.8.1 COPD GOLD Stage 0: areas of controversy

The main area of disagreement regarding GOLD Stage 0 is whether this stage has any prognostic significance (93). Previously published data have shown that an important proportion of patients with abnormal pulmonary function do not report respiratory symptoms (87). On the other hand, a large proportion of patients with normal lung function report respiratory symptoms but do not develop COPD (87). Another area of debate concerns the respiratory symptoms essentially required to define GOLD Stage 0, where most previous studies have used the MRC definition of CB of '*the presence of productive cough for three months in two successive years in a patient in whom other causes of chronic cough, have been excluded*' (94). Importantly, few studies suggest a more sensitive definition of GOLD Stage 0 by including a wider range of respiratory symptoms (cough, phlegm, wheeze, breathlessness), which are seen to occur on a recurrent basis (93, 95).

1.8.2 Natural history of COPD GOLD Stage 0

1.8.2.1 Earlier Epidemiology

The Fletcher and Peto prospective 8 year cohort of working men aged 30 to 59 years in London (96), was the first study aimed to clarify the risk factors for developing COPD other than smoking (96). They studied the independent effect of chronic mucous hypersecretion (CMH) on FEV_1 decline (96), finding no independent association between CMH and accelerated decline in FEV_1 following adjustment for smoking and other potential confounders (96). The study concluded that smoking remains the main risk factor for COPD (96) and that CMH lacks any predictive value for developing of COPD (28). A similar conclusion was drawn from Kauffmann *et al,* in their 12 year cohort study of male chemical factory workers in Paris from 1960 to 1972 (97). They studied a wider range of respiratory

symptoms than Fletcher and Peto by including exertional dyspnea *'even slight'* (97) with chronic cough and phlegm, finding a non-significant effect of respiratory symptoms on excess decline in FEV_1 and that they lack any predictive value for subsequent development of COPD (97).

1.8.2.2 More recent Epidemiology

More recently, contradictory findings have been reported from studies which examined GOLD Stage 0. Some studies have found that GOLD Stage 0 is lacking any independent predictive value of increased risk of developing COPD (86), whereas other studies have found it to be associated with an increased risk of developing COPD (98, 99). Moreover, GOLD Stage 0, in some studies, has been recognised as associated with a higher healthcare utilisation (90, 100, 101), lower HRoQL (85, 100, 102) and increased risk of mortality (95, 103). On the other hand, other studies do not observe an association between GOLD Stage 0 and increased mortality risk (104).

1.9 Rationale for studying GOLD Stage 0

1.9.1 Insufficient evidence

Generally, this condition of the presence of respiratory symptoms in the absence of airflow obstruction is an under-investigated area, with those patients representing a heterogeneous group with unclear aetiology and natural history (93). Moreover, the attention of researchers and clinicians is mainly focused on COPD (105), with most clinicians ignoring this condition and not managing it properly, assuming that it is benign since it is not currently classified as COPD (105). Furthermore, most previous research has focused on the coexistence of COPD and CB symptoms; unfortunately, however, such studies have failed to provide information for policy makers and healthcare providers concerning the relevance of the presence of

symptom even in the absence of diagnosed airflow obstruction (105). Moreover, sometimes symptomatic patients have been misdiagnosed as COPD based on their symptoms (60) and subsequently exposed to unnecessary medications that have been proven effective only in the case of COPD (60, 62).

1.9.2 Uncertainty about the predictive value of GOLD Stage 0 on the risk of developing COPD

Some studies have found that GOLD Stage 0 is associated with an increased risk of excess decline in FEV_1 (86, 93) and development of COPD (19, 98). Conversely, other studies found that GOLD Stage 0 *'is of little help in identifying subjects at risk of COPD'* (86).

1.9.3 Uncertainty about the prognostic value of GOLD Stage 0 on longer term outcomes

Although GOLD Stage 0 is no longer officially included in COPD staging scheme of the GOLD committee due to the inconsistent results from the previous studies (90), the presence of chronic respiratory symptoms could be an important predictor of long-term morbidity and mortality amongst affected subjects —even in the absence of diagnosed airflow obstruction (9).

1.10 Thesis aim and objectives

1.10.1 Aim

This thesis aims to clarify the uncertainty around the relevance and impact of chronic respiratory symptoms in the absence of airflow obstruction on patients' health in an effort to determine whether it is important to identify and target such patients with interventions.

1.10.2 Objectives

1. To examine the risk of developing COPD amongst patients with chronic respiratory symptoms compared to the normal population (Chapter 2).
2. To examine the overall prognosis and the prognostic factors of patients with chronic respiratory symptoms compared to diagnosed COPD patients (Chapter 3).
3. To investigate the relative importance of the presence of chronic respiratory symptoms *versus* airflow obstruction on quality of life (Chapter 4).
4. To compare the health-related characteristics and health outcomes of patients with chronic respiratory symptoms and those newly identified with COPD (Chapter 5).
5. To describe the magnitude and factors associated with COPD overdiagnosis in the UK primary care setting (Chapter 6).

1.11 Definition of GOLD Stage 0

In this thesis, GOLD Stage 0 will be defined broadly by the presence of any respiratory symptoms that occur on a frequent basis (including CB symptoms, dyspnoea and wheeze), with preserved normal lung function and without previous diagnosis of other respiratory diseases including asthma.

Cough and phlegm will be defined using the MRC definition of '*their presence on most days for three or more consecutive months during the year for more than two years'*, wheeze will be defined by '*ever had wheezing or whistling in the chest in the last twelve months*' and the presence of dyspnoea will be defined as Grade two and above of MRC Breathlessness Scale '*troubled by shortness of breath when hurrying on the level ground or walking up a slight hill'*. Although the term 'COPD GOLD Stage 0' no longer officially exists, for brevity it will be used in this thesis to refer to the study population of interest.

1.12 Thesis Structure

There are seven chapters: Chapter 1 provides the study background; Chapter 2 is a systematic review of the literature examining the risk of developing COPD amongst patients with chronic respiratory symptoms compared to the normal population; Chapter 3 consists of two systematic reviews, the first of which examines the prognosis of patients with chronic respiratory symptoms compared to COPD patients, whilst the second investigates factors affecting the prognosis of such patients; Chapter 4 provides a cross-sectional analysis of respiratory data from the 2010 Health Survey for England (HSE) to examine the independent impact of the presence of chronic respiratory symptoms *versus* airflow obstruction on self-assessed HRQoL; Chapter 5 is a cross-sectional analysis of the Birmingham COPD Cohort Study, comparing the difference in health-related characteristics and health outcomes of GOLD Stage 0 patients with a sample of recently identified COPD patients; Chapter 6 describes the magnitude and the main factors associated with COPD overdiagnosis in the UK primary care setting by analysing data from the Birmingham COPD Cohort Study; Chapter 7 provides a discussion of the main findings, the implications for research and clinical practice and the conclusion.

1.13 Contribution to research and clinical practice

This thesis will provide an evidence-base about the relevance of the presence of chronic respiratory symptoms in the absence of airflow obstruction and whether this condition warrants further attention. This research will also provide a platform for future health service-related research on GOLD Stage 0 and it can be used as a reference to help inform developing clinical management strategies for patients with GOLD Stage 0 symptoms.

2 GOLD STAGE 0 AND THE RISK OF DEVELOPING COPD: A SYSTEMATIC REVIEW

2.1 Abstract

Background: The predictive value of GOLD Stage 0 on the risk of developing COPD is uncertain. In this review the evidence on the following question will be evaluated: *Are people who have chronic respiratory symptoms but normal lung function at a higher risk of developing COPD compared to people who do not?*

Methods: Medline, Embase and other electronic databases (from inception to week 4 January 2014) were searched for relevant studies that examined the risk of developing COPD among adults aged 40 years and over, who have chronic respiratory symptoms but normal lung function in comparison with the normal population. Cohort studies were preferred but cross-sectional and case-control studies also accepted if they informed the review question. Two reviewers independently extracted data and assessed the quality of studies included. Analyses were descriptive.

Results: 38 studies were identified as potentially relevant; of which ten studies were eligible for inclusion. GOLD Stage 0 was found to be associated with an accelerated FEV_1 decline compared to the normal population. The findings from seven included cohort studies were contradictory regarding the risk of development of COPD among GOLD Stage 0 patients due to the instability of GOLD Stage 0 symptoms over time. Persistence of GOLD Stage 0 symptoms showed a higher adjusted risk (IRR, 2.88; CI 95%, 1.44 to 5.79) for developing COPD.

Conclusion: Compared to the normal population, GOLD Stage 0 is associated with a higher risk of excess decline in FEV_1. However, whether or not this necessarily leads to higher risk of developing COPD Stages 1+ remains unclear, although may be related to persistence of symptoms.

2.2 Introduction

The predictive value of the presence of chronic respiratory symptoms in the absence of airflow obstruction "GOLD Stage 0" has been a topic of argument (106) since the seminal study of Fletcher and colleagues (96). More recently, a wide range of views and some contradictory opinions have been observed, some studies have found it to be associated with an increased risk of developing COPD Stages 1+ in the future (98, 99), whilst other studies have found that GOLD Stage 0 lacks any predictive value of developing COPD (86). There has been no published systematic review studying the risk of developing COPD among GOLD Stage 0 patients. Therefore, this review aims at drawing together the currently available literature on Gold Stage 0 to provide an evidence-based summary and identify a scope for further research on this condition. These aims will be achieved by answering the following question: '*Are people who have chronic respiratory symptoms but normal lung function at a higher risk of developing COPD compared to people who do not?'*

2.3 Methods

2.3.1 Protocol and registration

The review protocol (Appendix A) for the present review and reviews 2 and 3 presented in the next chapter (Chapter 3), was prepared based on the guidelines of the Cochrane Collaboration (107) and the Centre for Reviews and Dissemination (108). The protocol was also registered with PROSPERO (Registration Number: CRD42014009146) (109).

2.3.2 Inclusion criteria

In the three systematic reviews, GOLD Stage 0 was defined by the presence of any respiratory symptoms that occur on frequent basis (including CB symptoms, wheeze and dyspnoea) with normal lung function. Table 5 below summarises the selection criteria (PECOS) for the present review:

2.3.2.1 Population

Studies were sought included adults aged 40 years and older who had chronic respiratory symptoms but normal lung function. Studies of younger age groups were included only if self-reported asthma was excluded (to minimise the potential of diagnostic bias by misclassification of bronchial asthma as COPD).

2.3.2.2 Exposure and comparator

Studies were included if they measured the presence of any chronic respiratory symptoms (This is defined in some studies as more than three consecutive months a year for two consecutive years, although it may not always be defined this way), and compared GOLD Stage 0 patients to a normal population (asymptomatic with normal lung function).

2.3.2.3 Outcome

The outcomes of interest were the decline in crude and percent predicted FEV_1 and the development of COPD.

2.3.2.4 Study Design

Ideally, cohort studies were sought; however, cross-sectional and case-control studies were also considered. Although cross-sectional studies do not allow causality to be proven or evaluation of prognosis, they may support the findings from the cohort studies.

Table 5: PECOS components of the review's question

Question components (PECOS)	Inclusion criteria	Exclusion criteria
Population	People aged 40 years and over with chronic respiratory symptoms and preserved normal lung function	Studies of younger age groups unless asthma excluded
"Exposure"	Any chronic respiratory symptoms	
Comparator	"Normal population" (asymptomatic with normal lung function)	
Outcome	Decline in FEV_1% and development of COPD	
Study design	Ideally cohort studies but cross-sectional and case-control studies might be considered	Reviews, editorials, case series and reports
Types of publication	All relevant studies with available full text, regardless of their publication status	

2.3.3 Search strategy

Due to the limited number of epidemiological studies on GOLD Stage 0 and because it is a poorly indexed term, the search was designed to be comprehensive and thorough, combining the search for this review and reviews 2 and 3 together. A wide range of key and MeSH terms, synonyms and spelling alternatives were used. Furthermore, there were no language or time restrictions applied to the search. An expert Librarian and an information specialist were consulted regarding the search terms before the actual search was initiated.

The electronic search for the three reviews was conducted by the first reviewer (HB) in February 2014, and initially involved searching the two key databases, Medline and Embase (from inception to week 4 January, 2014). The search terms used and different combinations with OR/AND, are presented in Table 43 (Appendix B). Thereafter, using the same search terms and combinations, the search also included CINAHL and databases for grey literature as Zetoc library, ETHOS library and SIGLE. The reference lists of identified relevant studies were also searched. The search was also supplemented by a database alert services subscription until April 2014.

2.3.4 Study selection

The resulting records were screened for relevant studies by the two reviewers (HB and NA) independently. This began by scanning through the titles, which was done by the first reviewer (HB), followed by an independent screening by the two reviewers through abstracts and then the full text against the predefined eligibility criteria. All excluded studies were listed and documented with the respective reasons for exclusion.

2.3.5 Data extraction

Two reviewers independently extracted the data from included studies, using a simple form (Table 6) adapted from the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist (110, 111) (Appendix C).The form was initially piloted on three articles.

2.3.6 Methodological quality assessment

Risk of bias assessment forms were generated from key quality assessment tools of non-randomised studies (112, 113). The QUIPS (Quality in Prognosis Studies) tool (112) (Appendix D) was adapted for the included cohort studies and the Newcastle Ottawa Scale (113) (Appendix E) was adapted for cross-sectional studies. The risk of bias was judged independently by the two reviewers with 'yes, partly, no and unclear' for each perspective. However, no studies were excluded based on the risk of bias.

2.3.7 Data synthesis process

The analyses were descriptive only, describing and comparing the main findings from the included studies as a formal meta-analysis was deemed not appropriate (Appendix A, section 8.5). There are clear difficulties involved with a formal meta-analysis of prognostic

systematic reviews, including high risk of publication bias, methodological quality and limitation in reporting quality of observational studies (114, 115).

In the present review, there was high clinical and statistical heterogeneity among the included studies, different patient groups were targeted (younger age, middle aged, men only, occupational cohorts); there was a variation in cut-off points used to define COPD (FEV_1/FVC<70% or FEV_1/FVC<60%); some studies measured crude FEV_1 values, others measured FEV_1% predicted and sometimes $FEV_{0.75}$ was measured. Moreover, the sample size in many studies was small; the analysis across studies adjusted for different variables (and sometimes was unadjusted) and in some cohort studies the completeness of follow-up was unknown.

2.4 Results

2.4.1 Study selection

The electronic searches resulted in 16,636 records, of which 5,832 duplicates were removed (Figure 1). Of the resulting 10,804 unique records, 641 records were identified by the two reviewers (HB and NA) as potentially eligible from their titles/abstracts and 73 records were identified for full article analysis, including seven non-English articles (two French, one Spanish, two Romanian, one Turkish and one German), which also were assessed through their full text after translation to English. Out of the 73 articles, 38 were identified as potentially relevant for inclusion in this review; ten studies were found eligible for inclusion, and 28 were excluded and documented with the reasons for exclusion. The two reviewers disagreed on four studies for inclusion, on which the third reviewer (RJ) was consulted.

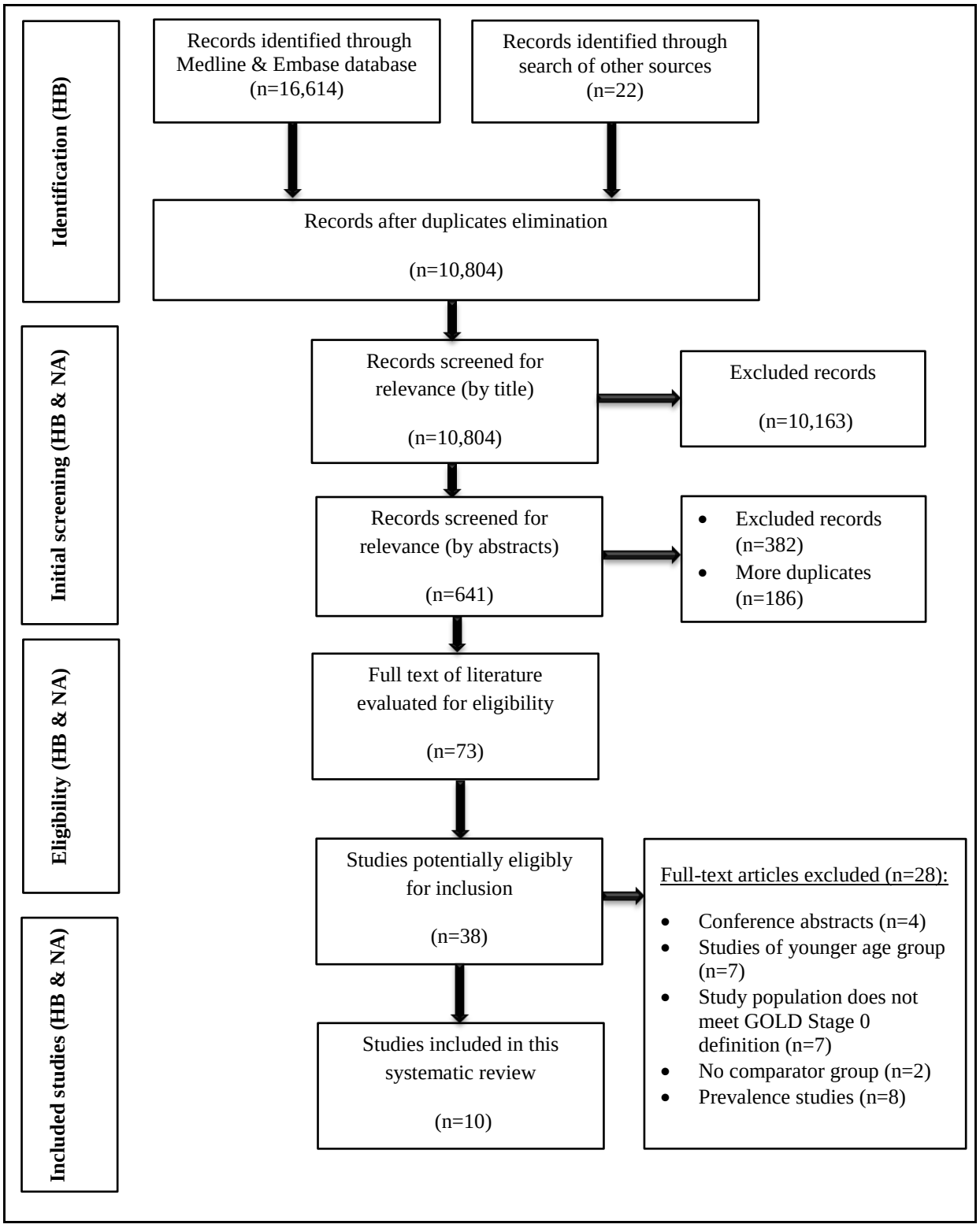

Figure 1: PRISMA flow diagram of study selection

2.4.2 The study characteristics

The characteristics and the main findings of the ten studies included are detailed in Table 6 below:

2.4.2.1 Study design and setting

Of the included studies, eight were cohort (19, 86, 89, 93, 98, 99, 116, 117), two were cross sectional studies (118, 119) (Table 6) but no relevant case-control studies were identified. The length of follow-up in the cohort studies ranged from 3.5 to 40 years, whilst the sample size across all studies ranged between 121 and 13,108 participants.

2.4.2.2 Population

Most of the included studies targeted adults aged 40 years and over, except in the case of four cohort studies (86, 93, 98, 117) where younger age groups were also targeted. GOLD Stage 0 patients who reported the presence of asthma were excluded in all of the included studies except in one study (19) (Table 6).

2.4.2.3 Exposure

In sex studies GOLD Stage 0 symptoms were defined using CB definition (86, 89, 93, 99, 116, 117), while the other four studies (19, 98, 118, 119) included wheeze and breathlessness, in addition to the CB symptoms (Table 6).

2.4.2.4 Comparator

GOLD Stage 0 patients were compared in all of the included studies to a reference group drawn from the normal population (asymptomatic with normal lung function). Although one cohort study (116) did not clearly define the baseline lung function, both subgroups had no airflow obstruction at the baseline.

2.4.2.5 Outcome

Amongst the cohort studies included, one study examined the effect of GOLD Stage 0 on rate of FEV_1 decline (99), four studies examined the effect of GOLD Stage 0 on the risk of development of COPD (19, 89, 98, 117) and three studies assessed the effect of GOLD Stage 0 on both of these outcomes (86, 93, 116). The included cross sectional studies examined the association between GOLD Stage 0 symptoms and absolute values of FEV_1 (118, 119) (Table 6). Incident COPD among GOLD Stage 0 patients was defined in all of the included studies using the GOLD committee fixed ratio definition (FEV_1/FVC <70%), except in one study (116), which did not clearly define the development of COPD. With the exception of two studies (93, 118), all studies defined COPD based on pre- rather than post-bronchodilator lung function testing (Table 6). Note that defining COPD based on pre-bronchodilator lung values leads to an overestimation of its prevalence (72).

Table 6: Study characteristics and the main findings

Vestbo *et al.*, 1996 (116)							
Design	**Population of interest**	**Definition of exposure**	**Comparator**	**Outcome**	**Confounders adjusted for**	**Results**	**General observations**
Retrospective cohort study of two surveys 5 years apart (Copenhagen City Heart Study) followed by 8-10 years follow-up of National Health Register for COPD development- Denmark	1,384 adults, aged 30-79 years (mean=53 years), reported CMH[2] and free from self-reported asthma	"*The presence of cough and phlegm for at least 3 months for more than 1 year*" and further classified in to: 1. CMH in the 1st survey but disappear in the 2nd 2. No CMH at the 1st survey but appeared at the 2nd 3. Persistent CMH in both surveys	8,051 subjects without CMH	The impact of CMH on excess decline in crude FEV_1 and on a subsequent hospitalisation due to COPD	• Smoking • Age • Height • Weight change • Sex	• A steeper FEV_1 decline in either groups with CMH than asymptomatic group, an excess FEV_1 decline of 22.8 ml/year (95% CI, 8.2 to 37.4) in men and of 12.6 ml/year (95% CI, 0.7 to 24.6) in women • Participants with persistent CMH over the study period showed a greater FEV_1 decline than those with recently occurred and with disappeared symptoms; among men, the FEV_1 decline was 18 ml/year (3.3-32.7), 15.2 ml/year (3.0-27.5) and 16.0 ml/year (0.3-31.8) respectively; among women, the decline was 7.9 ml/year (-4.1-19.8), 8.8 ml/year (-1.1-18.7) and 4.0 ml/year (-15.9-7.9) respectively. • CMH was significantly associated with increased subsequent hospitalisation with COPD recorded as the main diagnosis among men and women, with RR= 5.3 (2.9-9.6) and RR= 5.1 (2.5-10.3) respectively.	The study did not clearly define the baseline lung function and the development of COPD

[2] Chronic mucous hypersecretion (CMH)

Vestbo and Lange, 2002 (86)							
Design	**Population of interest**	**Definition of exposure**	**Comparator**	**Outcome**	**Confounders adjusted for**	**Results**	**General observations**
Retrospective cohort study- Denmark with 15 years follow-up (Copenhagen City Heart Study)	766 GOLD Stage 0 adults, aged ≥20 years (mean=52 years), reported the presence of productive cough, with FEV_1/FVC >70% and free from asthma	"*Productive cough for at least 3 months a year*"	10,441 normal adults (asymptomatic with normal lung function)	• FEV_1 Decline and progression from Stage 0 to COPD Stages 1+. • COPD was defined and classified using the GOLD criteria	• Age • Sex • Smoking • Inhalation habits	• After 5 years, the difference in the development of COPD among both groups was not statistically significant • After 15 years, the progression to COPD was more common among GOLD 0 than normal subjects (p=0.01 for total population and p=0.02 for smokers) • In multivariate logistic regression, the effect of GOLD 0 on the development of COPD Stages 1+ was small after 5 and 15 years; OR 1.1 (95% CI, 0.9-1.5) & 1.2 (95% CI, 0.8-1.5) respectively • The difference in the FEV_1 crude decline between the baseline and after 5 years among normal and GOLD 0 subjects were 36.8 ml/year and 59.6 ml/year respectively	• Pre-BD[3] values were used to define COPD • GOLD 0 symptoms were unstable over time; after 5 years, 39.6% of GOLD 0 subjects resolved to no symptoms and after 15 years, about 49.4% were persistent GOLD Stage 0 or developed COPD Stages 1+
Lindberg *et al.*, 2006 (19)							
Design	**Population of interest**	**Definition of exposure**	**Comparator**	**Outcome**	**Confounders adjusted for**	**Results**	**General observations**
7 years prospective cohort study- Sweden	963 adults, aged 46-77 and had chronic respiratory symptoms with normal lung	• "*Phlegm when coughing or phlegm which is difficult to*	Asymptomatic adults	Incident COPD defined using two definitions: • GOLD I (FEV_1/FVC< 0.70)	• Gender • Age • Smoking • Family history of COPD	• Incident cases of COPD reported significantly more respiratory symptoms at the baseline • The most significant symptoms preceding the development of COPD were sputum production	• Only Pre-BD spirometry performed • Asthma was not excluded

[3] Bronchodilator

	function (FEV_1/FVC >0.70%)	*bring up, most days during periods of at least 3 months, during at least the 2 last years"* • Wheeze • Dyspnea		• GOLD II (FEV_1/FVC < 0.70 and FEV_1<80% predicted)		and wheeze • In multivariable regression model, most of the symptoms were significant, or close to significant, as predictors of increased risk for incident COPD	
Pelkonen *et al.*, 2006 (99)							
Design	**Population of interest**	**Definition of exposure**	**Comparator**	**Outcome**	**Confounders adjusted for**	**Results**	**General observations**
Prospective cohort study with 40 years follow-up period- Finland	488 men aged 40- 59 years, had CB symptoms and free from other respiratory diseases	*"Productive cough for at least 3 months a year"*	1,223 subjects without CB	The effect of CB symptoms on the crude values of lung function measurements	• Smoking habit • Occupation	• The $FEV_{0.75}$ was 252 ml (95% CI, 211-293) lower in those with CB than subjects without CB • The $FEV_{0.75}$ was 309 ml (95% CI, 362-257) lower in subjects with persistent CB over the study period & 190 ml lower in subjects with non-persistent CB (95% CI, 245-134) • The excess decline in $FEV_{0.75}$ attributable to the presence of CMH was 13.2 ml/year	• $FEV_{0.75}$ was measured instead of FEV_1 • Targeted men only • Different definitions of GOLD 0 were used over the study period
de Marco *et al.*, 2007 (98)							
Design	**Population of interest**	**Definition of exposure**	**Comparator**	**Outcome**	**Confounders adjusted for**	**Results**	**General observations**
11 years prospective cohort study-the European Community	447 young adults aged 20–44years, had respiratory symptoms with	• *"The presence of chronic cough/ phlegm on*	4,533 asymptomatic adults	The incident COPD, defined as: FEV_1/FVC less than 70%	• Sex • Age • Smoking • Education	• The COPD incidence was 4 times greater in subjects who reported cough/phlegm at the end of follow-up than those never reported the presence of	• Only Pre-BD spirometry performed • GOLD 0 symptoms

Respiratory Health survey II	normal lung function (FEV_1/FVC >70%) and free from doctor-diagnosed asthma	*most days for as much as 3 months each year"* • Dyspnea *"even slight"*				cough/phlegm • Persistent symptomatic subjects had 3times greater risk for COPD (IRR, 2.88; 95% CI, 1.44-5.79) than asymptomatic after adjustment for confounders • Cough/phlegm was statistically significant independent predictor for incident COPD (IRR=1.85; 95% CI, 1.17-2.93) after adjustment for smoking and other confounders • Dyspnoea was a poor predictor of incident COPD (IRR=0.98; 95% CI, 0.64-1.50)	were unstable over time; among subjects reported the presence of symptoms at baseline, only 38% reported the persistence of symptoms at the end of the study
Guerra *et al.*, 2009 (117)							
Design	**Population of interest**	**Definition of exposure**	**Comparator**	**Outcome**	**Confounders adjusted for**	**Results**	**General observations**
Prospective Population-based cohort study with 12 years follow-up-USA (Tucson Epidemiological Study of Airway Disease Study)	97 white adults aged 21–80 years (mean =50 years), had CB symptoms with FEV_1/FVC ≥70% and free from diagnosed asthma	*"The presence of cough and sputum production on most days for at least 3 months in at least 2 consecutive years"*	1,315 asymptomatic adults	Incident COPD, defined as: FEV_1/FVC <70%	• Sex • Age • Pack-years smoking • Baseline FEV_1/FVC • BMI • Education	• At follow-up: 42% of GOLD 0 subjects developed AFO[4] compared to 23% of asymptomatic subjects (p<0.001) • In univariate analyses, the effect of GOLD 0 symptoms on incident COPD was significant (HR=1.94; 95% CI, 1.40-2.69). However, in multivariate model, this association became marginal (HR=1.37, 95% CI 0.98-1.92)	• Targeted white adults only • Only Pre-BD spirometry performed

[4] Airflow obstruction

Yamane *et al.*, 2010 (89)							
Design	**Population of interest**	**Definition of exposure**	**Comparator**	**Outcome**	**Confounders adjusted for**	**Results**	**General observations**
Prospective cohort study in Japan with 5 years follow up period (between 1993 and 2004)	69 GOLD Stage 0 men aged 40-69 years, had productive cough with normal lung function and free from any respiratory disease	'*Phlegm when coughing, or have phlegm which is difficult to bring up, for periods of at least three months, during at least the last two years?'*	536 normal subjects with normal lung function and without productive cough	FEV_1 decline and incident COPD, defined as: FEV_1/FVC <0.70	• Age • Height • FEV_1% • Pack years of smoking	• The cumulative COPD incidence rate was significantly higher among symptomatic men (10.1%) than asymptomatic (2.2%). • The COPD incidence rate was 28.9/1000 person-years among symptomatic group and 7.5/1000 person-years in asymptomatic group. • Current and ex-smoking individuals with productive cough had 1.8 times and 15.0 times higher risks for developing COPD, respectively compared to asymptomatic subjects • In multivariate analysis, productive cough was independent risk factor for the development of COPD in all subjects (HR=4.54, 95% CI 1.72-12.0, p=0.002) and among former smokers (HR=25.4, 95% CI 3.17-36.9, p=0.002) but not in current smokers (HR=0.49, 95% CI 0.05-4.49, p=0.53) • The annual FEV_1% decline was greatest among symptomatic subjects	• Targeted a specified population (men only)
Brito-Mutunayagam *et al.*, 2010 (93)							
Design	**Population of interest**	**Definition of exposure**	**Comparator**	**Outcome**	**Confounders adjusted for**	**Results**	**General observations**
5 years prospective	GOLD Stage 0 Adults; 584	• Cough	Normal adults: 2,769	FEV_1 decline and incident COPD,	• Smoking	• Persistent GOLD 0 symptoms	• Performed pre

cohort study- Australia	participants at baseline & 420 participants at follow-up, aged ≥18 years (mean=45.5 years), reported the presence of cough/phlegm with post-BD FEV_1/FVC >70% and free from asthma and restrictive disease	without sputum • Productive cough *"at least several table spoons per day on most or every day in the last 3 months"*	participants at baseline & 2,093 participants at follow-up	defined as post-BD FEV_1/FVC <70%	• Age • Sex • BMI	were associated with highest quartile of FEV_1 decline per year (OR 2.1; 95% CI, 1.2-3.7) in men • GOLD 0 defined by cough without sputum: in non-smoker males, persistent GOLD 0 was significantly associated with the highest quartile of annual FEV_1 decline (OR 3.16; 95% CI, 1.46-6.84), but this was not the case in non-smoker females. In current smokers, persistent GOLD 0 was associated with the highest quartile of annual FEV_1 declines in women (OR 5 4.86; 95% CI, 1.63-14.5) • GOLD 0 defined by cough & sputum: the mean annual decline in FEV_1 was 76 mL greater compared with GOLD 0 defined by cough without sputum. • The effect of GOLD 0 symptoms on incident COPD was non-significant (1.4%) among GOLD 0 subjects and the asymptomatic	& post-BD Spirometry • GOLD 0 symptoms were unstable over time; 39.8% of GOLD 0 subjects had persistent symptoms at the follow-up and 58.5% resolved to no symptoms
Shin *et al.*, 2005 (119)							
Design	**Population of interest**	**Definition of exposure**	**Comparator**	**Outcome**	**Confounders adjusted for**	**Results**	**General observations**
Cross-sectional study- Korea	7,518 symptomatic adults aged 40–69 years, with normal lung function and free from other lung diseases	Chronic cough, chronic phlegm, wheezing and dyspnoea	Asymptomatic adults with normal lung function	Difference in crude FEV_1 value between both groups	Age	• In men, the age-adjusted mean FEV_1 was lower among smokers and non-smokers with the presence of wheeze by 165 ml (95% CI 83-247, p<0.001) and 133ml (95% CI 17-249, p<0.05) respectively, by 210 ml (95% CI 38-382, p<0.05) among smokers	Only Pre-BD spirometry was performed

						with dyspnoea and lower by 56 ml (95% CI 5-107, p<0.05) among non-smokers with dyspnoea • In non-smoker women, the age-adjusted mean FEV_1 was significantly lower with the presence of wheeze: 89 ml (95% CI 44-134, p<0.001) and dyspnoea: 55 ml (95% CI 33-77, p<0.001). • There was no relationship between respiratory symptoms and FEV_1 among smoker women. However, only small number of women smoked cigarettes (3.5%) • Chronic cough and phlegm showed non-significant effect on FEV_1	
Komus *et al.*, 2008 (118)							
Design	**Population of interest**	**Definition of exposure**	**Comparator**	**Outcome**	**Confounders adjusted for**	**Results**	**General observations**
Cross-sectional study-Turkey	58 GOLD Stage 0 patients aged 40-95 years, had chronic respiratory symptoms, with post-BD FEV_1/FVC >0.70 and $FEV_1 \geq$ %80 and free from lung diseases	Any symptom of cough, phlegm and dyspnoea for >3 months	63 normal subjects	Difference in absolute values of FEV_1 between both groups	None	• Absolute and predicted values of FEV_1 and FEV_1/FVC were statistically significant lower among GOLD 0 group (p< 0.05): • Absolute FEV_1: 2.39 ± 0.62L among GOLD 0 & 2.69 ± 0.67L among the healthy (p=0.01) • FEV_1%: 87.36 ± 14.75 among GOLD 0 & 99.04 ± 18.23 among the healthy (p=0.00) • FEV_1/FVC: 73.36 ± 3.6862L among GOLD 0 and 78.46 ± 5.42 among the healthy (p=0.00)	• Performed post-BD spirometry • Small sample size • This study was translated from Turkish to English

2.4.3 Methodological quality of the included studies

The overall risk of bias in the cohort studies included is presented in Figure 2 (see Appendix F Table 44 for details of each study). All studies provided a clear description of study participants and the associated response rate. However, there was underreporting of study attrition in most of studies (n=7). Most studies accounted for the important confounders of age, sex and smoking in their analysis (n=7). Although the outcome of developing COPD was clearly defined in most of the studies (n=7), the measurement was not often reliable as lung function was tested only pre-bronchodilator (n=6). The methodological quality of the two included cross-sectional studies are detailed in Table 7 below; in one study there was a high risk of bias resulting from a poor study sample selection, whilst in the other, there was a lower risk of bias.

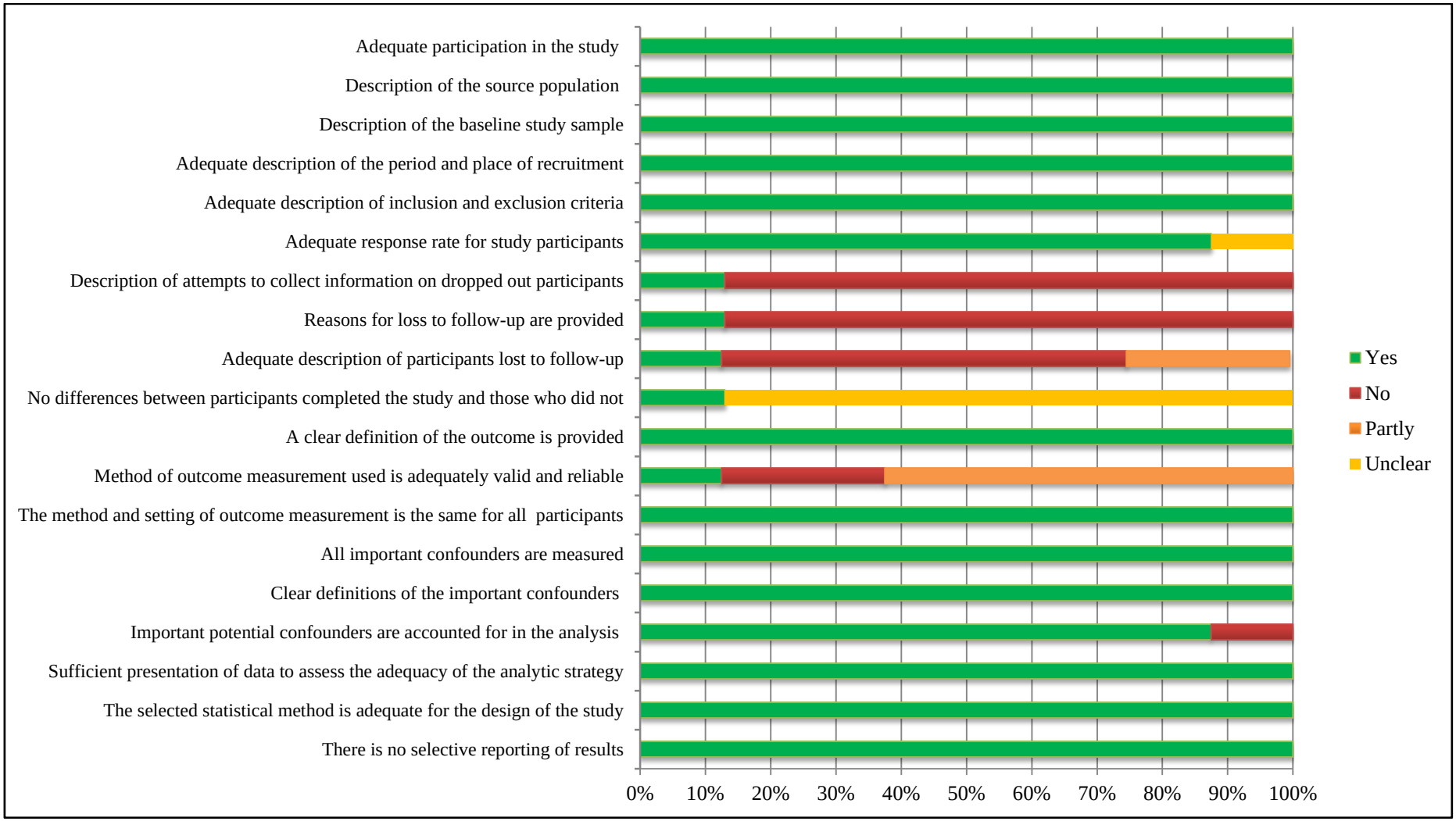

Figure 2: Overall risk of bias of the included cohort studies

Table 7: Risk of bias assessment for the included cross-sectional studies (113)

Study ID: (authors, year)		**Shin *et al.*, 2005**	**Komus *et al.*, 2008**
Domain	**Description**	**Judgement**	**Judgement**
1. Selection			
Representativeness of the sample	Truly representative sample of a target population	Y	U
	Full description of the sampling strategy is provided	Y	N
Sample size	Justified and satisfactory	Y	U
Non-respondents	Full description of the response rate or the characteristics of the responders and the non-responders is provided	Y	N
Ascertainment of the exposure	Validated measurement tool used	Y	Y
	Detailed description of the measurement tool is provided	Y	Y
2. Comparability	The subjects in different outcome groups are comparable, based on the study design or analysis	Y	Y
	The most important confounding factors are controlled	Y	N
3. Outcome			
Assessment of the outcome	Fully described	Y	Y
Statistical analysis	The statistical test used is clearly described and appropriate	Y	Y
	The measurement of the association is presented, including confidence intervals and p value	Y	Y

(Y=yes, N=no, U=unclear)

2.4.4 Main findings

2.4.4.1 GOLD Stage 0 and the excess decline in FEV_1

Table 6 above presents in detail the main findings from the six studies that examined the effect of respiratory symptoms on excess decline in FEV_1 (86, 93, 99, 116, 118, 119). All of these studies found that the presence of respiratory symptoms was significantly associated with excess FEV_1 decline. Pelkonen *et al.* who targeted only men in their cohort study, observed an excess decline in lung function values among symptomatic participants. They used the $FEV_{0.75}$ instead of FEV_1 and observed that the $FEV_{0.75}$ was 252 ml lower in subjects with symptoms at any point of the study period (95% CI, 211 to 293) than those without symptoms (99), 309 ml lower in subjects with persistent symptoms throughout the study period (95% CI, 257 to 362) but 190 ml lower in subjects with non-persistent symptoms (95% CI, 134 to 245) (99). By the end of their study, the excess decline in $FEV_{0.75}$ due to the presence of chronic cough and phlegm was 13.2 ml/year (99).

