Health-related quality of life; chronic obstructive pulmonary disease and smoking

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1 Abstract

This thesis explores and investigates the challenges around measurement of Quality of Life (QoL) / Health State Utility Value (HSUV) in Chronic Obstructive Pulmonary Disease (COPD), as a chronic disease and its major risk factor, smoking. This thesis is based upon four separate studies, which present original research of 1) systematic literature review on HSUV in COPD, 2) application of the HSUVs in COPD disease progression models, 3) economic evaluation study alongside a clinical trial aimed to improve HSUV in COPD and 4) econometric analysis of the effect of smoking habit transition on the HSUVs.

The first study investigates the mean HSUVs in COPD patients in general and specifically in each stage of the disease by using systematic literature review and meta-analysis of studies which reported patients-level utility values elicited by EQ-5D. In order to explore the degree of heterogeneity around the utility values, effects of a variety of clinical and study characteristics have been examined through subgroup analyses. This study represents one of the first meta-analysis and subgroup analysis of HSUV in COPD. It demonstrates considerable inconsistency in utility measures among COPD-related published literature. This study highlights that in case of high level of heterogeneity, appropriate sensitivity analyses are recommended for more accurate health economic appraisals.

The second study concerns the compatibility of available COPD progression models with good practices guideline for decision analytic modelling. This study conducts a systematic review of the HSUVs assigned to the different stages of COPD used in modelling studies and compares these with summary measures from meta-analyses of available utility studies. This study demonstrates that on average, COPD decision models used higher values than estimated mean HSUVs from the meta-analysis of the patient-level data. The study suggests that improvement

in the consistency of modelling studies may be achieved if published recommendations on good modelling practice, especially the data identification, are followed closely as suggested.

The third study is an economic evaluation of the telephone-based cognitive behavioural (TB-CBT) therapy for depression/anxiety comorbidities in COPD patients. Alongside a clinical trial, a cost-utility analysis is performed to measure cost and quality-adjusted life years gained based on the Assessment of Quality of Life (AQoL-4D) measure as a preference-based HSUV scale. This study shows that TB-CBT can be considered as a cost saving approach. This study, by using the concept of loss aversion from prospect theory which is based on individual preference, provides a distinctive interpretation of the incremental cost-effectiveness ratio (ICER) in the south-west quadrant of ICER plane.

The fourth study elucidates the effect of the transition from “Smoker” to “Ex-smoker” on QoL (measured by SF-36) in the general Australian population. Panel data from thirteen waves of a nationally representative longitudinal survey of Household Income and Labour Dynamics of Australia is used and piecewise two-way fixed effect linear regression models are adapted. Of the eight SF-36 dimensions, only physical health factors showed pervasively and significant improvements after the smoking transition, irrespective of age and sex and other related time-invariant covariates. This study is one of the first studies analysing the relationship between smoking and QoL measures in general population, taking the advantages of panel data which provides unique opportunity to account for individual heterogeneity and focuses on within-person changes in QoL as smoking status change while controlling for unobserved time-invariant individual characteristics (fixed effects) on observed covariates.

Declaration

This is to certify that:

(i) The thesis comprises only my original work towards the Ph.D. except where indicated in the Preface,

(ii) Due acknowledgement has been made in the text to all other material used and assistance received,

(iii) The thesis is fewer than 100,000 words in length, exclusive of tables, maps, bibliographies and appendices.

Signed:  Date: 10/04/2017

Preface

I gratefully acknowledge the guidance and work of many others in the two published and one submitted studies contained in this thesis. I was the primary author and contributed more than 70% of the content, including planning, data collection, data analysis, execution and preparation of manuscripts for each study.

Publications

This Ph.D. thesis has generated the following published and submitted papers in peer review journals:

- Foruhar Moayeri, Ya-Seng (Arthur) Hsueh, Philip Clarke & David Dunt. Outcome of smoking cessation; Piecewise two-way fixed effect linear regression models, using Australian population panel data; a close step to the notion of causality. It is going to be submitted for publication.

- Foruhar Moayeri, Ya-Seng (Arthur) Hsueh, David Dunt, Colleen Doyle. Cost-utility analysis of telephone-based cognitive behaviour therapy in Chronic Obstructive Pulmonary Disease (COPD) patients with anxiety and depression comorbidities: a randomized control trial. It is going to be submitted for publication.

- Foruhar Moayeri, Ya-Seng (Arthur) Hsueh, Philip Clarke & David Dunt. Do Model-Based Studies in Chronic Obstructive Pulmonary Disease Measure Correct Values of Utility? A Meta-Analysis. Value in Health Journal 2016; DOI: http://dx.doi.org/10.1016/j.jval.2016.01.012

  The pdf of the published article and the answers to the reviewers' comments were presented in Appendix G1.

Publications

- Foruhar Moayeri, Ya-Seng (Arthur) Hsueh, Philip Clarke, Xinyang Hua & David Dunt (2015): Health State Utility Value in Chronic Obstructive Pulmonary Disease (COPD); The Challenge of Heterogeneity: A Systematic Review and Meta-Analysis. COPD: Journal of Chronic Obstructive Pulmonary Disease 2015 DOI: http://dx.doi.org/10.3109/15412555.2015.1092953

  The pdf of the published article and the answers to the reviewers' comments were presented in Appendix G2.

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I would like to thank the unwavering support from my family; I wish to lovingly thank my beautiful wife Parisa for holding my hand on this journey and my beloved daughter, Maha.

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Acronyms and abbreviations

AIHW	Australian Institute of Health and Welfare
AQoL	Assessment of Quality of Life
AQ-20/30	Airway Questionnaire 20/30
AQ-20R	Airway Questionnaire 20 Revised
ATS	American Thoracic Society
ATT	Average Treatment effect on the Treatment
AUS$	Australian Dollar
BAI	Beck Anxiety Inventory
BODE	Body-mass index, airflow Obstruction, Dyspnoea, and Exercise capacity
BP	Bodily Pain
BTS	British Thoracic Society
CAT	COPD Assessment Test
CBT	Cognitive Behavioural Therapy
CCQ	Clinical COPD Questionnaire
CCOHTA	Canadian Cooperating Office for Health Technology Assessment
CD	Collection District
CEA	Cost-effectiveness Analysis
CEAC	Cost-effectiveness Acceptability Plane
CHEERS	Consolidated Health Economics Evaluation Reporting Standards
CI	Confidence Interval
COPDSS	COPD Severity Score
CRQ	Chronic Respiratory Questionnaire
CUA	Cost-Utility Analysis
df	degree of freedom
DID	difference-in-differences
EQ-5D	EuroQol-5 Dimension questionnaire
ERS	European Respiratory Society
EXACT	EXAcerbation of Chronic Pulmonary Disease Tool
EU	European Union
FACIT	Functional Impairment of Chronic Illness Therapy