An excess decline in lung function associated with the presence of respiratory symptoms was also observed in two more studies by Vestbo *et al.* (86, 116). In their1996 paper, they observed a steeper FEV_1 decline in subjects with symptoms compared to asymptomatic participants of both sexes (116). Amongst the three groups with symptoms; persistent, newly appeared and recovered symptoms, the FEV_1 decline was greater among those with persistent symptoms (116). Furthermore, in their 2002 study Vestbo and Lange observed a significant difference in decline in the crude FEV_1 value after 5 years follow-up between asymptomatic (36.8 ml/year) and GOLD Stage 0 subjects (59.6 ml/year) (86).

Komus *et al.* completed a cross-sectional study that also observed significantly lower crude and predicted values of FEV_1 and FEV_1/FVC ratio amongst GOLD Stage 0 subjects

compared to the normal subjects (118). However, in this study the sample size was relatively small, and these findings need to be considered with caution. Brito *et al*. in a cohort study compared the effect of cough without phlegm with the effect of productive cough (with sputum) on the excess decline in FEV_1 (93). Amongst those with productive cough, the mean annual excess decline in FEV_1 was greater (76ml/year) than those with cough only (42ml/year) (93). On the other hand, Shin *et al.* in their cross-sectional study reported a non-significant association between productive cough and age-adjusted mean FEV_1 amongst smoking and non-smoking GOLD Stage 0 subjects (119). However, this association was significantly positive with dyspnoea and wheeze (119).

2.4.4.2 GOLD Stage 0 and the risk of developing COPD

Table 6 presents the main findings from the seven cohort studies that examined the effect of respiratory symptoms on the risk of developing COPD (19, 86, 89, 93, 98, 116, 117). The findings from these studies were conflicting. Vestbo *et al.* in 1996, after ten years' follow-up, observed a statistically significant association between persistent respiratory symptoms and subsequent hospitalisation, with COPD recorded as the main diagnosis (116). Newly appeared CMH was also significantly associated with increased hospitalisation because of COPD (116). However, they acknowledged that there was potential for diagnostic bias due to the misclassification of other respiratory diseases or comorbid conditions as COPD in the hospital registers (116). In contrast, in their study of 2002, they concluded that '*GOLD Stage 0 is of little help in identifying subjects at risk of COPD*' (86), because after 5 years follow-up, the difference in the development of COPD Stages 1+ amongst GOLD Stage 0 (12.4%) and the normal population (9.7%) was small (86). Although, after 15 years, the progression to COPD was significantly more frequent among GOLD Stage 0 than asymptomatic subjects (18.5% *versus* 13.2%, p=0.01) (86) . However, the adjusted effect of GOLD Stage 0 on the risk of

development of COPD Stage 1+ after 5 years (OR 1.1; 95% CI, 0.9 to 1.5) and 15 years (OR 1.2; 95% CI, 0.8 to 1.5) was not statistically significant (86).

Although incident COPD was not the main emphasis of the cohort study by Brito *et al.*, they found that after five years follow-up, the rate of incident COPD was similar (1.4%) amongst GOLD Stage 0 and asymptomatic groups (93). On the other hand, Demarco *et al.* found that the incidence of COPD in a cohort of young adults was twice as great amongst GOLD Stage 0 subjects as asymptomatic (98). After adjustment for potential confounders, chronic cough and phlegm were still statistically significant independent predictors of incident COPD (IRR=1.85; 95% CI, 1.17 to 2.93) (98). This was in agreement with Lindberg *et al.*, (2006) and Yamane *et al.*, (2010), who also found, respectively, a significant effect of respiratory symptoms as predictors of increased risk of COPD development (19) and a higher cumulative COPD incidence rate amongst symptomatics (10.1%) compared to asymptomatic (2.2%) (89). In another epidemiological study, Guerra *et al.* found that 42% of GOLD Stage 0 subjects developed COPD compared to 23% of asymptomatic subjects (P<0.001) (117). Although the unadjusted effect of GOLD Stage 0 on incident COPD was significant (HR=1.94; 95% CI, 1.40 to 2.69), this became marginal after adjusted for potential confounders (HR=1.37; 95% CI, 0.98 to 1.92) (117).

2.4.4.3 Instability of GOLD Stage 0 symptoms

Although this was not a primary aim of this review, instability of GOLD Stage 0 symptoms over time has been highlighted in some of the included cohort studies (86, 93, 98, 116) as a potential determinant of the independent effect of GOLD Stage 0 symptoms on the subsequent risk of developing COPD. This feature of instability may explain to a large extent the contradictory results from different studies that examined GOLD Stage 0. Persistence of GOLD Stage 0 symptoms has shown to be associated with a highest quartile of annual FEV_1

decline (OR 2.1; 95% CI, 1.2 to 3.7) (93) and also with a higher risk of developing COPD than newly appeared and recovered GOLD Stage 0 symptoms (116). De Marco *et al*. study found following an adjustment for confounders that, persistence of GOLD Stage 0 symptoms was associated with three times higher risk for developing COPD (IRR, 2.88; 95% CI, 1.44 to 5.79) than asymptomatic subjects, compared to (IRR=1.40; 95% CI, 0.87 to 2.26) amongst those with newly occurred GOLD Stage 0 symptoms and (IRR=1.31; 95% CI, 0.71 to 2.43) amongst recovered GOLD Stage 0 subjects (98).

Summary Box 1:

1. **GOLD Stage 0 and FEV_1 decline:**
    - The presence of GOLD Stage 0 symptoms is associated with excess FEV_1 decline compared to the normal population (n=6 studies (4 cohort and 2 cross-sectional)).
    - The effect of symptoms on FEV_1 decline was 'dose dependent' i.e. those with persistent symptoms showed higher decline followed by those with newly appeared then recovered symptoms (n=3 cohort studies)
2. **GOLD Stage 0 and the risk of developing COPD**
    - 4 out of 7 cohort studies found a higher risk of COPD amongst GOLD Stage 0 subjects than the normal population, while the other 3 cohort studies found a non-significant effect.
    - The effect of GOLD Stage 0 symptoms on the risk of developing COPD was also "dose dependent" (n=2 cohort studies).
3. **Instability of GOLD Stage 0 symptoms**
    - This feature of instability was found to be the main determinant of the independent effect of GOLD Stage 0 symptoms on the excess FEV_1 decline and on the risk of developing COPD Stages 1+ (n=4 cohort studies).

2.5 Discussion

2.5.1 Summary of evidence

This is the first systematic review examining the risk of developing COPD amongst GOLD Stage 0 patients compared to the normal population. The presence of GOLD Stage 0 symptoms was found to be associated with an accelerated FEV_1 decline; however, this association was most marked among participants with persistent symptoms over time, followed by those with newly appeared then recovered GOLD Stage 0 symptoms than the normal population. On the other hand, inconsistent results were observed amongst cohort studies regarding the independent effect of GOLD Stage 0 on the risk of developing of COPD compared to the normal population. Four of the seven cohort studies included (19, 89, 98, 116) found a higher risk of COPD amongst GOLD Stage 0 subjects, whereas the other three cohort studies found no evidence of an effect of GOLD Stage 0 on the risk of developing COPD (86, 93, 117). However, the instability of GOLD Stage 0 could possibly contribute to these contradictory results.

2.5.2 Limitations

Undertaking a highly sensitive search strategy to retrieve articles for this review was complex; a broad spectrum of search terms was used. This subsequently resulted in a huge number of records, which was challenging and time consuming but was unlikely to have missed important studies. This review is also limited to being descriptive due to the high clinical and statistical heterogeneity amongst the studies included, resulting in practical difficulties for summarising and synthesising the data.

2.5.3 Implication for research and clinical practise

It seems that patients with GOLD Stage 0 symptoms do have worse lung function decline over time. However, the main factor affecting the significance of GOLD Stage 0 symptoms on risk of developing COPD is the feature of instability of symptoms over time. This finding may help to clarify the ongoing debate about the relevance of GOLD Stage 0. Future studies must account for this feature when examining the risk of COPD amongst this group of patients. In clinical practice, GOLD Stage 0 patients with persistent symptoms may need to be targeted for COPD screening and management.

2.5.4 Conclusion

GOLD Stage 0 is associated with a higher risk of accelerated FEV_1 decline than the normal population. However, whether or not this necessarily leads to a higher risk of developing COPD remains unclear. This could be explained by the instability of GOLD Stage 0 symptoms over time, as persistence of GOLD Stage 0 was associated with a higher risk of developing COPD GOLD Stages 1+.

3 PROGNOSIS AND PROGNOSTIC FACTORS OF GOLD STAGE 0: SYSTEMATIC REVIEWS

This chapter consists of two systematic reviews of literature, the first examining the prognosis of GOLD Stage 0 patients compared with established COPD patients and the second examining the main factors affecting GOLD Stage 0 patients' prognosis.

3.1 Abstract

Background: Information on the prognosis of patients with chronic respiratory symptoms is limited and conflicting. Two systematic reviews in this chapter aim to answer the following questions: *what is the prognosis of patients with chronic respiratory symptoms but normal lung function compared to established COPD patients?* And *what are the main factors that can affect the prognosis of patients with chronic respiratory symptoms but normal lung function?*

Methods: Medline, Embase and other bibliographic databases (from inception to week 4 January, 2014) were searched for relevant studies that examined the prognosis and prognostic factors among adults aged 40 years and above who had chronic respiratory symptoms but normal lung function, in comparison with confirmed COPD patients. Cohort studies were sought. But for review (2), cross-sectional and case-control studies were also considered if they informed the review question. Two reviewers independently extracted data and assessed the quality of studies included. Analyses were descriptive.

Results: There were 35 records identified as potentially relevant. Nine studies were eligible for inclusion in review (2), two cohort studies were eligible for inclusion in review (3) and 24 studies were excluded. The presence of GOLD Stage 0 symptoms was associated with increased mortality risk, high healthcare utilisation and increased risk of difficulties in daily

activities compared to the normal population and similar to that measured among those with mild COPD. Review (3) found insufficient evidence about the prognostic factors of GOLD Stage 0. However, the persistence of GOLD Stage 0 symptoms was proposed as the main factor affecting the risk of developing COPD among GOLD 0 patients in Chapter 2 and this review found that the main factors associated with the persistence of symptoms were persistent smoking, male gender, older women and metabolic syndrome amongst men.

Conclusion: GOLD Stage 0 is associated with increased risk of poor prognosis compared to the normal population and similar to those with mild COPD. However, the instability of symptoms over time was not fully accounted for and the effect of GOLD Stage 0 could therefore be underestimated. Prognostic factors affecting long-term morbidity and mortality among GOLD Stage 0 patients have not been entirely investigated and warrant more attention.

3.2 Introduction

GOLD Stage 0 had been excluded from the GOLD committee staging scheme of COPD since 2006 due to the inadequate evidence regarding the progression from GOLD Stage 0 to diagnosed COPD Stages 1+ (9). However, the presence of chronic respiratory symptoms could be an important predictor of long-term morbidity and mortality amongst affected subjects, even in the absence of diagnosed airflow obstruction (9). The natural history of unexplained chronic respiratory symptoms of GOLD Stage 0 in the general population is an under-investigated area (101), with little attention being given to this condition (105), despite being a common health problem across the population, especially amongst smokers (9, 101). In Chapter two, review (1) found that GOLD Stage 0 was associated with higher risk of excess decline of FEV_1 than the normal population. The risk of developing COPD among

GOLD Stage 0 population was not clear, although it might be related to persistence of symptoms. The following two systematic reviews of literature build on Chapter 2 and will be the first to gather the available evidence regarding the prognosis and prognostic factors of GOLD Stage 0 patients compared to confirmed COPD patients. In order to highlight gaps in knowledge and identify a scope for further research, the following two questions will be answered:

1. What is the prognosis of patients with chronic respiratory symptoms but normal lung function compared to established COPD patients?
2. What are the main factors affecting the prognosis of patients with chronic respiratory symptoms but normal lung function?

3.3 Methods

These reviews were conducted in parallel with systematic review (1), where there were shared methods for search strategy, study selection, data extraction and methodological quality assessment (See previous chapter for general review methods (Section 2.3). As it was the case with systematic review (1), the two reviews presented in this chapter are descriptive due to the practical difficulties involved with a formal meta-analysis of prognostic systematic reviews, including risk of publication bias, methodological quality and limitation in reporting quality of observational studies (114, 115).

As with review (1), there was high clinical and statistical heterogeneity among the included studies in the present two reviews, different patient groups were targeted (younger age, middle aged, men only, occupational cohorts); there was a variation in cut-off points used to define normal lung function and studies measured different outcomes. Moreover, the sample size in many studies was small, the analysis across studies adjusted for different variables

(and sometimes was unadjusted) and in some cohort studies the completeness of follow-up was unknown.

3.3.1 Inclusion criteria

Table 8 below summarises the selection criteria for the present reviews (2) and (3):

3.3.1.1 Population

Both reviews sought studies that assessed middle-aged and elderly populations (40 years and above) who had chronic respiratory symptoms with normal lung function.

3.3.1.2 Exposure and comparator

The exposure in review (2) was the presence of any chronic respiratory symptoms and in review (3) was any factor that might affect the prognosis of GOLD Stage 0 patients (excluding genetic factors and childhood respiratory infection). The comparator group in review (2) was patients with a confirmed COPD diagnosis.

3.3.1.3 Outcome

For both reviews, studies examining any health outcome were included.

3.3.1.4 Study Design

For review (2), ideally cohort studies were included. However, cross-sectional and case-control studies were also considered. Although cross-sectional studies do not allow causality to be proven or evaluation of prognosis, they may support the findings from the cohort studies. For review (3), only cohort studies were included.

Table 8: PECOS components for reviews 2 and 3

Question components (PECOS)	Review2: the prognosis of GOLD Stage 0	Review3: prognostic factors of GOLD Stage 0	Exclusion criteria
Population	People aged 40 years and above with chronic respiratory symptoms	People aged 40 years and above with chronic respiratory symptoms and normal lung function	Studies of younger age groups unless asthma excluded
"Exposure"	Chronic respiratory symptoms with normal lung function	Any prognostic factor; for e.g. age, sex, smoking status, air pollutions, BMI, biomarkers, occupational exposure, FEV_1 predicted and comorbidity	Childhood respiratory infections Genetic factors
Comparator	COPD patients	None	
Outcome	Any health outcome; for e.g. mortality, HRQoL, exacerbation and healthcare utilisation	Any health outcome	
Study design	Ideally cohort studies but case-control and cross-sectional studies might be considered	Cohort studies	Reviews, editorials, case series and reports
Types of publication	All relevant studies with available full text, regardless of their publication status		

3.4 Results

3.4.1 Study selection

The results of the study selection process (Figure 3) are detailed under section 2.4.1 within review (1) in the last chapter. Of the 73 articles, 35 were identified as potentially relevant studies for answering review 2 and 3 questions; nine studies were found to be eligible for inclusion in review (2), whilst two were eligible for inclusion in review (3). Overall, 24 studies were excluded with the reasons for exclusion documented. The two reviewers disagreed on four studies for inclusion in review (2), on which the third reviewer (RJ) was consulted.

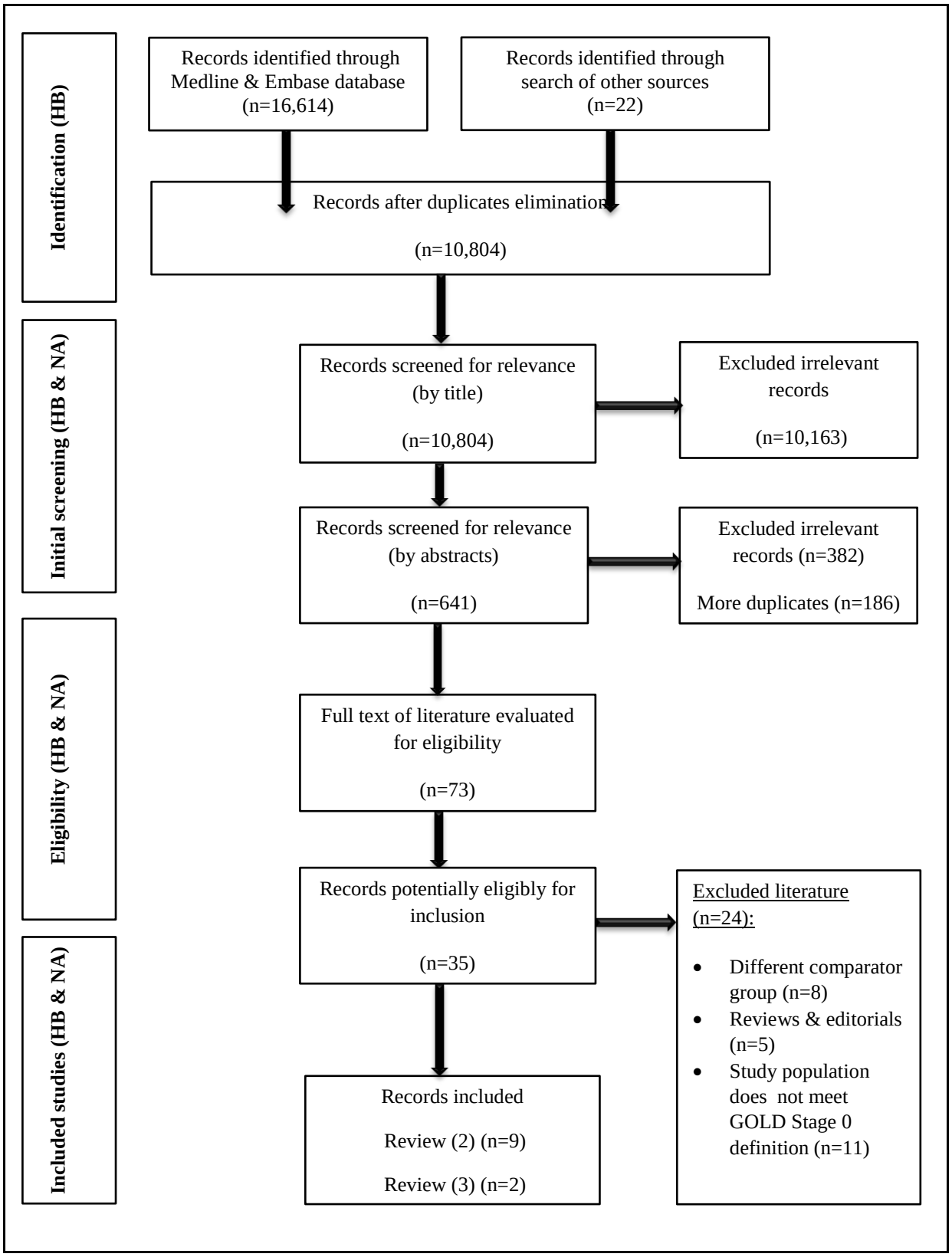

Figure 3: PRISMA flow diagram of study selection

3.5 Review (2): What is the prognosis of patients with chronic respiratory symptoms but normal lung function compared to confirmed COPD patients?

3.5.1 Results

3.5.1.1 The study characteristics

The characteristics and the main findings of the included nine studies are detailed in Table 9 below:

3.5.1.1.1 Study design and setting

Nine studies were identified as eligible to answer this review question: six cohort studies (9, 95, 100, 103, 104, 120), three cross-sectional studies (90, 101, 102) but no relevant case-control studies were identified. The length of follow-up in the cohort studies ranged from 4 to 30 years, whilst the sample size across all studies ranged between 115 and 15,440 participants.

3.5.1.1.2 Population

Most of the studies targeted middle-aged subjects (40 years and above), with the exception of one cross-sectional study, where a younger age group (20–44 years) was studied (90). Although, in this study, asthma was not excluded in the initial analysis, subsequently it was excluded in a secondary analysis (90).

3.5.1.1.3 Exposure

GOLD Stage 0 symptoms were defined in most of the included studies using the MRC definition of CB—*'the presence of chronic cough and sputum production 3 months a year in the last 2 years'*—with normal lung function ($FEV_1/FVC \geq 70\%$), except in two studies,

which also included wheeze and dyspnoea (95, 101), and one study included dyspnoea (104), in addition to cough and sputum production. Only one study confirmed the presence or absence of airflow obstruction using post-bronchodilator spirometry (101). The remainder performed only pre-bronchodilator spirometry.

3.5.1.1.4 Comparator

GOLD Stage 0 patients were directly compared to confirmed COPD patients only in two studies (100, 101) while in the other seven studies, GOLD Stage 0 patients and COPD patients were both compared with a reference group of normal population (9, 90, 95, 102-104, 120).

3.5.1.1.5 Outcome

Amongst the included cohort studies, four studies examined the risk of mortality amongst GOLD Stage 0 subjects (95, 103, 104, 120), one study assessed the rate of healthcare utilisation and the HRQoL (100), whilst one study examined the hospital admission rate (9). Amongst the included cross-sectional studies, one study (101) examined exacerbation-like events; one study assessed the rate of healthcare utilisation (90) and the third study (102) examined HRQoL.

Table 9: Study characteristics and the main findings (Review 2)

Petty *et al.*, 1976 (120)							
Design	**Population**	**Definition of exposure**	**Comparator**	**Outcome**	**Confounders adjusted for**	**Results**	**General observations**
Prospective cohort study with 6-7 years follow up period-USA	• 67 GOLD 0 subjects with a mean age of 47.1 years and had CB symptoms • 41 COPD patients as defined by FEV_1/FVC <60%	*"Bringing up mucous from the chest in the morning and/or during the day for at least 3 months of the year"*	111 healthy adults	All-cause mortality rates	None	Mortality rate over the follow-up period among patients with CB was 5.9% (with FEV_1/FVC>75%) and 10% (with FEV_1/FVC=60-74%) with an average of 8.0% and among COPD patients was 19.5%	• The study did not use the standard definition of COPD • Relatively small sample size • CB symptoms were unstable over the study period
Ekberg-Aronsson *et al.*, 2005 (103)							
Design	**Population**	**Definition of exposure**	**Comparator**	**Outcome**	**Confounders adjusted for**	**Results**	**General observations**
Prospective cohort study in Sweden (1974-2003)	• 493 GOLD Stage 0 subjects aged 27-61 years (mean age=46.5 years) and free from other comorbid conditions • 3,356 COPD patients Stages 1-4, classified according to the GOLD criteria	1. "*Daily cough lasting more than 3 months in more than 2 years"* 2. *"Ever symptoms of CB")* 3. *"Phlegm coming up from chest daily for more than three months"* 4. *"Recent symptoms of CB"*	Normal individuals	All-causes mortality risks	• Age • Sex • Smoking Inhalation habits	• Compared to normal population, smoking men Stage 0 patients showed an increased mortality risk, HR=1.65 (1.32–2.08) of similar magnitude to COPD Stage 2, HR=1.41 (1.31–1.70) and higher than COPD Stage 1 HR=1.13 (0.98–1.29). • No difference in mortality risk among GOLD 0 smoking men defined as "ever symptoms of CB", HR=1.62 (1.25–2.12 p<0.0001) or "recent	• Was not clear whether asthma was excluded • Lack of follow up respiratory data did not allow to determine the stability of GOLD 0 symptoms over the study period

						symptoms of CB" HR=1.74 (1.13–2.68 p= 0.012). • Among former and never smoker men, Stage 0 was associated with an increased mortality risk, but the number of deaths was small • Among smoking women, the HRs increased stepwise in Stage 1–4 (p for trend <0.0001). The HR was slightly increased in Stage 0, with a similar magnitude as in smoking men but of borderline significance	
Stavem *et al.*, 2006 (104)							
Design	**Population**	**Definition of exposure**	**Comparator**	**Outcome**	**Confounders adjusted for**	**Results**	**General observations**
25-27 years prospective cohort study in Norway	• 131 Gold Stage 0 subjects with $FEV_1/FVC \geq$ 70% & free from known respiratory and non-respiratory comorbidity • 265 COPD patients stages 1-4. COPD defined & classified using the GOLD criteria	*"Bring up phlegm on most days for as much as 3 months each year", "troubled by shortness of breath when hurrying on level ground or walking up a slight hill"* and *"short of breath walking with other people of your own age on level ground"*	1,223 normal reference	Long term mortality (all-cause)	• Age • Smoking habits • BMI • CVDs risk factors (systolic BP & serum cholesterol) • FEV_1 • Physical fitness	• GOLD Stage 0 subjects had a non-significantly increased adjusted risk of death (HR=1.19; 95% CI 0.91–1.57, p= 0.21) compared to the normal • GOLD Stage 1 patients (HR=1.30; 95% CI 1.0–1.69, p= 0.05) and Stage 2 (HR, 1.77; 95% CI 1.35–2.32, p < 0.0001) showed increased all-cause mortality than the normal. • When GOLD 0 defined	Targeted men only

						broadly by the presence of any respiratory symptom, the HR for mortality became significant (HR, 1.35, CI; 1.11–1.64 p=0.003) • In multivariate analysis, GOLD Stage 0 showed a better long-term prognosis than COPD patients Stages 1, 2, and 3, with non-significant excess risk of long-term mortality	
Mannino *et al.*, 2006 (95)							
Design	**Population**	**Definition of exposure**	**Comparator**	**Outcome**	**Confounders adjusted for**	**Results**	**General observations**
11 years prospective cohort study-USA	• 2,244 GOLD Stage 0 subjects, aged 43–66 years • 3,434 COPD patients classified into 4 severity stages using the GOLD criteria •	*"Presence of respiratory symptoms of cough, sputum, wheeze or dyspnoea in the absence of any lung function abnormality or disease"*	8,661 normal individuals	Mortality risk	• Age • Race • Sex • Smoking habit • Pack years • BMI • Education level	• Following adjustment for confounders, all GOLD stages predicted a higher risk of death compared to normal population: GOLD 0 (HR=1.5; 95% CI, 1.3-1.8), GOLD 1 (HR=1.4; 95% CI, 1.1-1.6), GOLD 2 (HR=2.4; 95% CI, 2.0-2.9) and GOLD 3 or 4 (HR=5.7; 95% CI, 4.4-7.3) • At each GOLD stage, patients reporting at least one respiratory symptom had a higher risk of death than asymptomatic	

Ekberg-Aronsson *et al.*, 2008 (9)							
Design	**Population**	**Definition of exposure**	**Comparator**	**Outcome**	**Confounders adjusted for**	**Results**	**General observations**
Prospective cohort study in Sweden (1974-2002)	• 493 Gold Stage 0 subjects with a mean age of 46.5 years • 3,356 COPD patients stages 1-4 classified using the GOLD criteria	*"Chronic productive cough lasting more than 3 months, for more than 2 consecutive years"*	2,792 normal individuals	All-causes hospital admission rates	• Age • Gender • Smoking habits	Compared to the normal, all-causes hospital admission rates showed statistically significant increase for smoking GOLD 0 men and women, smoking men with COPD Stages 1-4 and smoking women with COPD Stages 2 and 4. The rates did not increase among ex and never smoking GOLD 0 patients and COPD patients Stages 1–4	• Some cohorts did not perform a spirometry • The study did not account for the instability of GOLD 0 symptoms over the follow-up period
De Marco *et al.*, 2004 (90)							
Design	**Population**	**Definition of exposure**	**Comparator**	**Outcome**	**Confounders adjusted for**	**Results**	**General observations**
Cross sectional study- the European Community Respiratory Health Survey	• 1,751 GOLD Stage 0 patients aged 20–44 years (mean= 33.2 years) • 537 COPD patients Stages 1-4 classified using the GOLD criteria	*"Cough and/or phlegm from the chest, usually in winter and on most days for as long as 3 months each year"*	12, 567 normal population	Healthcare utilisation	• Smoking • Sex • Childhood respiratory infections • Occupation Socio-economic status	• Compared to the normal, all Stages, including Stage 0, showed higher proportion of doctor visits (32.6% *vs* 18.4%, p<0.001), prescribed medication (24.1% *vs* 14.0%, p<0.001), had at least one emergency department attendance/or hospital admission (10.8% *vs* 5.1%, p<0.001) because of respiratory problems • Following exclusion of patients with coexisting asthma, the relative	• Does not separate out GOLD 0 patients in the results of healthcare utilisation • Asthma was not excluded in the initial analysis but subsequently excluded in the secondary analysis

						pattern of utilisation remained unchanged	
Joo *et al.*, 2008 (100)							
Design	**Population**	**Definition of exposure**	**Comparator**	**Outcome**	**Confounders adjusted for**	**Results**	**General observations**
4 years prospective cohort study -USA	23 GOLD Stage 0 adults, aged 25-87 years (mean =71.5 years)	The presence of chronic cough and sputum production	49 COPD patients classified as GOLD Stages 1–2 and 44 patients as Stage 3–4	HRQoL & Healthcare utilization among both patients groups	• Age • Smoking status	• There was a statistically significant gradient of effect on HRQoL from GOLD Stage 0 through GOLD Stage 4. However, effects were not significantly different between GOLD Stage 0 and GOLD Stages 1 and 2 • GOLD 0 group had higher averages of outpatient visits/year of 14.4 (SD = 30.5), hospitalisations/year of 0.3 (SD = 0.8) and all-cause inpatient visits of 1.89 (SD = 1.36) than COPD patients, but the difference was not statistically significant	• 98% of GOLD 0 group were males • Small sample size
Kanervisto *et al.*, 2010 (102)							
Design	**Population**	**Definition of exposure**	**Comparator**	**Outcome**	**Confounders adjusted for**	**Results**	**General observations**
Cross-sectional study-Finland	• 630 GOLD Stage 0 patients aged ≥30 years277 COPD patients Stages1-4 classified using the GOLD criteria	*"Chronic cough and sputum production 3 months a year or in the last 2 years without airways obstruction*"	3,811 normal population	HRQoL	• Age • Gender • BMI • Socio-economic status • Smoking	Compared with the normal: • COPD patients and GOLD 0 patients had poorer adjusted activities in daily living (OR= 4.52 (3.33 to 6.15) and OR=2.01 (1.55 to 2.60)), respectively), reduced	Was not clear whether asthma was excluded

					habits • FEV_1% • Comorbid conditions	instrumental activities in daily living(OR=3.81(2.82 to 5.16) and OR= 2.15 (1.70 to 2.72), respectively) • GOLD 0 patients had difficulties in experiences of day to day life (OR= 1.58, 95%CI, 1.31 to 1.90), while COPD patients did not (OR= 1.11, 95%CI, 0.83 to 1.49) • GOLD 0 patients had fewer hobbies (OR= 1.38, 95%CI, 1.12 to 1.70) while COPD patients had not (OR= 1.24, 95%CI, 0.92 to 1.66)	
Tan *et al.*, 2014 (101)							
Design	**Population**	**Definition of exposure**	**Comparator**	**Outcome**	**Confounders adjusted for**	**Results**	**General observations**
Cross-sectional multisite population-based study in Canada	658 GOLD Stage 0 subjects aged ≥ 40 years and free from diagnosed respiratory diseases	*"Chronic cough or phlegm not occurring during a 'cold' and on most days for as much as 3 months each year for 2 years"*, or *'episodes of wheezing or whistling in the chest associated with feeling of shortness of breath, in the past 1 year not occurring during a cold"* or dyspnoea of MRC grade ≥ 2	838 COPD patients, defined using the GOLD committee's definition	Exacerbation like events	• Age • Gender • BMI • Education • Ever smoking • Comorbid conditions • Pulmonary function	Exacerbation in the last year were reported by 3.9% of GOLD 0 subjects compared with 8.2% of COPD patients (p<0.001). However the impact on healthcare utilisation was similar; among GOLD 0 group, 68% of exacerbations needed doctor visit and among COPD group, 62% needed a doctor visit	

3.5.1.2 Methodological quality of the included studies

The overall risk of bias in the included cohort studies is presented in Figure 4 (see Appendix F Table 45 for details of each study). Most studies provided a clear description of study participants and the associated response rate (n=5). Although all studies provided reasons for loss to follow-up, the description of participants lost to follow-up was inadequate in most of them (n=4). Most studies accounted for the important confounders in their analysis (n=5) and the outcome was clearly defined and accurately measured in most of these studies (n=5). The methodological quality of the three included cross-sectional studies is detailed in (Table 10). The overall risk of bias was low.

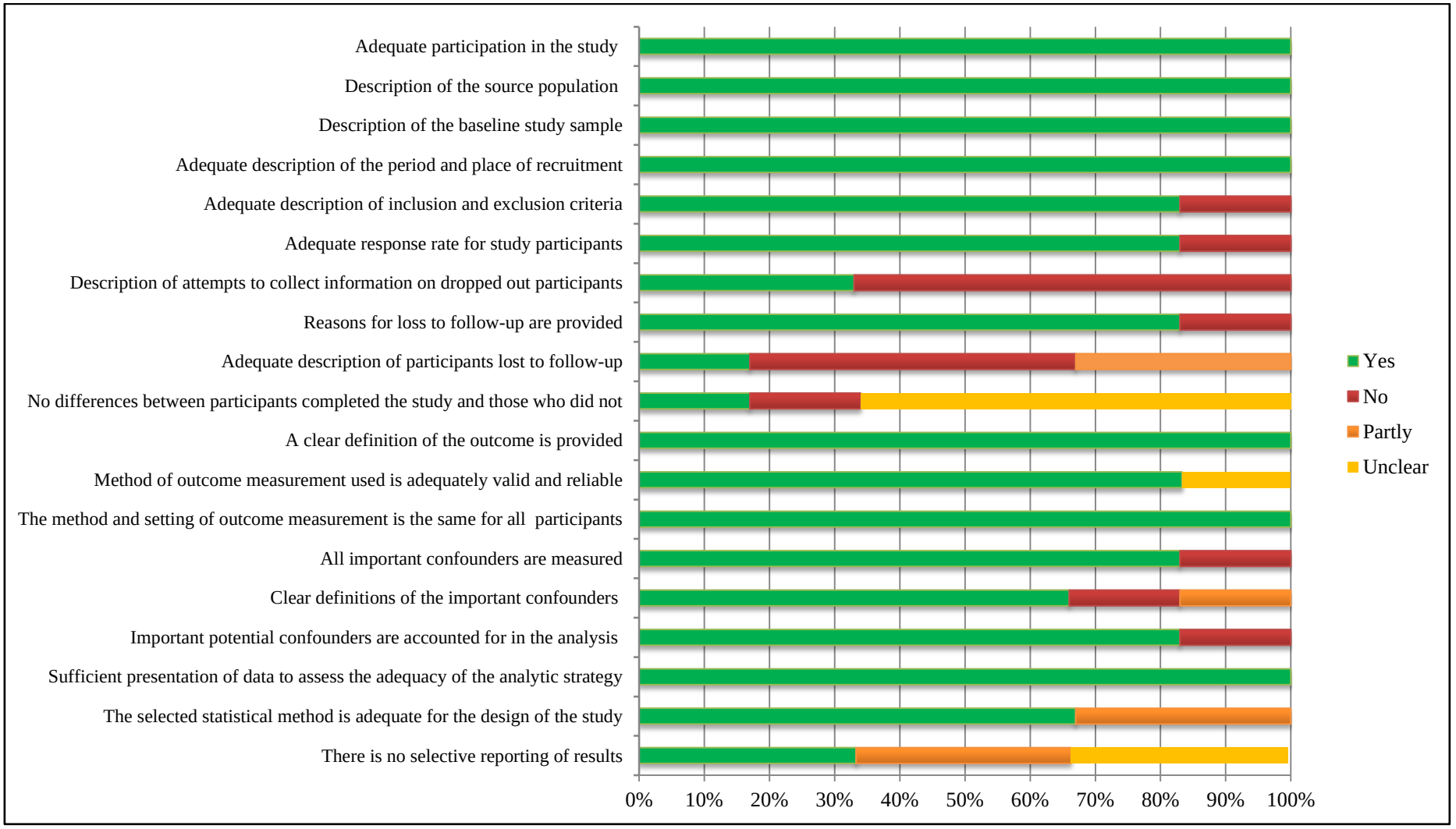

Figure 4: Overall risk of bias of the included cohort studies (Review 2)

Table 10: Risk of bias assessment for the included cross-sectional studies in review 2 (113)

Study ID: (authors, year)		**De Marco *et al.*, 2004**	**Tan *et al.*, 2014**	**Kanervisto *et al.*, 2010**
Domain	**Description**	**Judgement**	**Judgement**	**Judgement**
1. Selection				
Representativeness of the sample	Truly representative sample of a target population	Y	Y	Y
	Full description of the sampling strategy is provided	Y	Y	Y
Sample size	Justified and satisfactory	Y	Y	Y
Non-respondents	Full description of the response rate or the characteristics of the responders and the non-responders is provided	P	Y	P
Ascertainment of the exposure	Validated measurement tool used	Y	Y	Y
	Detailed description of the measurement tool is provided	Y	Y	Y
2. Comparability	The subjects in different outcome groups are comparable, based on the study design or analysis	Y	Y	Y
	The most important confounding factors are controlled	Y	Y	Y
3. Outcome				
Assessment of the outcome	Fully described	Y	Y	Y
Statistical analysis	The statistical test used is clearly described and appropriate	Y	Y	Y
	The measurement of the association is presented, including confidence intervals and p value	Y	Y	Y

(Y=yes, N=no, P=partly)

3.5.1.3 The main findings

3.5.1.3.1 GOLD Stage 0 and the risk of mortality

Four cohort studies examined the risk of mortality amongst GOLD Stage 0 subjects (95, 103, 104, 120) (Table 9). Mannino *et al.* (2006) cohort study found that compared with the normal population, the presence of GOLD Stage 0 respiratory symptoms was associated with an increased risk of mortality (HR=1.5, 95% CI; 1.3 to1.8) to a similar extent to COPD Stage 1 (HR=1.4, 95% CI; 1.1 to 1.6) (95). COPD GOLD Stage 2 (HR=2.4, 95% CI; 2.0 to 2.9) and COPD Stages 3 or 4 (HR= 5.7, 95% CI; 4.4 to 7.3) had a higher risk of mortality (95).