FEV1 % pred	predicted Forced Expiratory Volume in one second
GH	General Health
GOLD	Global Initiative for Chronic Obstructive Pulmonary Disease
HADS	Hospital Anxiety and Depression Scale
HEED	Health Economic Evaluations Database
HILDA	Household Income and Labour Dynamics of Australia
HSUV	Health State Utility Value
HR-QoL	Health Related Quality of Life
HUI	Health Utilities Index
ICUR	Incremental Cost-Effectiveness Ratio
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intention to Treat
LAS/VAS-8	Linear Analogue Scale/Visual Analogue Scale
LCOPD	Living with Chronic Obstructive pulmonary disease questionnaire
LTx	Lung Ttransplantation
MBS	Medicare Benefits Schedule
McGill COPD	McGill COPD Quality of Life Questionnaire
MCS	Mental component summary
MEPS	Medical Expenditure Panel Survey
MH	general Mental Health
MI	Multiple Imputation
MICE	Multiple Imputation Chained Equations
mMRC	Modified British Medical Research Council
MOOSE	Meta-analyses Of Observational Studies in Epidemiology
MOS-6A	Medical Outcomes Study 6-item general health survey
MPI	Minimal Psychological Intervention
MRC	Medical Research Council
MRF-28	Maugeri Respiratory Failure Questionnare-28
MYMOP	Measure Yourself Medical Outcome Profile
NICE	National Institute of Clinical Excellence
NE	North East
NHP	Nottingham Health Profile
NN	Nearest Neighbour

Acronyms and abbreviations

NW	North West
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PCS	Physical component summary
PF	Physical Functioning
PRP	Pulmonary Rehabilitation Program
PSM	Propensity Score Matching
PY	Person-Year
QALYs	Quality-Adjusted Life Years
QLICD-GM	Life Instruments for chronic Diseases-General Module
QoL	Quality of Life
QoL-RIQ	Quality of Life in Respiratory Illness Questionnaire
QWBSA	Quality of Well Being Self-Administered
PROs	Patient-Reported Outcomes
RCT	Randomized Control Trial
ResPers	Responding Person
RE	Role limitations due to Emotional problems
RP	Physical Functioning
RQLQ	Respiratory Quality of Life Questionnaire
SA	Sensitivity Analysis
SBU	The Swedish Council on Technology Assessment in Health Care
SD	Standard Deviation
SE	Standard Error; South East
SF-12	Short-Form Health Survey-12
SF-36	Short-Form Health Survey-36
SF-6D	Short Form-6 dimension
SG	Standard Gamble
SGRQ	St. George Respiratory Questionnaire
SF	Social Functioning
SIP	Sickness Impact Profile
SOLQ	Seattle Obstructive Lung Disease Questionnaire
SRI	Severe Respiratory Insufficiency
SSI	Supplemental Security Income

SSDI	Social Security Disability Insurance
SUTVA	Stable Unit Treatment Value Assumption
SW	South West
TB-CBT	Telephone-Based Cognitive Behavioural Therapy
TTO	Time Trade-Off
UK	United Kingdom
USA	United State of America
VAS	Visual Analogue Scale
VSRQ	Visual Simplified Respiratory Questionnaire
VT	Vitality
WHO	Wold Health Organization
WHOQOL-BREF	World Health Organization Quality Of Life short version list
WTA	Willingness-to-Accept
WTP	Willingness-to-Pay

1 Chapter 1 – Introduction

Chronic obstructive pulmonary disease (COPD) is a persistent, irreversible, progressive disease exacting a heavy toll on patients and health systems and is a leading cause of morbidity and mortality worldwide [1-4]. In 2013, COPD affected more than 329 million people or nearly five (4.8%) percent of the population [5, 6] and was the third leading cause of death in the world after ischemic heart diseases and stroke, with a 3.1 million deaths in 2012 [7]. It resulted in an estimated economic cost of $2.1 trillion in 2010 [8]. It affected women and men equally due to increased usage of tobacco among women in high-income countries [9]. The increased prevalence of the disease in developing countries in recent years was related to the increasing smoking habit, a growing population and an aging population due to the epidemiological transition [10]. It has been postulated that the global burden of the disease to continue increasing as the risk factors remain unchanged [11]. At this rate, the number of worldwide deaths associated with COPD is predicted to increase by more than 30% over the next decade [12].

In regard of international evidence, COPD was estimated as the fourth leading cause of death in Canada and a major determinant of morbidity[13]. A 2013 Ontario study has shown that one in eight people would likely experience COPD in their lifetime [14]. Estimates also indicated that more than 10% of the adult population were affected by COPD and one in four adults over 35 would develop COPD in their lifetime [15]. In addition, it was a leading cause of health care utilization, including hospitalizations and emergency room visits [16]. In the United States, chronic lower respiratory disease, primarily COPD, was already the third leading cause of death [17]. In 2013, 15.7 million (6.4%) of the USA adults were estimated to have COPD [18]; however, more than 24 million Americans have evidence of impaired lung function [19]. In England, an estimation of 0.84 million people out of 50 million population of was diagnosed with COPD in 2005 [20]. A recent study in the United Kingdom, conducted by GOLD 2013,

showed that the overall prevalence was 33.3 per 1,000 persons [21]. Evidence showed that the prevalence of stage II or higher COPD was 10.1% (SE 4.8) overall, 11.8% (7.9) for men, and 8.5% (5.8) for women [15] and the overall pooled estimate odds ratio was 1.94 (95% CI 1.80-2.10) per 10-year increment [15].

Treatment of COPD patients imposes a considerable burden on health care services. Studies have shown that health-care costs for management of COPD correlated strongly with the disease severity; health-care cost in severe cases are two to three times higher than those with the moderate disease and 7.5 to 10-fold greater than the cost of managing of the mild disease [22, 23]. This strong correlation was primary because of the hospitalizations and specific ICU care. The mean number of annual emergency department visits ranged from 1.4 (GOLD stages I and II) [1] to 1.8 (GOLD stages III and IV) in COPD patients with an exacerbation [24]. The cost of ICU services to total health care cost is about 8.4% to 47.7% in mild to severe COPD disease [23].

It has been estimated that 14.5% (95% CI, 12.4%–16.6%) or one in seven Australians 40 years or over (1.45 million Australians [25]) have airflow limitation of their lungs [26]. This prevalence was 7.5% (95% CI, 5.7%–9.4%) for GOLD stage II or higher among people aged over 40 years and 29.2% (95% CI, 18.1%–40.2%) among those aged over 75 years [26]. This figure showed that symptoms and spirometric evidence of COPD were common among people aged ≥40 years and increased with age [26]. There were 4,761 deaths (4% of all deaths) attributed to COPD in 2006 [27], and 160,346 years of life were lost due to COPD in 2011 [28], this figure was 47,207 in 2003 [29]. COPD was the second leading cause of avoidable hospital admissions (282.6 out of 2,847.5 avoidable admission in 100,000 population) [30]. In 2006-2007, there were 52,560 hospitalizations with COPD as the principal diagnosis with an

[1] GOLD is a severity staging system for COPD, based on the greatest volume of air that can be breathed out in the first second of a breath (FEV_1). It has been in described in Natural History of COPD section in this chapter.

average length of stay of 7 days [27]. COPD is the fourth biggest killer of Australians and COPD is the 3rd leading cause of human and economic burden of disease (following coronary heart disease and stroke) [31]. It has been estimated that half of the Australian people over 40 years who has progressed sufficiently to where symptoms may already be present and affecting daily life, will not know they have COPD and therefore not taking the important steps to slow down the progression of the disease [26]. About half of COPD patients were still in the period of their productive lives. If an effective measure has not been taken into account to change the current trend, in 2050 an estimated of 4.5 million of Australian people will suffer from COPD, with 2.5 million having moderate to very severe COPD [32]. COPD goes largely unrecognised and under-diagnosed. Nearly 700,000 Australians have a mild form of COPD where symptoms may not yet be present [25]. Many of these will go on to develop more severe COPD. Australian health report in 2014 showed that COPD is more common in areas of lowest socioeconomic status than in areas with the highest status (4% compared with 2%) [33].