The second cohort study (103) observed that GOLD Stage 0 was associated with a higher risk of mortality than the normal population, especially among current smoking men (HR=1.65, CI; 1.32 to 2.08) (103). This figure was comparable to that of COPD Stage 2 (HR=1.4, CI; 1.31 to 1.70) (103) and greater than that observed amongst COPD Stage 1 subjects (HR=1.13, CI; 0.98 to 1.29) (103). Similar effects were observed even with modified definitions of GOLD Stage 0 *'ever symptoms of CB'* (HR=1.62, CI; 1.25 to 2.12) or *'recent symptoms of CB'* (HR=1.74, CI; 1.13 to 2.68) (103). Amongst current smoking women, the HR was increased in GOLD Stage 0 compared with the normal population, demonstrating a similar magnitude to that observed amongst men but showing borderline statistical significance (103). Moreover, GOLD Stage 0 was associated with an increased risk of mortality amongst never and former smokers of both sexes (103), but the number of deaths was very small (103). However, in this study, there were no follow-up data on respiratory symptoms and it was not possible to determine the stability of GOLD Stage 0 symptoms over the study period. Therefore, the effect of symptoms on the risk of mortality might be even underestimated (103).

Although they did not adjust for the potential confounders, Petty *et al.,* (1976), when comparing the risk of death amongst GOLD Stage 0 and COPD patients compared to a healthy reference group showed that the mortality rate over a follow-up period of 7 years was 19.5% amongst COPD patients, and amongst patients with CB symptoms was lower, with an average of 8.0% (120). Stavem *et al*., (2006), who targeted men only, also found compared to a normal population that GOLD Stage 0 subjects did not have a statistically significant increased adjusted risk of mortality (HR=1.19, 95% CI; 0.91 to 1.57), whilst GOLD 1 and 2 showed a statistically significant increased risk of death (HR=1.30, 95% CI; 1.00 to 1.69 and HR=1.77, 95% CI; 1.35 to 2.32, respectively) (104). However, GOLD Stage 0 patients showed a statistically significant increased mortality risk similar COPD Stage 1 risk (HR=1.35, CI; 1.11 to 1.64) when a broadened definition of GOLD Stage 0 was used (by the presence of any phlegm or any breathlessness) (104).

3.5.1.3.2 Exacerbation-like events

One cross-sectional study examined the exacerbation like events amongst GOLD Stage 0 patients with persistent symptoms, compared to those with confirmed COPD (101). It found that the proportion of GOLD Stage 0 subjects who experienced exacerbations defined as *"a period of worsening of breathing problems that got so bad that it interfered with usual daily activities or caused the individual to miss work"* was lower (3.9% *versus* 8.2%, $p<0.001$) than amongst COPD patients (101). However, the influence on healthcare utilisation was equal or slightly greater amongst GOLD Stage 0 subjects, with 68% of exacerbations requiring a doctor consultation compared to 62% amongst COPD group (101). Furthermore, this study found that GOLD Stage 0 and COPD patients shared common predictors for respiratory exacerbation events (101) (Table 9).

3.5.1.3.3 HRQoL

Two studies examined HRQoL amongst GOLD Stage 0. The cohort study of Joo *et al.,* (2008) compared HRQoL amongst GOLD Stage 0 with those diagnosed with COPD (100). Following adjustment for the confounding of age and smoking, it was found that GOLD Stage 0 subjects had statistically significant better HRQoL scores than those with COPD Stages 1–2 and 3–4 (mean total score 29.14, 36.00 and 52.92, respectively, $p<0.001$) (100).

The cross-sectional work of Kanervisto *et al.,* (2010), found that compared to the normal population, both GOLD Stage 0 participants experienced a poorer physical functioning in daily living (OR=2.01; 95% CI, 1.55 to 2.60) than the normal population but better than COPD patients (OR=4.52; CI, 3.33 to 6.15). (102). However, GOLD Stage 0 subjects reported more difficulties in experiences of day to day life (OR=1.58; CI, 1.31 to 1.90) (102), whilst COPD patient did not (OR=1.11; CI, 0.83 to 1.49) (102).Furthermore, GOLD Stage 0 patients reported fewer hobbies (OR=1.38; CI, 1.12 to 1.70), whilst COPD patient did not (OR=1.24; CI, .92 to 1.66) (102).

3.5.1.3.4 Healthcare utilisation

Healthcare utilisation was examined in three studies, where the cohort study of Joo and colleagues (2008) suggested that GOLD Stage 0 subjects had a higher rate of all cause-inpatient visits, with an average of 1.89 (SD=1.36) visits per patient-year than COPD patients (100) and had a higher rate of all cause outpatient visits, with an average of 14.40 (SD=30.79) visits per patient-year (100) compared to an averages of 10.50 (SD=13.53) amongst COPD patients Stages 1–2 and 10.73 (SD=14.24) amongst COPD patients Stages 3–4 subjects (100). However, the differences between subgroups were not statistically significant (p=0.308) (100). The utilisation of respiratory medications in this study was higher among COPD patients (26% amongst GOLD Stage 0 subjects, 59% amongst COPD patient Stages 1–2 and

91% amongst COPD Stages 3–4) (100). However, due to the small sample size of this study, these findings should be viewed with caution.

The cross-sectional study by De Marco *et al.,* (2004) stated that, the use of healthcare resources, including physician visits, prescribed medications, emergency department visits and one or more hospital admission due to respiratory problems was similar amongst GOLD Stage 0 patients and those with COPD Stages 1+ (Table 9) and the trend remained unchanged, even after excluding those with self-reported asthma (90). The Ekberg-Aronsson *et al*., (2008) cohort reported generally increasing gradient of hospital admissions amongst current smokers from GOLD Stage 0 through COPD patients Stages 1–4 compared to the normal population (9). However, the rates did not increase amongst ex and never smoking GOLD Stage 0 patients (9) (Table 9). However, in this study, there were no follow-up data on respiratory symptoms; thus, the instability of GOLD Stage 0 symptoms over the study period was not accounted for (9).

Summary Box 2:

1. **GOLD Stage 0 and the risk of mortality**
    - Compared to normal population, GOLD Stage 0 patients showed a similar adjusted mortality risk to those with COPD Stage 1 (n=1 cohort study) and current smoking GOLD Stage 0 men showed a similar risk to COPD Stage 2 patients (n=1 cohort study).
    - Conversely in 2 other cohort studies, the mortality risk tended to be higher amongst confirmed COPD patients but not amongst GOLD Stage 0 patients compared to normal population.
    - However, using a broader definition of GOLD Stage 0 was associated with a higher mortality risk similar to COPD Stage 1 patients (n=1 cohort study).

2. **GOLD Stage 0 and exacerbation events**
    - GOLD Stage 0 subjects experienced fewer exacerbations but similar healthcare utilisation to COPD patients (n=1 cross-sectional study).
3. **HRQoL amongst GOLD Stage 0 patients**
    - Compared to COPD patients, GOLD Stage 0 subjects tended to have better total HRQoL scores (n=1 cohort study), although GOLD 1 and 2 did not show significant difference from GOLD 0.
    - Compared to normal population, GOLD Stage 0 and COPD subjects experienced a worse physical functioning, with the confirmed COPD patients tending to have worse outcomes (n=1 cross-sectional study).
4. **Healthcare utilisation amongst GOLD Stage 0**
    - Compared to confirmed COPD patients, GOLD Stage 0 subjects tended to have a higher rate of healthcare utilisation than COPD patients, although was not statistically significant (n=1 cohort study).
    - Compared to the normal, increased all-cause hospital admission rate showed a gradient of effect from GOLD Stage 0 through to diagnosed COPD patients (n=1 cohort study).
    - Healthcare utilisation due to respiratory problems amongst GOLD Stage 0 was similar to those with mild COPD (n=1 cross-sectional study).
5. None of the studies included accounted for the instability of GOLD Stage 0 symptoms over time.

3.5.2 Discussion

3.5.2.1 Summary of evidence

This is the first systematic review of literature to examine the prognosis of GOLD Stage 0 patients compared to those with confirmed COPD diagnosis. Generally there was a gradient of effect with increased risk of mortality, poor HRQoL and increased healthcare utilisation from the normal population through to diagnosed COPD patients. GOLD Stage 0 patients

have worse prognosis than the normal population but have similar outcomes to COPD Stages 1 and similar to COPD Stage 2 among smokers. Overall, GOLD Stage 0 patients tended to have similar mortality risk, better HRQoL, fewer exacerbations and similar consumption of healthcare resources to patient with mild COPD.

3.5.2.2 Limitations

The main limitation of this review is the paucity of cohort studies that examined the prognosis of GOLD Stage 0 patients and the inclusion of cross-sectional studies which does not allow for prognostic evaluation. However, the search was comprehensive and it was unlikely to have missed important cohort studies. Another limitation is the lack of studies that directly compared GOLD 0 patients with COPD patients, which resulted in the inclusion of studies that compared both patients groups with the normal population.

3.5.2.3 Implication for research and clinical practise

The findings from this review suggest that the GOLD Stage 0 could be associated with increased risk of poor prognosis and healthcare utilisation to a similar extent as mild COPD. However, there is limited evidence and the instability of GOLD Stage 0 symptoms was not fully accounted for when examining prognosis. Therefore, future studies must consider the instability of GOLD Stage 0 symptoms to fully examine their effects. Furthermore, a sensitivity analysis based on the different definitions of GOLD Stage 0 needs to be considered in future studies, in order to establish a consensus definition of this condition.

3.5.2.4 Conclusion

GOLD Stage 0 is associated with increased risk of poor prognosis compared to the normal population and similar to those with mild COPD. GOLD Stage 0 population showed a higher mortality risk to an extent which may be similar to patients with mild COPD, particularly

when broader definition of GOLD Stage 0 was used. Despite better reported HRQoL, GOLD Stage 0 patients tended to have similar restriction in daily activities and similar healthcare consumption to patients with mild COPD. However, the instability of symptoms over time was not fully accounted for and the effect of GOLD Stage 0 could even be underestimated.

3.6 Review (3): What are the main factors that can affect the prognosis of patients with chronic respiratory symptoms but normal lung function?

3.6.1 Results

3.6.1.1 The study characteristics

The characteristics and the main findings of the included two studies are detailed in Table 11:

3.6.1.1.1 Study design and setting

Two cohort studies were included. The length of the follow-up period ranged from 3 to 5 years, whilst the sample sizes ranged from 56 participants in one study (121) to 3,206 participants in the second (93).

3.6.1.1.2 Population

One study targeted middle-aged GOLD Stage 0 subjects (121), whilst in the other study, a younger age group was also studied (93). Patients reporting the presence of asthma were excluded. GOLD Stage 0 symptoms were defined in both studies using the MRC definition of CB.

3.6.1.1.3 Exposure and outcome

One cohort study (121) examined factors affecting the rate of FEV_1 decline including age, duration of CB symptoms, initial degree of airflow obstruction reversibility and the initial level of FEV_1. The second cohort study (93) investigated factors affecting the persistence of GOLD 0 symptoms over time including age, sex, smoking status, metabolic syndrome and body mass index (BMI).

Table 11: Study characteristics and the main findings (Review 3)

Barter *et al.*, 1974 (121)

Design	Population of interest	Exposure	Outcome	Results	General observations
4.5 years prospective cohort study- Australia	56 Ex-servicemen with CB symptoms, aged 40- 68 years, had pre and post-BD FEV_1 of > 60% predicted and free from asthma and other lung diseases	• Age • Initial degree of reversible bronchospasm • Duration of CB • Initial level of FEV_1	Factors affecting the annual decline rate of FEV_1	• FEV_1 annual decline rate showed a significant positive correlation with the initial degree of reversible bronchospasm and with the duration of CB symptoms ($p<0.05$) but showed a non-significant correlation with the initial value of FEV_1 • Age was weakly but significantly related to the FEV_1 annual decline ($p<0.05$) • There was an individual variation in FEV_1 decline rate; the highest decline was 0.23L/year	• Small sample size • The used cut off of ≥ 60% define moderate AFO according to the GOLD • Targeted a specified population

Brito Mutunayagam *et al.*, 2010 (93)

Design	Population of interest	Exposure	Outcome	Results	General observations
3.5 years prospective cohort Study- Australia	584 GOLD Stage 0 adults, aged ≥18 years (mean=45.5 years) and free from asthma and restriction (the total study sample was 3,206 participants)	• Age • Sex • Smoking status • BMI • Metabolic syndrome	Factors affecting the persistence or resolution of symptoms	• Persistence of GOLD 0 symptoms at follow-up was associated with persistent smoking (men: OR 11.9, 95% CI, 6.4-22.1; women: OR 4.0, 95% CI, 2.1-7.4), depressive symptoms (men: OR 3.8, 95% CI, 1.9-7.6; women: OR 3.2, 95% CI, 1.7-5.9), with highest quartile of annual FEV_1 decline (mL) (OR 2.1, 95% CI, 1.2-3.7) and with metabolic syndrome in men (OR 5 1.7, 95% CI, 1.01-3.0) and with older age in women • Resolving of GOLD 0 symptoms was associated with smoking cessation (OR 13.7; 95% CI, 4.6-40.1), FEV_1 decline (mL) per year below the median (OR 2.0; 95% CI, 1.1-3.5), normal BMI (OR 1.8; 95% CI, 1.03-3.13), and younger age groups	Relatively short follow-up period

3.6.1.2 Methodological quality of the included studies

The overall risk of bias in the included two cohort studies is presented in Figure 5 (see Appendix F Table 46 for details of each study). Both studies provided a clear description of study participants and the associated response rate. However, description of study attrition and participants lost to follow-up was generally underreported in both studies. The prognostic factors examined were adequately defined and reliably measured in both studies included. Furthermore, both studies accounted for the important confounders in their analysis and the outcome was clearly defined and measured.

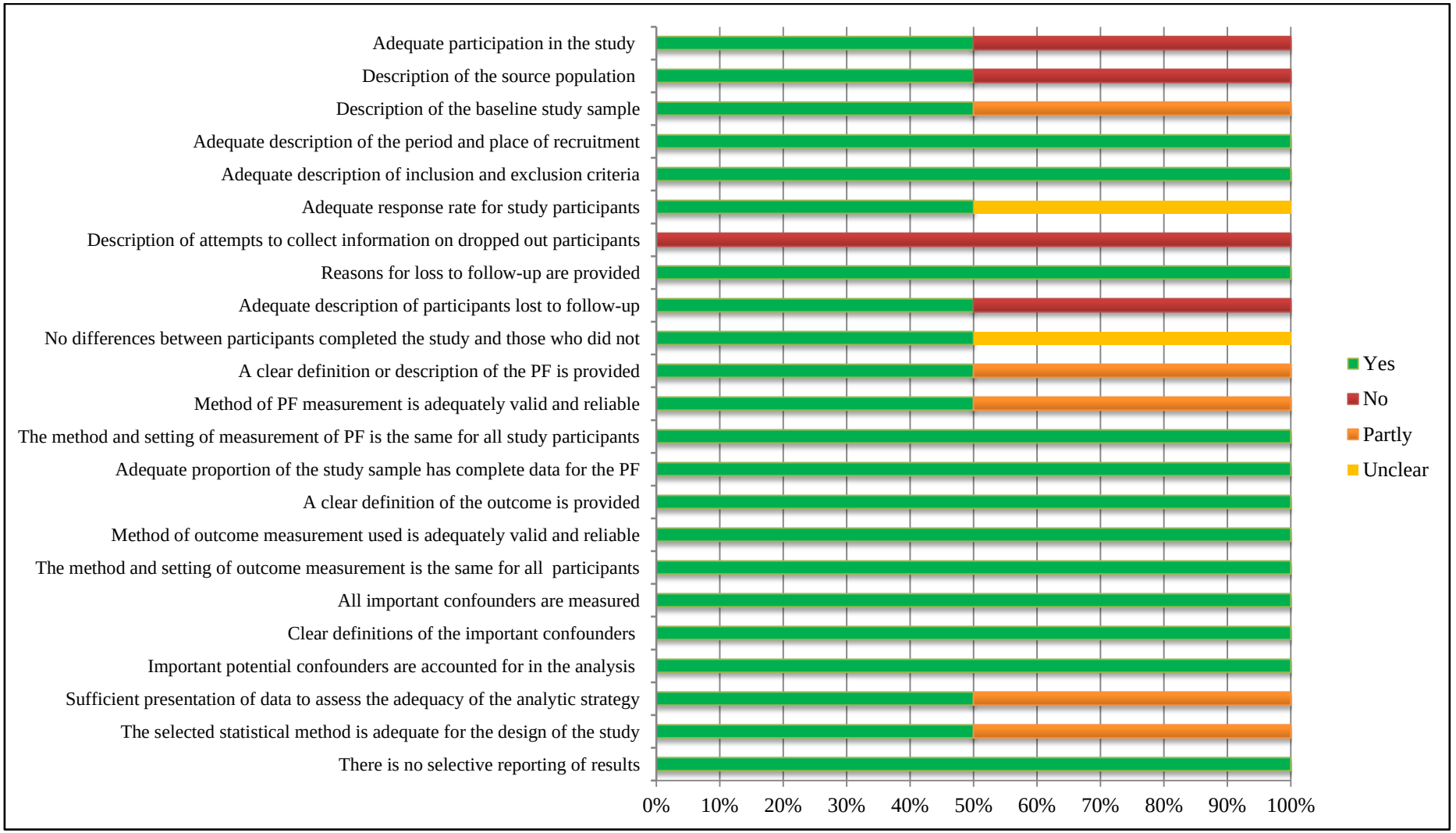

Figure 5: Overall risk of bias of the included two cohort studies (Review 3)

3.6.1.3 The main findings

3.6.1.3.1 Factors affecting the rate of FEV_1 decline

The cohort study of Barter *et al.,* (1974) (121) found that increasing age ($p<0.05$) and the greater initial degree of airway obstruction reversibility ($p=0.001$) were the main factors that showed a significant relationship with the increasing rate of FEV_1 decline among GOLD Stage 0 patients (121). Another observation from this study was that the longer duration of CB symptoms has been found to be a significant predictor of FEV_1 decline ($p<0.05$) (121). Furthermore, there was also an individual variation in FEV_1 decline rates observed in this study, some of GOLD Stage 0 subjects had an annual decline in FEV_1 of 0.23L, many subjects had a negligible FEV_1 decline and few subjects had an annual increase of 0.06L (121). The effect of baseline initial level of FEV_1 on the annual rate of its decline was also examined in this study, which suggested a possible correlation with FEV_1 annual decline rate, although this was not statistically significant ($r=0.16$) (121). However, the sample size of this study was relatively small (56 Ex-servicemen) and these findings need to be considered with caution (Table 11).

3.6.1.3.2 Factors affecting the persistence of GOLD Stage 0 symptoms

Systematic review (1) in the previous chapter suggested that the feature of instability of GOLD Stage 0 symptoms over time is possibly the main determinant of the independent predictive value of GOLD Stage 0 on the risk of developing COPD (please refer to section 2.4.4.3).

The present review identified one cohort study by Brito *et al.,* (2010) (93), which investigated the main factors affecting the persistence of GOLD Stage 0 symptoms over time. Brito *et al.,* found that persistent smoking and male gender (smoking men: OR=11.9; 95% CI, 6.4 to 22.1; smoking women: OR=4.0, 95% CI, 2.1 to 7.4) (93), older age in women and the presence of

metabolic syndrome amongst men (OR=51.7; 95% CI, 1.01 to 3.0) were the main factors associated with the persistence of GOLD Stage 0 symptoms (93). While smoking cessation, normal BMI and younger age were the main factors associated with a resolution of GOLD Stage 0 symptoms (93) (Table 11).

Summary box 3:

1. **Factors affecting FEV_1 decline rate (n=1 cohort study):**
    - Increasing age
    - The higher initial degree of airway obstruction reversibility
    - The longer duration of CB symptoms
    - An individual variations
2. **Factors affecting the persistence of GOLD Stage 0 symptoms (n=1 cohort study):**
    - Persistent smoking
    - Male gender
    - Older women
    - Metabolic syndrome amongst men

3.6.2 Discussion

3.6.2.1 Summary of evidence

This is the first systematic review to examine the main factors affecting the prognosis of GOLD Stage 0 patients. However, only two cohort studies were identified relevant to answer the review's question and therefore this systematic review draws attention to the lack of good data on the prognostic factors of this condition of GOLD Stage 0 and that reliable answer to this question requires more evidence and better studies.

This review confirmed through one cohort study (93) that the persistence of GOLD Stage 0 symptoms was more common among those who were persistent smokers, amongst males, older females and males with metabolic syndrome (93). Through the other included cohort study (121), this review found that increasing age, the longer duration of CB symptoms and the presence of airway obstruction reversibility were the main factors associated with excess decline in FEV_1 (121). However, the sample size of the latter study was small and a specified population was targeted (56 Ex-servicemen).

3.6.2.2 Limitations

Undertaking a comprehensive search strategy was challenging but unlikely to have missed important studies. However, the main limitation of this review was the lack of enough evidence to answer the review question, with only two cohort studies identified relevant. This makes it difficult to draw a conclusion with certainty.

3.6.2.3 Implication for research and clinical practise

Future longitudinal studies are required in order to explore the main factors affecting the prognosis of GOLD Stage 0 patients. However, as recommended in the last two reviews, factors affecting the instability of GOLD Stage 0 symptoms over time need to be explored through future studies. This will allow for developing interventions targeting GOLD Stage 0 adults at a higher risk of persistence of their symptoms; for instance, strengthening of the smoking cessation programmes.

3.6.2.4 Conclusion

This systematic review found insufficient evidence to answer its question on the factors that could affect the individual's susceptibility to poor prognosis among GOLD Stage 0 patients. Therefore, these factors warrant further attention and future studies are needed. Particularly,

on the factors affecting the persistence of GOLD Stage 0 symptoms over time, which may in part be moderated by persistence of smoking.

4 CHRONIC RESPIRATORY SYMPTOMS *VERSUS* AIRFLOW OBSTRUCTION: THE EFFECT ON PATIENT'S QUALITY OF LIFE—THE HEALTH SURVEY FOR ENGLAND (2010)

4.1 Abstract

Background: The severity of airflow obstruction is considered to be inadequate in capturing the eventual COPD-related adverse health outcomes and patient's perception of ill health. The primary aim of this study was to compare the independent impact of respiratory symptoms and obstructive lung function on patients' HRQoL, with a secondary aim to explore those symptoms that contribute most to patients' general health.

Methods: Cross-sectional analysis of the 2010 data of the HSE on 2,046 adult participants classified into four groups according to the presence or absence of respiratory symptoms and the presence or absence of airflow obstruction as based on the LLN criteria. Logistic regression analysis adjusted for age, sex, smoking, BMI and comorbidity was used to quantify the effects of symptoms on HRQoL.

Results: Patients with chronic respiratory symptoms had significantly poorer HRQoL across a number of measures than the normal population, and those with symptoms and airflow obstruction were even more affected. Conversely, asymptomatic patients with airflow obstruction only showed no significant differences from the normal population.

Conclusion: These results emphasise the importance of the effect of respiratory symptoms on patients' quality of life, regardless of the presence of airflow obstruction, which may not capture the entire picture of COPD.

4.2 Introduction

Patients with COPD usually have poor HRQoL that worsens over time (122), with the main determinants requiring identification in order to develop intervention strategies which could improve patients' HRQoL (122). Most existing guidelines for COPD management and monitoring are primarily based on the degree of airflow obstruction (123). However, COPD is a multidimensional systematic syndrome (123), with this approach considered inadequate in terms of capturing the multiple components of COPD (26, 124, 125). Moreover, the severity of airflow obstruction does not adequately predict the eventual COPD-related adverse health outcomes (125); therefore, calls for considering multidimensional indices of COPD—such as the BODE index (comprising BMI, airflow obstruction, dyspnoea and exercise tolerance), ADO index (age, dyspnoea and airflow obstruction) and many other indices are increasing (123).

HRQoL has become an important outcome measure for chronic diseases, including COPD (126) and improvement of the HRQoL of affected patients is an important goal of their management (122). Previously published studies that examined the HRQoL among COPD patients have reported that the degree of severity of airflow obstruction is the main contributor to poor HRQoL (127, 128). However, few studies have examined the effects of symptoms on HRQoL among COPD patients (94, 122, 126, 129-131). Therefore, it has not yet been clarified whether poor HRQoL in COPD is attributed to the degree of airflow obstruction, to the presence of symptoms, or to both. Furthermore, evidence is inadequate and has shown conflicting results regarding the impact of respiratory symptoms in the absence of airflow obstruction on HRQoL, that is the group formerly defined as COPD GOLD Stage 0 (100, 102). Additionally, in previously published studies, patients with diagnosed asthma and other respiratory conditions were not always excluded among GOLD Stage 0 group and the

presence of these conditions was not accounted for in examining the impact of symptoms on HRQoL (supplementary Table 19).

This population-based study is the first to compare the independent impact of respiratory symptoms and obstructive lung function as measured using the LLN criteria on different measures of patients' HRQoL amongst three groups of "exposure" of the English population compared to healthy reference group, with a secondary aim to explore in more details those symptoms that contribute most to patients' self-assessed general health.

4.3 Methods

4.3.1 Study design

Cross-sectional analysis of respiratory data from the 2010 HSE (132).

4.3.2 Study setting

The 2010 HSE was the twentieth annual cross-sectional health survey carried out in the UK as a part of the NHS Information Centre for Health and Social Care surveys programme (132). The HSE provides annual data at a national level, using a representative sample of the UK general population, chosen through multistage stratified random sampling, made up of 8,736 addresses of private households across England (132). The 2010 HSE was mainly focused on respiratory health and lung diseases (132). More detailed information on the HSE is available at: http://www.hscic.gov.uk/pubs/hse10trends.

4.3.2.1 Sampling strategy

In the 2010 HSE, a multistage stratified random sampling strategy was used (132). The sampling frame was the small user Postcode Address File (132). At the first stage, a random sample of 840 primary sampling units was selected based on the postcode sectors (132). In the

second stage, a random sample of postal addresses (known as delivery points) was then drawn from within each selected primary sampling unit (132). Within each selected household, all adults (up to a maximum of ten adults) were selected to take part in the survey (132).

4.3.2.2 Measurements and data collection

During the first stage of the HSE, eligible adults who gave consents to participate undertook a standard computer-assisted interview including questions on general health, smoking status, and respiratory health (132). The interview also included a self-completion questionnaire, including a shortened 12-item general health questionnaire (GHQ12) and the EQ-5D. Height and weight measurements were also taken at the interview (132). Stage 2 involved nurse visits to the participants' houses, during which the spirometry testing was performed.

4.3.2.2.1 Pulmonary function tests

Pre-bronchodilator spirometry was performed to measure the three key lung function parameters: FEV_1, FVC and FEV_1/FVC ratio (132). Participants were excluded from performing the spirometry if they were pregnant, were currently being treated for tuberculosis, had a resting pulse rate of more than120 beats per minute, had been admitted to hospital with a heart complaint during the preceding month, or if they had had a heart attack, detached retina or major surgery on their chest, abdomen, ears, eyes or brain in the preceding three months (132). However, detailed information on the measurement protocol for spirometry is given in Volume two of the HSE report available at:

www.ic.nhs.uk/pubs/HSE10report

4.3.3 Study Population

This study considered the 2010 data of the HSE adult participants who were aged 40 years and above, of white ethnicity, free from asthma and other doctor-diagnosed respiratory

conditions and who had valid spirometry results available. The eligible participants were then classified into four "exposure" groups according to the presence or absence of any respiratory symptoms and the presence or absence of airflow obstruction based on the LLN criteria: normal population (asymptomatic with normal lung function), AFO only group (asymptomatic but had obstructive lung function), symptoms only group "GOLD Stage 0" (reported the presence of chronic respiratory symptoms but had normal lung function) and symptomatic AFO group (reported the presence of chronic respiratory symptoms and had obstructive lung function).

4.3.4 Definitions

4.3.4.1 Chronic Respiratory Symptoms

The presence of respiratory symptoms of cough, sputum, dyspnoea and wheezing was assessed using the MRC questionnaire (132). Cough and phlegm were defined by the positive response to the question '*Do you usually cough or bring up phlegm on most days for three consecutive months or more during the year?'* (132). Wheeze was defined by a positive response to the question *'Have you had wheezing or whistling in the chest in the last 12 months?'* (132). Dyspnoea was defined as grade two or above of the MRC breathlessness scale *'Short of breath when hurrying or walking up a slight hill'* (132).

4.3.4.2 Airflow obstruction

Airflow obstruction was defined based on the LLN criterion using the Stanojevic (2009) all-ages equations (132), as FEV_1/FVC ratio below the 5^{th} percentile of predicted value for age, sex, height and ethnicity (41). However, at the time at which the HSE was conducted, the all-age reference equations were available only for white ethnicity and those for other ethnicities

were not yet developed (132); therefore, this study considered participants of white ethnicity only.

4.3.4.3 Covariates

Participants were categorised according to their smoking status (current, former, never). BMI was estimated by dividing patient weight in kilograms by the square of their height in metres (132) and further categorised using the World Health Organisation (WHO) BMI classification standard into: underweight (BMI less than 18.5 kg/m²), normal (BMI= 18.5 to 24.9 kg/m²), overweight (BMI=25 to 29.9 kg/m²) and obese (BMI ≥ 30 kg/m²). Doctor diagnosed long standing comorbidities were assessed using self-completed questionnaires, which included cardiovascular diseases (CVDs), cancer, diabetes and mental illnesses. Multiple comorbidities were defined by the presence of three or more of these comorbidities.

4.3.4.4 HRQoL

HRQoL was examined using self-completion questionnaires (132) on:

4.3.4.4.1 Self-reported general health

General health was investigated by asking participants to rate their general health on a five point Likert scale as either: very good, good, fair, bad or very bad (132).

4.3.4.4.2 GHQ12

The GHQ12 contains twelve items that capture information on psychosocial health, such as depression, anxiety, sleep disturbance and ability to cope over the recent few weeks (132). The twelve items are graded on a four points response scale, where a score of 0 is given to responses such as those stating the symptom as present ‘not at all’ or ‘no more than usual’, whilst a score of 1 is given to responses such as ‘rather more than usual’ or ‘much more than

usual' (132). A GHQ12 score of 4 or higher is indicated as a 'High GHQ12 score', demonstrating probable psychological disturbance or ill mental health (132).

4.3.4.4.3 Three level EQ-5D

The EQ-5D has two components, the first of which is a descriptive system including five different dimensions, namely pain/discomfort, anxiety/depression, self-care, ability to perform usual activities, and mobility (132). Participants were asked to indicate whether they had no problems, some problems or severe problems (132). The second component is the EQ visual analogue scale (EQ VAS), which records participant's self-assessed health through the use of a vertical visual scale, where endpoints are categorised as 'Best imaginable health state' (100) and 'Worst imaginable health state' (0) (132).

4.3.5 Statistical Analysis

STATA v.13 was used for all statistical analyses. In order to account for the complex sampling design and to minimise bias from individual non-response within households, the survey dataset was weighted using individual level weights provided by the HSE, which were a combination of the household weight and a component that adjusted for the sample technique (132). Due to the way in which the questions were formulated, missing data on respiratory symptoms were treated as the absence of symptoms. Descriptive data were presented as mean and standard error (SE) for continuous variables and as frequency and percentage for categorical variables.

In order to examine the independent effect of respiratory symptoms and airflow obstruction on HRQoL amongst the three groups of "exposure" compared with normal population, linear and multiple logistic regression were undertaken and associations presented as the odds ratios (ORs), with 95% confidence interval (CI) and p value. Age, sex and smoking status were

defined as potential confounders and adjusted for in an initial model. To account for the clinical significance of BMI and comorbidity and their potential influence on the association, further adjustment with BMI, cardiovascular comorbidity and the number of comorbidities was performed in a second model.

Due to the small numbers of observations in level 3, the domains of the EQ-5D were dichotomised in the regression model combining levels 2 and 3. In order to examine the respiratory symptom that had the most significant effect on general health, symptoms were examined individually using multiple logistic regression adjusted as above and further the symptoms were adjusted for each other.

4.3.5.1 Statistical power of the analysis

There were 2,046 participants with data available for this analysis (see results section 4.4.1). This would provide 85% power to observe an odds ratio of 2.0 for the proportion of non-normals (combined symptoms only, AFO only and both) reporting bad to very bad health, assuming that 3% of the normal population reports bad to very bad health. This assumes that the population sizes are 1,369 for normals, 68 for AFO only, 522 for symptoms only and 87 for presence of both (see next section).

4.4 Results

4.4.1 Study sample

There were 2,303 HSE participants who met the inclusion criteria for this study. Of those, 2,046 participants (88.8%) had spirometry data available and were included (Figure 6). Among those included, 1,369 participants were classified as “normal”, 68 classified as “AFO only”, 522 classified as symptoms only “GOLD Stage 0”, and 87 classified as “AFO with symptoms".

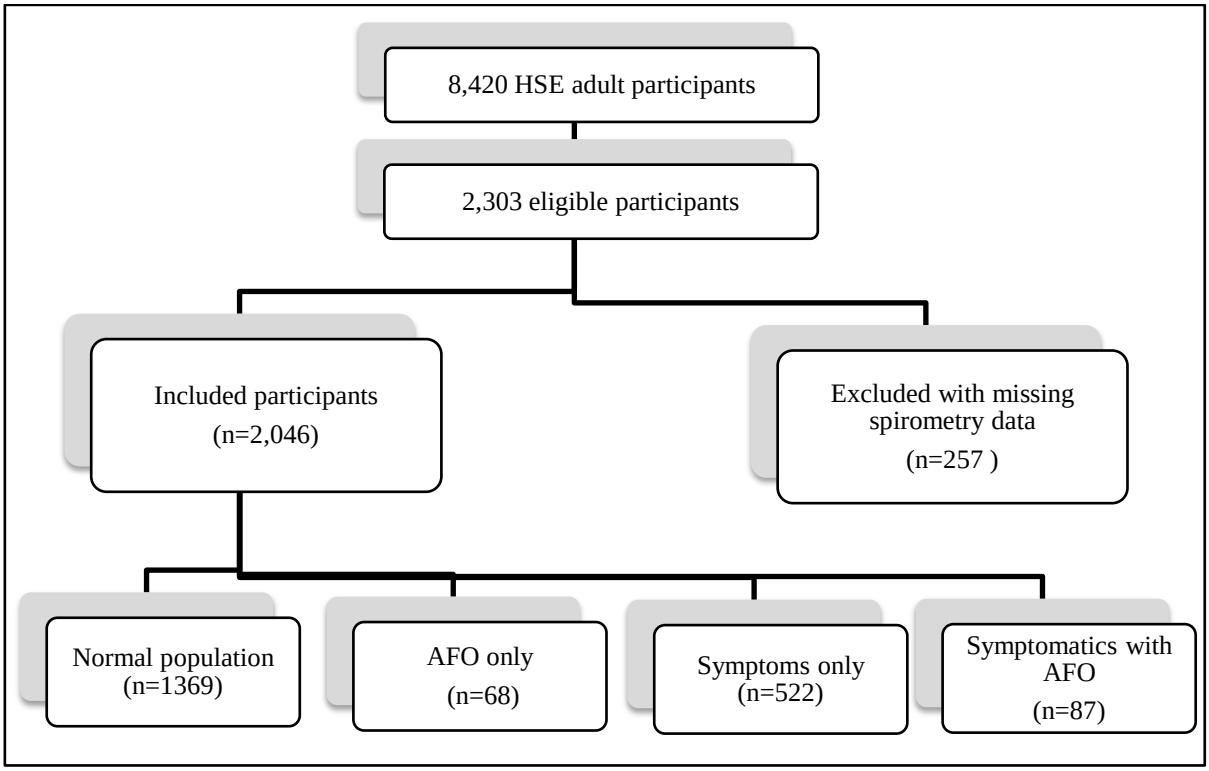

Figure 6: Flow diagram of patient selection procedure

4.4.2 Description of patient characteristics

4.4.2.1 Socio-demographics and clinical characteristics

Compared with the normal group (mean age 56.9 years), GOLD Stage 0 patients and those with AFO only were significantly older (both groups mean age 60.2 years) and those with both symptoms and AFO were the oldest (64.3 years, $p<0.0001$). Patients with both AFO and symptoms were more likely to be males than the normal group (66.7% *versus* 47.3%, $p<0.0001$). All groups were more likely to be current smokers than the normal group, but participants with AFO were most likely to be current smokers. Participants with both AFO and symptoms were also more likely to be ex-smokers than normal (51.7% *versus* 33.7%, $p<0.0001$). Overall, participants with AFO were much more likely to be ever smokers (Table 12).

Compared to the normal, GOLD Stage 0 participants were more likely to be obese (37.5% *versus* 22.2%, $p<0.0001$). GOLD Stage 0 participants showed similar trends to those with both AFO and symptoms in the higher rates of the following self-reported diagnosed comorbidities than the normal group: cardiovascular diseases (24.7% and 23.0%, respectively, *versus* 10.8%), high blood pressure (45.2% and 46.0%, respectively, *versus* 29.9%), diabetes (11.3% and 9.2%, respectively, *versus* 4.4%), mental health comorbidities (5.4% and 5.7%, respectively, *versus* 2.0%) and multiple comorbidities of two conditions (21.1% and 25.3%, respectively, *versus* 10.5%) or three or more conditions (12.5% and 14.9%, respectively, *versus* 3.7%). Participants with AFO only showed similar comorbidity profiles to the normal group, except for the neoplasm (7.4% *versus* 2.1% among the normal) (Table 12).

Table 12: Univariable socio-demographics and clinical characteristics by groups of "Exposure" compared to the normal population

	Normal population (n=1369)	AFO only (n=68)	GOLD Stage 0 (n=522)	AFO with symptoms (n=87)
Age−Mean (SE)	56.9 (0.3)	60.2 (1.6); P=0.05	60.2 (0.5); P<0.0001	64.3 (1.2); P<0.0001
Sex[1]				
Males	648 (47.3%)	30 (44.1%)	244 (46.7%)	58 (66.7%)
Females	721 (52.7%)	38 (55.9%)	278 (53.3%)	29 (33.3%)
P value	-	P=0.6	P=0.8	P< 0.0001
Smoking status[2]				
Current smokers	119 (8.7%)	23 (33.8%)	117 (22.4%)	32 (36.8%)
Ex-smokers	462 (33.7%)	21 (30.9%)	189 (36.2%)	45 (51.7%)
Never smokers	788 (57.6%)	24 (35.3%)	216 (41.4%)	10 (11.5%)
P value	-	P<0.0001	P<0.0001	P<0.0001
BMI[3]				
Normal	365 (26.7%)	23 (33.8%)	85 (16.3%)	32 (36.8%)
Underweight	5 (0.4%)	0	1 (0.2)	2 (2.3%)
Overweight	594 (43.4%)	27 (39.7%)	186 (35.6%)	29 (33.3%)
Obese	304 (22.2%)	11 (16.2%)	196 (37.5%)	17 (19.5%)
P value	-	P= 0.1	P< 0.0001	P=0.03
Self-reported doctor diagnosed comorbidities				
CVDs	148 (10.8%)	8 (11.8%); P=0.7	129 (24.7%); P<0.0001	20 (23.0%); P<0.0001
Heart failure	0	0	4 (0.8%)	2 (2.3%)
High blood pressure	410 (29.9%)	16 (23.5%); P=0.2	236 (45.2%); P<0.0001	40 (46.0%); P=0.002
Neoplasm	28 (2.1%)	5 (7.4%); P=0.01	21 (4.0%); P=0.01	7 (8.1%); P=0.001
Diabetes	60 (4.4%)	3 (4.4%); P=0.9	59 (11.3%); P<0.0001	8 (9.2%); P=0.05
Mental	27 (2.0%)	1 (1.5%); P= 0.3	28 (5.4%); P<0.0001	5 (5.7%); P=0.006
Number of comorbid conditions[4]				
No comorbidity	812 (59.3%)	39 (57.4%)	202 (38.7%)	23 (26.4%)
1 comorbidity	363 (26.5%)	18 (26.5%)	145 (27.8%)	29 (33.3%)
2 comorbidities	144 (10.5%)	6 (8.8%)	110 (21.1%)	22 (25.3%)
≥ 3 comorbidities	50 (3.7%)	5 (7.4 %)	65 (12.5%)	13 (14.9%)
P value	-	P=0.7	P<0.0001	P<0.0001

- Normal population is the reference group for all comparisons
- Values presented are numbers with percentages unless otherwise stated
- Reference categories: 1=male, 2=current smokers, 3= normal BMI and 4=No comorbidity
- P value is for the difference between each patient group and the normal population

4.4.2.2 Profile of individual respiratory symptom

The relative prevalence of individual respiratory symptoms was compared in the two groups with any symptoms. For each of the individual symptoms, prevalence was significantly higher

amongst participants with AFO than those with normal lung function except for dyspnoea MRC Grade two (Table 13).