According to the report of Australian Lung Foundation, the relative risk (RR) of death attributed to COPD has been calculated equal to 3.2 times more than the Australian general population [34]. It has been assumed that, due to under-diagnosis and complications associated with comorbidities, the actual number of death from COPD is significantly lower than the attributable mortality estimate in the report [28]. Based on the Australian health report 2014, the death rate from COPD for males has decreased markedly over the past 40 years, with the age-standardised rate in 2011 less than one-third of that in 1970 falling from 95 to 30 per 100,000 populations [33]. In contrast, there was a small rise in the death rate for females over this period (from 13 to 18 per 100,000 populations). This may reflect differences in smoking prevalence and history among males and females [33].

1.1 Natural History of COPD

COPD is a progressive, irreversible inflammatory disease of lung tissue [35]. The progression rate may vary depending on risk factors such as continues exposure to noxious particles (e.g. tobacco smoke)[9, 35]. It is thought that exposure to environmental factors is the major underlying cause of COPD, with smoking being the most important risk factor [36-38]. COPD has different phenotype; it can represent itself in a variable combination of emphysema and chronic bronchitis [9, 39]. The major manifestation of disease is persistent expiratory airflow limitation leading to the following symptoms: shortness of breath with exertion, wheezing, and chronic productive cough [11, 40, 41]. The clinical course of COPD is highlighted by frequent exacerbations which are sudden deterioration of health condition and worsening respiratory symptoms that required a change in the medication [42]. Predictors of two or more exacerbations annually, in stable COPD, include older age, chronic mucus hypersecretion and decreased forced expiratory volume in the first second of expiration (FEV_1) [43]. It has been shown that hospitalization for COPD exacerbations escalate the risk of mortality regardless of baseline pulmonary function [44]. Patients suffering from other major diseases such as diabetes and coronary artery disease are more susceptible to be hospitalized for exacerbations [45].

Although a small degree of reversible pulmonary obstruction may be achieved in some COPD cases, in most the airway obstruction is close to irreversible [46]. Progression of COPD may be decelerated by smoking cessation and avoiding exposure to other harmful agents, but optimal management is proven to reduce exacerbations and enhance the quality of life [4, 47]. The diagnosis of COPD is based on the clinical symptoms and history of risk factors, confirmed by spirometry test [11, 41, 48]. There are several systems for severity classification of the COPD [11]; one of the most widely accepted is the Global Initiative for Chronic Lung Disease (GOLD) combined assessment criteria that are based on four aspects of COPD disease: current level of patient's symptoms, severity of the spirometric abnormality, exacerbation risk and presence of comorbidities [11]. Assessment of symptoms can be undertaken by using validated questionnaires, the recommended ones are COPD assessment Test (CAT) [49] and Modified

British Medical Research Council (mMRC). Spirometric assessment measures forced expiratory volume in one second which is the greatest volume of air that can be breathed out in the first second of a breath (FEV_1) after post-bronchodilator therapy [48]. According to the previous version of the GOLD severity classification which was only based on FEV1, there are four stages, ranging from mild to very severe (Table 1-1).

Table 1-1 GOLD COPD Severity classification, based on post-bronchodilator forced expiratory volume in one second (FEV_1)

Stage	Severity	FEV_1/FVC	FEV_1	Symptoms
I	Mild	< 0.70	FEV_1 ≥ 80% predicted	Symptoms may or may not be present Possible symptoms include a chronic cough and sputum production
II	Moderate	< 0.70	50% ≤ FEV_1 < 80% predicted	Shortness of breath on exertion A cough and sputum production are sometimes present
III	Severe	< 0.70	30% ≤ FEV_1 < 50% predicted	Greater shortness of breath, reduced exercise capacity, fatigue, and repeated exacerbations
IV	Very severe	< 0.70	FEV_1 < 30% predicted or FEV_1 < 50% predicted plus chronic respiratory failure	Respiratory failure, which may also lead to cor-pulmonale

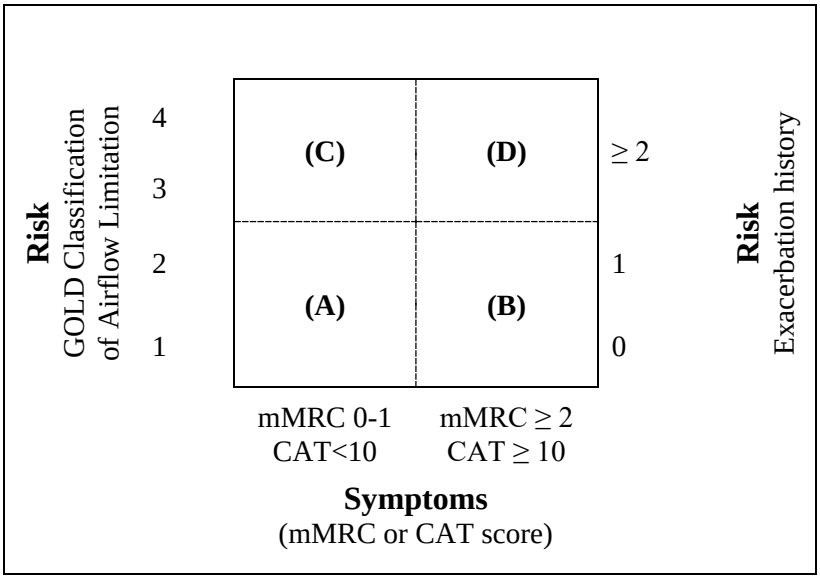
Adapted from Global Initiative for Chronic Lung Disease (GOLD) guideline: [50]

In a recent revision of the GOLD guideline, the association between FEV1, symptoms and patients quality of life impairment was assumed to be weak. Assessment of exacerbation risk reflects the risk of poor prognosis in COPD patients [51, 52]. And the reason is due to the effect of exacerbation on declining of lung function. Frequent exacerbation, more than two events annually, is well predicted by a medical history of previously treated events and is associated with increased risk of hospitalization and death [53]. Assessment of comorbidities is an important aspect of COPD management. COPD can impose itself as a leading factor to other multisystem chronic diseases including sarcopenia, nutritional abnormalities, metabolic disorders, osteoporosis, depression and anxiety, cardiovascular disease and lung cancer [54-

61]. Systemic inflammation is likely the key factor in the development of these concomitant diseases; in addition, an elevated level of biomarkers such as C-reactive protein is proven to be associated with an increased risk of comorbidities [62]. Comorbidities such as cardiovascular disease have a major impact on management, course of diseases, health care utilization and quality of life [11] and contribute to the vast majority of COPD deaths [63-65].

The new multi-attribute index of assessing severity disease and risk of exacerbation was released by GOLD guideline 2013 [11] (Figure 1-1), indicating the importance of comprehensive consideration of patient's situation. According to this index, absence of frequent exacerbations in past medical history or even absence of FEV_1 abnormality alone cannot predict a better chance of survival [34].