Table 13: Self-reported respiratory symptoms by lung function

	GOLD Stage 0 (n=522)	AFO with symptoms (n=87)	P value
Chronic cough	175 (33.5%)	45 (51.7%)	<0.0001
Chronic phlegm	97 (18.6%)	24 (27.6%)	<0.0001
Wheeze	188 (36.0%)	53 (60.9%)	<0.0001
Dyspnoea			
MRC Grade 2	212 (40.6%)	24 (27.6%)	<0.0001
MRC Grades 3-5	99 (19.0%)	27 (31.0%)	<0.0001
Values presented are numbers with percentages unless otherwise stated			

4.4.2.3 Measures of HRQoL

Table 14 below shows the distribution of HRQoL between subgroups. In unadjusted analyses, compared to the normal, participants with both symptoms and AFO and GOLD Stage 0 participants were significantly more likely to report bad to very bad general health (16.1% and 10.5%, respectively, *versus* 2.9%) and worse GHQ12 (4+) scores (16.1% and 18.0%, respectively, *versus* 9.3%).

Within the EQ-5D, the frequency of moderate anxiety was higher amongst GOLD Stage 0 group (27.0%), followed by the AFO only group (20.6%) and the symptoms with AFO group (18.4%). GOLD Stage 0 participants (44.8%) and those with both symptoms and AFO (43.7%) showed higher frequencies of mild to moderate problems with pain compared to (28.9%) in the normal group. Similar patterns were observed for self-care, usual activities and mobility. There was also a similar gradient of scores observed with the EQ-5D VAS general health scale, with the worst scores amongst the group reporting both symptoms and AFO.

Table 14: Univariable measures of HRQoL by groups of "Exposure" compared to the normal population

	Normal population (n=1369)	AFO only (n=68)	GOLD Stage 0 (n=522)	AFO with symptoms (n=87)	P value
Self-assessed general health					<0.0001
Very good to good	1,174 (85.8%)	53 (77.9%)	309 (59.2%)	46 (52.9%)	
Fair	155 (11.3%)	15 (22.1%)	158 (30.3%)	27 (31.0%)	
Bad to very bad	40 (2.9%)	1 (1.5%)	55 (10.5%)	14 (16.1%)	
Psychosocial wellbeing (GHQ12 score)					<0.0001
Score 0	915 (66.8%)	47 (69.1%)	279 (53.5%)	47 (54.0%)	
Score 1-3	275 (20.1%)	11 (16.2%)	113 (21.7%)	20 (23.0%)	
Score 4+	128 (9.3%)	8 (11.8%)	94 (18.0%)	14 (16.1%)	
EQ-5D dimensions					
• **Anxiety/depression**					<0.0001
Not anxious/depressed	1,093 (79.8%)	51 (75.0%)	337 (64.6%)	61 (70.1%)	
Moderately anxious	203 (14.8%)	14 (20.6%)	141 (27.0%)	16 (18.4%)	
Extremely anxious	15 (1.1%)	0	11 (2.1%)	3 (3.5%)	
• **Pain/discomfort**					<0.0001
No pain/discomfort	898 (65.6%)	43 (63.2%)	237 (45.4%)	39 (44.8%)	
Moderate pain	396 (28.9%)	24 (35.3%)	234 (44.8%)	38 (43.7%)	
Extreme pain	34 (2.5%)	0	34 (6.5%)	4 (4.6%)	
• **Self-care**					<0.0001
No problems	1,287 (94.0%)	64 (94.1%)	456 (87.4%)	71 (81.6%)	
Some problems with washing or dressing	34 (2.5%)	3 (4.4%)	45 (8.6%)	8 (9.2%)	
Unable to wash or dress my self	1 (0.1%)	0	1 (0.2%)	0	
• **Usual activities**					<0.0001
No problems	1,168 (85.3%)	59 (86.8%)	374 (71.6%)	54 (62.1%)	
Some problems	146 (10.7%)	9 (13.2%)	113 (21.6%)	24 (27.6%)	
Unable to perform usual activities	13 (0.9%)	0	16 (3.1%)	4 (4.6%)	
• **Mobility**					<0.0001
No problems	1,265 (92.4%)	60 (88.2%)	370 (70.9%)	52 (59.8%)	
Some problems	180 (13.2%)	11 (16.2%)	179 (34.3%)	30 (34.5%)	
Severe problems	7 (0.5%)	0	1 (0.2%)	0	
EQ-5D VAS −Mean (SE)	82.8 (0.4)	81.9 (1.8)	74.7 (0.7)	71.4 (1.9)	<0.0001
Values presented are numbers with percentages unless otherwise stated					

4.4.3 The independent effect of symptoms and airflow obstruction on HRQoL

4.4.3.1 Self-assessed general health

Following an adjustment for age, sex and smoking status, the risk of self-assessed 'bad to very bad' general health was significantly higher amongst symptomatic participants with AFO (OR=4.1; 95% CI, 2.1 to 7.9) and GOLD Stage 0 group (OR=3.3; 95% CI, 2.1 to 5.1)

compared to the normal group. On the contrary, the AFO only group showed a lower risk than the normal population. Similar patterns were observed following further adjustment for the confounding of the BMI, cardiovascular comorbidity and the number of comorbidities (Table 15).

Table 15: The adjusted difference in general health between "Exposure" groups compared to the normal population

	Bad to very bad self-assessed general health			
	Number (%)	**Unadjusted OR (95% CI)**	**Adjusted OR[1] (95% CI)**	**Adjusted OR[2] (95% CI)**
Normal population	40 (2.9%)	1.0	1.0	1.0
AFO only	1 (1.5%)	0.2 (0.02 to 1.3)	0.13 (0.02 to 0.9)	0.1 (0.01 to 0.9)
GOLD Stage 0	55 (10.5%)	3.9 (2.6 to 5.9)	3.3 (2.1 to 5.1)	2.1 (1.3 to 3.4)
AFO with Symptoms	14 (16.1%)	6.5 (3.5 to 11.9)	4.1 (2.1 to 7.9)	2.5 (1.1 to 5.5)

- Normal population is the reference group for all comparisons
- Reference category: good/very good to fair general health
- OR[1]:Adjusted for age, sex and smoking status
- OR[2]: Adjusted for age, sex and smoking status, BMI, CVDs and the number of comorbidities

4.4.3.2 Self-assessed Psychosocial Wellbeing

The adjusted risk of worse GHQ12 (4+) scores was significantly higher amongst participants with both symptoms and AFO (OR=2.4; 95% CI, 1.3 to 4.4) and GOLD Stage 0 participants (OR=2.3; 95% CI, 1.7 to 3.2) compared to the normal group. Conversely, the AFO only group showed non-significant difference from the normal group. Similar patterns were observed following further adjustment for the confounding of the BMI, cardiovascular comorbidity and the number of comorbidities (Table 16).

Table 16: The adjusted difference in psychosocial wellbeing between 'Exposure' groups compared to the normal population

	Psychosocial wellbeing (GHQ12 scores 4+)			
	Number (%)	**Unadjusted OR (95% CI)**	**Adjusted OR[1] (95% CI)**	**Adjusted OR[2] (95% CI)**
Normal population	128 (9.3%)	1.0	1.0	1.0
AFO only	8 (11.8%)	1.3 (0.6 to 2.7)	1.3 (0.6 to 2.7)	1.2 (0.5 to 2.6)
GOLD Stage 0	94 (18.0%)	2.2 (1.7 to 2.9)	2.3 (1.7 to 3.2)	1.9 (1.4 to 2.7)
AFO with Symptoms	14 (16.1%)	2.0 (1.1 to 3.5)	2.4 (1.3 to 4.4)	1.6 (0.8 to 3.2)

- Normal population is the reference group for all comparisons
- Reference category: GHQ12 scores 0-3
- OR[1]:Adjusted for age, sex and smoking status
- OR[2]: Adjusted for age, sex and smoking status, BMI, CVDs and the number of comorbidities

4.4.3.3 EQ-5D

Table 17 below presents the adjusted risks for each domain of the EQ-5D. Compared to the normal, the risk of moderate to extreme anxiety was higher amongst GOLD Stage 0 participants (OR=2.3; 95% CI, 1.8 to 2.9). Moreover, participants with both AFO and symptoms (OR=1.8; 95% CI, 1.1 to 2.8) and GOLD Stage 0 participants (OR=2.1; 95% CI, 1.7 to 2.6) showed a higher risk of moderate to extreme pain and discomfort. Similar patterns were confirmed for moderate to severe problems with self-care, usual activities and mobility. The lower mean EQ-5D VAS scores were also significantly associated with the presence of symptoms. Similar patterns were observed following further adjustment for the confounding of the BMI, cardiovascular comorbidity and the number of comorbidities (Table 17).

Table 17: The adjusted difference in the EQ-5D domains between "Exposure" groups compared to the normal population

	EQ-5D			
	Number (%)	**Unadjusted OR (95% CI)**	**Adjusted OR[1] (95% CI)**	**Adjusted OR[2] (95% CI)**
Moderate/extreme anxiety and depression[1]				
Normal population	218 (15.9%)	1.0	1.0	1.0
AFO only	14 (20.6%)	1.3 (0.7 to 2.5)	1.3 (0.7 to 2.4)	1.2 (0.6 to 2.3)
GOLD Stage 0	152 (29.1%)	2.3 (1.8 to 2.9)	2.3 (1.8 to 2.9)	2.0 (1.5 to 2.6)
AFO with Symptoms	19 (21.9%)	1.6 (0.9 to 2.6)	1.6 (0.9 to 2.8)	1.3 (0.8 to 2.3)
Moderate/extreme pain and discomfort[2]				
Normal population	430 (31.4%)	1.0	1.0	1.0
AFO only	24 (35.3%)	1.2 (0.7 to 1.97)	1.02 (0.6 to 1.8)	1.0 (0.6 to 1.8)
GOLD Stage 0	268 (51.3%)	2.4 (1.9 to 2.9)	2.1 (1.7 to 2.6)	1.5 (1.2 to 1.9)
AFO with Symptoms	42 (48.3%)	2.2 (1.4 to 3.4)	1.8 (1.1 to 2.8)	1.2 (0.7 to 2.1)
Moderate/severe problems with self-care[3]				
Normal population	35 (2.6%)	1.0	1.0	1.0
AFO only	3 (4.4%)	1.9 (0.6 to 5.4)	1.4 (0.5 to 3.9)	1.3 (0.4 to 5.0)
GOLD Stage 0	45 (8.8%)	3.7 (2.4 to 5.6)	3.0 (1.9 to 4.7)	1.9 (1.1 to 3.3)
AFO with Symptoms	8 (9.2%)	4.4 (2.1 to 8.9)	2.9 (1.3 to 6.2)	1.7 (0.8 to 3.9)
Moderate/severe problems with usual activities[4]				
Normal population	159 (11.6%)	1.0	1.0	1.0
AFO only	9 (13.2%)	1.2 (0.6 to 2.3)	0.95 (0.5 to 1.9)	0.8 (0.3 to 1.5)
GOLD Stage 0	129 (24.7%)	2.5 (1.97 to 3.2)	2.2 (1.7 to 2.9)	1.4 (1.0 to 1.9)
AFO with Symptoms	28 (32.2%)	3.8 (2.4 to 6.0)	3.0 (1.8 to 4.8)	1.6 (1.0 to 2.8)
Moderate/severe problems with mobility[5]				
Normal population	187 (13.7	1.0	1.0	1.0
AFO only	11 (16.2%)	1.2 (0.6 to 2.3)	0.9 (0.5 to 1.9)	1.0 (0.5 to 2.2)
GOLD Stage 0	180 (34.5%)	2.3 (2.6 to 4.1)	2.8 (2.2 to 3.6)	1.8 (1.4 to 2.4)
AFO with Symptoms	30 (34.5%)	3.9 (2.5 to 6.1)	2.7 (1.7 to 4.4)	1.9 (1.1 to 3.3)
EQ-5D VAS (Best/worst imaginable health state)				
	Mean (SE)	**Unadjusted regression coefficient (95% CI)**	**Adjusted regression coefficient[1] (95% CI)**	**Adjusted regression coefficient[2] (95% CI)**
Normal population	82.8 (0.4)	1.0	1.0	1.0
AFO only	81.9 (1.8)	-0.8 (-4.4 to 2.7)	0.2 (-3.3 to 3.7)	0.9 (-2.2 to 3.9)
GOLD Stage 0	74.7 (0.7)	-8.1 (-9.7 to -6.4)	-7.4 (-9.1 to -5.7)	-4.0 (-5.5 to -2.4)
AFO with Symptoms	71.4 (1.9)	-11.3 (-15.1 to -7.5)	-9.5 (-13.3 to -5.7)	-6.4 (-9.9 to -2.8)

- Normal population is the reference group for all comparisons
- Reference categories:1= not anxious/depressed, 2= no pain/discomfort, 3, 4 and 5= no problems
- OR[1]:Adjusted for age, sex and smoking status
- OR[2]: Adjusted for age, sex and smoking status, BMI, CVDs and the number of comorbidities

4.4.4 The effect of individual symptoms on self-assessed general health

The effect of individual symptoms was explored on participants' perception of general health. In unadjusted analyses, the risk of bad to very bad general health was significantly associated with each individual symptom except for chronic phlegm which showed similar direction but

did not reach statistical significance. After adjustment for age, sex and smoking status, the associations remained similarly significant, although after further adjustment for cardiovascular comorbidity, BMI and each other, only dyspnoea (OR=4.5; 95% CI, 2.2 to 9.4) and wheeze (OR=3.3; 95% CI, 1.3 to 8.7) remained statistically significant (Table 18).

Table 18: The adjusted individual effect of respiratory symptoms on general health

	Bad to very bad general health			
	Unadjusted OR (95% CIs)	**Adjusted OR[1] (95% CIs)**	**Adjusted OR[2] (95% CIs)**	**Adjusted OR[3] (95% CIs)**
Chronic cough	1.7 (1.1 to 2.7)	1.7 (1.1 to 2.7)	1.3 (0.7 to 2.3)	1.7 (0.8 to 3.6)
Chronic phlegm	1.5 (0.9 to 2.2)	1.4 (0.9 to 2.2)	1.2 (0.7 to 2.1)	1.0 (0.5 to 1.8)
Wheeze	2.9 (2.1 to 4.3)	2.8 (1.9 to 4.0)	1.9 (1.2 to 3.1)	3.3 (1.3 to 8.7)
Dyspnoea (MRC grade ≥2)	6.3 (5.0 to 7.9)	5.9 (4.6 to 7.5)	4.0 (2.9 to 5.4)	4.5 (2.2 to 9.4)

- OR[1]: Adjusted for age, sex and smoking status
- OR[2]: Further adjustment for BMI, CVD and the number of comorbidities
- OR[3]: The symptoms were adjusted for each other

4.5 Discussion

4.5.1 Main Findings

The findings from this study of population-based data demonstrate that the presence of respiratory symptoms has more negative impact on patient's HRQoL than the presence of airflow obstruction. GOLD Stage 0 patients had similar, although slightly better HRQoL across a number of different measures to symptomatic patients with airflow obstruction. In contrast, participants with airflow obstruction without symptoms consistently presented non-significant differences from the normal population in their HRQoL.

Additionally, upon further examination of patients' perception of their health, the most important symptoms affecting quality of life appear to be dyspnoea and wheeze, with chronic cough having little independent impact.

4.5.2 Comparison with the Existing Evidence

The present study was the first to examine the independent impact of chronic respiratory symptoms and airflow obstruction on HRQoL through classifying the participants in to three groups of "exposure" compared with the normal population. However, findings from this study are in line with previously published cross-sectional studies (94, 122, 129, 130), which also observed that lower quality of life scores were more strongly related to the respiratory symptoms than to the severity of COPD as measured using the GOLD fixed ratio criteria. On the other hand, Xie *et al*. (2005), in a Chinese context, found that only patients with both airflow obstruction and symptoms had higher risk of poor HRQoL, when patients with symptoms only and those with airflow obstruction only had a mild risk of poor HRQoL (131).

Furthermore, the present study confirms the results of Voll-Aanerud *et al*. (126, 129, 130), who also found that dyspnoea and wheeze had a greater negative effect than other symptoms on the HRQoL and with Wheaton *et al*., study (122), which showed that wheeze but not cough was associated with poor HRQoL after adjustment for relevant confounders. However, they found that phlegm still had a significant effect on poor HRQoL (122).

4.5.3 Strengths and Limitations

This study has some limitations. First, the analysis was limited to those of white British and Irish ethnicity; therefore, the results may not be generalisable to other ethnic groups. The second limitation was the smaller number of patients in groups with airflow obstruction which suggests that caution needs to be considered in terms of interpreting some of the effect estimates. The strength of this study is centred on using a large national representative data from the HSE with the advantage of applying generalisability to the English population.

4.5.4 Implications for research and clinical practise

Future longitudinal studies targeting this relevant group of patients with chronic respiratory symptoms in the absence of identified clear pathological origin are required. Such studies can contribute to better understanding of their prognosis, in particular to identify patients who may progress to formal diagnoses of COPD and those who may have a non-COPD treatable condition. In clinical practice, the importance of questioning the presence of respiratory symptoms (particularly dyspnoea and wheeze) is emphasised. This is simple, feasible and better describes patients' quality of life than the severity of airflow obstruction. Furthermore, symptomatic patients without airflow obstruction must be investigated for any underlying respiratory and non-respiratory conditions and treated accordingly. As they are more likely to be obese, referral to weight management programmes might be beneficial. Although pulmonary rehabilitation is usually only available for patients with diagnosed respiratory conditions, perhaps this group of symptomatic patients might also benefit from pulmonary rehabilitation by improving their management of dyspnoea.

4.5.5 Conclusion

This study emphasises the significance of the impact of respiratory symptoms on patients' quality of life, regardless of the presence of airflow obstruction, where FEV_1 may not capture the entire picture of COPD. Consequently, those patients with symptoms without clear identified underlying pathology perhaps are more of a concern than those with a known cause, as they are recognised as having a similarly poor quality of life, which cannot be explained by impaired lung function. The cause for their breathlessness should be investigated and appropriately treated.

4.6 Acknowledgments

The cooperation of the UK Data Service Archive, University of Essex, University of Manchester and the Health Survey for England 2010 in providing access to their data is acknowledged and appreciated.

4.7 Supplementary Tables

Table 19: Summary of the available evidence on the chapter's topic

Study ID	Design	Outcome	Study population	Gaps in knowledge
Xie *at al.*, 2005 **(131)**	9 years prospective cohort study in China	• The relationship between baseline pulmonary function and HRQoL 9 years later • HRQoL was measured using the Chinese 35-Item Quality of Life Instrument	• 1,356 middle aged adults • Normal lung function was defined as: FEV_1/FVC ratio ≥ 0.70, $FEV_1 \geq 80\%$ predicted & FVC $\geq 80\%$ predicted	• The primary objective of this study was the effect of lung function on HRQoL and symptoms were included in the model as a confounder factor. However, the study population were further classified in to 4 groups normal, impaired pulmonary function only and impaired pulmonary function with chronic respiratory symptoms but this was a secondary objective and was briefly presented • Included asthma in symptomatic group • COPD was defined and classified using the GOLD criteria
Voll-Aanerud *et al*., 2007 **(126)**	Longitudinal population-based cohort study in Norway	• The effect of incidence, remission, and persistence of 6 respiratory symptoms (morning cough, chronic cough, phlegm cough, wheeze, dyspnea attacks, and dyspnea grade 2) on HRQoL compared to no symptoms • HRQoL was measured by the SF^5-12 questionnaire	3,786 subjects aged 15 to 70 years	Examined the negative impact of symptoms on HRQoL irrespective to the lung function
Voll-Aanerud *et al*., 2008 **(129)**	Cross sectional study, Norway	• The association between 6 respiratory symptoms and COPD severity (based on the GOLD criteria) with HRQoL compared to healthy subjects • HRQoL was measured by the SF-12 questionnaire	2,306 subjects, aged 15 to 70	• HRQoL was examined in relation to individual symptom, number of symptoms and to the COPD severity • COPD was defined and classified using the GOLD criteria

[5] Short-Form questionnaire

Study ID	Design	Outcome	Study population	Gaps in knowledge
Voll-Aanerud *et al*., 2010 **(130)**	Cross sectional study of the European Community Respiratory Health Study data	• The association of respiratory symptoms with HRQoL in subjects with and without asthma or COPD • HRQoL was measured by the SF-36 questionnaire	6,009 adults aged 20-44 years in	• Asthma was not excluded • HRQoL was examined in relation to individual symptom and persistent symptoms in subjects with and without diagnosed asthma or COPD • COPD was defined and classified using the GOLD criteria
De Oca *et al*., 2012 **(94)**	Cross sectional study in Latin America	• The effect of the coexisting CB symptoms and COPD on patient's perceptions of their HRQoL • HRQoL was measured by the SF-12 questionnaire	• 5,571 subjects, aged ≥40 years and classified in to 2 groups: COPD and non-COPD and each group further classified into with and without CB groups • CB defined as; phlegm on most days at least 3 months per year for ≥ 2 years	• Did not exclude asthma • COPD was defined and classified using the GOLD criteria • Although performed parallel analysis using the LLN but data was not shown
Wheaton *et al*., 2013 **(122)**	Cross sectional study in the US	• The association of impaired lung function and respiratory symptoms with the HRQOL • HRQOL was measured using questions on general health, physical health and mental health	5,139 participants, aged 40–79 years categorised into: • Normal lung function • Restrictive impairment • Mild obstruction • Moderate to severe obstruction And further classified according to their reported symptoms into: • Cough • Phlegm • Wheeze • Any symptoms • No symptoms	• HRQoL was examined in relation to lung function category, individual symptom, any symptom and no symptom separately • COPD was defined and classified using the GOLD criteria

5 COPD GOLD STAGE 0 AND NEWLY DIAGNOSED COPD PATIENTS: HEALTH-RELATED CHARACTERISTICS AND OUTCOMES−BIRMINGHAM COPD COHORT STUDY

5.1 Abstract

Introduction: Although the association between the presence of chronic respiratory symptoms and the development of COPD remains uncertain, these symptoms may have a relevant impact on patients' health even in the absence of airflow obstruction. The aim of this study was to compare the health-related characteristics and health outcomes of GOLD Stage 0 patients and those newly diagnosed with COPD, both groups identified through a COPD case-finding trial in the UK.

Methods: Cross-sectional analysis of baseline data from the Birmingham COPD Cohort Study including 281 GOLD Stage 0 patients and 215 new COPD patients. Characteristics and health outcomes of patient in both groups were compared using logistic regression analysis adjusted for age, sex, smoking status and comorbidity.

Results: Compared to newly diagnosed COPD patients, GOLD Stage 0 patients were younger (mean age 62.3 *versus* 66.1 years, OR=0.9; 95% CI, 0.94 to 0.98), more likely to be never smokers (22.1% *versus* 15.3%, adjusted OR=4.3; 95% CI, 2.3 to 7.9) and more likely to be obese (43.8% *versus* 29.8%, adjusted OR=2.3; 95% CI, 1.3 to 4.0). GOLD Stage 0 patients showed possibly fewer exacerbation events, but similar overall patterns in HRQoL, healthcare utilisation, and exercise capacity to that reported by newly diagnosed COPD patients.

Conclusion: GOLD Stage 0 patients showed similar patterns of poor health outcomes to those diagnosed with COPD. Longitudinal studies are needed to better describe the long-term prognosis of GOLD Stage 0.

5.2 Introduction

Previous epidemiological studies have found that the prevalence of GOLD Stage 0 is relatively high (101). In the European Community Respiratory Health Survey, the prevalence of GOLD Stage 0 in the participating countries ranged from 7.2% in Australia to 23.7% in Spain (90), whilst the UK prevalence was found to be 9.8% (90). However, due to the uncertainty about the association between GOLD Stage 0 and the risk of development of COPD (9, 133), little attention has been directed to this condition compared with COPD (101).

There are four published studies (Supplementary Table 29) that have examined the health outcomes of HRQoL (133), exacerbation events (101) and healthcare utilisation (9, 90) among GOLD Stage 0 patients, mostly compared with healthy controls (9, 90, 133). In the previous chapter 4, cross-sectional analyses of the Health Survey for England suggest that chronic respiratory symptoms, particularly dyspnoea and wheeze, are more important than airflow obstruction in affecting patients' HRQoL. However, data were not available on other health-related outcomes such as healthcare utilisation, exacerbations and exercise capacity. In addition, those comparisons concern patients at all stages of COPD, some of whom may have had COPD for a long while and be in more advanced stages. It would be useful to compare patients identified contemporaneously from the same base population at the same point in time.

This will be the first study to examine the health-related characteristics of GOLD Stage 0 patients with those newly identified with COPD. This study will also bring all different measures together to directly compare the health outcomes of GOLD Stage 0 patients with newly identified COPD patients.

5.3 Methods

5.3.1 Study Design

Cross-sectional analysis of baseline data from the Birmingham COPD Cohort Study in the UK (134).

5.3.2 Setting

Participants in the Birmingham COPD cohort are drawn from two sources: (1) The Target COPD Case Finding Trial and (2) patients on the COPD registers of 71 participating general practices:

5.3.2.1 The Target COPD Case Finding Trial

The full protocol of the Birmingham COPD Case Finding Trial has been described elsewhere (135). Briefly, it was a pragmatic randomised controlled trial of COPD case finding intervention in 54 general practices in the West Midlands, UK (135). The patients targeted were identified as eligible if they fit the following criteria: registered with the participating practices, aged 40–79 years, and had no previous diagnosis of COPD (135). Thereafter, the eligible patients who positively responded to the respiratory symptom questions (chronic cough or phlegm for three or more months of the year for two or more years, wheeze in the last 12 months, or dyspnoea of MRC Grade two or above) were invited for spirometry testing (135). Patients were defined as having COPD using the GOLD/current NICE definition of

FEV_1/FVC <0.7 (135). Later, patients who met the definition of GOLD Stage 0 (reported the presence of chronic respiratory symptoms but had normal lung function), as well as those newly identified with COPD within the study (reported the presence of chronic respiratory symptoms with demonstrated airflow obstruction), were further invited to take part in the linked Birmingham COPD Cohort Study (134).

5.3.2.2 The Birmingham COPD Cohort Study

The Birmingham COPD Cohort Study is a prospective primary care based cohort study in the West Midlands, UK (134). It includes patients with existing COPD on GP disease registers (prevalent cases), but also patients with respiratory symptoms, with (incident cases) and without airflow obstruction (GOLD Stage 0) (134).

The eligible prevalent COPD patients were identified through standardised electronic searches of the COPD QoF register (COPD14) (134). The baseline assessment of this cohort was undertaken between May 2012 and June 2014 in 71 participating general practices (134).

5.3.3 Patient included in this analysis

The present study analysed the baseline data of the Birmingham COPD Cohort Study for GOLD Stage 0 patients, as well as those newly diagnosed with COPD. These two groups of patients were identified through the Birmingham COPD Case Finding Trial (135) and subsequently agreed to participate in the cohort study.

5.3.4 Measurements and data collection

Clinical assessment was undertaken at the patients' practices by trained research assistants and included a wide range of clinical measures including anthropological measurements, blood pressure and heart rate, spirometry and exercise capacity (134). Spirometry was performed pre and post-bronchodilator (20 minutes after 400 micrograms salbutamol

administered through a spacer) using the Easy One spirometer (ndd, Switzerland) to attain three acceptable expiratory manoeuvres according to the ATS/ERS (2005) guidelines (136). Validated questionnaires were used to collect data on patient demographics, background, lifestyle, occupational history, coexisting comorbidities, respiratory symptoms, prescribed medications, healthcare utilisation, exacerbation events and HRQoL (COPD assessment test (CAT), EQ-5D (5 level version) and self-assessed general health). Parts of the questionnaires were self-completed, other parts interviewer-led as appropriate (134).

5.3.5 Study Variable Definitions

5.3.5.1 Exposure variables

5.3.5.1.1 Smoking

Patients were classified as never, current and ex-smokers according to their response to the question: *Have you ever smoked a cigarette, cigar or pipe regularly*? *(Regularly means at least 1 cigarette/day or 7 cigarettes/ week for at least 6 months)* (134). Pack years of smoking were calculated based on the cigarette history using the following equation: number of cigarettes per day multiplied by the number of years smoked divided by 20 (137) and further categorised into <5, 5-19, 20-49 and 50+ pack years.

5.3.5.1.2 BMI

Patient's weight was measured using an electronic scale (Tanita BC-420SMA Body Composition Scale) and standing height was measured in metres using a portable Stadiometer (Leicester Height Monitor) by well-trained research assistants during the clinical assessment (134). BMI was calculated using the formula of (weight in kilograms divided by the square of the height in metres) (138) and categorised using the WHO/NICE cut-off points into:

underweight (BMI <18.5 kg/m²), normal (BMI= 18.5-24.9 kg/m²), overweight (BMI=25-29.9 kg/m²) and obese (BMI ≥ 30 kg/m²) (139).

5.3.5.1.3 Respiratory symptoms

The presence of respiratory symptoms was assessed using a self-completed questionnaire (134). Cough and phlegm were defined by '*their presence on most days for three or more consecutive months during the year for more than two consecutive years',* wheeze defined by '*ever had wheezing or whistling in the chest in the last twelve months*' and dyspnoea defined as Grade two and above of MRC Breathlessness Scale '*troubled by shortness of breath when hurrying on the level ground or walking up a slight hill?'* (134).

5.3.5.1.4 Coexisting comorbidities

The presence of coexisting comorbid conditions was also self-reported. Cardiovascular comorbidity was defined by the presence of any cardiovascular diseases of coronary heart disease, heart failure, stroke, high blood pressure, or other heart problems ever diagnosed by a doctor.

5.3.5.2 Health outcome variables

5.3.5.2.1 Self-reported HRQoL

Self-reported HRQoL was measured using the self-completed CAT score (140) as a disease specific HRQoL measure (Appendix G), and self-completed EQ-5D (5 level version) (141) (Appendix H) and a 5-point Likert scale of self-assessed general health as general HRQoL measures. Self-reported general health was assessed by the question, '*How is your health in general?*' and classified as good to very good, fair or bad to very bad (134).

5.3.5.2.2 Self-reported exacerbation-like events

Self-reported exacerbations were defined by an affirmative answer to one of the following questions: (1) In the last 12 months have you had one or more courses of oral steroids (prednisolone) for your lung problems? (2) In the last 12 months have you had one or more courses of antibiotics for your lung problems? (134).

5.3.5.2.3 Self-reported healthcare utilisation

Self-reported healthcare utilisation included hospital admissions and accident and emergency department (A & E) attendance over the last 12 months and the number of healthcare personnel consultations for lung disease in the past 14 days using the following questions: (1) In the last 12 months have you been admitted to hospital (spent at least one night) for your lung problems? (2) In the last 12 months have you been admitted to hospital (spent at least one night) for a reason other than your lung problems? (3) During the last 12 months did you ever attend casualty or A & E for your lung problems? (4) During the last 12 months did you ever attend as a patient at the casualty or A & E department of a hospital for a reason other than your lung problems? (4) Have you consulted healthcare personnel regarding your respiratory (lung) disease during the past 14 days? (134).

5.3.5.2.4 Exercise capacity

Exercise capacity was assessed by the one minute sit to stand test, it involves the number of complete sittings and standings undertaken by the patient over one minute, as counted by the research assistant during the clinical assessment (134). This test has been proved as a valid substitute to the six minute walking test in COPD patients (142).

5.3.6 Diagnostic criteria

GOLD Stage 0 was defined by the presence of any of the above respiratory symptoms, with preserved lung function (post-bronchodilator $FEV_1/FVC \geq 0.7$) and free from self-reported asthma and other diagnosed respiratory diseases. New COPD cases were diagnosed through the Case Finding Trial using the GOLD/current NICE definition of post-bronchodilator $FEV_1/FVC < 0.7$. Patients with self-reported asthma were also excluded from the COPD group. Predicted lung function values were calculated using the Global Lung Initiative (GLI)-2012 equations (143). These equations calculate predicted LLN spirometric indices for the entire age range (3-95 years) and for different ethnic and geographic groups all over the world (143, 144). These equations were derived based on 74,187 records from healthy non-smoking males and females from 26 countries across five continents (143) and therefore considered more generalisable across different population (143, 144).

Patients with no post-bronchodilator spirometry data available because of reported spirometry contraindications (Table 20), inability to perform spirometry or reported a history of salbutamol allergy were excluded. Reversible airflow obstruction was defined using the GOLD/ATS definition of '*a change of greater than 12% of the baseline FEV_1 if this also exceeds 200 ml*' (6). Participants who had taken their bronchodilator medications four hours before the spirometry testing were excluded from the reversibility analysis.

Table 20: Spirometry contraindications (134)

- Patient who had coughed up any blood in the last month prior to the study
- Currently taking any medications for the treatment of tuberculosis within the last month
- Being told by a Doctor or other health professional to have:
    - A heart attack in the last 3 months
    - A detached retina in the last 3 months?
- Reported any major surgery on chest, abdomen, brain, ears or eyes, e.g. cataract surgery in the last 3 months
- Have been in hospital with severe angina in the last month

5.3.7 Statistical analysis

STATA v.13 was used in this analysis. Descriptive data were presented as mean and standard deviation (SD) or as median and interquartile range (IQR) for continuous variables and as frequency and percentage for categorical variables. Logistic regression was used to examine the significance of difference between patients groups and association was presented as ORs with 95% CI and p values. Age, sex, smoking status and comorbidity were defined as potential confounders.

5.4 Results

5.4.1 Patients recruitment

Figure 7 summarises the selection procedure of patients included in this study. A total sample of 496 patients was included, 281 of whom met the definition of GOLD Stage 0 (56.7%), whilst 215 were newly diagnosed COPD patients (43.3%). Both patients' subgroups identified through the Birmingham COPD Case Finding Trial and agreed to participate in the linked cohort study.

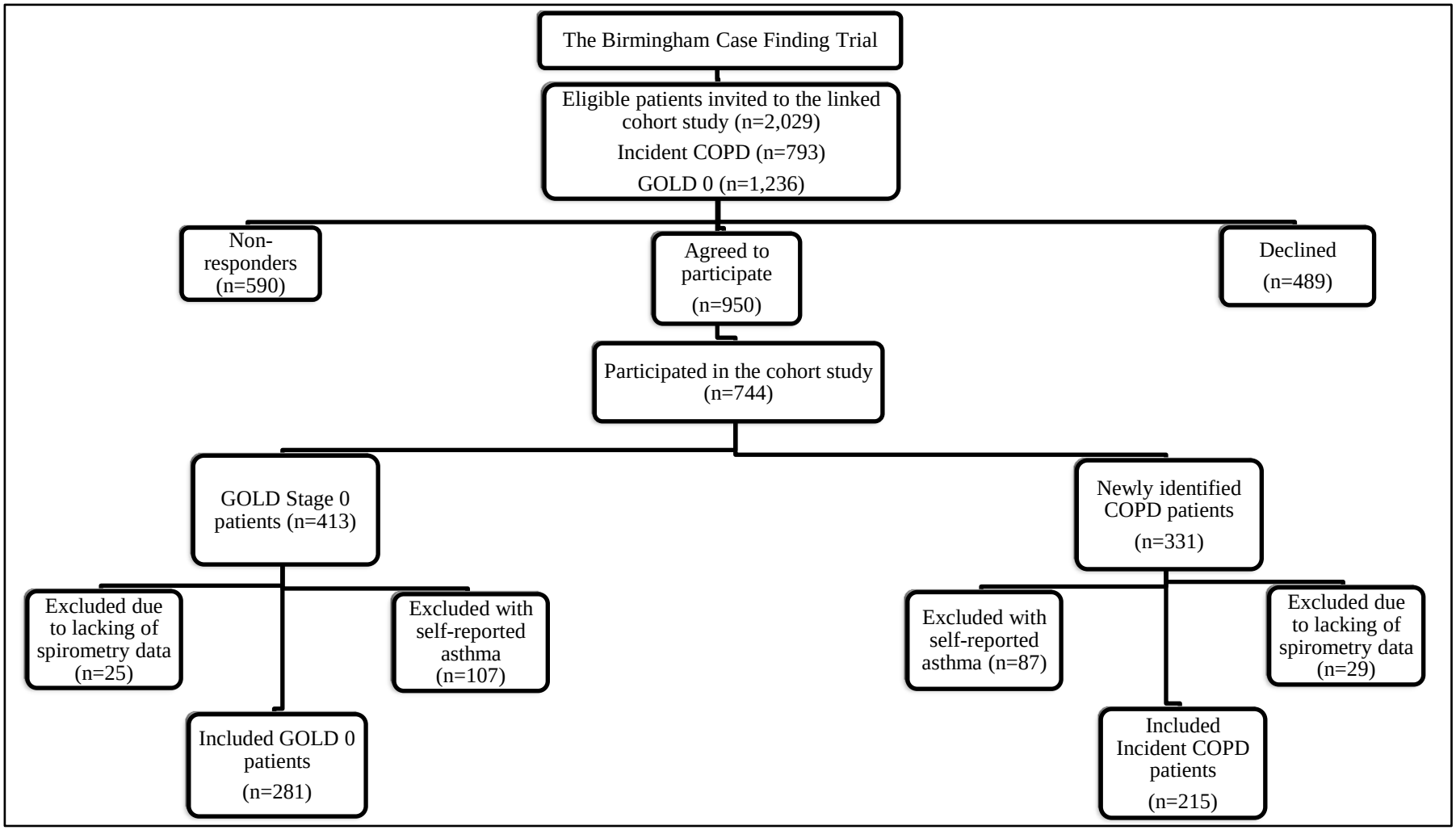

Figure 7: Flow diagram of patient recruitment procedure

5.4.2 Characteristics of participants and non-participants

Compared to non-participants, those who participated were slightly older, more likely to be males and more likely to be of white ethnicity. However, the difference between both groups was not statistically significant (Table 21).