Figure 1-1 Approach to combined assessment of COPD severity



Adapted from Global Initiative for Chronic Lung Disease (GOLD) guideline: [11]
CAT: COPD Assessment Test; **mMRC**: Modified British Medical Research Council

At the end-stage, COPD patients are characterised by continuous deteriorating dyspnoea during daily life activities and even at rest [46]. Other symptoms such as, cough, loss of energy, insomnia, weight loss and difficulty in expectoration are seen. Depression, anxiety and

panic conditions are frequent. Patients become more dependent on hospital admission and intensive care [4, 46]. Predictors of survival factors for the end-stage COPD patients are current smoking, low body mass index, hypoxia and comorbidities [46, 66].

1.2 Social and economic burden of COPD

As a deliberating and chronic disease, COPD imposes a significant and substantial economic burden on individual and society. According to the Murray and Lopez 30-year disease projection [67], COPD is going to worsen as a third most common cause of death in the world by 2020. Continued tobacco use combined with the overall increase in life expectancy, which allows people to expose to COPD risk factors, are responsible for this progressive growth in COPD cases [1, 4]. Evidence showed that in the USA, COPD mortality has increased dramatically in men and women since 1964 [68]. The number of women dying from COPD now surpasses the number of men. It is suggested that women are more susceptible to develop severe COPD at younger ages [68]. The most recent smoking-related mortality assessment in the USA [69], which evaluated the gender-specific smoking mortality across three time periods (1959−1965, 1982−1988, 2000−2010) in seven large cohorts, showed that male and female current smokers had similar risk ratios for mortality from COPD (26.61 and 22.35 respectively) in the current period, while this risk ratio for women was almost half the risk in the time period 1982-1988 [69].

The economic burden of COPD can be categorized as direct and indirect costs. In 2010, almost 70,000 hospitalizations, 10.3 million outpatients visits, and 1.5 million emergency visits occurred for COPD in the USA [70]. As would be expected, there was a direct relationship between severity of COPD and the overall medical costs at the individual level [1, 71]. Hospitalization was the most important cost driver of COPD across all stages of the disease,

accounted for 45%-50% of the total direct costs of COPD [71, 72]. The importance of exacerbations on direct costs of COPD is alarming, there was a strong association between exacerbation and hospital admission [73]. In the USA, COPD made itself as one of the leading causes of hospital admission with more than one million patients' admission in 2012 [74]; at an average of US$ 11,195 per admission and more than US$ 40,000 if the patient needs mechanical ventilation [34]. Estimated medical costs incurred by people with COPD increased during recent years: US$37.2 billion in 2004 [75], US$42.6 billion in 2007 [76], and a project of US$49.9 billion in 2010 [77]. A recently published study by using the population-based US Medical Expenditure Panel Survey (MEPS) revealed that the average annual per person medical costs among person with COPD were US$9,800, comparing with the US$3,770 among those without COPD [78] in 2010. The total medical costs sustained by COPD patients were estimated US$101 billion [78]. After adjustment for demographic disparities and 11 medical comorbidities, the medical costs were US$ 32.1 billion. The costs increased by age and were higher among women (US$21.0 billion) than among men (US$11.1 billion) [78]. This study projected that national cost will increase to US$49.0 billion in 2020, representing an increase of 53% [78].

In Canada, the average total cost per patient ranged between CAN$2444.17 – CAN$4391.16 (patient perspective) and CAN$3910.39 – CAN$6693.37 (societal perspective) annually (accounting for inflation) [79]. The average cost per an acute COPD exacerbation ranged from CAN$718 – CAN$11,156 and the cost was found to increase with the severity of exacerbation [3, 80]. Studies showed the substantial effect of patient characteristics on COPD cost; female COPD patients incurred more costs compared to male patients (additional CAN$985 per patient from a patient perspective, CAN$1513 – CAN$2138 per patient from a societal perspective) [1, 81].

COPD is a major contributor to the work absenteeism [82-84]. It is estimated that 16.4 million days of absenteeism were due to COPD in 2010 in the USA [78], with an attributed cost of US

$3.9 billion. Thornton et al [85], revealed that COPD was associated with a decrease in the likelihood of employment of 8.6 percentage points (OR = 0.58, 95% CI 0.50-0.67). Furthermore, COPD was associated with a 3.9 percentage point (OR 2.52, 95% CI 2.00-3.17) increase in the likelihood of collecting Social Security Disability Insurance (SSDI), as well as a 1.7 percentage point (OR 2.87, 95% CI 2.02-4.08) increase in the likelihood of collecting Supplemental Security Income (SSI) [85]. This association was equal that of stroke and was larger than those of heart disease, cancer, hypertension, and diabetes [85].

In 2008, the total economic impact of COPD was estimated to be AUS $98.2 billion of which AUS $8.8 billion was attributed to financial costs and $89.4 billion to the loss of wellbeing [86]. Of the financial costs, a large proportion was due to the loss of productivity due to COPD, ie lower employment, absenteeism and the workplace impact of the premature death of Australians with COPD [86]. The direct cost to the Australian health care system was estimated to be $900 million with hospital use contributing the largest share of health spending (at around $473.1 million) [86]. Pharmaceuticals made up the next largest share at $147.3 million or 19.6% [86]. The remainder ($130.0 million or 17.3%) was made up of out of the hospital and other expenditure such as aged care homes, allied health professionals and research [86]. In terms of overall costs, COPD was more costly per case than cardiovascular disease, osteoporosis or arthritis [86].

1.3 Quality of life in COPD patients

The quality-adjusted life year (QALY) is routinely used as a summary measure of health outcome for economic evaluation, which incorporates the impact on both the quantity (life expectancy) and quality of life [87]. In order to generate QALYs, health utilities (or HR-QoL weights) are needed. Utility or Health State Utility Values (HSUV) are cardinal values that represent the strength of an individual's preferences for specific health-related outcomes [88]. These HSUV weights are derived from a valuation process by using cardinal preferences

measures such as time rating scale (RS), standard gamble (SG) and trade-off (TTO) methods, called holistic (or composite) instruments, through applying a specific algorithm or tariff to individual responses on the instruments which describe health states [89, 90]. During this process, members of the general population rank between 0 (representing death) and one (representing full health), the different health states, called as scenarios or vignettes, described by the instruments [91].

HSUV is measured on an interval scale with zero reflecting the state of health equivalent to death and one reflecting perfect health [92-94]. HSUV measures can bring complementary information on effectiveness. HSUV reflects not only the presence, frequency, or intensity of symptoms, abilities, or feeling as measured by psychometric instruments [95] but also represents an individual's preferred value for specific health states relative to full health, whether they are patients suffering from the condition in question, physicians, or the general population [96].

Several alternative approaches can be used to measure utility. They can be categorised as direct methods such as multi-attribute utility system instruments (MAUS), for example the Euro-Qol Group's EQ-5D [97], the Australian Assessment of Quality of Life AQoL [98-100], the 15D from Finland [101, 102], the Health Utilities Index version 2 or 3 from Health Utilities Index (HUI2 or HUI3) [103], and the UK's SF-6D [104-106]. MAUSs are feasible alternatives for holistic instruments and allow the rapid estimation of utilities in the context of a longitudinal trial [90]. This approach is capable of describing a wide range of health states and utility weights are attached to every possible state. This is normally done by measuring a limited number of health states and using these to calibrate a model which is then used to infer the utility values of every other health state in the 'descriptive system [107]. These generic (descriptive) preference-based measures are beneficial in facilitating to calculate QALYs for preceding cost-utility analysis; moreover, it can be used for comparison of HR-QoL across different health conditions [91]. Additionally, there is an indirect way to map HSUV from

disease-specific measures such as St. George Respiratory Questionnaire (SGRQ), or non-preference-based scales such as Visual Analogue Scale (VAS) and the commonly used SF-36 and SF-12 into one of the preference-based measures, using published transformation algorithms [108-110].

According to the recent published systematic literature review [111] (23 intsruments), and some added inputs (14 new instruments) from the systematic literature reviews conducted in this thesis, 37 instruments have been used to measure QoL in COPD patients: 16 disease-specific, 10 generic instruments and 11 utility measures (Appendix A Table A1). The table shows the instrument characteristics such as number of items, response options, completion time, and way of administration.

I have conducted a comprehensive literature review and meta-analysis of HSUVs in COPD reported by patient-level studies; which was accompanied by subgroup analysis. Chapter 2 was concentrated on this concept. The following aims were taken into consideration in this chapter:

(i) To conduct a meta-analysis of utility values estimated by using EQ-5D measure in the included studies, the most widely used instrument to determine mean utility scores for COPD,

(ii) To explore the degree of heterogeneity in the mean utility values across a variety of clinical and study characteristics.

1.4 Simulation models in COPD

Nowadays, decision-analytic models are used as a basis for economic evaluations of health care technologies and interventions. Modelling is a useful tool to combine available evidence and knowledge in order to estimate and extrapolate outcomes of the interventions in COPD. A central component of such analysis is the QALY, which is formed by the arithmetic product of

quantity and quality of life [87]. In the last three decades, several COPD progression models have been published [110, 112-129], with the first one in 1993 [130] and the most recent one in 2013 [131]. They substantially differ in model structure, inclusion of risk factors, epidemiology and comorbidities data, the length of the COPD health status and differentiation of exacerbation severities.

Chapter 3 and 4 of this thesis were concentrated on the COPD progression models and the following aims were taken into consideration:

(i) To review the main features of the published COPD progression models

(ii) To examine how decision model COPD studies follow good modelling practice recommendations

(iii) to conduct a systematic review of the utilities assigned to the different stages of COPD used in modelling studies and to compare these with summary measures from meta-analyses of available utility studies

(iv) To estimate the implications of differences between utility used in COPD models and estimates of the average utility for health states that were derived from a meta-analysis of the available literature of patient-derived values

1.5 Economic evaluation in COPD

Anxiety and depression are important psychological co-morbidities in COPD patients. The presence of anxiety and/or depression in COPD patients is associated with worse survival, earlier hospitalization, the length of hospital stay, exacerbation rates, decreased QoL and functional status [132, 133]. Anxiety and/or depressive symptoms were a risk factor independent of physiological measure of disease severity [134]. Cognitive behaviour therapy (CBT) is an effective treatment for anxious and depressive symptoms and disorders in the physically healthy, and there is evidence of its usefulness in patients with COPD [135-141].

But there is a scarcity of evidence regarding the cost-effectiveness of CBT in this group of patient with depression/anxiety comorbidities.

Chapter 5 and 6 were constructed to address this issue. The following aims were considered:

(i) To perform a systematic literature review on CBT-based intervention studies for anxiety and/or depression problem in patients with COPD

(ii) To conduct an economic evaluation alongside a clinical trial to assess, from a health service payer perspective, the cost-utility of the Telephone-Based Cognitive Behavioural Therapy (TB-CBT) compared with a standard care without CBT in COPD patient with psychological comorbidities.

1.6 Smoking as the major risk factor for COPD

Smoking remains the main risk factor for the progress of COPD [10, 99, 142]. It was responsible for 75% of the COPD disability-adjusted life year (DALY) in Australia [28]. Epidemiological and clinical evidence provides enough support to believe that smoking has a biologic linkage with respiratory tissue damages [143, 144]; smoking is associated with 70 percent higher all-cause mortality rates in men, a cause of lung cancer and laryngeal cancer in men and the most important cause of chronic bronchitis [68]. A national wide survey in the USA demonstrated that prolonged tobacco use was associated with respiratory symptoms and COPD, after controlling for current smoking behaviour [145]. Several studies [146, 147] investigated the relationship of smoking with self-perception of the quality of life [148-152]. Among participants older than 18 years old, current smokers were 70% more likely than never smoker to describe poor or fair health [150]. Ostbye et al [149] observed that a dose-response relationship existed for self-reported poor or fair health among current smokers compared with never smokers, on a scale of excellent, very good, good, fair or poor; compared with never smokers, current light smokers and current heavy smokers had odds ratios of 1.47 and 2.06 in

reporting fair or poor health respectively. Former smokers were more likely to have poor or fair health than never smoker [151], their health report was inversely related to the time of abstinence as well [149]. A decline in risk for reporting poor health, with increasing time since quitting was discovered by Arday et al, 2003 [152] . This study showed that the risk of reporting poor health in former smoker was similar to the never smoker after 15 years of abstinence. Former smokers who quit within the last three years were twice more likely than never smokers [152]. In Australia, a recent study [153] showed that current smokers had adjusted risk ratio of mortality of 2.96 (95% CI 2.69–3.25) compared to never-smokers and it was similar in men and women, 2.82 (95% CI 2.49–3.19) and 3.08 (95% CI 2.63–3.60) respectively. Mortality risk ratios increased with increasing smoking intensity, with around two- and four-fold in current smokers of ≤14 (mean 10/day) and ≥25 cigarettes/day, respectively, compared to never-smokers [153].

There is consistent evidence in the literature that smoking is related to the poor physical and mental function measured by SF-36 or SF-12 [152, 154-160]. Furthermore, current smokers showed more symptoms of psychological comorbidities than ex/non-smoking COPD patients [161]. In a cohort study, current smokers had lower physical and emotional functioning than never smokers and this score declined as the number of cigarettes per day increased [162]. Self-reported limited ability to work due to health problems was more than twice more common in current heavy smokers than in never smokers [149]. This figure was 73% increase in the risk of disability in current light smokers compared with never smokers. In a 3-years follow-up study [163], current smokers were at risk to experience a decline in mental and physical health over five times more than never smokers. Several studies revealed that the status of physical and mental functioning in ex-smokers tends to fall in between those of current and never smokers [155-157, 160, 164]. SF-36 physical and mental component summary scores improved with longer time since quitting [162].

Several other health and well-being measures have also been evaluated in relation to smoking; current smokers showed significant difficulty in walking a short distance than never smokers [149, 165]. Overall quality of life [166] and life satisfaction [151] appear to be reduced by smoking. Furthermore; it was revealed that smoking cessation may improve QoL scores [167, 168]. Never smokers were 29% more likely to have successful aging than smokers [169]; where successful aging was defined as having good cognitive, respiratory and cardiovascular functioning, and the absence of disability, mental health problems, and chronic disease.

By using Australian general population panel data, chapter 7 and the data presented in Appendix F to Chapter 7 were constructed to cover the effect of smoking habit and smoking transition on QoL. It aimed to address the following goals:

(i) To explore the effect of the transition from “Smoker” to “Ex-smoker” status (smoking cessation) on QoL and discover the temporal trajectories of QoL following this transition. This aim implies the following assumptions: a change in smoking status from smoker to ex-smoker is in accordance with the improvement of QoL (presented in Chapter 7).

(ii) To estimate the net values of health-related quality of life, as measured by SF-36 and Short Form-6 dimension (SF-6D), in different smoking status in the Australian general population (presented in Appendix F).