Table 21: Univariable characteristics of participants and non- participants

	Participants (n=744)	Non-participants (n=1,285)	Unadjusted OR	p value	95% CI
Age – mean (SD)	62.3 (9.6)	59.2 (10.9)	1.0	<0.0001	1.02 to 1.04
Male sex [1]	413 (55.5%)	667 (51.9%)	1.2	0.07	0.9 to 1.4
White ethnicity[2]	477 (64.1%)	788 (61.3%)	1.1	0.2	0.9 to 1.4

- Non-participants is the reference group
- Values presented are numbers with percentages unless otherwise stated
- Reference categories:1=Female and 2=Non-white

5.4.3 Comparison of the health-related characteristics between GOLD Stage 0 patients and newly diagnosed COPD patients

5.4.3.1 Socio-demographics

Compared to the newly diagnosed COPD patients, GOLD Stage 0 patients were younger (mean age 62.3 *versus* 66.1 years, OR=0.9; 95% CI 0.94 to 0.98), more likely to be females (although not statistically significant), more likely to be never smokers (22.1% *versus* 15.3%, adjusted OR=4.3; 95% CI, 2.3 to 7.9) and ex- smokers (58.4% *versus* 47.9%, adjusted OR=3.7; 95% CI, 2.3 to 5.9) and less likely to be of white ethnicity (86.5% *versus* 87.9%, OR=0.4; 95% CI, 0.2 to 0.9) (Table 22).

Table 22: The adjusted socio-demographic characteristics of the study population

	GOLD Stage 0 (n=281)	Newly diagnosed COPD (n=215)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Age −Mean (SD)	62.3 (10.3)	66.1 (8.8)	0.9 (0.94 to 0.98)	-
Sex[1]				
Females	119 (42.3%)	81 (37.7%)	1.0	-
Males	160 (56.9%)	131 (60.9%)	0.8 (0.6 to 1.2)	-
Ethnicity[2]				
Non-white	25 (9.0%)	7 (3.3%)	1.0	-
White	243 (86.5%)	189 (87.9%)	0.4 (0.2 to 0.9)	-
Highest education level[3]				
No formal qualification	79 (28.1%)	88 (40.9%)	1.0	1.0
Primary level (GCSE)	68 (24.2%)	49 (22.8%)	1.5 (0.95 to 2.5)	1.1 (0.7 to 1.9)
Secondary (A-level)	25 (8.9%)	9 (4.2%)	3.1 (1.4 to 7.0)	2.5 (0.9 to 6.1)
Degree level or higher	54 (19.2%)	31 (14.4%)	1.9 (1.1 to 3.3)	1.6 (0.9 to 2.8)
Currently in work	106 (37.7%)	58 (27.0%)	1.7 (1.1 to 2.4)	1.1 (0.7 to 1.8)
Smoking status[4]				
Current smoker	54 (19.2%)	76 (35.3%)	1.0	1.0
Ex-smoker	164 (58.4%)	103 (47.9%)	2.2 (1.5 to 3.4)	3.7 (2.3 to 5.9)
Never smoker	62 (22.1%)	33 (15.3%)	2.6 (1.5 to 4.6)	4.3 (2.3 to 7.9)
Pack years smoking amongst smokers[5]				
<5	37 (13.2%)	9 (4.2%)	1.0	1.0
5-19	73 (26.0%)	44 (20.5%)	0.4 (0.2 to 0.9)	0.4 (0.2 to 0.8)
20-49	81 (28.8%)	77 (35.8%)	0.3 (0.1 to 0.6)	0.2 (0.1 to 0.5)
50+	52 (18.5%)	21 (9.8%)	0.6 (0.3 to 1.5)	0.6 (0.3 to 1.6)

- Newly diagnosed COPD group is the reference for all comparisons
- Values presented are numbers with percentages unless otherwise stated
- White ethnicity includes white British, Irish & other white backgrounds
- Reference categories: 1=Female, 2=Non-white, 3= No formal qualification, 4= Current smoker and 5=<5 Pack years
- *Adjusted for age, sex and smoking status
- Smoking outcomes were adjusted only for age and sex

5.4.3.2 Respiratory symptoms, BMI and coexisting comorbidities

Overall, 63.7 % of GOLD Stage 0 patients and 73.0% of newly diagnosed COPD patients reported the presence of any of the relevant respiratory symptoms in the baseline cohort questionnaire. This had changed from their original status in the Case Finding Trial where all had reported relevant chronic symptoms. Dyspnoea was the most common symptom among GOLD Stage 0 patients (55.5%) followed by wheeze (37.7%). GOLD Stage 0 patients reported a similar distribution of chronic cough and phlegm to new COPD patients, although

wheeze was more common among COPD patients (37.7% *versus* 51.2%, adjusted OR=0.6; 95% CI, 0.4 to 0.9). Dyspnoea was more frequently reported among COPD patients, but this was not statistically significant. GOLD Stage 0 patients were more likely to be obese than COPD patients (43.8% *versus* 29.8%, adjusted OR=2.3; 95% CI, 1.3 to 4.0). It is possible that GOLD Stage 0 patients were more likely to have diabetes and depression, however, the difference between groups was not statistically significant (Table 23).

Table 23: The adjusted difference in respiratory symptoms, BMI and comorbidities by patients group

	GOLD Stage 0 (n=281)	**Newly diagnosed COPD (n=215)**	**Unadjusted OR (95% CI)**	**Adjusted OR* (95% CI)**
Self-reported respiratory symptoms				
Chronic cough	95 (33.8%)	75 (34.9%)	0.9 (0.6 to 1.4)	1.1 (0.7 to 1.7)
Chronic phlegm	58 (20.6%)	57 (26.5%)	0.8 (0.5 to 1.2)	0.8 (0.5 to 1.4)
Wheeze	106 (37.7%)	110 (51.2%)	0.6 (0.4 to 0.8)	0.6 (0.4 to 0.9)
Dyspnoea[1] (MRC grade ≥ 2)	156 (55.5%)	136 (63.3%)	0.8 (0.5 to 1.1)	0.8 (0.5 to 1.2)
Any symptom	179 (63.7%)	157 (73.0%)	0.3 (0.1 to 0.9)	0.4 (0.1 to 1.02)
BMI[2]				
Normal	41 (14.6%)	49 (22.8%)	1.0	1.0
Underweight	2 (0.7%)	2 (0.9%)	1.2 (0.2 to 8.9)	0.4 (0.02 to 7.9)
Overweight	87 (31.0%)	72 (33.5%)	1.4 (0.9 to 2.4)	1.4 (0.8 to 2.5)
Obese	123 (43.8%)	64 (29.8%)	2.3 (1.4 to 3.8)	2.3 (1.3 to 4.0)
Self-reported comorbidity				
Cardiovascular comorbidities				
CVDs	140 (49.8%)	117 (54.4%)	0.8 (0.6 to 1.2)	0.9 (0.6 to 1.4)
High blood pressure	113 (40.2%)	95 (44.2%)	0.8 (0.6 to 1.2)	0.9 (0.6 to 1.3)
Coronary heart disease	29 (10.3%)	21 (9.8%)	1.0 (0.6 to 1.8)	1.3 (0.7 to 2.5)
Heart failure	17 (6.1%)	14 (6.5%)	0.9 (0.4 to 1.9)	1.1 (0.5 to 2.5)
Stroke	14 (5.0%)	16 (7.4%)	0.6 (0.3 to 1.3)	0.8 (0.4 to 1.7)
Other heart diseases	29 (10.3%)	20 (9.3%)	1.1 (0.6 to 1.9)	1.2 (0.6 to 2.3)
Other comorbidities				
Cancer	30 (10.7%)	27 (12.6%)	0.8 (0.5 to 1.4)	0.9 (0.5 to 1.7)
Diabetes	39 (14.0%)	23 (10.7%)	1.3 (0.8 to 2.3)	1.3 (0.7 to 2.2)
Depression	81 (28.8%)	50 (23.3%)	1.3 (0.9 to 2.0)	1.2 (0.8 to 1.8)
Number of comorbidities[3]				
No comorbidity	68 (24.2%)	53 (24.7%)	1.0	-
1 comorbidity	108 (38.4%)	77 (35.8%)	1.1 (0.7 to 1.7)	1.2 (0.7 to 1.9)
2 comorbidities	65 (23.1%)	54 (25.1%)	0.9 (0.6 to 1.6)	1.0 (0.6 to 1.8)
≥ 3 comorbidities	40 (14.2%)	31 (14.4%)	1.0 (0.6 to 1.8)	0.96 (0.5 to 1.8)

- Newly diagnosed COPD group is the reference for all comparisons
- Values presented are numbers with percentages unless otherwise stated
- Reference categories:1= MRC Grade 1, 2= Normal BMI and 3= No comorbidity
- *Adjusted for age, sex and smoking status

5.4.3.3 FEV_1 reversibility

Compared to COPD patients, GOLD Stage 0 patients were less likely to have a significant post-bronchodilator FEV_1% reversibility that might indicate the presence of asthma (6.9% *versus* 21.3%, OR=0.3; 95% CI, 0.2 to 0.5) (Table 24).

Table 24: Univariable post-bronchodilator reversibility by patients group

	GOLD Stage 0 (n=275)	Newly diagnosed COPD (n=204)	Unadjusted OR	p value	95% CI
Reversible AFO	19 (6.9%)	41 (21.3%)	0.3	<0.0001	0.2 to 0.5

- Newly diagnosed COPD is the reference group
- Values presented are numbers with percentages unless otherwise stated
- Participants who had their bronchodilator medications 4 hours before the spirometry testing were excluded (11 newly diagnosed COPD and 6 GOLD Stage 0 patients)

5.4.4 Comparison of the health outcome measures between GOLD Stage 0 patients and newly diagnosed COPD patients

5.4.4.1 HRQoL

As shown in Table 25 below, GOLD Stage 0 patients reported very similar HRQoL to newly diagnosed COPD patients across all measures, even after adjustment for the confounding of age, sex, smoking status and comorbidities.

Table 25: The adjusted difference in HRQoL between patients group

	GOLD Stage 0 (n=281)	Newly diagnosed COPD (n=215)	Unadjusted OR (95% CI)	Adjusted OR[1] (95% CI)	Adjusted OR[2] (95% CI)
Self-assessed general health[1]− Number (%)					
Fair	82 (29.2%)	68 (31.6%)	0.9 (0.6 to 1.3)	0.9 (0.6 to 1.3)	0.9 (0.6 to 1.3)
Bad/very bad	16 (5.7%)	8 (3.7%)	1.5 (0.6 to 3.6)	1.4 (0.5 to 3.4)	1.2 (0.5 to 3.1)
EQ-5D Index value−Median (IQR)					
	0.84 (0.31)	0.84 (0.31)	0.7 (0.3 to 1.6)	0.8 (0.3 to 1.8)	0.9 (0.4 to 2.1)
CAT score−Mean (SD)					
	13.3 (7.0)	13.5 (6.7)	1.0 (0.9 to 1.03)	1.0 (0.9 to 1.03)	0.9 (0.9 to 1.03)

- Newly diagnosed COPD group is the reference for all comparisons
- Reference categories: 1=Good to very good general health
- OR[1]: Adjusted for age, sex and smoking status
- OR[2]: Adjusted for age, sex, smoking status and comorbidity (CVDs, diabetes & depression)

5.4.4.2 Exacerbation-like events

Compared to new COPD patients, GOLD Stage 0 subjects were less likely to have exacerbation events (as defined by ever had two or more courses of oral steroids or antibiotics for lung problems), although the difference was at the margins of statistical significance (13.5% *versus* 19.5%, OR=0.6; 95% CI 0.4 to 1.1). The reporting of prescribed oral steroids and antibiotics of more than two courses was almost similar between subgroups (Table 26).

Table 26: The adjusted difference in self-reported exacerbation events by patients group

	GOLD Stage 0 (n=281)	**Newly diagnosed COPD (n=215)**	**Unadjusted OR (95% CI)**	**Adjusted OR[1] (95% CI)**	**Adjusted OR[2] (95% CI)**
Exacerbations in the last 12 months					
	38 (13.5%)	42 (19.5%)	0.7 (0.4 to 1.1)	0.6 (0.4 to 1.0)	0.6 (0.4 to 1.1)
Prescribed steroids[1] (≥ 2 courses)					
	270 (96.1%)	205 (95.4%)	2.2 (0.5 to 9.3)	2.0 (0.4 to 9.9)	1.8 (0.3 to 9.6)
Prescribed antibiotics[1] (≥ 2 courses)					
	251 (89.3%)	186 (86.5%)	1.5 (0.8 to 2.8)	1.8 (0.9 to 3.5)	1.8 (0.9 to 3.4)

- Newly diagnosed COPD group is the reference for all comparisons
- Values presented are numbers with percentages unless otherwise stated
- Reference categories: 1= one course
- OR[1]: Adjusted for age, sex and smoking status
- OR[2]: Adjusted for age, sex, smoking status and comorbidity (CVDs, diabetes & depression)

5.4.4.3 Healthcare utilisation

The difference between both patient subgroups in healthcare utilisation across different measures was small and not statistically different (Table 27).

Table 27: The adjusted difference in self-reported healthcare utilisation between patients group

	GOLD Stage 0 (n=281)	Newly diagnosed COPD (n=215)	Unadjusted OR (95% CI)	Adjusted OR[1] (95% CI)	Adjusted OR[2] (95% CI)
All cause hospital admissions					
	19 (6.8%)	19 (7.6%)	0.7 (0.4 to 1.4)	0.7 (0.3 to 1.4)	0.7 (0.3 to 1.4)
Hospital admissions due to lung problems					
	3 (1.1%)	3 (1.4%)	0.7 (0.2 to 3.7)	0.7 (0.1 to 3.4)	0.6 (0.1 to 3.2)
Hospital admissions due to other health problems					
	16 (5.7%)	16 (7.4%)	0.7 (0.4 to 1.5)	0.7 (0.3 to 1.5)	0.7 (0.3 to 1.6)
All cause A & E attendance					
	44 (15.7%)	43 (20.0%)	0.7 (0.5 to 1.2)	0.7 (0.4 to 1.1)	0.7 (0.4 to 1.1)
A & E attendance due to lung problems					
	2 (0.7%)	1 (0.5%)	1.5 (0.1 to 16.6)	1.6 (0.1to 17.8)	1.5 (0.1 to 17.4)
A & E attendance due to other health problems					
	43 (15.3%)	42 (19.5%)	0.7 (0.5 to 1.2)	0.7 (0.4 to 1.2)	0.7 (0.4 to 1.1)
Number of consultations due to respiratory disease[1] (≥ 2 times)					
	2 (0.7%)	0			

- Newly diagnosed COPD group is the reference for all comparisons
- Values presented are numbers with percentages unless otherwise stated
- Reference categories: 1=1 time
- OR[1]: Adjusted for age, sex and smoking status
- OR[2]: Adjusted for age, sex, smoking status and comorbidity (CVDs, diabetes & depression)

5.4.4.4 Exercise capacity

The mean of exercise capacity was also similar between both groups of patients (Table 28).

Table 28: The adjusted difference in exercise capacity between patients group

	GOLD Stage 0 (n=281)	Newly diagnosed COPD (n=215)	Unadjusted OR (95% CI)	Adjusted OR[1] (95% CI)	Adjusted OR[2] (95% CI)
Mean (SD)	22 (7.9)	21.6 (7.2)	1.0 (0.9 to 1.03)	1.1 (0.9 to 1.03)	1.0 (0.9 to 1.03)

- Newly diagnosed COPD group is the reference for all comparisons
- OR[1]: adjusted for age, sex and smoking status
- OR[2]: adjusted for age, sex, smoking status and comorbidity (CVDs, diabetes & depression)

5.5 Discussion

5.5.1 Main findings

There were some important differences in the characteristics of patients in each of the categories. GOLD Stage 0 patients tended to be slightly younger and twice as likely to be

obese than newly diagnosed COPD patients identified contemporaneously from the same base population. Although less common than among the COPD patients, about 78% reported having ever smoked which could help to explain their symptoms. However, the symptoms amongst GOLD Stage 0 patients had a tendency to be slightly less severe than those newly diagnosed with COPD. Obesity might be another explanation for the presence of GOLD Stage 0 symptoms. Obesity has been identified as one of the major aetiological factors for the presence of respiratory symptoms, particularly exertional dyspnoea independently of airflow obstruction (145-147). The main symptoms associated with obesity are usually dyspnoea (145) and wheeze (146), but an association with productive cough has been also observed (145).

Although the importance of GOLD Stage 0 has been debated due to inconsistencies on whether such patients progress to develop COPD (133), in this study, this group of patients showed similar overall patterns cross-sectionally for outcome measures of HRQoL, healthcare utilisation and exercise capacity to that reported by patients newly identified with COPD. Thus, the presence of chronic respiratory symptoms—even in the absence of diagnosed airflow obstruction—could have a relevant impact on patients' health, and the utilisation of healthcare system resources. Although exacerbation events were lower amongst GOLD Stage 0 compared to COPD patients, both patient groups reported similar proportions of steroid and antibiotic prescriptions (indicative of acute respiratory events).

5.5.2 Comparison with the existing evidence

The present study supports the view that the presence of symptoms has a negative impact on affected patients' health, through examining different health outcome measures amongst GOLD Stage 0 patients compared with those newly identified with COPD in a contemporary

and representative primary care population. Tan *et al*., (2014) study, was the only to compare cross-sectionally the exacerbation events between GOLD Stage 0 patients and those with COPD. Importantly, they found in line with this study that symptomatic patients had less frequent self-reported exacerbations than COPD patients (3.9% *versus* 8.2%, $p<0.001$) (101), but were seen to have a similar or even higher healthcare utilisation (68% *versus* 62%) (101). In the other studies (9, 90, 133), when compared to the normal population, GOLD Stage 0 patients and newly identified COPD patients showed similar impairment in HRQoL (133), increased all cause and obstructive lung disease-related hospital admissions (9) and similar healthcare utilisation (90).

5.5.3 Strengths and Limitations

This study has some limitations. Firstly, the cross-sectional design does not allow inspection of longer-term prognosis between the two patient groups. Secondly, some of the study variables were self-reported and examined retrospectively, meaning they may be subject to recall bias. Another limitation is a lack of imaging data within the Birmingham COPD Cohort Study, meaning it is not possible to rule out the potential of the presence of other underlying pathology (such as emphysema or bronchiectasis), which could help to explain the presence of respiratory symptoms and their association with poor health outcomes among GOLD Stage 0 patients. The strength of this study is its use of data with high quality measures from a prospective cohort study on a large representative sample of patients in the West Midlands, UK. Also patients in both groups were selected from the same underlying population at the same point in time, and therefore should be more comparable than having patients at different stages of COPD.

5.5.4 Implications for research and clinical practise

This study has emphasised the need for further longitudinal studies on GOLD Stage 0 patients with the aim of better understanding their prognosis and to confirm whether the results observed cross-sectionally are reflected longitudinally. Furthermore, GOLD Stage 0 patients are more likely to be obese and in clinical practice they may benefit from weight management programmes and probably pulmonary rehabilitation programmes to improve their symptoms.

5.5.5 Conclusion

The impact of the chronic respiratory symptoms in the absence of airflow obstruction on patients and on the healthcare system should not be ignored. GOLD Stage 0 patients showed similar patterns of poor health outcomes to COPD patients and might also need to be identified and targeted with appropriate interventions. However, further longitudinal studies are needed to better understand their long-term prognosis.

5.6 Supplementary Table

Table 29: Summary of the available evidence on the chapter's topic

Study ID	Design	Outcome	Sample size	Population	Comparator I	Comparator II	Gaps in knowledge
Tan *et al.*, 2014 (101)	A cross sectional multisite population-based study-Canada	The prevalence of exacerbation events	4,890 adults aged ≥ 40 years	Non-COPD patients with "*chronic cough or chronic phlegm not occurring during a cold and on most days for as much as 3 months each year for 2 years*", "*the presence of episodes of wheezing or whistling in the chest associated with feeling of shortness of breath, in the past 1 year not occurring during a cold"* and "*troubled by shortness of breath when hurrying on the level or walking up a slight hill'*	COPD patients, defined using the GOLD criteria	None	• Exacerbation was defined as *"a period of worsening of breathing problems that got so bad that it interfered with usual daily activities or caused the individual to miss work"* • Did not ask about antibiotic/steroids use
Miravitlles *et al.*, 2009 (133)	Cross-sectional population-based study-Spain	HRQoL	4,274 adults aged 40–80 years	GOLD Stage 0 patients defined by the presence of chronic cough and sputum with normal spirometry	Healthy reference group	COPD patients (Stages 1-4), defined using the GOLD criteria	The primary objective was to measure the prevalence and burden of undiagnosed COPD in the general population
Ekberg-Aronsson *et al.*, 2008 (9)	23 years follow up study-Sweden	Hospital admission rates	22,044 middle aged adults (mean=47.5 years)	Gold Stage 0 individuals reported "*chronic productive cough for ≥ 3 months for > 2 consecutive years*" with FEV_1/FVC >0.70 and FEV_1>80% predicted	Control group of asymptomatic smokers with normal lung function	COPD patients, defined as FEV_1/FVC <0.70 with and without symptoms	Asthma was not excluded among GOLD 0 patients and asthma-related hospital admissions were included in the analyses
De Marco *et al.*, 2004 (90)	Cross-sectional study	Healthcare resources utilisation	18,000 young adults aged 20-44 years	GOLD Stage 0 patients reported "*the presence of chronic cough+/-phlegm usually in winter and on most days for as long as 3 months each year*" with FEV_1/FVC >70%	Healthy control group	COPD patients, defined using the GOLD criteria	The primary focus was to measure the prevalence of COPD

6 COPD OVERDIAGNOSIS IN THE UK: THE BIRMINGHAM COPD COHORT STUDY

6.1 Abstract

Introduction: Overdiagnosis is a growing concern for a wide range of diseases including COPD. The aim of this study is to examine the magnitude of COPD overdiagnosis in the UK primary care settings and investigate the main factors associated with COPD overdiagnosis.

Methods: Cross-sectional analysis of data on 1,473 GP diagnosed COPD patients aged 40 years and over who participated in the Birmingham COPD Cohort Study-UK. Patients were classified as non-COPD or confirmed-COPD based on post-bronchodilator spirometry results. Characteristics were compared using logistic regression adjusted for age, sex and smoking status.

Results: Based on GOLD/current NICE, LLN and NICE (2004) criteria, 13.7%, 28.1% and 32.3% of participants were potentially overdiagnosed with COPD, respectively. A restrictive pattern of lung disease was observed in 18.9% of non-COPD patients by using the current NICE definition. Compared to confirmed-COPD, non-COPD patients were more likely to be females (52.2% *versus* 35.4%, OR=2.0; 95% CI, 1.5 to 2.7), never smokers (22.9% *versus* 13.8%, OR=2.4; 95% CI, 1.5 to 3.9), obese (39.3% *versus* 31%, OR=1.6; 95% CI, 1.1 to 2.4), have multiple comorbidities (23.9% and 16.4% with three or more comorbidities respectively, OR=1.7; 95% CI, 1.1 to 2.7) but have less FEV_1 reversibility (10% *versus* 21.4%, OR=0.4; CI, 0.2 to 0.7). Although not statistically significant, non-COPD participants reported more diagnosed coronary heart disease (18.4% *versus* 14.2%), asthma (47.3% *versus* 38.7%),

diabetes (18.9% *versus*14.2%) and depression (21.4% *versus* 16.8%). Applying the LLN definition made a little difference to these characteristics.

Conclusion: COPD overdiagnosis is common. Female sex, obesity and restrictive lung function were identified as potential explanations for COPD overdiagnosis. A follow-up assessment to examine for the possibility of physiological spirometry variability is recommended.

6.2 Introduction

In recognition of the increasing burden of COPD in the UK, both diagnosed and undiagnosed, two key initiatives were established (148). Firstly, NICE published its guidelines for COPD management (148); which included the recommendation that COPD diagnosis should be confirmed only with spirometry (148). Secondly, the introduction of QOF section to the new General Medical Services contract, in which General Practices would receive extra payments for providing a high standard care for COPD patients and for creating detailed patients registers including documented spirometry data, annual reviews and treatment plans (73, 148, 149). Since then, an increase in the prevalence of registered diagnoses of COPD and in the prescription of inhaler medications have been observed (148). Furthermore, most COPD research is usually focused on COPD under diagnosis in primary care, but less is known about COPD overdiagnosis and its consequences, particularly the potential for overtreatment.

A correct diagnosis of COPD is essential because of the therapeutic and prognostic consequences on diagnosed patients and on the healthcare system (60). The inappropriate use of COPD medications to treat patients who do not have the disease exposes them to potentially harmful adverse effects of these medications (62, 63). For example, ICS have been associated with an increased risk of pneumonia (64, 65) and LABAs may cause adverse

cardiovascular effects (61, 66). This is of particular concern as patients at higher risk for receiving a false diagnosis of COPD (e.g. those with undiagnosed heart conditions) are those who may be at higher risk for these adverse effects (61). Moreover, available evidence suggests that symptomatic patients misdiagnosed with COPD are more likely to have higher hospital admission rates and have more diagnostic tests than correctly diagnosed COPD patients indicating missed opportunities for intervention (61) and an increased cost to the NHS (68). Consequently, patients are suffering from chronic respiratory symptoms because of other underlying causes and not receiving the appropriate management (60, 62).

There are a number of studies which suggest that COPD is overdiagnosed in the UK and elsewhere (36, 60, 62, 68, 72, 73, 80, 150-153) (Table 30). However, evidence is limited on the most important factors leading to COPD overdiagnosis, particularly the patient's clinical and lung function-related factors. This study will be the first to examine the magnitude of COPD overdiagnosis and overtreatment in UK primary care settings using three different criteria to define COPD. It will also examine the main factors associated with COPD overdiagnosis, by comparing the clinical and lung function-related characteristics of "overdiagnosed" patients and those with confirmed COPD diagnosis using two criteria. The secondary aim of this study is to compare the health outcomes of "overdiagnosed" patients and confirmed COPD patients.

Table 30: Summary of available evidence on COPD overdiagnosis

Study ID	Setting	Outcome	Sample size	Rate of COPD overdiagnosis	Factors associated with COPD overdiagnosis	Gaps in knowledge
Van Dijk *et al.*, 2015 (36)	Cross-sectional population-based study-Canada	The clinical relevance of the GOLD and LLN criteria on patient-reported outcomes of symptoms, health status, disability, exacerbations and cardiovascular comorbidity	4,882 people aged ≥ 40 years	Was not measured	Have not been examined	The main focus was to compare the clinical relevance of the GOLD and the LLN criteria
Ghattas *et al.*, 2013 (68)	Retrospective cohort study-US	The prevalence of COPD overdiagnosis among underserved population	80 people aged ≥ 40 years	42.5%	• Less smoking exposure • Asthma	• Small sample size • Targeted specified population • Used the GOLD criteria only to define COPD
Buffels *et al.*, 2012 (80)	Prospective cohort study-Belgium	The diagnostic accuracy of COPD in primary care	312 patients aged > 40 years	28.6%	Have not been examined	Used the GOLD criteria only
Melbye *et al.*, 2011 (150)	General practice-based study-Norway	The agreement between spirometry findings and GPs diagnosis of COPD	74 registered COPD patients aged ≥ 40 years	25.8%	Have not been examined	Used the GOLD criteria only to define COPD Small sample size
Jones *et al.*, 2008 (72)	Cross-sectional study in primary care practices-UK	The diagnostic accuracy of COPD registers in general practices	580 patients	27.2%	• Restrictive function • Asthma	Used the former NICE (2004) criteria only
Walters *et al.*, 2011 (60)	Cross-sectional study in primary care practices- Australia	The misclassification of COPD	341 patients	31%	• Obesity • Self-reported allergic rhinitis and hay fever • Age, sex and smoking status • Respiratory symptoms • Restrictive function	Used the GOLD criteria only

Study ID	Setting	Outcome	Sample size	Rate of COPD overdiagnosis	Factors associated with COPD overdiagnosis	Gaps in knowledge
Bolton *et al.*, 2005 (73)	Questionnaire based survey-UK	The agreement between the diagnostic label of COPD in primary care and the study's spirometric results	125 GP-diagnosed COPD patients without spirometry, aged ≥ 40 years	31%	• Restrictive function • Asthma	Used the NICE (2004) criteria only
Sichletidis *et al.*, 2007 (151)	Prospective study in general practices-Greece	The validity of COPD diagnosis in general practices	319 diagnosed COPD patients, aged ≥ 40 years	49.8%	• Restrictive function • Asthma	Used the GOLD criteria only
Zwar *et al.*, 2011 (62)	Conducted in a context of a randomised controlled trial-Australia.	The practitioner, practice and patients-related factors that affect the agreement between COPD diagnostic label and the study's spirometry results	445 COPD patients aged 40-80 years.	42.2%	• Younger age • Multiple comorbidities • Restrictive function • Asthma	Used the GOLD criteria only
Ta´lamo *et al.*, 2007 (152)	PLATINO study of COPD prevalence in Latin America	The agreement between prior diagnostic label and the study's spirometry findings	237 COPD patients aged ≥ 40 years	63.7%	• Spirometry underuse • Restrictive function • Female sex • Less smoking exposure	Used the GOLD criteria only
Centurion *et al.*, 2012 (153)	Multi-centre study-US	The utility of confirmatory spirometry for COPD diagnosis in patients hospitalised with exacerbation	36 adults age ≥18 years admitted with COPD exacerbations	28%	• High BMI	Used the LLN criteria only Small sample size

6.3 Methods and Materials

6.3.1 Study design/setting

Cross-sectional analysis of baseline assessment data from the Birmingham COPD Cohort Study, a prospective primary-care based cohort study in the West Midlands-UK (134). The baseline assessment was undertaken between May 2012 and June 2014, across 71 participating general practices (134).

6.3.1.1 Patient recruitment

As mentioned in the previous chapter (section 5.3.2.2), prevalent COPD patients participated in the Birmingham COPD Cohort Study were identified through a standardised electronic search of the COPD QoF register (COPD14) of the participating general practices (134). Thereafter, GPs reviewed the search results and identified eligible patients who were registered with COPD diagnosis, aged 40 years and over and able to give a written consent (134). At the GP's discretion, patients with terminal illness, unable to give informed consent or with other social factors (e.g. recent bereavement) were excluded (134). All of the identified eligible patients were invited by their GPs to participate in the study, with a maximum of two reminders sent to non-respondents (134). Information on how the COPD diagnosis was made and the date of diagnosis was not obtained (134).

6.3.2 Measurements and data collection

Clinical assessment was undertaken at the patients' practices by trained research assistants and included a wide range of clinical measures (134). Spirometry was performed pre and post-bronchodilator according to the ATS/ERS guidelines (136). Validated questionnaires were used to collect data on patient demographics, lifestyle, coexisting comorbidities,

respiratory symptoms, prescribed medications, healthcare utilization, exacerbation events and HRQoL (134).

6.3.3 Study variables definitions

6.3.3.1 Exposure variables

Exposure variables of smoking, BMI, self-reported respiratory symptoms and self-reported coexisting comorbidities were examined using the same measures and definitions detailed in Chapter 5 (Section 5.3.4.1).

6.3.3.2 Health outcome variables

Health outcomes examined in this study included; self-reported HRQoL, self-reported exacerbation-like events, self-reported healthcare utilisation and a measured exercise capacity. All were assessed using the same measures and definitions detailed in Chapter 5 (Section 5.3.4.2).

6.3.4 Diagnostic criteria

6.3.4.1 Confirmation of COPD diagnosis

The diagnosis of COPD was confirmed using three different criteria: the current NICE/the GOLD committee criteria of post-bronchodilator FEV_1/FVC ratio <0.7 (6, 7), the former NICE (2004) criteria of $FEV_1/FVC<70\%$ and $FEV_1<80\%$ (154) and the LLN criteria of '*post-bronchodilator FEV_1/FVC ratio falls below the 5^{th} percentile of the predicted values for patient's age, height, sex and ethnicity, with a reference to healthy non-smoker population*' calculated using the GLI-2012 equations (143).

Patients with no post-bronchodilator spirometry data available because of reported spirometry contraindications, inability to perform spirometry or reported history of salbutamol allergy were excluded from this study.

6.3.4.2 Reversible airflow obstruction

Reversible airflow obstruction was defined using the GOLD/ATS definition of '*a post bronchodilator increase of the baseline FEV_1 of more than 12% if this also exceeds 200 ml*' (6). Participants who had taken their bronchodilator medications four hours prior to spirometry testing were excluded from the reversibility analysis.

6.3.4.3 Restrictive lung function pattern

Restrictive lung function is *'a condition in which the total lung capacity is reduced, on the basis of an abnormally low vital capacity in combination with a normal or high FEV_1/FVC ratio'* (144). It was measured as FVC below 80% predicted and FEV_1/FVC ratio equal to or higher than 70% (155) and secondly as FVC% predicted below the LLN but FEV_1/FVC% predicted within or higher than the LLN (156). All predicted lung function values were calculated using the GLI equations.

6.3.5 Statistical analyses

STATA v.13 was used for all statistical analyses. Descriptive data of patients with and without COPD, were presented as mean and SD or as median and IQR for continuous variables and as frequency and percentage for categorical variables. Logistic regression was used to examine the patient-related factors associated with COPD overdiagnosis and presented as ORs with 95% CI and p values adjusted for age, sex, smoking status and cardiovascular comorbidities.

6.4 Results

6.4.1 Patient recruitment

From the QOF register of 71 participating general practices, 6,383 diagnosed COPD patients were identified as eligible and invited to participate in the cohort study. Of those, 2,014 (31.6%) did not respond after two reminders, 2,171 (34.0%) agreed to participate and 2,198 (34.5%) declined. Amongst those patients who agreed to the invitation, 1,558 gave written consent and were assessed. 85 patients (5.5%) were excluded from this study due to missing post-bronchodilator spirometry data (Figure 8).

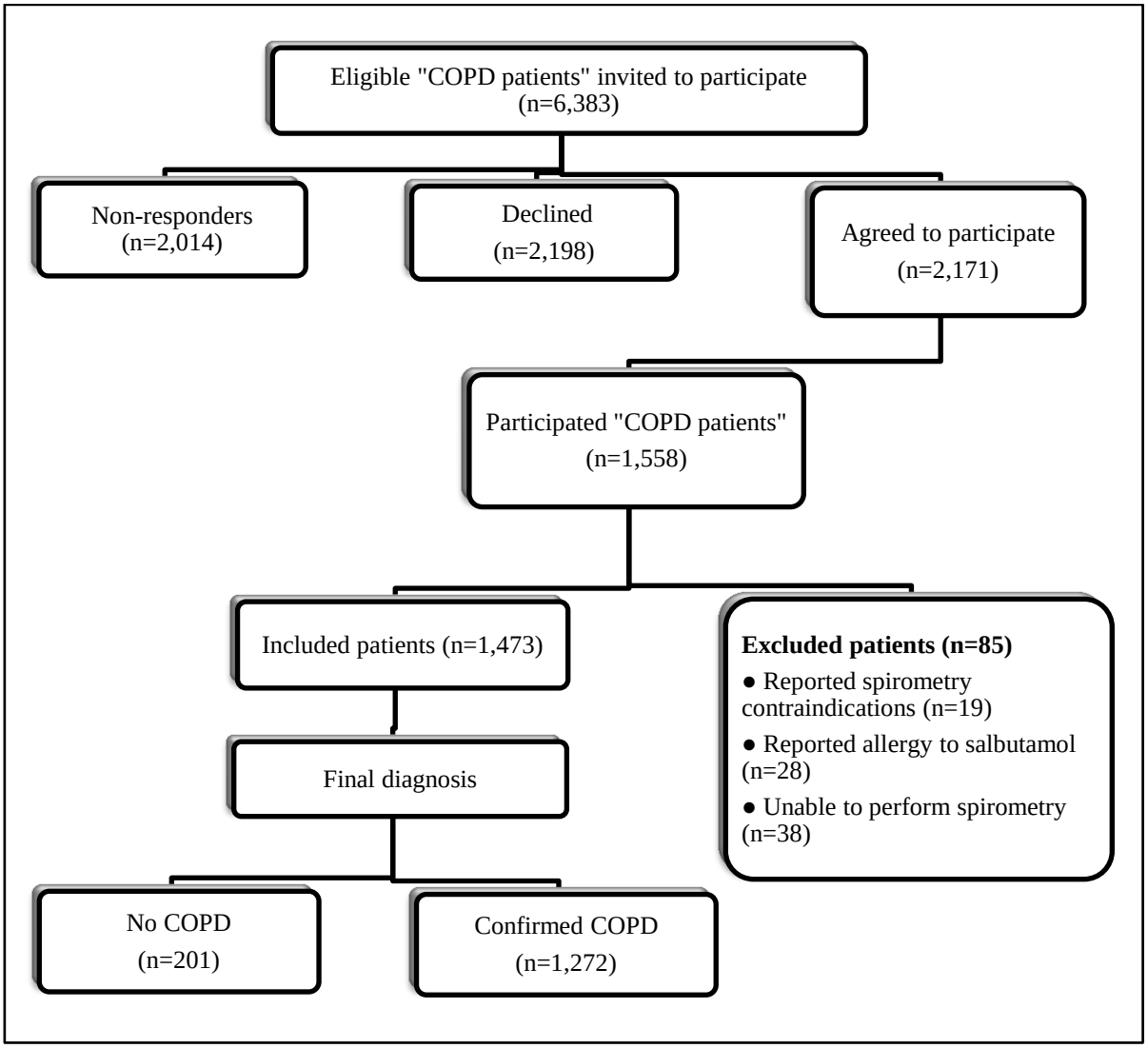

Figure 8: Flow diagram of patient recruitment procedure

6.4.2 Characteristics of participants and non-participants

Compared to non-participants, those who participated were more likely to be males (57.1% *versus* 46.5%, OR=1.6; 95% CI, 1.4 to 1.8) and more likely to be of white ethnicity (70.2% *versus* 67.4%, OR=1.5; 95% CI, 1.1 to 2.2). However, the mean age was similar (Table 31).

Table 31: Univariable characteristics of participants and non-participants

	Participants (n=1,558)	Non-participants (n=4,825)	Unadjusted OR	p value	95% CI
Age – Mean (SD)	68.5 (9.9)	69.3 (11.4)	1.0	0.007	1.0 to 1.1
Male sex [1]	890 (57.1%)	2,246 (46.5%)	1.6	<0.0001	1.4 to 1.8
White ethnicity[2]	1,094 (70.2%)	3,253 (67.4%)	1.5	0.03	1.1 to 2.2

- Non- participants is the reference group
- Values presented are numbers with percentages unless otherwise stated
- Reference categories:1=Female and 2=Non-white

6.4.3 Magnitude of COPD overdiagnosis

6.4.3.1 Prevalence of COPD overdiagnosis

A total of 1,473 registered GP-diagnosed COPD patients were included in this study, the prevalence of COPD overdiagnosis amongst them varied according to the criteria being applied. Using the current NICE/GOLD criteria, 201 patients (13.7%, 95% CI; 0.12 to 0.16) did not meet the definition of COPD. With the LLN criteria, 413 participants (28.1%, 95% CI; 0.26 to 0.30) did not have COPD; similarly, using the former NICE (2004) criteria, 458 participants (32.3%, 95% CI; 0.30 to 0.35) did not meet the criteria (Figure 9).