(iii) To find out which dimensions of QoL are affected by smoking, and if so, to which degree they were affected (presented in Appendix F).

2 Chapter 2 – Utility-based quality of life in Chronic Obstructive Pulmonary Disease (COPD); the challenge of heterogeneity: A systematic review and meta-analysis

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2.1 Abstract

Chronic obstructive pulmonary disease (COPD) has a considerable impact on quality of life and wellbeing of patients. Health state utility value (HSUV) is a recognized measure for health economic appraisals and is extensively used as an indicator for decision-making studies.

This study is a systematic literature review aimed to estimate mean utility value in COPD using meta-analysis and explore the degree of heterogeneity in the utility values across a variety of clinical and study characteristic.

The literature review covers studies that used EQ-5D to estimate utility value for patient level research in COPD. Studies that reported utility values elicited by EQ-5D in COPD patients were selected for random-effect meta-analysis addressing inter-study heterogeneity and subgroup analyses.

Thirty-two studies were included in the general utility meta-analysis. The estimated general utility value was 0.673 (95% CI 0.653 to 0.693). Meta-analyses of COPD stages utility values showed the influence of airway obstruction on utility value. The utility values ranged from 0.820 (95% CI 0.767 to 0.872) for stage I to 0.624 (95% CI 0.571 to 0.677) for stage IV. There was substantial heterogeneity in utility values: I^2=97.7%.

A more accurate measurement of utility values in COPD is needed to refine valid and generalizable scores of HSUV. Given the limited success of the factors studied to reduce heterogeneity, an approach needs to be developed how best to use mean utility values for COPD in health economic evaluation.

2.2 Introduction

The quality of life can be defined as an individual's perception of their position in life or life satisfaction. It is a complex entity incorporating physical health, psychological condition, independent living, social relationships and personal judgement [170]. Health status, functional status, well-being, quality of life (QoL), health-related quality of life (HR-QoL) and health state utility value (HSUV) are used interchangeably, but despite some differences in meaning, all these concepts are classified as patient-reported outcomes (PROs) [171]. In clinical practice, HSUV instruments are used to design clinical management guidelines, prioritizing patient complaints, screening possible problems and making decisions about treatment modalities.

Nowadays, Quality Adjusted Life Years (QALYs) are commonly applied as a measure of health in economic appraisals and are extensively used as outcomes for resource allocation decisions. Cost-effectiveness of medical intervention in Chronic Obstructive Pulmonary Disease (COPD) utilizes generic (such as EQ-5D, SF-36) [172, 173] or diseases-specific measures of QoL (such as St. George Respiratory Questionnaire [SGRQ] and Clinical COPD Questionnaire [CCQ]) [174, 175].

Generic instruments such as EQ-5D have the advantage of having value-sets which facilitate the quantification of patient-rated health status into measures of utility. This health-state utility reflects not only the presence, frequency or intensity of symptoms, abilities, or feeling as measured by psychometric instruments [95] but also represents a social or individual's preferred value or judgment for specific health states relative to full health [96, 176]. The EQ-5D is the most widely used generic measure across all diseases. In order to convert patient responses to the health descriptors used on the scale to a single index of HSUV, a preference-based set of weights is applied. These descriptors comprise five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). In EQ-5D-5L (version 2005),

each dimension has five levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. In addition to the descriptive system, the EQ-5D contains a 25 centimetres vertical visual analogue scale (EQ-VAS) that records the respondent's self-rated health, and can be used as a quantitative measure of health outcome. Based on societal preferences for health states, country-specific algorithms or tariffs have been generated [177, 178]. The minimally important clinical difference for the EQ-5D Index has been estimated to be: ±0.074 [179].

Overviews and meta-analyses of the utility-based quality of life have been undertaken in a variety of diseases including diabetes [180], various types of cancer [95, 181, 182], HIV/AIDS [183], chronic kidney disease [184], neuropathic pain [185] and orthopaedic diseases [186]. The main purposes of these reviews were to examine the applicability of these utility measures in patients with the diseases and to attempt to summarize mean utility scores according to the disease states.

The utility-based health-related quality of life in patients with COPD (necessarily together with their common comorbidities) has been measured using surveys of COPD patients, but values differ significantly across studies. For instance, the reported average utility values for stage II COPD range from 0.579 [187] to 0.929 [188]. Different methods of utility elicitation measures explain part of this variability. A recent study [176] examining the role for meta-analysis for utility values has noted that combining reported utilities can be problematic, due to for example valuation methods and have recommended only combining studies reporting utility values that are derived in a similar fashion (e.g. using the same generic quality of life instrument). For this reason, we confine our review to studies that employ the EQ5D to measure utility values for COPD patients. While this may reduce some variation, the diversity in COPD patient population characteristics may also have other imposed effects on the value of utility measured in different studies.

The first aim of this study is to conduct a meta-analysis using EQ-5D, the most widely used instrument to determine mean utility scores for COPD. The second aim of this study is to explore the degree of heterogeneity in the mean utility values across a variety of clinical and study characteristics.

2.3 Methods

2.3.1 Study selection

The literature review of HSUV studies in COPD comprises studies that use EQ-5D to estimate utility value for patient level research in COPD; simulation-based studies were not included.

Studies with the following criteria were included:

- studies on health utility that were published prior to July 2015,
- studies in which their sample population was specifically categorized as COPD as defined by standard criteria for COPD diagnosis and spirometric confirmation (should clearly be addressed in the methodology of included studies),
- English language studies and non-English language studies with English abstracts,
- abstracts (e.g. seminar abstracts) and reports if adequate data for analysis were provided.
- studies with more than 10 participants

Exclusion was applied for the following criteria:

- editorials /opinion pieces, letters, systematic reviews, and meta-analyses,
- studies that reported utilities from proxies, not individual participant data (e.g. reported by a family member or a health professional),

- studies that obtained utility estimates from the literature, if there was not enough information on the derivation of utility,
- studies that did not distinguish COPD from other types of obstructive pulmonary disease such as asthma or cystic fibrosis,
- papers using utility values mapped from other reported Quality of Life studies,
- Studies that reported utility values from non-stable and exacerbation state COPD patients.

Studies with different designs (i.e. case control, randomized control trial (RCT), cohort, etc.) were included. It is not always feasible to conduct utility data collection within a clinical trial, so utility data from non-clinical trial studies was also included. In order to eliminate the additive effect of studies using the same data source, the special effort made to only include the study with the largest sample size.

This systematic review followed MOOSE guideline for observational studies [189]. A search strategy was employed for MEDLINE database (Appendix 1) and was adapted for other databases. A hand search and citation-tracking were also conducted.

In order to ensure consistency in a literature review of utility elicitation methodology, general recommendations of the Peasgood et al [176] were followed.

EndNote X7.3.1 was used to download citation, and to identify and extract duplicate studies.

2.3.2 Search Methods

The systematic literature review on utility values for COPD was part of a wider systematic review of economic evidence on COPD, related pharmacological and psychological interventions and progression modelling for patients with COPD. The following electronic databases were searched for relevant articles: MEDLINE, EMBASE (for the period of 1898–

2015), Web of Science, CINAHL, ProQuest (which includes PsycINFO and other 61 databases), the Cochrane Library Database (which includes NHS Economic Evaluation Database, Health Technology Assessment Database, Cochrane Database of Systematic Reviews and other three databases), International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and Google Scholar. An attempt was made to decrease the likelihood of publication bias [190] by using dissertation abstracts, authors and websites of key academic institutions such as NICE (National Institute for Clinical Excellence), CCOHTA (Canadian Cooperating Office for Health Technology Assessment), SBU (The Swedish Council on Technology Assessment in Health Care), Health Economic Evaluations Database (HEED, ceased publishing in 2014) and the Cost-Effectiveness Analysis Registry at Tufts-New England Medical Centre.

2.3.3 Data extraction and management

Data from included articles were extracted into Excel and Stata spreadsheets. The following variables were obtained from each citation: principal author, year of publication, clinical characteristics and demographic of patients, the number of patients, country of origin, study design, data collection method, health state utility value measure and utility estimate (mean and standard deviation). In intervention studies, such as randomized control trials, baseline QoL value were used to avoid the potential effect of the intervention on the quality of life estimates. When a demographic or clinical factor splits intervention groups, the entire number of the whole was used where possible.

Assessment of study eligibility and extraction of information from each study were carried out by two independent reviewers.

2.3.4 Data analysis

In order to estimate a single mean utility score value for COPD, a meta-analysis was conducted. This was done for COPD as a general condition and for the stages of the disease separately. Point estimates and 95% Confidence Intervals (CI) for utility scores were calculated and displayed in forest plots. Possible publication biases were investigated using funnel plots. Meta-analysis was restricted to EQ-5D Index-elicited utility values, as this was the only utility measure that existed in sufficient numbers for it to be feasible to undertake a meta-analysis. This restriction avoided heterogeneity imposed by elicitation methodology diversity [176].

Meta-analysis was conducted with the command "metan" [191], using Stata version 13.1. The between-study variability was considered through incorporating random effects model and a mean of a distribution of true effects was estimated. Heterogeneity among the studies was measured using I2 statistic = 100% × (Q - df)/Q and 95% CI, indicating the proportion of observed variance due to real differences in utility scores rather than sampling error. Values of 30%–60%, 50%–90% and 75%–100% were considered as moderate, substantial and considerable heterogeneity. If standard errors of utility values were not reported, they were calculated from 95% confidence intervals or standard deviations, in accordance with the recommendation of Cochran handbook[2]. If any study did not present enough data for measuring standard error, it was excluded. "metabias" and "metafunnel" commands were used to perform the Egger regression asymmetry test for publication bias and draw the funnel plot [192, 193]. In order to demonstrate the influence of outlier studies on the overall meta-analysis "metaninf," command was used.

To conduct pre-specified subgroup analyses, study variables including clinical/participant and conduct of study factors were selected to define subgroups as follows: age, gender, FEV1%

[2] Standard deviation can be obtained from the standard error of a mean by multiplying by the square root of the sample size.
The standard deviation for each group is obtained by dividing the length of the confidence interval by 3.92, and then multiplying by the square root of the sample size.

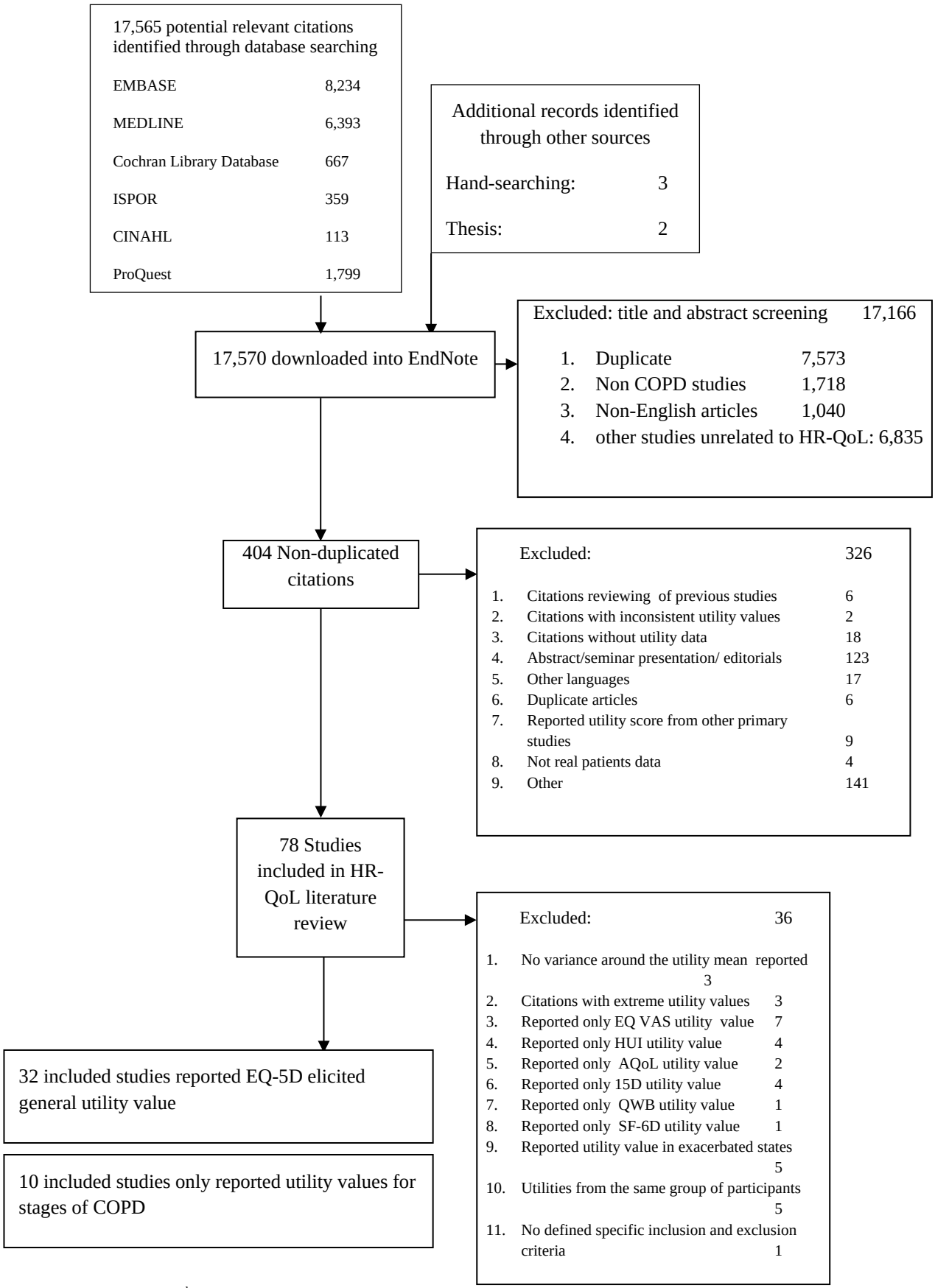
predicted, pack-years number of cigarette smoking, number of patients per study, Hospital Anxiety and Depression Scale (HADS) depression index, Borg dyspnoea index, Charlson comorbidity index, level of literacy, length of COPD and Body-mass index, airflow Obstruction, Dyspnoea, and Exercise capacity (BODE) index scores. Interaction tests were conducted only if there were at least two studies in each of the subgroups. Meta-regression was abandoned because of an insufficient number of studies in some subgroups. Interaction models to some subgroups of interest were applied and changes in magnitude or direction of the utility values and heterogeneity were reported. T-test and analysis of variance (ANOVA) were applied for comparing estimated utility means between subgroups.