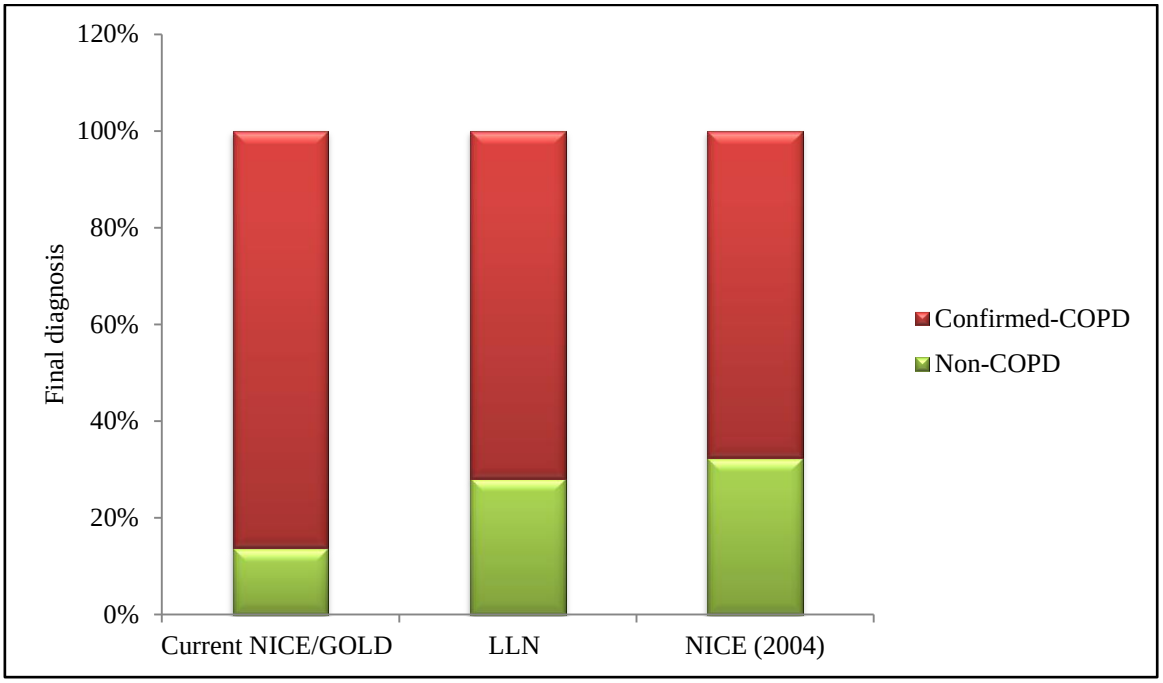

Figure 9: Rate of COPD overdiagnosis based on three different definitions

6.4.3.2 Consequence of COPD overdiagnosis: medication prescriptions

Although 77.6% of patients without COPD were prescribed inhaled medications, this was lower than those with confirmed COPD (88.5%). Some respiratory medications were significantly less likely to be prescribed for non-COPD compared with confirmed COPD participants: Combinhaler (31.8% *versus* 56.8%, p<0.0001), LAMA (28.9% *versus* 50.6%, p<0.0001) and SABA (69.2% *versus* 76.4%, p=0.03). However, both sets of patients had similar levels of prescribed single ICS, LABA and SAMA (Table 32).

Table 32: Prescribed respiratory medications by lung function group using the current NICE criteria

Prescribed respiratory medications	Non-COPD (n=201)	Confirmed COPD (n=1,272)	P value
Combinhaler	64 (31.8%)	723 (56.8%)	<0.0001
LAMA	58 (28.9%)	643 (50.6%)	<0.0001
SABA	139 (69.2%)	972 (76.4%)	0.03
ICS	11 (5.5%)	45 (3.5%)	0.18
LABA	12 (6%)	77 (6.1%)	0.96
SAMA	9 (4.5%)	62 (4.9%)	0.81
Any of the above inhaler medication	156 (77.6%)	1,126 (88.5%)	<0.0001

- Confirmed COPD group is the reference for all comparisons
- Values presented are numbers with percentages unless otherwise stated
- ICS: inhaled corticosteroids. Combinhaler: ICS combined with one of the other inhalers. LABA: long-acting beta2 agonist. LAMA: long-acting muscarinic antagonist. SABA: Short-acting beta2 agonists. SAMA: short-acting muscarinic antagonists

6.4.4 Comparing the clinical and lung function related characteristics of non-COPD and confirmed COPD groups using the current NICE criteria

6.4.4.1 Clinical characteristics

6.4.4.1.1 Socio-demographics

Table 33 below presents the socio-demographic characteristics of participants potentially overdiagnosed with COPD based on the current NICE criteria. Compared to confirmed COPD patients, non-COPD participants were slightly younger (although not statistically significant), more likely to be females (52.2% *versus* 35.4%, OR=2.0; 95% CI, 1.5 to 2.7) and more likely to be never smokers (22.9% *versus* 13.8%, OR=2.4; 95% CI, 1.5 to 3.9).

Table 33: The adjusted socio-demographic characteristics by lung function group using the current NICE criteria

	Non-COPD (n=201)	Confirmed COPD (n=1,272)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Age −Mean (SD)	67.2 (10.8)	69.5 (9)	1.0 (0.9 to 1.0)	
Sex[1]				
Males	96 (47.8%)	822 (64.6%)	1.0	
Females	105 (52.2%)	450 (35.4%)	2.0 (1.5 to 2.7)	
Ethnicity[2]				
White	180 (89.6%)	1, 141 (89.7%)	1.1 (0.5 to 3.0)	
Non-white	5 (2.6%)	37 (3.0%)	1.0	
Highest education level[3]				
No formal qualification	108 (53.7%)	695 (54.6%)	1.0	1.0
Primary level (GCSE)	34 (16.9%)	196 (15.4%)	1.1 (0.7 to 1.7)	1.0 (0.7 to 1.6)
Secondary (A-level)	7 (3.5%)	43 (3.4%)	1.1 (0.5 to 2.4)	1.0 (0.4 to 2.3)
Degree level or higher	8 (4.0%)	82 (6.5%)	0.6 (0.3 to 1.3)	0.6 (0.3 to 1.3)
Currently in work	36 (17.9%)	203 (16.0%)	1.2 (0.8 to 1.7)	1.0 (1.0 to 1.1)
Smoking status[4]				
Current smoker	42 (20.9%)	343 (27%)	1.0	1.0
Ex-smoker	107 (53.2%)	727 (57.2%)	1.2 (0.8 to 1.8)	1.5 (1.0 to 2.2)
Never smoker	46 (22.9%)	175 (13.8%)	2.2 (1.4 to 3.4)	2.4 (1.5 to 3.9)
Pack years smoking amongst smokers[5]				
<5	18 (8.9%)	80 (6.3%)	1.0	1.0
5-19	40 (19.9%)	187 (14.7)	0.9 (0.5 to 1.8)	0.8 (0.4 to 1.5)
20-49	61 (30.3%)	496 (39.1%)	0.5 (0.3 to 1.0)	0.5 (0.3 to 0.8)
50+	33 (16.4%)	106 (8.3%)	1.3 (0.7 to 2.6)	1.2 (0.6 to 2.3)

- Confirmed COPD group is the reference for all comparisons
- Values presented are numbers with percentages unless otherwise stated
- White ethnicity includes white British, Irish & other white backgrounds
- Reference categories: 1=male, 2=non-white, 3= no formal qualification, 4= current smoker and 5=<5 pack years
- *Adjusted for age, sex and smoking status
- Smoking outcomes were adjusted only for age and sex

6.4.4.1.2 Respiratory symptoms, BMI and coexisting comorbidities

There was little difference in the frequency of reported respiratory symptoms between the two groups (Table 34). However, compared with confirmed COPD participants, those without COPD were more likely to be obese (39.3% *versus* 31%, adjusted OR=1.6; 95% CI, 1.1 to 2.4) and have multiple comorbidities (23.9% and 16.4% with three or more comorbidities respectively, adjusted OR=1.7; 95% CI, 1.1 to 2.7). Although not statistically significant, non-

COPD participants reported more doctor-diagnosed coronary heart disease (18.4% *versus* 14.2%), asthma (47.3% *versus* 38.7%), diabetes (18.9% *versus* 14.2%) and depression (21.4% *versus* 16.8%).

Table 34: The adjusted difference in respiratory symptoms, BMI and comorbidities by lung function group using the current NICE criteria

	Non-COPD (n=201)	Confirmed COPD (n=1,272)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Self-reported respiratory symptoms				
Chronic cough	107 (53.2%)	645 (50.7%)	1.2 (0.8 to 1.6)	1.3 (0.9 to 1.8)
Chronic phlegm	77 (38.3%)	519 (40.8%)	0.8 (0.6 to 1.1)	0.9 (0.6 to 1.3)
Wheeze	141 (70.1%)	918 (72.2%)	0.8 (0.6 to 1.2)	0.8 (0.6 to 1.2)
Dyspnoea[1] (MRC grade 2)	49 (24.4%)	276 (21.7%)	1.0 (0.5 to 1.3)	1.0 (0.6 to 1.6)
Dyspnoea[1] (MRC 3-5)	112 (55.7%)	722 (56.8%)	0.9 (0.6 to 1.7)	0.8 (0.5 to 1.3)
Any symptom	173 (86.1%)	1,120 (88.1%)	0.5 (0.2 to 1.4)	0.5 (0.2 to 1.4)
BMI[2]				
Normal	38 (18.9%)	313 (24.6%)	1.0	1.0
Underweight	3 (1.5%)	29 (2.3%)	0.9 (0.3 to 2.9)	0.9 (0.3 to 3.1)
Overweight	66 (32.8%)	468 (36.8%)	1.2 (0.8 to 1.8)	1.2 (0.8 to 1.9)
Obese	79 (39.3%)	394 (31%)	1.7 (1.1 to 2.5)	1.6 (1.1 to 2.4)
Self-reported comorbidity				
Cardiovascular comorbidities				
CVD	116 (57.7%)	710 (55.8%)	1.02 (0.7 to 1.4)	1.2 (0.9 to 1.7)
High blood pressure	89 (44.3%)	556 (43.7%)	0.9 (0.7 to 1.3)	1.0 (0.8 to 1.4)
Coronary heart disease	37 (18.4%)	180 (14.2%)	1.3 (0.9 to 2.0)	1.5 (0.9 to 2.3)
Heart failure	17 (8.5%)	87 (6.8%)	1.2 (0.7 to 2.1)	1.4 (0.8 to 2.4)
Stroke	16 (8%)	96 (7.5%)	1.03 (0.6 to 1.8)	1.1(0.6 to 1.9)
Other heart diseases	19 (9.5%)	106 (8.3%)	1.2 (0.7 to 1.96)	1.2 (0.7 to 2.1)
Respiratory comorbidities				
Asthma	95 (47.3%)	492 (38.7%)	1.3 (0.9 to 1.8)	1.1 (0.8 to 1.6)
Hay fever	32 (15.9%)	199 (15.6%)	1.0 (0.7 to 1.5)	0.9 (0.6 to 1.3)
Tuberculosis	3 (1.5%)	48 (3.8%)	0.4 (0.1 to 1.2)	0.3(0.1 to 1.1)
Other comorbidities				
Cancer	19 (9.5%)	157 (12.3%)	0.7 (0.4 to 1.2)	0.8 (0.5 to 1.3)
Diabetes	38 (18.9%)	180 (14.2%)	1.4 (0.9 to 2.0)	1.3 (0.9 to 2.0)
Depression	43 (21.4%)	214 (16.8%)	1.4 (0.9 to 2.0)	1.1 (0.7 to 1.6)
Number of comorbidities[3]				
No comorbidity	45 (22.4%)	330 (25.9%)	1.0	1.0
1 comorbidity	59 (29.4%)	429 (33.7%)	1.0 (0.7 to 1.5)	1.1 (0.7 to 1.7)
2 comorbidity	49 (24.4%)	304 (24%)	1.2 (0.8 to 1.8)	1.3 (0.8 to 2.0)
≥ 3 comorbidity	48 (23.9%)	209 (16.4%)	1.7 (1.1 to 2.6)	1.7 (1.1 to 2.7)

- Confirmed COPD group is the reference for all comparisons
- Values presented are numbers with percentages unless otherwise stated
- CVD includes high blood pressure, coronary heart disease, heart failure, stroke or any other heart problems
- Reference categories:1= MRC 1, 2= normal BMI and 3= no comorbidity
- *Adjusted for age, sex and smoking status

6.4.4.2 Lung function-related characteristics

According to spirometric measurements at the cohort baseline assessment, approximately 18.9% of non-COPD participants had restrictive lung function. 69.6% reported the presence of respiratory symptoms with normal lung function (met the definition of GOLD Stage 0), whereas, 2.5% were asymptomatic with normal lung function (Table 35). Post-bronchodilator FEV_1 reversibility was less likely amongst non-COPD participants than confirmed COPD participants (10% *versus* 21.4%, OR=0.4; 95% CI, 0.2 to 0.7) (Table 35).

Table 35: Univariable spirometry findings by lung function group using the current NICE criteria

	Non-COPD (n=201)	**Confirmed COPD (n=1,272)**	**Unadjusted OR**	**P value**	**95% CI**
Restrictive lung function	38 (18.9%)	0			
"GOLD Stage 0"	140 (69.6%)	0			
Asymptomatic with normal PFT	6 (3.0%)	0			
Post-bronchodilator AFO reversibility					
	Non-COPD (n=170)[1]	**Confirmed COPD (n=907)[2]**			
Reversible AFO	17 (10%)	194 (21.4%)	0.4	0.001	0.2 to 0.7

- Confirmed COPD is the reference group
- Values presented are numbers with percentages unless otherwise stated
- PFT=pulmonary function test
- 1=Excluding 28 participants who had their bronchodilator medications 4 hours prior to the spirometry
- 2=Excluding 352 participants who had their bronchodilator medications 4 hours prior to the spirometry

6.4.4.3 Potential explanations for COPD overdiagnosis using the current NICE definition

Being female, a never smoker, having obesity and having multiple comorbidities were the main clinical factors significantly associated with COPD overdiagnosis. However, when further adjusted for each another, the reported multiple comorbidities of more than three conditions no longer remained significant, although the point estimate remained the same (Table 36).

Table 36: Adjusted clinical factors associated with COPD overdiagnosis based on the current NICE criteria

	Non-COPD (n=201)	Confirmed COPD (n=1,272)	Unadjusted OR (95% CI)	Adjusted OR[1] (95% CI)	Adjusted OR[2] (95% CI)
Female sex	105 (52.2%)	450 (35.4%)	2.0 (1.5 to 2.7)	-	1.8 (1.3 to 2.5)
Never smoker	46 (22.9%)	175 (13.8%)	2.2 (1.4 to 3.4)	2.4 (1.5 to 3.9)	2.5 (1.5 to 4.1)
Obesity	79 (39.3%)	394 (31%)	1.7 (1.1 to 2.5)	1.6 (1.1 to 2.4)	1.6 (1.01 to 2.4)
≥ 3 comorbidities	48 (23.9%)	209 (16.4%)	1.7 (1.1 to 2.6)	1.7 (1.1 to 2.7)	1.6 (0.9 to 2.6)

- Confirmed COPD is the reference group
- Values presented are numbers with percentages unless otherwise stated
- OR[1] adjusted for age, sex and smoking status
- OR[2] adjusted for age, sex, smoking status, BMI and number of comorbidities

6.4.5 Comparing the health outcome measures between non-COPD and confirmed COPD using the current NICE definition

There were no statistically significant differences between non-COPD participants and those with confirmed COPD for HRQoL, healthcare utilisation or exercise capacity (Table 37). However, compared with the confirmed COPD group, non-COPD participants reported significantly fewer exacerbation events (50.2% *versus* 58.1%, OR=0.6; 95% CI, 0.5 to 0.9) but were more likely to report antibiotics and steroids prescriptions of two courses or more (Although not statistically significant) (Table 37).

Table 37: The adjusted difference in health outcome measures by lung function group using the current NICE criteria

	Non-COPD (n=201)	Confirmed COPD (n=1,272)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
HRQoL				
Self-assessed general health[1]				
Fair	91 (45.3%)	575 (45.2%)	1.0 (0.7 to1.3)	1.0 (0.7 to 1.4)
Bad/very bad	23 (11.4%)	166 (13.1%)	0.8 (0.5 to 1.4)	0.9 (0.5 to 1.6)
EQ-5D Index value − Median (IQR)				
	0.71 (0.34)	0.74 (0.28)	0.8 (0.4 to 1.5)	0.8 (0.4 to 1.5)
CAT score−Mean (SD)				
	19.2 (8.4)	20 (8.8)	1.0 (0.9 to 1.0)	1.0 (0.9 to1.0)
Self-reported exacerbation events				
Exacerbations in the last 12 months	101 (50.2%)	739 (58.1%)	0.7 (0.5 to 0.9)	0.6 (0.5 to 0.9)
Prescribed steroids[2] (≥ 2 courses)	164 (81.6%)	1,004 (78.9%)	1.1 (0.7 to 1.7)	1.2 (0.8 to 1.9)
Prescribed antibiotics[2] (≥ 2 courses)	164 (81.6%)	971 (76.3%)	1.2 (0.8 to 1.8)	1.2 (0.8 to 1.8)
Self-reported healthcare utilisation				
All-cause hospital admissions	30 (14.9%)	203 (16%)	0.9 (0.6 to 1.4)	1.0 (0.7 to 1.6)
Hospital admissions due to lung problems	8 (4%)	87 (6.8%)	0.6 (0.3 to 1.2)	0.7 (0.3 to 1.4)
Hospital admissions due to other health problems	24 (11.9%)	132 (10.4%)	1.2 (0.8 to 1.9)	1.3 (0.8 to 2.1)
All cause A & E attendance	46 (22.9%)	268 (21.1%)	1.1 (0.8 to 1.6)	1.2 (0.8 to 1.7)
A & E attendance due to lung problems	11 (5.5%)	81 (6.4%)	0.9 (0.4 to 1.6)	0.8 (0.4 to 1.7)
A & E attendance due to other health problems	39 (19.4%)	206 (16.2%)	1.2 (0.8 to 1.8)	1.3 (0.8 to 1.9)
Number of consultations due to respiratory disease[3]				
1 time	13 (6.5%)	83 (6.5%)	1.0	1.0
≥ 2 times	5 (2.5%)	30 (2.4%)	1.1 (0.3 to 3.2)	1.1 (0.3 to 3.4)
Exercise capacity (sit to stand test)−Mean (SD)				
	18.7 (6.8)	17.9 (6.0)	1.0 (1.0 to 1.1)	1.0 (1.0 to 1.1)

- Confirmed COPD is the reference group
- Values presented are numbers with percentages unless otherwise stated
- Reference categories: 1=good/very good general health, 2= one course and 3=1 time
- *Adjusted for age, sex, smoking status and cardiovascular comorbidity

6.4.6 The implications of applying the LLN criteria

By applying the LLN criteria to define COPD in place of the current NICE/GOLD criteria (Table 38), broadly similar patterns observed except that there was no longer any difference in the sex distribution but there were now more ex-smokers in the non-COPD group than

confirmed COPD (59.1% *versus* 55.8%, adjusted OR=1.7; 95% CI, 1.3 to 2.3) and non-COPD patients were less likely to have severe dyspnoea of MRC grades 3-5 (51.3% *versus* 58.6%, adjusted OR=0.7; 95% CI 0.5 to 0.9). Although the difference in post-bronchodilator FEV_1 reversibility between groups was not statistically significant, the effect was in the same direction as with the current NICE criteria. Among the overdiagnosed group, a larger proportion had restrictive lung function than with using the current NICE criteria (31.5% *versus* 18.9%) and a larger proportion had reversible airflow obstruction (16.3% *versus* 10%). This resulted in a smaller proportion (53.8% *versus* 69.6%) who reported symptoms with no lung function abnormality (i.e. COPD GOLD Stage 0) (Table 38).

Table 38: The adjusted difference in clinical and spirometry-related characteristics by lung function group using the LLN criteria

	Non-COPD (n=413)	**Confirmed COPD (n=1,059)**	**Unadjusted OR (95% CI)**	**Adjusted OR* (95% CI)**
• **Clinical factors**				
Age −Mean (SD)	70.2 (9.8)	68.7 (9.2)	1.0 (1.0 to 1.03)	-
Sex[1]				
Male	246 (59.6%)	672 (63.5%)	0.9 (0.7 to 1.1)	-
Female	167 (40.4%)	387 (36.5%)	1.0	-
Ethnicity[2]				
White	367 (88.9%)	953 (90%)	1.2 (0.6 to 2.5)	-
Non-white	10 (2.4%)	32 (3.1%)	1.0	-
Highest education level[3]				
No formal qualification	217 (52.5%)	585 (55.2%)	1.0	1.0
Primary level	69 (16.7%)	161 (15.2%)	1.2 (0.8 to 1.6)	1.3 (0.9 to 1.8)
Secondary level	16 (3.9%)	34 (3.2%)	1.3 (0.7 to 2.3)	1.4 (0.8 to 2.6)
Degree level or higher	23 (5.7%)	67 (6.3%)	0.9 (0.6 to 1.5)	1.0 (0.6 to 1.6)
Currently in work	57 (13.8%)	182 (17.2%)	0.8 (0.6 to 1.1)	0.9 (0.7 to 1.3)
Smoking status[4]				
Current smoker	72 (17.4%)	313 (29.7%)	1.0	1.0
Ex-smoker	244 (59.1%)	590 (55.8%)	1.8 (1.3 to 2.4)	1.7 (1.3 to 2.3)
Never smoker	86 (20.8%)	134 (12.4%)	2.8 (1.9 to 4.1)	2.6 (1.8 to 3.8)
Pack years smoking amongst smokers[5]				
<5	36 (8.7%)	62 (5.9%)	1.0	1.0
5-19	69 (16.7%)	158 (14.9%)	0.8 (0.5 to 1.2)	0.8 (0.5 to 1.3)
20-49	132 (32%)	425 (40.1%)	0.5 (0.3 to 0.8)	0.6 (0.4 to 0.9)
50+	59 (14.3%)	79 (7.5%)	1.3 (0.8 to 2.2)	1.2 (0.7 to 2.1)
BMI[6]				
Normal	70 (16.9%)	281 (26.5%)	1.0	1.0
Underweight	5 (1.2%)	27 (2.5%)	0.7 (0.3 to 2.0)	0.9 (0.4 to 2.6)
Overweight	140 (33.9%)	393 (37.1%)	1.4 (1.0 to 2.0)	1.4 (1.0 to 1.9)
Obese	165 (40%)	308 (29.1%)	2.2 (1.6 to 3.1)	2.2 (1.6 to 3.0)

	Non-COPD (n=413)	Confirmed COPD (n=1,059)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Respiratory symptoms				
Chronic cough	215 (52.1%)	536 (50.6%)	1.1 (0.9 to 1.4)	1.3 (1.0 to 1.6)
Chronic phlegm	155 (37.5%)	440 (41.5%)	0.8 (0.6 to 1.1)	0.9 (0.7 to 1.2)
Wheeze	279 (67.6%)	779 (73.6%)	0.7 (0.6 to 0.9)	0.8 (0.6 to 1.1)
Dyspnoea[7] (MRC grade 2)	103 (24.9%)	222 (21.5%)	0.9 (0.6 to 1.3)	0.9 (0.6 to 1.3)
Dyspnoea (MRC grade 3-5)	212 (51.3%)	621 (58.6%)	0.7 (0.5 to 0.9)	0.7 (0.5 to 0.9)
Any symptom	363 (88.0%)	985 (93.0%)	0.5 (0.4 to 0.8)	0.8 (0.4 to 1.9)
Self-reported comorbidity				
Cardiovascular comorbidities				
CVDs	241 (58.4%)	584 (55.1%)	1.2 (0.9 to 1.5)	1.1 (0.9 to 1.5)
High blood pressure	194 (47%)	450 (42.5%)	1.2 (0.9 to 1.5)	1.2 (0.9 to 1.5)
Coronary heart disease	69 (16.7%)	148 (14%)	1.2 (0.9 to 1.7)	1.2 (0.9 to 1.7)
Heart failure	36 (8.7%)	68 (6.4%)	1.4 (0.9 to 2.2)	1.4 (0.9 to 2.0)
Stroke	28 (6.8%)	84 (7.9%)	0.9 (0.5 to 1.3)	0.9 (0.6 to 1.4)
Other heart diseases	35 (8.5%)	90 (8.5%)	1.0 (0.7 to 1.5)	1.0 (0.6 to 1.5)
Respiratory comorbidities				
Doctor diagnosed asthma	173 (41.9%)	413 (39%)	1.1 (0.9 to 1.5)	1.1 (0.9 to 1.4)
Hay fever	65 (15.7%)	165 (15.6%)	1.0 (0.8 to 1.4)	1.0 (0.7 to 1.4)
Tuberculosis	11 (2.7%)	40 (3.8%)	0.7 (0.4 to 1.4)	0.6 (0.3 to 1.3)
Other comorbidities				
Cancer	51 (12.3%)	125 (11.8%)	1.1 (0.7 to 1.5)	1.0 (0.7 to 1.5)
Diabetes	73 (17.7%)	145 (13.7%)	1.4 (1.0 to 1.9)	1.3 (0.9 to 1.7)
Depression	74 (17.9%)	183 (17.3%)	1.1 (0.8 to 1.5)	1.1 (0.8 to 1.6)
Number of comorbidities[8]				
No comorbidity	100 (24.2%)	275 (26%)	1.0	1.0
1 comorbidity	117 (28.3%)	370 (34.9%)	0.9 (0.6 to 1.2)	0.9 (0.6 to 1.2)
2 comorbidity	108 (26.2%)	245 (23%)	1.2 (0.9 to 1.7)	1.2 (0.9 to 1.7)
≥ 3 comorbidity	88 (21.3%)	169 (16%)	1.4 (1.01 to 2.0)	1.4 (1.0 to 2.0)
• **Lung function-related factors**				
Restrictive lung function	130 (31.5%)	308 (29.1%)	1.1 (0.7 to 1.7)	
"GOLD Stage 0"	222 (53.8%)	0		
Asymptomatic with normal PFT	8 (1.9%)	0		
Post-bronchodilator reversibility				
	Non-COPD (n=332)[9]	**Confirmed COPD (n=740)[10]**		
Reversible AFO	54 (16.3%)	157 (21.2%)	0.7 (0.5 to 1.02)	

- Confirmed COPD is the reference group
- Values presented are numbers with percentages unless otherwise stated
- White ethnicity includes white British, Irish & other white backgrounds
- Reference categories: 1=Female, 2=Non-white, 3= No formal qualification, 4= Current smoker, 5=<5 Pack years, 6=Normal BMI, 7=MRC Grade 1 and 8=No comorbidity
- *Adjusted for age, sex and smoking status
- PFT=pulmonary function test
- 9=excluding 81 non-COPD participants who had their bronchodilator medications 4 hours prior to the spirometry testing
- 10=excluding 319 confirmed COPD participants who had their bronchodilator medications 4 hours prior to the spirometry testing

6.5 Discussion

6.5.1 Main findings and comparison with the existing evidence

6.5.1.1 Magnitude of COPD overdiagnosis

Using data from a unique primary care cohort of COPD patients, this study shows that 13.7% were potentially overdiagnosed with COPD based on the current NICE criteria (approximately one in every seven diagnosed patients). Published prevalence rates from the UK using the former NICE criteria are similar to the rate of 32.3% observed in this study, where 5 to10 years ago rates of 31% (73) and 27.2% (72) were reported. Overdiagnosis in the UK however does appear to be less of a problem than in some other countries. Even in more recent international studies, most of which used the GOLD criteria (equivalent to the current NICE definition), a rate of 25.8% was reported in Norway (150), 28.6% in Belgium (80) and 49.8% in Greece (151). In the US, the figure has been found to be 42.5% amongst the uninsured population (68) and 28% amongst patients admitted to hospital with a diagnosis of COPD exacerbation by using the LLN criteria (153). In Australia, rates of 31% (60) and 42.2% have been reported (62). In Latin America, a rate of 63.7% was reported (152). However, the current NICE/GOLD definition of COPD is controversial as it does not account for normal age related airflow limitation (39) and may overestimate the COPD prevalence by up to 50% in older people (40). If the LLN criterion is used, which may be accepted in future guidelines; up to one-third of patients will be classified as overdiagnosed.

6.5.1.2 Consequences of COPD overdiagnosis

Overdiagnosis has consequences such as over treating individuals with normal spirometry with COPD medications, thus exposing them to the adverse effects, as well as the unnecessary cost to those patients and to the national healthcare systems (62). In this study, by excluding

participants who had shown FEV_1 reversibility indicating asthma (10%), around 68% of non-COPD individuals were potentially over treated with bronchodilators. This accords with previous observations from a survey of GP practices in South West England (72). A previously published study in Belgium observed that 49% of GPs prescribed ICS to all of their COPD patients irrespective of the guidelines (157).

6.5.1.3 Clinical factors associated with COPD overdiagnosis

There is a lack of published information on the clinical factors associated with COPD overdiagnosis. In this study, using the current NICE definition, non-COPD participants were more likely to be females, never smokers, obese and with multiple comorbidities. These findings are in line with the few published studies that found a significant association of COPD overdiagnosis with multiple comorbidities (62), obesity (60, 153), female sex (152), and with less smoking exposure (68, 152) by using the GOLD criteria.

Female sex was found to be associated with higher restrictive lung function pattern than male sex (158). Published studies (158, 159) have also shown that males and females perceive and report symptoms differently (158) and females are more likely to report symptoms than males (160). Furthermore, female sex found to be associated with a higher risk for comorbidities of diabetes, heart failure and depression than male sex (161).

Obesity is also one of the etiological factors of restrictive lung function (85), it also causes exertional dyspnoea and reduced exercise capacity (146) and obese patients usually have limited expiratory flow (60) despite normal airway function (162). Previously published studies have shown a negative association between increased BMI and obstructive lung function (146, 163) but a positive association with restrictive lung function (145). However, the assessment of COPD in obese patients remains challenging in primary care (145), due to

the presence of dyspnoea (147), which is usually the main symptom of COPD but also can be caused by obesity (147). This usually leads to overdiagnosis, over dosing of obese patients with bronchodilators (163) and missed opportunities to appropriately manage obesity induced dyspnoea (163). Published evidence (162, 163) have reported a higher prescription of inhaled bronchodilators among obese patients despite the absence of diagnosed COPD or asthma. There is a lack of supporting evidence on the use of bronchodilators in treating dyspnoea unrelated to airflow obstruction (146).

The presence of self-reported diabetes was also more common among overdiagnosed patients in this study, which is also known to be one of the aetiological factors of restrictive lung function (164).

6.5.1.4 Lung function-related factors associated with COPD overdiagnosis

When using the current NICE definition, approximately 19% of non-COPD participants showed restrictive patterns of lung disease, 10% had FEV_1 reversibility indicating asthma and 71% had normal spirometry. Of the latter, 2.5% did not report the presence of any symptom and the rest reported the presence of symptoms and met the definition of GOLD Stage 0. Although other studies reported a range of values for spirometry related factors amongst misdiagnosed COPD patients, the present study was broadly consistent. Restrictive lung function was reported at about 4% (72, 73, 151), 18% to 20% (62, 152), up to 37% (60). Post-bronchodilator reversibility (indicating asthma) ranged from about 4% to 22.5% (62, 68, 72, 73, 151). However, the present study identified more subjects without lung function abnormalities compared with other studies which reported rates of 16% to 56% (60, 62, 72, 151, 152).

Although non-COPD participants were more likely to report previous asthma, this might be explained by reporting of childhood asthma as they showed less airflow obstruction reversibility and therefore COPD overdiagnosis in this study cannot be explained by current misdiagnosed asthma.

6.5.1.5 Difference in health outcome measures

There are little published data on the health outcomes of patients overdiagnosed with COPD. In the present study, there was no evidence of a difference between the groups in their HRQoL, healthcare utilisation or exercise capacity. This indicates that those patients are ill with other underlying conditions but not with COPD. These findings were in line with Walters *et al.*, (2011) study, which also found a non-significant difference in the frequency of respiratory-related emergency department attendance or hospital admission between both patient subgroups (60).

6.5.2 Strengths and Limitations

The limitations of this study include a lack of data on the date of COPD diagnosis and how it was diagnosed, whether based on spirometry or only on smoking history and clinical symptoms. However, the quality of spirometry performed in the Birmingham COPD cohort was found to be exceptionally high. It was performed by well-trained research assistants with real-time and post-assessment quality assurance (134, 135). Another limitation is the exclusion of homebound patients and those with end stage COPD. However, this study has much strength, using data from a prospective cohort study on a large sample of different stages COPD patients from 71 participating practices in the West Midlands that were purposively selected to provide a study population that comprised different ethnicities, socioeconomic backgrounds and rural/urban patterns and broadly representative of the region's primary care COPD patients (134).

6.5.3 Implications for research and clinical practise

The prevalence of COPD overdiagnosis reported by this study is considerable and requires more attention, given the impact on patients' health and on the healthcare system. However, the current diagnostic criteria of COPD remain controversial and need to be superseded by more restructured criteria. In clinical practise, the diagnosis of COPD should be confirmed only by the post-bronchodilator spirometry rather than relying upon the nonspecific respiratory symptoms and smoking history. GPs need to pay more attention to differential diagnoses of respiratory symptoms, particularly dyspnoea and consider coexisting comorbidities and restrictive lung diseases, especially with the presence of obesity.

With the high rates of obesity, which may account for much of the overdiagnosis, interventions to reduce weight and improve physical activity could help in improving patients' symptoms. Furthermore, evidence on COPD overdiagnosis is limited. Therefore, future longitudinal research aiming at exploring the factors which contribute to overdiagnosis and also examine for physiological lung function variability would be advised. An economic analysis is also required to estimate the extra expenditure of the NHS resources on the unnecessary over medicalisation.

6.5.4 Conclusion

COPD overdiagnosis is common in UK primary care settings. Subsequently, inappropriate use of respiratory medications occurs with potential risk to patients and unnecessary waste of the national healthcare system resources. The true underlying causes of reporting respiratory symptoms need to be identified and managed appropriately. In particular, obesity, restrictive lung function, undiagnosed heart disease or other comorbidities. A follow-up lung function assessment is also recommended to examine for the potential reversal of lung function values

between obstructed and non-obstructed patterns due to daily and seasonal physiological variations.

7 DISCUSSION AND CONCLUSION

7.1 Background and context

In 2001, the GOLD committee included an additional "at risk" stage in the description of COPD patients with a view to considering early interventions (90). Patients in this stage (known as COPD GOLD Stage 0) were included because they had relevant chronic respiratory symptoms (86), and were thought to be 'at risk' of developing COPD in the future (19). However, in 2006, GOLD Stage 0 was subsequently excluded due to lack of supporting evidence regarding its progression to diagnosed COPD (91). However, it remains an open area of debate, because there are many patients in the population (especially amongst smokers) with such symptoms (87, 135, 165). Furthermore, it is known that a certain proportion of patients in primary care with a formal diagnosis of COPD may not meet the spirometric criteria (72), but have relevant respiratory symptoms and therefore may fit the criteria for "GOLD Stage 0". It is possible that these patients represent a group at risk of developing COPD, although it is also possible that they may have other conditions which could explain their symptoms. This thesis uses a range of primary and secondary data sources to provide further evidence to help clarify these questions.

7.2 Key findings

7.2.1 Risk of developing COPD among individuals with GOLD Stage 0 symptoms

The systematic review in chapter 2 showed evidence on that there are relatively few published studies in this area and that they are heterogeneous in design, populations and outcomes measured. There are a mixture of cohort studies and small cross-sectional studies. However, there are some useful conclusions which can be tentatively drawn. Individuals with GOLD

Stage 0 symptoms appear to show faster decline in FEV_1 than the normal population (86, 93, 99, 116, 119), although risk of development of COPD is not consistent across studies (19, 86, 89, 93, 98, 116, 117). GOLD Stage 0 symptoms are not always stable over time. Development of COPD and FEV_1 decline appears to be associated with persistence of GOLD Stage 0 symptoms (93, 98, 116), and the inconsistent cohort findings may reflect this phenomenon. Persistence of symptoms was associated with persistent smoking and among males, older females and males with metabolic syndrome (93) (Chapter 3).

7.2.2 Prognosis of individuals with GOLD Stage 0 symptoms

The systematic reviews in chapter 3 again identified few studies which explored the prognosis of GOLD Stage 0 patients. In two of the four relevant cohort studies, GOLD Stage 0 participants had a similar risk of mortality to patients with COPD GOLD Stage 1 (95), and current smoking GOLD Stage 0 participants had similar risks to those with GOLD Stage 2 (103). Across four studies (9, 90, 100, 101), healthcare use among GOLD Stage 0 patients was found to be similar to those with established COPD. In one cross-sectional study (102), GOLD Stage 0 participants reported poorer functioning than their diagnosed counterparts. None of these studies accounted for the instability of GOLD Stage 0 symptoms over time, and therefore the effects may even be underestimated.

These findings were explored in more depth in cross-sectional analyses of the 2010 HSE (Chapter 4) and of data from the Birmingham COPD Cohort (Chapter 5). Analyses of the Birmingham COPD Cohort also showed that patients with GOLD Stage 0 symptoms had similar consumption of healthcare resources to those newly identified with COPD, but also reported similar quality of life, exercise capacity and exacerbation-like events.

The HSE analyses allowed examination of three groups of participants. In addition to the normal population, a "GOLD Stage 0" group and a group which fitted COPD criteria, there was a group of participants without symptoms but recorded as having airflow obstruction only (AFO only). There was a gradient of effect from normal through to patients with "COPD". The "GOLD Stage 0" group was again quite similar to the "COPD" group in terms of quality of life, and even appeared to have worse anxiety and depression. The AFO only group, however, was much more similar to the normal population.

Exploration of the importance of different symptoms showed that dyspnoea and wheeze were more strongly associated with poor quality of life than chronic productive cough.

In general, the prognosis, quality of life and healthcare utilisation of GOLD Stage 0 patients is quite similar to those with milder COPD.

7.2.3 Health related characteristics of GOLD Stage 0 patients

The clinical characteristics of GOLD Stage 0 patients were explored in several primary analyses (Chapters 4-6). There were some important differences in the characteristics of patients in each of the categories. Overall, GOLD Stage 0 patients were of older age compared to the normal population (Chapter 4) but younger than diagnosed COPD patients (Chapter 5). A similar gradient was observed with smoking exposure. Furthermore, compared with diagnosed COPD patients, GOLD Stage 0 patients were more likely to be female, obese and have multiple comorbidities. Across all analyses, they were more likely to report cardiovascular diseases, high blood pressure, diabetes and depression, although this was not statistically significant. Additionally, they were less likely to show reversibility when tested spirometrically, suggesting that asthma is not more common in GOLD Stage 0 patients.

Obesity is a major aetiological factor of the presence of respiratory symptoms, particularly exertional dyspnoea (145-147). Moreover, obesity is a major contributor to the functional capacity restriction (145, 146, 163). However, the potential interrelationships between obesity, airflow obstruction, and respiratory symptoms or exercise limitations are not fully understood (145).

7.2.4 COPD overdiagnosis in the UK primary care setting

The work in chapter 6 identified a substantial proportion of patients in primary care with a diagnosis of COPD who did not meet the required spirometric criteria. The magnitude of COPD overdiagnosis varied according to the criteria being used; 13.7%, 28.1% and 32.3% using the current NICE, the LLN and the former NICE criteria, respectively. Previous UK studies which used the former NICE criteria (72, 73), reported comparable rates of overdiagnosis. It is also noteworthy that the extent of diagnosis varies substantially with the COPD criteria used. The current NICE criterion, which employs the fixed ratio, apparently diminishes the proportion of people thought to be overdiagnosed. However, these criteria themselves are suggested to be too inclusive (39, 40) and therefore the actual extent of overdiagnosis may be far greater. Consequently, patients are suffering from symptoms and not receiving the appropriate treatment which has several implications of missed opportunities (60, 62), increased cost to the NHS, false lifelong disease labels and the side effects of inappropriate medications (68).

Patients who were overdiagnosed were more likely to be female, never smokers, obese and possibly have multiple comorbidities. Exploration of the overdiagnosed revealed that approximately 70% met the GOLD Stage 0 criteria, 19% had a restrictive pattern of lung function (which could be related to the excess obesity) and 2.5% were asymptomatic with normal lung function. 10% had reversible airflow obstruction, but this was significantly lower

than those with confirmed COPD, and therefore it is unlikely that misdiagnosed asthma would explain the findings. It is also possible that some of these overdiagnosed patients might have undiagnosed heart disease, but this was not measured. The features of the overdiagnosed group are very similar to the GOLD Stage 0 patients in the previous chapters. Quality of life, exacerbations, exercise capacity and healthcare utilisation were similar between the confirmed and the overdiagnosed groups. This may indicate that many of those patients are ill but not necessarily with COPD.

7.3 Strengths and limitations

This thesis has some limitations. First, the cross-sectional design of the primary analyses (Chapters 4-6) has limitation in terms of causality. Second, most of the study populations were of white ethnicity; therefore, the results may not be generalisable to patients of other ethnicities. The presence of doctor-diagnosed comorbidity was self-reported and therefore, there is a potential for under or overdiagnosed chronic disease among GOLD Stage 0 patients. Another limitation is a lack of imaging data, thus it is not possible to rule out the possibility of the presence of underlying respiratory or cardiac pathology, which could explain the presence of respiratory symptoms and their association with poor health outcomes. The strengths of this thesis are centred on the first systematic reviews of literature on COPD GOLD Stage 0 carried out to the high standards of the Cochrane collaboration. Secondly, the use of a large national representative data from the HSE with the advantage of applying generalisability to the English population. Thirdly, the use of data from the Birmingham prospective COPD Cohort Study on a large sample of patients from 71 participating practices in the West Midlands.

7.4 Implication for research

Although this thesis was based on cross-sectional studies, it can be used as a platform for future prospective population-based studies to confirm the cross-sectional findings and explore the prognosis of GOLD Stage 0. There is still a big gap in knowledge on this condition. Further work is needed to determine the main factors affecting the persistence of GOLD Stage 0 symptoms over time– smoking seems important so can we target smoking cessation to these people. Moreover, future studies examining GOLD Stage 0 must account for the instability of its symptoms. The relationship between the GOLD Stage 0 symptoms, obesity, diabetes and restrictive spirometry function also warrants further investigations. Studies investigating the effect of reducing obesity by targeted weight intervention on reducing patients' symptoms are also needed.

7.5 Implication for clinical practice

This thesis emphasises the importance of questioning the presence of respiratory symptoms even in the absence of airflow obstruction. There may be no clear management pathways, but their health seems to be as poor as patients with mild COPD. Initially, persistence of symptoms should be established. For those patients with persistent symptoms who do not meet criteria for obstruction, alternative causes of their symptoms should be investigated. Furthermore, GOLD Stage 0 patients with persistent symptoms and frequent exacerbation may need to be identified and targeted for COPD screening. Clinicians should also consider other strategies to treat symptomatic patients, including weight management interventions and pulmonary rehabilitation rather than focusing on labelling patients falsely with a diagnosis of COPD. Moreover, further improvement in the use and interpretation of spirometry in diagnosing COPD in primary care is needed. Lastly, the desire to strengthen smoking cessation support programmes in clinical practice is always beneficial.

7.6 Conclusion

The findings from this thesis emphasise that the presence of respiratory symptoms is an epidemiologically and clinically relevant regardless of the presence of lung function abnormalities. People with GOLD Stage 0 symptoms have similar poor quality of life and healthcare consumption when compared to those with mild COPD. It is still uncertain whether this group will develop COPD or whether they are ill because they have other conditions, or whether the lung function criteria for defining COPD is rather arbitrary. Some GOLD Stage 0 patients showed similar characteristics to COPD patients but others may have other conditions (e.g. obesity and restrictive lung disease) responsible for their symptoms. It is therefore important to further investigate GOLD Stage 0 through longitudinal studies. Such works would also help in developing management guidelines aiming at improving patients' quality of life, reduce the risk of misdiagnosis and reduce the inappropriate consumption of healthcare resources.

APPENDICES

8 APPENDIX A: A SYSTEMATIC REVIEW PROTOCOL

8.1 Step 1: the Review's Topic

8.1.1 Background and Rationale for the Topic

8.1.1.1 Definition of COPD

COPD is a heterogeneous disease consisting of a number of chronic respiratory disorders that progress gradually into air flow obstruction (AFO) as a consequence of different disease mechanisms (4); therefore, there is more than one definition for COPD (4) .The widely used definition is that of the Global Initiative for Chronic Obstructive Lung Disease (GOLD), which defines COPD as *"a common preventable and treatable disease, . . . characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and co morbidities contribute to the overall severity in individual patients"*(6, 7).

8.1.1.2 Classification of COPD

The GOLD guidelines, published in 2001, aimed to provide a standard global framework for COPD prevention, severity staging, diagnosis and management (86, 87) . The GOLD guidelines classified five stages of COPD severity based on post-bronchodilator spirometric lung function measurements, as summarised in Table 39.

Table 39: 2001 GOLD classification of COPD severity (69, 73)

Gold Stage	Characteristics	
	Post-bronchodilator spirometry	**Chronic respiratory symptoms (cough, sputum production)**
GOLD Stage 0 (At risk)	Normal spirometry ($FEV_1/FVC > 0.70$)	+
GOLD Stage I (Mild COPD)	$FEV_1/FVC < 0.70$ $FEV_1 \geq 80\%$ predicted	±
GOLD Stage II (Moderate COPD)	$FEV_1/FVC < 0.70$ $FEV_1 < 80\%$ but $\geq 50\%$ predicted	±
GOLD Stage III (Severe COPD)	$FEV_1/FVC < 0.70$ $FEV_1 < 50\%$ but $\geq 30\%$ predicted	±
GOLD Stage IV (Very Severe COPD)	$FEV_1 \leq 30\%$ predicted or $FEV_1 <$ 50% predicted plus chronic respiratory failure[6]	±

FEV_1: forced expiratory volume in one second. FVC: forced vital capacity

8.1.1.3 GOLD Stage 0

Many components of the original GOLD guidelines and staging system are controversial (86), particularly COPD GOLD stage 0, which defines individuals who have preserved normal lung function (FEV1/FVC > 70%) but chronic respiratory symptoms (such as cough and sputum production) as being "at risk" of developing COPD in the future (86). The main idea behind the inclusion of this stage was to allow for early intervention, before the progression to stage 1 or even more advanced stages of COPD (90). However, due to limited epidemiological studies and a lack of supporting evidence regarding the progression from GOLD stage 0 to stage 1 COPD, GOLD stage 0 has been excluded from GOLD staging of COPD since 2006 (91). Meanwhile, the significance of the public health message that chronic respiratory symptoms are abnormal and that their underlying causes must be identified remains unchanged (91).

[6]Respiratory failure is defined as "arterial partial pressure of oxygen (PaO2) less than 8.0 kPa (60 mm Hg) with or without arterial partial pressure of CO2 (PaCO2) greater than 6.7 kPa (50 mm Hg) while breathing air at sea level" .

8.1.1.4 Areas of Arguments on GOLD Stage 0

The main areas of disagreement regarding GOLD stage 0 COPD are whether this stage exists or not (87) and by what means subjects with normal pulmonary function (no obstruction) can be classified as COPD and included in GOLD staging (87). The data from preceding surveys have shown that a large proportion of patients with abnormal pulmonary function do not report respiratory symptoms (87). On the other hand, a large proportion of patients with normal lung functions do report respiratory symptoms (87). Another area of debate is that regarding the respiratory symptoms essentially required to define Gold Stage 0, most previous studies have used the following definition of chronic bronchitis: "*the presence of productive cough for 3 months in two successive years in a patient in whom other causes of chronic cough, have been excluded*" (94). Some other studies have suggested a more sensitive definition of GOLD Stage 0 by including a wider range of respiratory symptoms (cough, phlegm, wheeze, breathlessness) that happen on a recurrent basis (87).

8.1.1.5 The Scoping Search on GOLD Stage 0: Existing Literature

There is a wide range of views and some contradictory opinions from relevant studies that exist on the risk factors and prognosis of GOLD stage 0. Some studies have found GOLD stage 0 to be associated with an increased risk of developing COPD in the future (98, 99), a higher utilisation of health care (90), lower HRoQL and increased risk of long-term mortality (87), especially among smoking males (103). Furthermore, some studies have found that the presence of chronic respiratory symptoms increases the risk of mortality in all stages of COPD, including stage 0 patients with preserved lung function (95). Two studies by de Marco et al and one by Pelkonen et al have concluded that chronic cough and phlegm predict an increased risk of developing COPD, independent of smoking behaviours (98, 99), due to the significant risk of respiratory symptoms in excessive FEV1 decline (86, 99, 119). In their

study, Mannino et al have shown that respiratory symptoms with normal lung function are associated with functional restriction and poor health status to a similar degree as moderate COPD (85). On the other hand, in their analysis of data collected over 15 years of the course of three surveys in The Copenhagen City Heart Study, Vestbo and Lange have concluded that GOLD Stage 0 "is of little help in identifying subjects at risk of COPD" (86). They state that GOLD Stage 0 lacks any predictive prognostic value (even though it was associated with excess FEV_1 decline), and that it does not considerably increase the risk of developing AFO later in life (86).

8.1.2 Rationale for a systematic review

To the best of knowledge, there has as of yet been no systematic review studying GOLD Stage 0 and assessing the natural history of this group of patients. Therefore, this proposed systematic review will be the first to gather the available literature on GOLD Stage 0.

8.1.3 Review aims and Questions

The proposed systematic review aims to:

a. Draw together the currently available literature on Gold Stage 0 and provide an evidence-based summary.
b. Identify the scope for further research on COPD Gold stage 0.

These aims will be achieved by answering the following questions:

1. Are people who have chronic respiratory symptoms but normal lung function at a higher risk of developing COPD compared to people who do not?
2. What is the prognosis of patients with chronic respiratory symptoms but normal lung function compared to established COPD patients?
3. What are the main factors that can affect the prognosis of patients with chronic respiratory symptoms but normal lung function?

8.1.4 Selection Criteria for Considering Studies for this Review

Although, the term GOLD Stage 0 does not officially exist, it will be used in this review to refer to the study population (instead of using its long definition every single time). Furthermore, the term chronic bronchitis (CB) may be also used to refer to GOLD Stage 0. Table 40 below summarises the PECOS components of the review's questions:

8.1.4.1 Population

This review will particularly include studies that have assessed middle-aged and elderly populations (40 years and above) who have chronic respiratory symptoms but preserved normal lung function. Studies of younger age groups will be included if self-reported asthma was excluded, due to the potential of diagnostic bias by misclassification of bronchial asthma as COPD.

8.1.4.2 Exposure

For questions 1 and 2, studies should include any chronic respiratory symptoms as cough, phlegm, dyspnoea and wheeze, which occur on a frequent basis. (This is defined in some studies as more than three consecutive months a year for two consecutive years (95), although it may not always be defined this way). For questions 3, studies which measure any factors that affect the prognosis of GOLD Stage 0 patients such as age, sex, ethnic group, smoking status, passive smoking, body mass index (BMI), biomarkers, occupational exposure, FEV_1 predicted and comorbidity. Studies of genetic factors and childhood respiratory infection will not be included.

8.1.4.3 Comparator

For question 1, studies that compared GOLD Stage 0 to normal population (asymptomatic with normal lung function) will be included. For question 2, studies that compared GOLD Stage 0 to clinically diagnosed COPD patient's stages 1+ will be included.

8.1.4.4 Outcome

For question 1, the outcome of interest is the decline in FEV_1% and development of COPD. For question 2 and 3, any outcome, it will include: mortality, symptoms exacerbation and hospitalisation, health care utilisation, development of comorbidities and HRQOL.

8.1.4.5 Study Design

For questions 1 and 2, ideally cohort studies will be included as a reliable prognostic/aetiological systematic review necessitates an accurate cohort of patients at the same stage of their disease (115). However, cross-sectional studies will also be considered, due to the likelihood of limited cohort studies on GOLD Stage 0. For question 3, only cohort studies will be included.

8.1.4.6 Types of Publication

The proposed review will include all relevant studies for which full text is available, regardless of their publication status. There will be no language or time restrictions, relevant grey literature will be included and also conference abstracts and ongoing studies will be included if the full article can be obtained (authors will be contacted for full articles).

Table 40: PECOS components of the review questions

Question components (PECOS)	Q1: GOLD Stage 0 and the risk of developing COPD	Q2: Prognosis of GOLD Stage 0	Q3: Prognostic factors of GOLD Stage 0	Exclusion Criteria
Population	People aged ≥40 years with normal lung function	People aged ≥40 years with normal lung function	People aged ≥40 years with chronic respiratory symptoms and normal lung function	Studies of younger age groups unless asthma excluded
"Exposure"	Any chronic respiratory symptoms	Chronic respiratory symptoms	Any; for e.g. age, sex, ethnic group, smoking status, passive smoking, air pollutions, BMI, biomarkers, occupational exposure, FEV_1 predicted and comorbidity	• Genetic factors • Childhood respiratory infections
Comparator	"Normal population"	COPD patients with or without chronic respiratory	None	
Outcome	Decline in FEV_1% and development of COPD	Any outcome; for e.g. mortality, HRQOL, exacerbation and healthcare utilisation	Any outcome	
Study Design	Ideally cohort studies, but case-control studies and cross-sectional studies might be considered	Ideally cohort studies, but case-control and cross-sectional studies will be considered	Cohort studies	Reviews, editorials, case series and reports
Types of Publication	All relevant studies with available full text, regardless of their publication status			

8.2 Step 2: Search strategy and identifying relevant literature

8.2.1 Selection of Relevant Databases to Search

8.2.1.1 Identifying Ongoing Systematic Reviews

Initially, the following databases will be searched and checked for both existing and ongoing systematic reviews on COPD GOLD stage 0 and to identify the nature and numbers of significant studies on this topic: the Database of Abstracts of Reviews of Effects (DARE), the

Cochrane Database of Systematic Reviews (CDSR), the Centre for Reviews and Dissemination (CRD) and the International Prospective Register of Systematic Reviews (PROSPERO), MEDLINE, EMBASE and websites of the National Institute for Health and Clinical Excellence (NICE) and the NIHR Health Technology Assessment (NIHR HTA) Programme.

8.2.1.2 Search for Relevant Literature

The following sources will be searched:

8.2.1.2.1 Bibliographic Electronic Databases

MEDLINE and EMBASE via Ovid, MEDLINE in process, CINAHL, Web of Sciences, PubMed and Cochrane (Wiley) Central will be accessed and searched through the University of Birmingham library catalogue.

8.2.1.2.2 Searching the Internet

Searches will also be conducted on selected websites such as GOLD, NICE, ERS and ATS for conferences abstracts over the last two years.

8.2.1.2.3 Searching Reference Lists

Reference lists of relevant studies will also be searched in order to identify other significant studies that can be included.

8.2.1.2.4 Searching Other Sources

This will include searching for grey literature, which is not usually included in the main databases. However, much of this literature can be searched and accessed via SIGLE (System for Information on Grey Literature), ETHOS library, ZETOC library, and Conference Proceedings Citation Index- Science (CPCI-S) within Web of Sciences.

8.2.1.2.5 Seeking Experts' Input

In order to ensure a comprehensive literature search, advice and support from information specialists and expert librarians will be sought throughout the proposed systematic review period.

8.2.1.2.6 Hand searching of a selection of relevant journals

If advised by the review team

8.2.1.3 Search Strategy

8.2.1.3.1 Search Term Combinations for Electronic Databases

In order to maximise the sensitivity of the search to obtain the largest possible number of relevant studies, the following steps will be taken:

a. Identification and inclusion of a comprehensive list of key search terms for each component of the question and a range of synonyms with spelling alterations.
b. Identification of relevant MeSH terms by looking at the keywords recommended at the end of abstracts of relevant studies and searching for how they are indexed in the database.
c. Combination of simple key terms and the MeSH terms selected previously.

The following (Table 41) shows an example of search term combinations for the MEDLINE (Ovid) database;

Table 41: Questions components and search terms

Population: Patients aged 40 and over with chronic respiratory symptoms but normal lung function (GOLD Stage 0)		
Key terms	**MeSH terms**	**Search term combinations**
GOLD Stage 0 Respiratory symptoms Respiratory disease$ Cough Phlegm Dyspnoea Wheeze Chronic bronchitis	exp chronic respiratory tract disease exp bronchitis	**OR (captures Population)**
Exposure: Risk factors		
Key terms	**MeSH terms**	**OR (captures Exposure)**
Risk factors Determinant$ Cohort Epidemiological studies	exp risk factors exp epidemiologic studies exp predictive value	
Comparator: COPD Stages 1+		
Key terms	**MeSH terms**	**OR (captures Comparator)**
Chronic obstructive lung disease Global initiative for obstructive lung disease GOLD stages	exp pulmonary disease exp chronic obstructive lung disease exp pulmonary disease, chronic obstructive [classification, complications, aetiology, mortality]	
Outcome: Prognosis of GOLD Stage 0		
Key terms	**MeSH terms**	**OR (captures outcome)**
Prognosis Predict$ Prognos$ course Predictive value Outcomes	Exp cohort studies exp disease progression exp mortality exp follow-up studies	
AND combines all the question components		

Adapted from (166)

8.2.1.4 Identifying Relevant Studies

The search for a literature will be conducted by the first reviewer and the screening for eligibility of inclusion will be conducted independently by two reviewers. The searching will be done over three stages, as follows:

Stage1: Searching databases and other previously mentioned sources using key and MeSH terms combinations, importing obtained records to EndNoteX7 reference software and eliminating duplicates.

Stage2: Screening the searched literatures' titles and abstracts against the predefined inclusion/exclusion criteria.

Stage 3: A detailed assessment of the full text of potentially significant studies yielded from the initial screening, as well as questionable studies about which the final judgment cannot be made through title and abstract screening alone. If a final decision on the eligibility of questionable studies cannot be made, or in cases of disagreement between the two reviewers, a third reviewer will be consulted. However, to avoid major disagreement between the two reviewers, the review's eligibility criteria was first piloted on some studies (n=14) (Table 42). Excluded studies will be listed and documented with the reasons for exclusion. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (167) schematic flow diagram will be used to report different phases of identifying relevant literature to be included.

Table 42: Piloting some studies against the selection criteria

Study ID	The population	The exposure	The outcomes	The study design	Comments
Mannino *et al.*, 2005	Adult subjects aged 43–66 years	• Chronic respiratory symptoms • Pack-years of smoked cigarettes • Age, sex and race • BMI • Education level	The predictive risk of abnormal lung function on the subsequent mortality	11 years cohort study	This study categorised the participants according to the Pre-BD spirometry
Antonelli-Incalzi *et al.*, 2003	Individuals aged 73±6 years	• Sex, age • Living condition • Comorbidity	The correlation between different GOLD stages of COPD and changes in health status	Cross-sectional study	
Stroband *et al.*, 2007	45–75 years old patients	• Chronic respiratory symptoms • Smoking and ≥10 pack-years of smoked cigarette	The variation in inflammatory biomarkers between COPD patients with and without respiratory symptoms of chronic bronchitis	Cross-sectional study	
Tsushima et al., 2005	No selection criteria were applied (general population health survey)	• Chronic respiratory symptoms • Smoking • Demographic data, lifestyle and past medical histories	The clinical difference between GOLD stage 0 and normal individuals	Cross-sectional study	• Young age groups included • The exclusion of bronchial asthma relied only on self-reported questionnaires without testing for reversibility
Vestbo and Lange, 2002	Subjects aged 20 years or above	• Age sex • Smoking • * Changes in smoking habits (smoking cessation)	Decline in FEV_1 and Progression from stage 0 to COPD 1+	Prospective 15 years cohort study	
Stavem *et al.*, 2005	Healthy males aged 40- 59 years (have no other comorbidities including severe pulmonary diseases)	• Respiratory symptoms • BMI • Age • Serum cholesterol and BP • Smoking habits • Physical fitness	Risk of mortality in GOLD stage 0 compared with GOLD stages I and II	Occupational 8 years cohort study	

Study ID	The population	The exposure	The outcomes	The study design	Comments
Aronsson *et al.*, 2005	Subjects aged 27-61 years	• Chronic respiratory symptoms • Smoking • Age • Sex • Comorbidity	Over-all mortality risks in GOLD stages 0–4 and the influence of chronic respiratory symptoms on mortality risks	The study analysed previously collected data from 18 years health screening survey in Sweden, then prospectively followed up all participants through the national registers to assess the total mortality	
Shin *et al.*, 2005	Adults aged 40–69 years	• Chronic respiratory symptoms • Sex • Age • Smoking	Relationship between chronic respiratory symptoms and deterioration in lung function	Cross-sectional study	
Pelkonen *et al.*, 2006	Men aged 40 to 59 years	• Chronic bronchitis • Smoking • Age	The effect of chronic bronchitis on lung function and the risk of mortality	Cohort study	
de Marco *et al.*, 2004	Young adults aged 20–44 years	• Chronic cough and phlegm • Childhood respiratory infection • Smoking • Asthma • Occupational exposure • Socioeconomic class • Sex • Age	Shared common risk factors and difference in health care utilisation between stage 0 and more advanced stages of COPD	Cross sectional analysis of data from the European Community Respiratory Health Survey (ECRHS)	Classification bias of asthma as COPD
de Marco *et al.*, 2007	Young adults aged 20–44 years	• Chronic cough and phlegm • Sex • Age • Smoking habits • Educational level	The incidence of COPD among young adults and the value of chronic cough and phlegm as independent predictors of COPD	ECRHSII	Classification bias of asthma as COPD

Study ID	The population	The exposure	The outcomes	The study design	Comments
Albers *et al.*, 2007	Adults aged 20-70 years with no history of COPD, asthma or other chronic respiratory disease	• Early respiratory symptoms • Age • Gender • Pack years • Smoking behaviour	The predictive value of chronic respiratory symptoms, lung function below normal range and reversibility	Prospective 5 years cohort study	
Cerveri *et al.*, 2003	Individuals aged 20–44 years	• Respiratory symptoms • Asthma • Socioeconomic status • Smoking habits • Age • Gender	The prevalence and characteristic of chronic cough and phlegm	Multicentre cross-sectional survey	The assessment and characterisation of the respiratory symptoms was done by using simple screening questionnaire without performing spirometry

8.3 Step 3: Data extraction and management

The data extraction will be done independently by the two reviewers. The form will be adapted from the STOBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist (110, 111) (Appendix C). It puts the primarily emphasis on population, exposure/comparator, outcomes and study designs. The form will be piloted first on some papers and then if no modification is required, it will be used to collect data from the identified eligible studies. In cases of discrepancy between the two reviewers, the third reviewer will be consulted. The author of the primary study may be contacted at this stage for any missing data.

8.4 Step 4: Methodological Quality Assessment

Assessment of the quality of studies to be included in the proposed review will be performed independently by the two reviewers. Because of lack of consensus comprehensive critical appraisal tool of observational studies, the assessment forms were generated from two key quality assessment tools of non-randomised studies; QUIPS tool (Appendix D) will be used for included cohort studies (112) and Newcastle Ottawa tool (Appendix E) for cross sectional studies (113). According to the Cochrane Collaboration recommendations (107) a scale rating will not be generated as the rating system does not always reflect the validity of the study finding. The risk of bias will be judged by yes, no, partly and unclear for each perspective.

8.5 Step 5: Data synthesis and analysis

There are clear difficulties involved with a formal meta-analysis of prognostic systematic reviews. These challenges are mainly attributed to the high risk of publication bias, the methodological quality and the reporting quality of the primary observational studies to be included in the systematic review (114, 115). Furthermore, the results of a meta-analysis of a

systematic review of prognostic studies are usually misleading and not convincing even when the meta-analysis is conducted with great precision (108, 115, 168), except when the individual patients data (IPD) can be accessed and used for synthesis (115) which might not be feasible. Therefore, this review will be a descriptive review and will not consider a meta-analysis.

8.6 Step 6: Protocol Registration and Plan of Dissemination

Once finalised and agreed upon by the review team, the protocol will be registered with PROSPERO. After completion, both the protocol and the systematic review will be submitted for publication and will also be presented and disseminated through seminars and conference

9 APPENDIX B: LIST OF THE SEARCH TERMS USED IN THE SYSTEMATIC REVIEWS

Table 43: Search terms for systematic reviews 1, 2 and 3

	Search term
1	"gold stage 0".mp.
2	chronic respiratory symptoms.mp.
3	bronchitis.mp.
4	exp bronchitis/
5	exp cough/
6	cough.mp.
7	exp mucus
8	phlegm.mp.
9	exp dyspnea/
10	Dyspnea.mp.
11	Wheeze.mp.
12	exp wheezing/
13	epidemiology.mp.
14	exp epidemiology/
15	exp cohort studies/
16	cohort.mp.
17	exp cross-sectional studies/
18	cross-sectional.mp.
19	exp case-control Studies/
20	Case-control.mp.
21	copd.mp.
22	exp pulmonary disease, chronic obstructive/
23	airflow obstruction.mp.
24	exp airway obstruction/
25	FEV_1 decline.mp.
26	predict$.mp.
27	exp Prognosis/
28	prognosis.mp.
29	prognos$.mp.
30	outcome.mp.
31	age.mp.
32	sex.mp.
33	exp smoking/
34	smoking.mp.
35	BMI.mp.
36	ethnicity.mp.
37	comorbidity.mp.
38	biomarkers.mp.
39	air pollution.mp.
40	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
41	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
42	21 or 22 or 23 or 24 or 25
43	40 and 41 and 42
44	26 or 27 or 28 or 29 or 30
45	40 and 41 and 44
46	31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
47	13 or 14 or 15 or 16
48	26 or 27 or 28 or 29
49	40 and 46 and 47 and 48

10 APPENDIX C: STRENGTHENING THE REPORTING OF OBSERVATIONAL STUDIES IN EPIDEMIOLOGY CHECKLIST (STROBE)

No	Item	Recommendation
1	**Study ID**	The title, author, year and journal
Methodology		
2	**Study design**	Present key elements of study design
3	**Setting**	Describe the study locations, periods of recruitment, exposure, follow-up, and data collection
4	**Participants**	a) ***Cohort study*****:** Give the eligibility criteria, sources and methods of selection of participants and methods of follow-up/ for matched cohort studies, the matching criteria and number of exposed and unexposed ***Cross-sectional study*****:** Give the eligibility criteria, and the sources and methods of selection of participants ***b) Sample size:*** Explain how the study size was arrived at
5	**Variables**	a) Clearly define all exposures, predictors, potential confounders, and diagnostic criteria b) For each variable of interest, give sources of data and methods of measurement c) Describe comparability of assessment methods if there is more than one group
6	**Outcome measures**	a) Define outcomes of interest b) Describe statistical methods used to control for confounding c) Describe statistical methods used to examine subgroups and interactions d) Describe statistical methods used to deal with missing data e) ***Cohort study*****:** Describe methods used to address loss to follow-up f) ***Cross-sectional study*****:** Describe the analytical methods taking account of sampling strategy

No	Item	Recommendation
Results		
7	**Participants**	a) Report numbers of individuals at each stage of study; numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed b) Give reasons for non-participation at each stage
8	**Variables**	a) Give the demographic, clinical and social characteristics of the study participants b) Give information on exposures and potential confounders c) Indicate the number of participants with missing data for each variable of interest d) Adjustment and justification of potential confounders e) ***Cohort study*****:** Summarise follow-up time (average and total amount)
9	**Outcome data**	a) Report the outcome measures b) Addressed potential sources of bias c) ***Cohort study*****:** Report numbers of outcome events over time/ attrition rate d) ***Cross-sectional study:*** Report numbers of outcome events or summary measures

Source:(110)

11 APPENDIX D: QUALITY IN PROGNOSIS STUDIES (QUIPS) TOOL

Summary of the Bias Domains, Prompting Items, and Ratings of the QUIPS Tool (112)						
Variable	Bias Domains					
	1. Study Participation	**2. Study Attrition**	**3. Prognostic Factor Measurement**	**4. Outcome Measurement**	**5. Study Confounding**	**6. Statistical Analysis and Reporting**
Optimal study or characteristics of unbiased study	The study sample adequately represents the population of interest	The study data available (i.e., participants not lost to follow-up) adequately represent the study sample	The PF is measured in a similar way for all participants	The outcome of interest is measured in a similar way for all participants	Important potential confounding factors are appropriately accounted for	The statistical analysis is appropriate, and all primary outcomes are reported
Prompting items and considerations†	a. Adequate participation in the study by eligible persons	a. Adequate response rate for study participants	a. A clear definition or description of the PF is provided	a. A clear definition of the outcome is provided	a. All-important confounders are measured	a. Sufficient presentation of data to assess the adequacy of the analytic strategy
	b. Description of the source population or population of interest	b. Description of attempts to collect information on participants who dropped out	b. Method of PF measurement is adequately valid and reliable	b. Method of outcome measurement used is adequately valid and reliable	b. Clear definitions of the important confounders measured are provided	b. Strategy for model building is appropriate and is based on a conceptual framework or model
	c. Description of the baseline study sample	c. Reasons for loss to follow-up are provided	c. Continuous variables are reported or appropriate cut points are used	c. The method and setting of outcome measurement is the same for all study participants	c. Measurement of all important confounders is adequately valid and reliable	c. The selected statistical model is adequate for the design of the study
	d. Adequate description of the sampling frame and recruitment	d. Adequate description of participants lost to follow-up	d. The method and setting of measurement of PF is the same for all study participants		d. The method and setting of confounding measurement are the same for all study participants	d. There is no selective reporting of results

	e. Adequate description of the period and place of recruitment	e. There are no important differences between participants who completed the study and those who did not	e. Adequate proportion of the study sample has complete data for the PF		e. Appropriate methods are used if imputation is used for missing confounder data	
	f. Adequate description of inclusion and exclusion criteria		f. Appropriate methods of imputation are used for missing PF data		f. Important potential confounders are accounted for in the study design	
					g. Important potential confounders are accounted for in the analysis	
Ratings						
High risk of bias	The relationship between the PF and outcome is very likely to be different for participants and eligible nonparticipants	The relationship between the PF and outcome is very likely to be different for completing and non-completing participants	The measurement of the PF is very likely to be different for different levels of the outcome of interest	The measurement of the outcome is very likely to be different related to the baseline level of the PF	The observed effect of the PF on the outcome is very likely to be distorted by another factor related to PF and outcome	The reported results are very likely to be spurious or biased related to analysis or reporting
Moderate risk of bias	The relationship between the PF and outcome may be different for participants and eligible nonparticipants	The relationship between the PF and outcome may be different for completing and non-completing participants	The measurement of the PF may be different for different levels of the outcome of interest	The measurement of the outcome may be different related to the baseline level of the PF	The observed effect of the PF on outcome may be distorted by another factor related to PF and outcome	The reported results may be spurious or biased related to analysis or reporting
Low risk of bias	The relationship between the PF and outcome is unlikely to be different for participants and eligible nonparticipants	The relationship between the PF and outcome is unlikely to be different for completing and non-completing participants	The measurement of the PF is unlikely to be different for different levels of the outcome of interest	The measurement of the outcome is unlikely to be different related to the baseline level of the PF	The observed effect of the PF on outcome is unlikely to be distorted by another factor related to PF and outcome	The reported results are unlikely to be spurious or biased related to analysis or reporting

12 APPENDIX E: NEWCASTLE-OTTAWA SCALE

Selection: (Maximum 5 stars)

1) Representativeness of the sample:

a) Truly representative of the average in the target population. * (all subjects or random sampling)

b) Somewhat representative of the average in the target population. * (non-random sampling)

c) Selected group of users.

d) No description of the sampling strategy.

2) Sample size:

a) Justified and satisfactory. *

b) Not justified.

3) Non-respondents:

a) Comparability between respondents and non-respondents characteristics is established, and the response rate is satisfactory. *

b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory.

c) No description of the response rate or the characteristics of the responders and the non-responders.

4) Ascertainment of the exposure (risk factor):

a) Validated measurement tool. **

b) Non-validated measurement tool, but the tool is available or described.*

c) No description of the measurement tool.

Comparability: (Maximum 2 stars)

1) The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled.

a) The study controls for the most important factor (select one). *

b) The study control for any additional factor. *

Outcome: (Maximum 3 stars)

1) Assessment of the outcome:

a) Independent blind assessment. **

b) Record linkage. **

c) Self report. *

d) No description.

2) Statistical test:

a) The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value). *

b) The statistical test is not appropriate, not described or incomplete.

13 APPENDIX F: METHODOLOGICAL QUALITY OF INDIVIDUAL COHORT STUDIES INCLUDED IN THE SYSTEMATIC REVIEWS

Table 44: Risk of bias assessment for the included cohort studies (systematic review 1)

Bias Domain	Description	Judgment							
Study ID: (authors, year)		**Yamane *et al.*, 2010**	**Lindberg *et al.*, 2006**	**Guerra *et al.*, 2009**	**Pelkonen *et al.*, 2006**	**Vestbo *et al.*, 1996**	**Vestbo and Lange, 2002**	**Brito-Mutunayagam *et al.*, 2010**	**de Marco *et al.*, 2007**
Study participation	Adequate participation in the study by eligible persons	Y	Y	Y	Y	Y	Y	Y	Y
	Description of the source population or population of interest	Y	Y	Y	Y	Y	Y	Y	Y
	Description of the baseline study sample	Y	Y	Y	Y	Y	Y	Y	Y
	Adequate description of the period and place of recruitment	Y	Y	Y	Y	Y	Y	Y	Y
	Adequate description of inclusion and exclusion criteria	Y	Y	Y	Y	Y	Y	Y	Y
Study attrition	Adequate response rate for study participants	U	Y	Y	Y	Y	Y	Y	Y
	Description of attempts to collect information on participants who dropped out	N	N	N	Y	N	N	N	N
	Reasons for loss to follow-up are provided	N	N	N	N	N	N	Y	N
	Adequate description of participants lost to follow-up	N	N	N	P[7]	P	N	Y	N
	There are no important differences between participants who completed the study and those who did not	U	U	U	U	U	U	Y	U

[7] Only the number of lost to follow up was reported

Bias Domain	Description	Judgment							
Study ID: (authors, year)		**Yamane *et al.*, 2010**	**Lindberg *et al.*, 2006**	**Guerra *et al.*, 2009**	**Pelkonen *et al.*, 2006**	**Vestbo *et al.*, 1996**	**Vestbo and Lange, 2002**	**Brito-Mutunayagam *et al.*, 2010**	**de Marco *et al.*, 2007**
Outcome measurement	A clear definition of the outcome is provided	Y	Y	Y	Y	Y	Y	Y	Y
	Method of outcome measurement used is adequately valid and reliable	P[8]	P	P	P	N	P	Y	P
	The method and setting of outcome measurement is the same for all study participants	Y	Y	Y	Y	Y	Y	Y	Y
Study confounding	All-important confounders are measured	Y	Y	Y	Y	Y	Y	Y	Y
	Clear definitions of the important confounders measured are provided	Y	Y	Y	Y	Y	Y	Y	Y
	Important potential confounders are accounted for in the analysis	Y	Y	Y	Y	Y	Y	Y	Y
Statistical analysis and reporting	Sufficient presentation of data to assess the adequacy of the analytic strategy	Y	Y	Y	Y	Y	Y	Y	Y
	The selected statistical method is adequate for the design of the study	Y	Y	Y	Y	Y	Y	Y	Y
	There is no selective reporting of results	Y	Y	Y	Y	Y	Y	Y	Y

(Y=yes, N=no, P=partly, U=unclear)

[8] Only pre-BD spirometry was performed

Table 45: Risk of bias assessment for the included cohort studies (systematic review 2)

Bias Domain	Description	Judgment					
Study ID: (authors, year)		**Ekberg-Aronsson *et al.*, 2005**	**Ekberg-Aronsson *et al.*, 2008**	**Petty *et al.*, 1976**	**Mannino *et al.*, 2006**	**Stavem *et al.*, 2006**	**Joo *et al.*, 2008**
Study participation	Adequate participation in the study by eligible persons	Y	Y	Y	Y	Y	Y
	Description of the source population or population of interest	Y	Y	Y	Y	Y	Y
	Description of the baseline study sample	Y	Y	Y	Y	Y	Y
	Adequate description of the period and place of recruitment	Y	Y	Y	Y	Y	Y
	Adequate description of inclusion and exclusion criteria	Y	Y	Y	Y	Y	N
Study attrition	Adequate response rate for study participants	Y	Y	Y	Y	Y	N
	Description of attempts to collect information on participants who dropped out	N	N	Y	Y	N	N
	Reasons for loss to follow-up are provided	Y	Y	Y	Y	Y	N
	Adequate description of participants lost to follow-up	P[9]	P	Y	N	N	N
	There are no important differences between participants who completed the study and those who did not	U	U	Y	U	U	N
Outcome measurement	A clear definition of the outcome is provided	Y	Y	Y	Y	Y	Y
	Method of outcome measurement used is adequately valid and reliable	Y	Y	U	Y	Y	Y
	The method and setting of outcome measurement is the same for all study participants	Y	Y	Y	Y	Y	Y

[9] Only the number of lost to follow up was reported

Bias Domain	Description	Judgment					
Study ID: (authors, year)		**Ekberg-Aronsson *et al.*, 2005**	**Ekberg-Aronsson *et al.*, 2008**	**Petty *et al.*, 1976**	**Mannino *et al.*, 2006**	**Stavem *et al.*, 2006**	**Joo *et al.*, 2008**
Study confounding	All-important confounders are measured	Y	Y	N	Y	Y	Y
	Clear definitions of the important confounders measured are provided	Y	Y	N	Y	Y	P
	Important potential confounders are accounted for in the analysis	Y	Y	N	Y	Y	Y
Statistical analysis and reporting	Sufficient presentation of data to assess the adequacy of the analytic strategy	Y	Y	Y	Y	Y	Y
	The selected statistical method is adequate for the design of the study	Y	Y	P	Y	Y	P
	There is no selective reporting of results	P	P	Y	Y	U	U

(Y=yes, N=no, P=partly, U=unclear)

Table 46: Risk of bias assessment for the included cohort studies (systematic review 3)

Bias Domain	Description	Judgment	
Study ID: (authors, year)		**Barter *et al.*, 1974**	**Brito Mutunayagam *et al.*, 2010**
Study participation	Adequate participation in the study by eligible persons	N	Y
	Description of the source population or population of interest	N	Y
	Description of the baseline study sample	P	Y
	Adequate description of the period and place of recruitment	Y	Y
	Adequate description of inclusion and exclusion criteria	Y	Y
Study attrition	Adequate response rate for study participants	U	Y
	Description of attempts to collect information on participants who dropped out	N	N
	Reasons for loss to follow-up are provided	Y	Y
	Adequate description of participants lost to follow-up	N	Y
	There are no important differences between participants who completed the study and those who did not	U	Y
Prognostic Factor (PF) Measurement	A clear definition or description of the PF is provided	P	Y
	Method of PF measurement is adequately valid and reliable	P	Y
	The method and setting of measurement of PF is the same for all study participants	Y	Y
	Adequate proportion of the study sample has complete data for the PF	Y	Y
Outcome measurement	A clear definition of the outcome is provided	Y	Y
	Method of outcome measurement used is adequately valid and reliable	Y	Y

Bias Domain	Description	Judgment	
Study ID: (authors, year)		**Barter *et al.*, 1974**	**Brito Mutunayagam *et al.*, 2010**
	The method and setting of outcome measurement is the same for all study participants	Y	Y
Study confounding	All-important confounders are measured	Y	Y
	Clear definitions of the important confounders measured are provided	Y	Y
	Important potential confounders are accounted for in the analysis	Y	Y
Statistical analysis and reporting	Sufficient presentation of data to assess the adequacy of the analytic strategy	P	Y
	The selected statistical method is adequate for the design of the study	P	Y
	There is no selective reporting of results	Y	Y

(Y=yes, N=no, P=partly, U=unclear)

14 APPENDIX G: COPD ASSESSMENT TEST (CAT)

Example: I am very happy | 0 | √ 1 | 2 | 3 | 4 | 5 | I am very sad

I never cough	0	1	2	3	4	5	I cough all the time
I have no phlegm (mucus) in my chest at all	0	1	2	3	4	5	My chest is completely full of phlegm
My chest does not feel tight at all	0	1	2	3	4	5	My chest feels very tight
When I walk up a hill or one flight of stairs I am not breathless	0	1	2	3	4	5	When I walk up a hill or one flight of stairs I am breathless
I am not limited doing any activities at home	0	1	2	3	4	5	I am very limited doing activities at home
I am confident leaving home despite my lung condition	0	1	2	3	4	5	I am not confident leaving my home because of my lung condition
I sleep soundly	0	1	2	3	4	5	I don’t sleep soundly because of my lung condition
I have lots of energy	0	1	2	3	4	5	I have no energy at all

15 APPENDIX H: EQ-5D (5 LEVEL VERSION)

MOBILITY	
I have no problems in walking about	☐
I have slight problems in walking about	☐
I have moderate problems in walking about	☐
I have severe problems in walking about	☐
I am unable to walk about	☐
SELF-CARE	
I have no problems washing or dressing myself	☐
I have slight problems washing or dressing myself	☐
I have moderate problems washing or dressing myself	☐
I have severe problems washing or dressing myself	☐
I am unable to wash or dress myself	☐
USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*	
I have no problems doing my usual activities	☐
I have slight problems doing my usual activities	☐
I have moderate problems doing my usual activities	☐
I have severe problems doing my usual activities	☐
I am unable to do my usual activities	☐
PAIN / DISCOMFORT	
I have no pain or discomfort	☐
I have slight pain or discomfort	☐
I have moderate pain or discomfort	☐
I have severe pain or discomfort	☐
I have extreme pain or discomfort	☐
ANXIETY / DEPRESSION	
I am not anxious or depressed	☐
I am slightly anxious or depressed	☐
I am moderately anxious or depressed	☐
I am severely anxious or depressed	☐
I am extremely anxious or depressed	☐

16 APPENDIX I: COPD OVERDIAGNOSIS CONFERENCE ABSTRACT (ORAL PRESENTATION AT SAPC, POD AND THE ERS CONFERENCES)

Halima Buni, Rachel Jordan, Peymane Adab, Alexandra Enocson, Kar Keung Cheng.

European Respiratory Journal 46 (suppl 59):OA3288 · September 2015

Introduction: Overdiagnosis is a growing concern for a wide range of diseases. We aimed to assess the magnitude of COPD overdiagnosis in the UK primary care settings and examine the characteristics of patients potentially overdiagnosed with COPD.

Methods: We analysed data on 1,473 GP diagnosed COPD patients aged 40 years and over who participated in the Birmingham COPD cohort study-UK. Patients were classified as non-COPD or confirmed-COPD based on post-bronchodilator spirometry results. Characteristics were compared using logistic regression adjusted for age, sex and smoking status.

Results: Based on GOLD, LLN (GLI-2012 equations) and NICE 2004 definitions, 13.7%, 28.1% and 32.3% of participants were potentially overdiagnosed with COPD respectively. Restrictive pattern of lung disease was observed in 18.9% of non-COPD. Compared to confirmed-COPD, non-COPD were younger (mean age 67.2 *versus* 69.5 years, OR 0.98; 95% CI 0.96 - 0.99), more likely to be female (52.2% *versus* 35.4%, OR 0.5; CI 0.4 - 0.7), never smokers (22.9% *versus* 13.8%, OR 2.2; CI 1.4-3.4), obese (39.3% *versus* 31%, OR 1.7; CI 1.1 - 2.5), with multiple comorbidities (23.9% *versus* 16.4%, OR 1.7; CI 1.1 - 2.6) and showed less FEV_1 reversibility (10% *versus* 21.4%, OR 0.4; CI 0.2 - 0.7). Non-COPD participants were more likely to report previous asthma (47.3% *versus* 38.7%), coronary heart diseases

(18.4% *versus* 14.2%), diabetes (18.9% *versus* 14.2%) and depression (21.4% *versus* 16.8%). But the difference between groups was insignificant.

Conclusion: Overdiagnosis was common. We identified female sex, obesity, restrictive lung pattern and multiple comorbidities as potential predictors for COPD overdiagnosis but recommend a follow-up assessment for spirometry variability.

17 List of References

1. Cazzola M, Hanania NA, MacNee W, Rudell K, Hackford C, Tamimi N. A review of the most common patient-reported outcomes in COPD--revisiting current knowledge and estimating future challenges. Int J Chron Obstruct Pulmon Dis. 2015;10:725-38.
2. Snoeck-Stroband JB, Lapperre TS, Gosman MM, Boezen HM, Timens W, ten Hacken NH, et al. Chronic bronchitis sub-phenotype within COPD: inflammation in sputum and biopsies. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology. 2008;31(1):70-7.
3. Dutta N. Diagnosis of COPD. InnovAiT: Education and inspiration for general practice. 2013;6(4):223-31.
4. Mannino DM. COPDepidemiology, prevalence, morbidity and mortality, and disease heterogeneity. CHEST Journal. 2002;121(5_suppl):121S-6S.
5. Liu Y, Pleasants RA, Croft JB, Wheaton AG, Heidari K, Malarcher AM, et al. Smoking duration, respiratory symptoms, and COPD in adults aged >/=45 years with a smoking history. Int J Chron Obstruct Pulmon Dis. 2015;10:1409-16.
6. Global Initiative for Chronic Obstructive Lung Disease (2015). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. [cited 2015]. Available from: http://www.goldcopd.org/uploads/users/files/GOLD_Report_2015_Feb18.pdf.
7. National Institute for Health and Clinical Excellence. London (2010). Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care. [cited 2014]. Available from: http://guidance.nice.org.uk/CG101/Guidance/pdf/English.
8. Ford ES, Croft JB, Mannino DM, Wheaton AG, Zhang X, Giles WH. COPD surveillance—United States, 1999-2011. CHEST Journal. 2013;144(1):284-305.
9. Ekberg-Aronsson M, Lofdahl K, Nilsson JA, Lofdahl CG, Nilsson PM. Hospital admission rates among men and women with symptoms of chronic bronchitis and airflow limitation corresponding to the GOLD stages of chronic obstructive pulmonary disease-A population-based study. Respir Med. 2008;102(1):109-20.
10. Lange P, Celli B, Agustí A, Boje Jensen G, Divo M, Faner R, et al. Lung-function trajectories leading to chronic obstructive pulmonary disease. N Engl J Med. 2015;373(2):111-22.
11. Halbert RJ, Natoli JL, Gano A, Badamgarav E, Buist AS, Mannino DM. Global burden of COPD: Systematic review and meta-analysis. Eur Respir J. 2006;28(3):523-32.
12. Albers M, Schermer T, Heijdra Y, Molema J, Akkermans R, van Weel C. Predictive value of lung function below the normal range and respiratory symptoms for progression of chronic obstructive pulmonary disease. Thorax. 2008;63(3):201-7.
13. Holguin F, Folch E, Redd SC, Mannino DM. Comorbidity and mortality in COPD-related hospitalizations in the United States, 1979 to 2001. Chest Journal. 2005;128(4).
14. Balcells E, Gimeno-Santos E, de Batlle J, Ramon MA, Rodriguez E, Benet M, et al. Characterisation and prognosis of undiagnosed chronic obstructive pulmonary disease patients at their first hospitalisation. BMC Pulm Med. 2015;15:4.
15. Health & Social Care Information Centre (2014). Quality and Outcomes Framework (QOF) for April 2013 - March 2014, England. [cited 2014]. Available from: http://www.hscic.gov.uk/catalogue/PUB15751/qof-1314-prevalence-all-levels.xlsx.

16. Raluy-Callado M, Lambrelli D, MacLachlan S, Khalid JM. epidemiology, severity, and treatment of chronic obstructive pulmonary disease in the United Kingdom by gOlD 2013. International journal of chronic obstructive pulmonary disease. 2015;10:925.
17. Britton M. The burden of COPD in the UK: results from the Confronting COPD survey. Respir Med. 2003;97:S71-S9.
18. Pauwels PRA, Rabe KF. Burden and clinical features of chronic obstructive pulmonary disease (COPD). Lancet. 2004;364(9434):613-20.
19. Lindberg A, Eriksson B, Larsson L-G, Ronmark E, Sandstrom T, Lundback B. Seven-year cumulative incidence of COPD in an age-stratified general population sample. Chest. 2006;129(4):879-85.
20. Speizer FE, Ware JH. Exploring Different Phenotypes of COPD. N Engl J Med. 2015;373(2):185-6.
21. Eisner MD, Anthonisen N, Coultas D, Kuenzli N, Perez-Padilla R, Postma D, et al. An official American Thoracic Society public policy statement: Novel risk factors and the global burden of chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine. 2010;182(5):693-718.
22. Balmes J, Becklake M, Blanc P, Henneberger P, Kreiss K, Mapp C, et al. American Thoracic Society Statement: Occupational contribution to the burden of airway disease. American Journal of Respiratory and Critical Care Medicine. 2003;167(5):787-97.
23. Andersen ZJ, Hvidberg M, Jensen SS, Ketzel M, Loft S, Sorensen M, et al. Chronic obstructive pulmonary disease and long-term exposure to traffic-related air pollution: a cohort study. Am J Respir Crit Care Med. 2011;183(4):455-61.
24. Berglund DJ, Abbey DE, Lcbowitz MD, Knutscn SF, McDonncll WF. Respiratory symptoms and pulmonary function in an elderly nonsmoking population. Chest. 1999;115(1):49-59.
25. Hu G, Zhou Y, Tian J, Yao W, Li J, Li B, et al. Risk of COPD from exposure to biomass smoke: a metaanalysis. Chest. 2010;138(1):20-31.
26. Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. The Lancet. 2007;370(9589):765-73.
27. Vestbo J, Prescott E. Update on the 'Dutch hypothesis' for chronic respiratory disease. Thorax. 1998;53(SUPPL. 2):S15-S9.
28. Vestbo J, Hogg JC. Convergence of the epidemiology and pathology of COPD. Thorax. 2006;61(1):86-8.
29. Barnes PJ. Against the Dutch hypothesis: asthma and chronic obstructive pulmonary disease are distinct diseases. American journal of respiratory and critical care medicine. 2006;174(3):240-3.
30. Postma DS, Bush A, van den Berge M. Risk factors and early origins of chronic obstructive pulmonary disease. Lancet. 2015;385(9971):899-909.
31. Mannino DM. Looking beyond the cigarette in COPD. Chest. 2008;133(2):333-4.
32. Hanania NA, Müllerova H, Locantore NW, Vestbo J, Watkins ML, Wouters EFM, et al. Determinants of Depression in the ECLIPSE Chronic Obstructive Pulmonary Disease Cohort. American Journal of Respiratory and Critical Care Medicine. 2011;183(5):604-11.
33. Nussbaumer-Ochsner Y, Rabe KF. SYstemic manifestations of copd. Chest. 2011;139(1):165-73.
34. Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. Eur Respir J. 2009;33(5):1165-85.
35. Wust RC, Degens H. Factors contributing to muscle wasting and dysfunction in COPD patients. Int J Chron Obstruct Pulmon Dis. 2007;2(3):289-300.

36. van Dijk W, Tan W, Li P, Guo B, Li S, Benedetti A, et al. Clinical relevance of fixed ratio vs lower limit of normal of FEV1/FVC in COPD: patient-reported outcomes from the CanCOLD cohort. The Annals of Family Medicine. 2015;13(1):41-8.
37. Marcus BS, McAvay G, Gill TM, Vaz Fragoso CA. Respiratory symptoms, spirometric respiratory impairment, and respiratory disease in middle-aged and older persons. J Am Geriatr Soc. 2015;63(2):251-7.
38. Swanney MP, Ruppel G, Enright PL, Pedersen OF, Crapo RO, Miller MR, et al. Using the lower limit of normal for the FEV1/FVC ratio reduces the misclassification of airway obstruction. Thorax. 2008.
39. Garcia-Rio F, Soriano JB, Miravitlles M, Munoz L, Duran-Tauleria E, Sanchez G, et al. Overdiagnosing subjects with COPD using the 0.7 fixed ratio: correlation with a poor health-related quality of life. Chest. 2011;139(5):1072-80.
40. Jordan RE, Miller MR, Lam KB, Cheng KK, Marsh J, Adab P. Sex, susceptibility to smoking and chronic obstructive pulmonary disease: the effect of different diagnostic criteria. Analysis of the Health Survey for England. Thorax. 2012;67(7):600-5.
41. Culver BH. How should the lower limit of the normal range be defined? Respir Care. 2012;57(1):136-45; discussion 43-5.
42. Miller MR, Levy ML. Chronic obstructive pulmonary disease: missed diagnosis versus misdiagnosis. Bmj. 2015;351.
43. Scanlon PD, Connett JE, Waller LA, Altose MD, Bailey WC, Buist AS, et al. Smoking cessation and lung function in mild-to-moderate chronic obstructive pulmonary disease. The Lung Health Study. Am J Respir Crit Care Med. 2000;161(2 Pt 1):381-90.
44. Anthonisen NR, Connett JE, Kiley JP, Altose MD, Bailey WC, Buist AS, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. The Lung Health Study. Jama. 1994;272(19):1497-505.
45. Kanner RE, Connett JE, Williams DE, Buist AS. Effects of randomized assignment to a smoking cessation intervention and changes in smoking habits on respiratory symptoms in smokers with early chronic obstructive pulmonary disease: the Lung Health Study. Am J Med. 1999;106(4):410-6.
46. Bauld L, Bell K, McCullough L, Richardson L, Greaves L. The effectiveness of NHS smoking cessation services: a systematic review. Journal of Public Health. 2010;32(1):71-82.
47. Crockett AJ, Cranston JM, Moss JR, Alpers JH. A review of long-term oxygen therapy for chronic obstructive pulmonary disease. Respir Med. 2001;95(6):437-43.
48. Lacasse Y, Goldstein R, Lasserson TJ, Martin S. Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2006(4):Cd003793.
49. Puhan MA, Scharplatz M, Troosters T, Steurer J. Respiratory rehabilitation after acute exacerbation of COPD may reduce risk for readmission and mortality–a systematic review. Respir Res. 2005;6(1):54.
50. Poole P, Chacko EE, Wood-Baker R, Cates CJ. Influenza vaccine for patients with chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2009;(4)(CD002733).
51. Calderon-Larranaga A, Carney L, Soljak M, Bottle A, Partridge M, Bell D, et al. Association of population and primary healthcare factors with hospital admission rates for chronic obstructive pulmonary disease in England: national cross-sectional study. Thorax. 2011;66(3):191-6.
52. Sethi S. Infectious etiology of acute exacerbations of chronic bronchitis. Chest. 2000;117(5 SUPPL. 2):380S-5S.

53. Walters JA, Smith S, Poole P, Granger RH, Wood-Baker R. Injectable vaccines for preventing pneumococcal infection in patients with chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2010(11):Cd001390.
54. Bourbeau J, Nault D, Dang-Tan T. Self-management and behaviour modification in COPD. Patient Education and Counseling. 2004;52(3):271-7.
55. Monninkhof E, van der Valk P, van der Palen J, van Herwaarden C, Partridge MR, Zielhuis G. Self-management education for patients with chronic obstructive pulmonary disease: a systematic review. Thorax. 2003;58(5):394-8.
56. Zwerink M, Brusse-Keizer M, van der Valk PD, Zielhuis GA, Monninkhof EM, van der Palen J, et al. Self management for patients with chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2014;3:Cd002990.
57. Bourbeau J, Julien M, Maltais F, et al. Reduction of hospital utilization in patients with chronic obstructive pulmonary disease: A disease-specific self-management intervention. Arch Intern Med. 2003;163(5):585-91.
58. Bourbeau J, van der Palen J. Promoting effective self-management programmes to improve COPD. Eur Respir J. 2009;33(3):461-3.
59. Moynihan R, Glasziou P, Woloshin S, Schwartz L, Santa J, Godlee F. Winding back the harms of too much medicine. Bmj. 2013;346.
60. Walters JA, Haydn Walters E, Nelson M, Robinson A, Scott J, Turner P, et al. Factors associated with misdiagnosis of COPD in primary care. Prim. 2011;20(4):396-402.
61. Collins BF, Feemster LC, Rinne ST, Au DH. Factors predictive of airflow obstruction among veterans with presumed empirical diagnosis and treatment of COPD. Chest. 2015;147(2):369-76.
62. Zwar NA, Marks GB, Hermiz O, Middleton S, Comino EJ, Hasan I, et al. Predictors of accuracy of diagnosis of chronic obstructive pulmonary disease in general practice. Med J Aust. 2011;195(4):168-71.
63. Moynihan R, Doust J, Henry D. Preventing overdiagnosis: how to stop harming the healthy. Bmj. 2012;344.
64. Joo MJ, Au DH, Fitzgibbon ML, Lee TA. Inhaled corticosteroids and risk of pneumonia in newly diagnosed COPD. Respir Med. 2010;104(2):246-52.
65. McKeever T, Harrison TW, Hubbard R, Shaw D. Inhaled corticosteroids and the risk of pneumonia in people with asthma: a case-control study. Chest. 2013;144(6):1788-94.
66. Gershon A, Croxford R, Calzavara A, To T, Stanbrook MB, Upshur R, et al. Cardiovascular safety of inhaled long-acting bronchodilators in individuals with chronic obstructive pulmonary disease. JAMA Intern Med. 2013;173(13):1175-85.
67. Chiolero A, Paccaud F, Aujesky D, Santschi V, Rodondi N. How to prevent overdiagnosis. Swiss Med Wkly. 2015;145:w14060.
68. Ghattas C, Dai A, Gemmel DJ, Awad MH. Over diagnosis of chronic obstructive pulmonary disease in an underserved patient population. International journal of chronic obstructive pulmonary disease. 2013;8:545.
69. Mitsiki E, Bania E, Varounis C, Gourgoulianis KI, Alexopoulos EC. Characteristics of prevalent and new COPD cases in Greece: the GOLDEN study. Int J Chron Obstruct Pulmon Dis. 2015;10:1371-82.
70. Lucas AE, Smeenk FJ, Smeele IJ, van Schayck OP. Diagnostic accuracy of primary care asthma/COPD working hypotheses, a real life study. Respir Med. 2012;106(8):1158-63.
71. Jones RCM, Freegard S, Reeves M, Hanney K, Dobbs F. The role of the practice nurse in the management of chronic obstructive pulmonary disease (COPD). Prim. 2001;10:106.

72. Jones RC, Dickson-Spillmann M, Mather MJ, Marks D, Shackell BS. Accuracy of diagnostic registers and management of chronic obstructive pulmonary disease: the Devon primary care audit. Respir Res. 2008;9:62.
73. Bolton CE, Ionescu AA, Edwards PH, Faulkner TA, Edwards SM, Shale DJ. Attaining a correct diagnosis of COPD in general practice. Respir Med. 2005;99(4):493-500.
74. Schermer TR, Smeele IJ, Thoonen BP, Lucas AE, Grootens JG, van Boxem TJ, et al. Current clinical guideline definitions of airflow obstruction and COPD overdiagnosis in primary care. Eur Respir J. 2008;32(4):945-52.
75. Davis KJ, Landis SH, Oh Y-M, Mannino DM, Han MK, van der Molen T, et al. Continuing to Confront COPD International Physician Survey: physician knowledge and application of COPD management guidelines in 12 countries. International journal of chronic obstructive pulmonary disease. 2015;10:39.
76. Fromer L. Diagnosing and treating COPD: understanding the challenges and finding solutions. International journal of general medicine. 2011;4:729-39.
77. Lucas AE, Smeenk FW, Smeele IJ, van Schayck CP. Overtreatment with inhaled corticosteroids and diagnostic problems in primary care patients, an exploratory study. Fam Pract. 2008;25(2):86-91.
78. Marklund B, Tunsater A, Bengtsson C. How often is the diagnosis bronchial asthma correct? Fam Pract. 1999;16(2):112-6.
79. Izquierdo JL, Martin A, de Lucas P, Rodriguez-Gonzalez-Moro JM, Almonacid C, Paravisini A. Misdiagnosis of patients receiving inhaled therapies in primary care. Int J Chron Obstruct Pulmon Dis. 2010;5:241-9.
80. Buffels J, Degryse J, Liistro G, Decramer M. Differential diagnosis in a primary care population with presumed airway obstruction: a real-life study. Respiration. 2012;84(1):44-54.
81. Drazen JM, Postma DS, Rabe KF. The Asthma–COPD Overlap Syndrome. N Engl J Med. 2015;373(13):1241-9.
82. Pearson M, Ayres JG, Sarno M, Massey D, Price D. Diagnosis of airway obstruction in primary care in the UK: the CADRE (COPD and Asthma Diagnostic/management REassessment) programme 1997-2001. Int J Chron Obstruct Pulmon Dis. 2006;1(4):435-43.
83. Tinkelman DG, Price DB, Nordyke RJ, Halbert RJ. Misdiagnosis of COPD and asthma in primary care patients 40 years of age and over. J Asthma. 2006;43(1):75-80.
84. Johnson JD, Theurer WM. A stepwise approach to the interpretation of pulmonary function tests. Am Fam Physician. 2014;89(5):359-66.
85. Mannino DM, Ford ES, Redd SC. Obstructive and restrictive lung disease and functional limitation: data from the Third National Health and Nutrition Examination. J Intern Med. 2003;254(6):540-7.
86. Vestbo J, Lange P. Can GOLD Stage 0 provide information of prognostic value in chronic obstructive pulmonary disease? Am J Respir Crit Care Med. 2002;166(3):329-32.
87. Mannino DM. GOLD stage 0 COPD: is it real? Does it matter? Chest. 2006;130(2):309-10.
88. Global Initiative for Chronic Obstructive Lung Disease (2001). Global Strategy for the Diagnosis, Management and Prevention of COPD NHLBI/WHO Workshop Report. [cited 2013]. Available from: http://www.goldcopd.org/uploads/users/files/GOLDWkshp2001.pdf.
89. Yamane T, Hattori N, Kitahara Y, Haruta Y, Sasaki H, Yokoyama A, et al. Productive cough is an independent risk factor for the development of COPD in former smokers. Respirology. 2010;15(2):313-8.

90. De Marco R, Accordini S, Cerveri I, Corsico A, Sunyer J, Neukirch F, et al. An international survey of chronic obstructive pulmonary disease in young adults according to GOLD stages. Thorax. 2004;59(2):120-5.
91. Global Initiative for Chronic Obstructive Lung Disease (2006). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. [cited 2013]. Available from: http://www.goldcopd.org/uploads/users/files/GOLDReport2006_0122.pdf.
92. Mannino DM, Kiri VA. Changing the burden of COPD mortality. International journal of chronic obstructive pulmonary disease. 2006;1(3):219.
93. Brito-Mutunayagam R, Appleton SL, Wilson DH, Ruffin RE, Adams RJ. Global initiative for chronic obstructive lung disease stage 0 is associated with excess FEV1 decline in a representative population sample. Chest. 2010;138(3):605-13.
94. de Oca MM, Halbert RJ, Lopez MV, Perez-Padilla R, Talamo C, Moreno D, et al. The chronic bronchitis phenotype in subjects with and without COPD: the PLATINO study. Eur Respir J. 2012;40(1):28-36.
95. Mannino DM, Doherty DE, Buist AS. Global Initiative on Obstructive Lung Disease (GOLD) classification of lung disease and mortality: Findings from the Atherosclerosis Risk in Communities (ARIC) study. Respir Med. 2006;100(1):115-22.
96. Fletcher C, Peto R. The natural history of chronic airflow obstruction. Br Med J. 1977;1(6077):1645-8.
97. Kauffmann F, Drouet D, Lellouch J, Brille D. Twelve years spirometric changes among Paris area workers. Int J Epidemiol. 1979;8(3):201-12.
98. de Marco R, Accordini S, Cerveri I, Corsico A, Anto JM, Kunzli N, et al. Incidence of chronic obstructive pulmonary disease in a cohort of young adults according to the presence of chronic cough and phlegm. Am J Respir Crit Care Med. 2007;175(1):32-9.
99. Pelkonen M, Notkola I-L, Nissinen A, Tukiainen H, Koskela H. Thirty-year cumulative incidence of chronic bronchitis and COPD in relation to 30-year pulmonary function and 40-year mortality: a follow-up in middle-aged rural men. Chest. 2006;130(4):1129-37.
100. Joo MJ, Lee TA, Bartle B, van de Graaff WB, Weiss KB. Patterns of healthcare utilization by COPD severity: a pilot study. Lung. 2008;186(5):307-12.
101. Tan W, Bourbeau J, Hernandez P, Chapman K, Cowie R, FitzGerald J, et al. Exacerbation-like respiratory symptoms in individuals without chronic obstructive pulmonary disease: results from a population-based study. Thorax. 2014:thoraxjnl-2013-205048.
102. Kanervisto M, Saarelainen S, Vasankari T, Jousilahti P, Heistaro S, Heliovaara M, et al. COPD, chronic bronchitis and capacity for day-to-day activities: negative impact of illness on the health-related quality of life. Chron. 2010;7(4):207-15.
103. Ekberg-Aronsson M, Pehrsson K, Nilsson JA, Nilsson PM, Lofdahl CG. Mortality in GOLD stages of COPD and its dependence on symptoms of chronic bronchitis. Respir Res. 2005;6(98).
104. Stavem K, Sandvik L, Erikssen J. Can global initiative for Chronic Obstructive Lung Disease stage 0 provide prognostic information on long-term mortality in men? Chest. 2006;130(2):318-25.
105. National Heart, Lung, and Blood Institue (2011). Non-obstructive Chronic Bronchitis (NCB): A Syndrome in Need of Better Definition and Treatment. [cited 2014]. Available from: https://www.nhlbi.nih.gov/research/reports/2011-bronchitis.htm.
106. Vestbo J. Chronic cough and phlegm in young adults: Should we worry? American Journal of Respiratory and Critical Care Medicine. 2007;175(1):2-3.

107. Higgins JPT GSe. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration 2011. Available from: www.cochrane-handbook.org.
108. Centre for Reviews and Dissemination University of York (2009). Systematic Reviews: CRD's guidance for undertaking reviews in health care. [cited 2013]. Available from: http://www.york.ac.uk/inst/crd/pdf/Systematic_Reviews.pdf.
109. PROSPERO: International prospective register of systematic reviews York: Centre for Reviews and Dissemination, University of York. [cited 2014]. Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014009146.
110. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Prev Med. 2007;45(4):247-51.
111. Vandenbroucke JP, Von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. Gaceta Sanitaria. 2009;23(2):158e1-e28.
112. Hayden JA, van der Windt DA, Cartwright JL, CÃ P, Bombardier C. Assessing bias in studies of prognostic factors. Ann Intern Med. 2013;158(4):280-6.
113. Wells G, Shea B, O'connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2000.
114. Altman DG. Systematic reviews of evaluations of prognostic variables. Bmj. 2001;323(7306):224-8.
115. Egger M, Smith GD, Altman D. Systematic reviews in health care: meta-analysis in context: John Wiley & Sons; 2008.
116. Vestbo J, Prescott E, Lange P. Association of chronic mucus hypersecretion with FEV1 decline and chronic obstructive pulmonary disease morbidity. Copenhagen City Heart Study Group. Am J Respir Crit Care Med. 1996;153(5):1530-5.
117. Guerra S, Sherrill DL, Venker C, Ceccato CM, Halonen M, Martinez FD. Chronic bronchitis before age 50 years predicts incident airflow limitation and mortality risk. Thorax. 2009;64(10):894-900.
118. Komus N, Tertemiz KC, Sevinc C. The importance of the at risk COPD patients (Stage 0) and clinical differences. [Turkish] KOAH riski altinda olan (Evre 0) olgularin onemi ve klinik farkliliklari. Tuberk. 2008;56(4):382-9.
119. Shin C, Lee S, Abbott RD, Je HK, Sang YL, Kwang HI, et al. Relationships between respiratory symptoms and FEV1 in men and women with normal lung function: The Korean health and genome study. Lung. 2005;183(5):301-9.
120. Petty TL, Pierson DJ, Dick NP. Follow up evaluation of a prevalence study for chronic bronchitis and chronic airway obstruction. Am Rev Respir Dis. 1976;114(5):881-90.
121. Barter CE, Campbell AH, Tandon MK. Factors affecting the decline of FEV1 in chronic bronchitis. Aust N Z J Med. 1974;4(4):339-45.
122. Wheaton AG, Ford ES, Thompson WW, Greenlund KJ, Presley-Cantrell LR, Croft JB. Pulmonary function, chronic respiratory symptoms, and health-related quality of life among adults in the United States--National Health and Nutrition Examination Survey 2007-2010. BMC Public Health. 2013;13:854.
123. Mannino DM, Diaz-Guzman E, Pospisil J. A new approach to classification of disease severity and progression of COPD. Chest. 2013;144(4):1179-85.

124. Cerveri I, Corsico A, Zoia MC, Carrozzi L, Beccaria M, Marinoni A, et al. Chronic cough and phlegm in young adults. Eur Respir J. 2003;22(3):413-7.
125. Lam DC, Hui CK, Ip MS. Issues in pulmonary function testing for the screening and diagnosis of chronic obstructive pulmonary disease. Curr Opin Pulm Med. 2012;18(2):104-11.
126. Voll-Aanerud M, Eagan TM, Wentzel-Larsen T, Gulsvik A, Bakke PS. Changes in respiratory symptoms and health-related quality of life. Chest. 2007;131(6):1890-7.
127. Stahl E, Lindberg A, Jansson S-A, Ronmark E, Svensson K, Andersson F, et al. Health-related quality of life is related to COPD disease severity. Health Qual Life Outcomes. 2005;3(1):56.
128. Pereira EDB, Pinto R, Alcantara M, Medeiros M, Mota RMS. Influence of respiratory function parameters on the quality of life of COPD patients. Jornal Brasileiro de Pneumologia. 2009;35(8):730-6.
129. Voll-Aanerud M, Eagan TM, Wentzel-Larsen T, Gulsvik A, Bakke PS. Respiratory symptoms, COPD severity, and health related quality of life in a general population sample. Respir Med. 2008;102(3):399-406.
130. Voll-Aanerud M, Eagan TML, Plana E, Omenaas ER, Bakke PS, Svanes C, et al. Respiratory symptoms in adults are related to impaired quality of life, regardless of asthma and COPD: results from the European community respiratory health survey. Health Qual Life Outcomes. 2010;8:107.
131. Xie G, Li Y, Shi P, Zhou B, Zhang P, Wu Y. Baseline pulmonary function and quality of life 9 years later in a middle-aged Chinese population. Chest. 2005;128(4):2448-57.
132. NatCen Social Research and Royal Free and University College Medical School. Department of Epidemiology and Public Health HSfE, 2010 [computer file]. Colchester, Essex: UK Data Archive [distributor], April 2012. SN: 6986 http://dx.doi.org/10.5255/UKDA-SN-6986-1
133. Miravitlles M, Soriano JB, Garcia-Rio F, Munoz L, Duran-Tauleria E, Sanchez G, et al. Prevalence of COPD in Spain: impact of undiagnosed COPD on quality of life and daily life activities. Thorax. 2009;64(10):863-8.
134. P. Adab, D. Fitzmaurice, A.P. Dickens, J. Ayres, H. Buni, K.K. Cheng, et al. Cohort profile: The Birmingham COPD Cohort Study 2016. Available from: www.birmingham.ac.uk/bliss.
135. Jordan RE, Adab P, Jowett S, Marsh JL, Riley RD, Enocson A, et al. TargetCOPD: a pragmatic randomised controlled trial of targeted case finding for COPD versus routine practice in primary care: protocol. BMC Pulm Med. 2014;14:157.
136. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319-38.
137. Guidelines in Prctice, UK [cited 2015]. Available from: http://www.guidelinesinpractice.co.uk/.
138. NHS Choices, UK [cited 2015]. Available from: www.nhs.uk.
139. Danielle Morrisa, Kamlesh Khuntia, Laura Grayb, Naveed Sattarc, Daviesa M. What are the cut-off points for body mass index (BMI) and waist circumference among adults from black, Asian and other minority ethnic groups living in the UK that are 'risk equivalent' to the current thresholds set for white European populations? Analyses from the ADDITION-Leicester Study[cited 2015. Available from: https://www.nice.org.uk/guidance/ph46/evidence/ph46-bmi-and-waist-circumference-black-asian-and-minority-ethnic-groups-expert-report-1-analyses-from-the-addition-leicester-study-aic-removed2.

140. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. Eur Respir J. 2009;34(3):648-54.
141. Hurst NP, Kind P, Ruta D, Hunter M, Stubbings A. Measuring health-related quality of life in rheumatoid arthritis: validity, responsiveness and reliability of EuroQol (EQ-5D). Br J Rheumatol. 1997;36(5):551-9.
142. Ozalevli S, Ozden A, Itil O, Akkoclu A. Comparison of the Sit-to-Stand Test with 6 min walk test in patients with chronic obstructive pulmonary disease. Respir Med. 2007;101(2):286-93.
143. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3–95 year age range: the Global Lung Function 2012 Equations: Report of the Global Lung Function Initiative (GLI), ERS Task Force to establish improved Lung Function Reference Values. The European respiratory journal. 2012;40(6):1324-43.
144. Quanjer PH, Stanojevic S, Stocks J, Cole TJ. GLI-2012 All-Age Multi-Ethnic Reference Values for Spirometry2012 [cited 2015. Available from: http://www.ers-education.org/lrmedia/2012/pdf/266696.pdf.
145. Zutler M, Singer JP, Omachi TA, Eisner M, Iribarren C, Katz P, et al. Relationship of obesity with respiratory symptoms and decreased functional capacity in adults without established COPD. Prim. 2012;21(2):194-201.
146. Sin DD, Jones RL, Man SF. Obesity is a risk factor for dyspnea but not for airflow obstruction. Arch Intern Med. 2002;162(13):1477-81.
147. Van Den Bemt L, Schermer T. Obesity: Another good reason to question the fixed FEV1/FVC ratio when diagnosing COPD. Chest. 2012;141(2):568-9.
148. Smith CJP, Gribbin J, Challen KB, Hubbard RB. The impact of the 2004 NICE guideline and 2003 General Medical Services contract on COPD in primary care in the UK. Qjm. 2008;101(2):145-53.
149. Walker PP, Mitchell P, Diamantea F, Warburton CJ, Davies L. Effect of primary-care spirometry on the diagnosis and management of COPD. Eur Respir J. 2006;28(5):945-52.
150. Melbye H, Drivenes E, Dalbak LG, Leinan T, Høegh-Henrichsen S, Østrem A. Asthma, chronic obstructive pulmonary disease, or both? Diagnostic labeling and spirometry in primary care patients aged 40 years or more. International journal of chronic obstructive pulmonary disease. 2011;6:597.
151. Sichletidis L, Chloros D, Spyratos D, Chatzidimitriou N, Chatziiliadis P, Protopappas N, et al. The validity of the diagnosis of chronic obstructive pulmonary disease in general practice. Primary care respiratory journal: journal of the General Practice Airways Group. 2007;16(2):82-8.
152. Talamo C, de Oca MM, Halbert R, Perez-Padilla R, Jardim JR, Muino A, et al. Diagnostic labeling of COPD in five Latin American cities. Chest. 2007;131(1):60-7.
153. Centurion V, Huang F, Naureckas E, Camargo C, Jr., Charbeneau J, Joo M, et al. Confirmatory spirometry for adults hospitalized with a diagnosis of asthma or chronic obstructive pulmonary disease exacerbation. BMC polm. 2012;12(1):1-7.
154. Gruffydd-Jones K, Jones MM. NICE guidelines for chronic obstructive pulmonary disease: Implications for primary care. Br J Gen Pract. 2011;61(583):91-2.
155. Global Initiative for Chronic Obstructive Lung Disease (2010). Spirometry for health care providers. [cited 2015]. Available from: http://www.goldcopd.org/uploads/users/files/GOLD_Spirometry_2010.pdf.

156. Quanjer PH, Brazzale DJ, Boros PW, Pretto JJ. Implications of adopting the Global Lungs Initiative 2012 all-age reference equations for spirometry. Eur Respir J. 2013;42(4):1046-54.
157. Decramer M, Bartsch P, Pauwels R, Yernault JC. Management of COPD according to guidelines. A national survey among Belgian physicians. Monaldi Arch Chest Dis. 2003;59(1):62-80.
158. Lamprecht B, Vanfleteren LE, Studnicka M, Allison M, McBurnie MA, Vollmer WM, et al. Sex-related differences in respiratory symptoms: results from the BOLD Study. Eur Respir J. 2013;42(3):858-60.
159. Han MK, Postma D, Mannino DM, Giardino ND, Buist S, Curtis JL, et al. Gender and chronic obstructive pulmonary disease: Why it matters. American Journal of Respiratory and Critical Care Medicine. 2007;176(12):1179-84.
160. Dimich-Ward H, Camp PG, Kennedy SM. Gender differences in respiratory symptoms-does occupation matter? Environ Res. 2006;101(2):175-83.
161. Lopez Varela MV, Montes de Oca M, Halbert R, Muino A, Talamo C, Perez-Padilla R, et al. Comorbidities and health status in individuals with and without COPD in five Latin American cities: the PLATINO study. Arch Bronconeumol. 2013;49(11):468-74.
162. Sin DD, Jones RL, Man SFP. Obesity is a risk factor for dyspnea but not for airflow obstruction. Arch Intern Med. 2002;162(13):1477-81.
163. Cecere LM, Littman AJ, Slatore CG, Udris EM, Bryson CL, Boyko EJ, et al. Obesity and COPD: associated symptoms, health-related quality of life, and medication use. Copd. 2011;8(4):275-84.
164. Mannino DM, Thorn D, Swensen A, Holguin F. Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. Eur Respir J. 2008;32(4):962-9.
165. Allinson JP, Hardy R, Donaldson GC, Shaheen SO, Kuh D, Wedzicha JA. The Presence of Chronic Mucus Hypersecretion Across Adult Life in Relation to COPD Development. Am J Respir Crit Care Med. 2015.
166. Khan K, Kunz R, Kleijnen J, Antes G. Systematic reviews to support evidence-based medicine: CRC Press; 2011.
167. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151(4):264-9.
168. Egger M, Schneider M, Smith GD. Meta-analysis Spurious precision? Meta-analysis of observational studies. Bmj. 1998;316(7125):140-4.