2.4 Results

2.4.1 Study characteristics

The flow diagram (Figure 2-1) summarises the selection process of articles to be included. The initial pool of studies comprised 17,565 entries, including three citations captured through hand search [194-196]. Of these, 17,570 were excluded from scanning of abstracts. Full-text examination of 404 studies was conducted and, after incorporating inclusion and exclusion criteria, 78 studies were selected for review. Thirty-two studies with 49 observations gave estimates of general utility values for COPD population as a whole. Included articles in the meta-analysis are tabulated in Table 2-1 and Table 2-2. In order to adhere to Cochrane handbook recommendation on including studies with multiple intervention groups (multiple observations) in a particular meta-analysis, observations of a single study were combined to create a single value.

Figure 2-1 Flow diagram for papers included in meta-analysis *



*Last search was done in 25th June 2015

Table 2-1 Characteristics of studies included in meta-analysis

First author (year)	Country	Number of patients	Population	Comorbidities	Study design	Age		Male (%)	FEV1/FVC		FEV1 % pred		intervention
					Design	mean	SD or range		Mean	SD or Range	Mean	SD or range	
Wu et al, [197] 2015	China	678	COPD in community health centre & spirometry test	-	Cross-sectional	70.4	10.1	72.9	-	-	54.5	23.0	-
Wilson et al, [172] 2015	UK	In 73 Co 75	COPD registries, after spirometry tests	-	RCT	67.3 69.3	15.1 8.9	41.0 50.0	-	-	-	-	Pulmonary rehabilitation
Sundh et al, [198] 2015	Sweden	373	COPD registry in hospitals	Cardiovascular disease, Chronic bronchitis, Diabetes, Renal failure, depression	Cross-sectional	71.25	-	44.24	-	-	34.72.	-	-
Stoddart et al, [199] 2015	UK	In 128 Co 128	COPD registers in hospitals	-	RCT	69.4 68.4	8.8 8.4	25 35	-	-	44.0 40.0	18.8 17.0	Telemonitoring
McDowell et al [200] 2015	Ireland	In 55 Co 55	COPD registers in hospitals	-	RCT	69.8 70.2	7.1 7.4	41.8 45.5	-	-	45.5 43.4	13.7 11.3	Telemonitoring
Donohue et al, [201] 2014	Multi, 11 countries	Trial1 353 353 Trial2 349 348	COPD confirmed by spirometry	-	RCT	62.5 63.0 63.2 64.0	9.05 8.91 8.57 8.53	72 69 76 76	47.5 46.8 47.3 47.0	10.61 10.78 10.73 10.72	49.2 49.6 49.4 49.5	10.82 10.88 10.81 10.87	Pharmaceutical

Lin et al, [202] 2014	USA	670	COPD patients from a multicentre study, after spirometry test	Hypertension, Diabetes, Cancer, Dementia, Depression	Cross-sectional	68.5	10.4	57.8	-	-	-	-	-
Ferreira et al, [203] 2014	Portugal	72	COPD registers in hospital recruited by pneumologists	-	Cross-sectional	68.6	9.5	97.2	-	-	-	-	-
Chen et al, [204] 2014	Hong Kong	154	COPD out-patient respiratory specialist clinic	Hypertension, Heart disease, diabetes, cancer liver disease …	Cross-sectional	42.9	8.1	98.7	-	-	32.7	9.2	-
Gillespie et al. [205] 2013	Ireland	In 178 Co 172	COPD general practice + spirometry test (diagnosed as defined as GOLD guidelines)	-	RCT	68.4 68.8	10.3 10.2	61.6 65.7	55.4 52.9	11.9 11.5	59.7 57.6	13.8 14.3	structured education pulmonary rehabilitation
Browne, et al, [206] 2013	UK	In 73 Co 75	COPD (Diagnosed by physician + spirometry test)	-	RCT	69.3 67.3	8.9 15.1	50.0 41.0	-	-	41 *	16 *	Maintenance pulmonary rehabilitation
Kruis et al, [207] 2013	The Netherlands	1086	COPD diagnosed (GP medical records) & spirometry test	Hypertension, Diabetes, Depression, Cardiovascular disease	Cluster RCT	68.3	11.2	53.9	-	-	67.8	-	Integrated COPD management
Taylor et al, [208] 2012	UK	In 61 Co 30	COPD registers or community respiratory clinic & spirometry test	-	RCT	69.0 70.5	9.8 10	51.28 34.2	0.55	0.15	53.9	22.6	Self-Management
Garcia-Polo , et al [209] 2012	Spain	All 115 HR 64 Co 51	Stable COPD, & spirometry test	Depression, anxiety	Cross-sectional	66.90 66.6 67.2	8.70 9.4 8.0	93.00 93.8 92.2	46.40	12.80	43.70 39.6 46.9	15.10	-
Naberan, et al [210] 2012	Spain	4552	Stable COPD & spirometry test	No comorbidity	Cross-sectional observational	67.10	10.00	83.30	59.00	20.00	48.30	21.00	-

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Egan, et al [211] 2012	Ireland	47	Stable COPD	No comorbidity	longitudinal	-	-	-	-	-	46.8	16.6	Rehabilitation
Starkie et al [109] 2011	Multi country	3640	COPD registers & spirometry test	-	RCT - TORCH	64.70	8.40	71.00	-	-	-	-	Pharmaceutical
Fletcher, et al [187] 2011	Multi, 6 countries	2426	COPD diagnosed by physician, no spirometry	Hypertension, arthritis, anxiety, depression, diabetes	Cross-sectional	56.4		49.00	-	-	-	-	-
Janssen, et al [212] 2011	The Netherlands	105	COPD out-patient clinic & spirometry test	-	Cross-sectional	66.30	9.20	61.90	-	-	34.10	13.50	-
Khdour, et al [213] 2011	Ireland	In Co	COPD out-patient clinic & spirometry test	-	RCT	66.20 66.60	9.80 9.10	42.20 45.00	56.50 56.10	9.50 10.80	53.40 51.30	16.00 16.30	Self-management program
Pickard, et al [214] 2011	USA	120	Diagnosed COPD & spirometry test	-	Cross-sectional	71.20	10.30	98.30	59	22	58.40	24.80	-
Agh T, et al [215] 2011	Hungary	170	Outpatient COPD diagnosed & spirometry test	-	Cross-sectional	63.83	11.24	41.8	-	-	64.21	17.34	-
Heyworth, et al [216] 2009	UK	280	COPD in general practice. No spirometry test	-	Cross-sectional	-	-	-	-	-	-	-	-
Miravitlles, et al [217] 2009	Spain	827	Stable COPD patients Primary Care & spirometry test	-	Cross-sectional	69	10	86.5	56.9	10.1	54.6	17.7	-
Skoupá J. et al [218] 2009	Czech Republic	Co: 90 In: 90	In and outpatient	CHD, Depression Diabetes	Cross-sectional	65.7 67.1	10.9 10.4	69 61	-	-	-	-	-
Ringback, et al [196] 2008	Denmark	218	COPD outpatients & spirometry test	Musculoskeletal Cardiac disease	Cross-sectional	69.10	8.10	31.90	-	-	34.10	12.20	Rehabilitation
Stellefson M, et al [219] 2008	USA (control)	41	COPD registers in health clinic	-	RCT	61.51	6.29	39	-	-	-	-	Education
Punekar, et al [220] 2007	Multi 5 EUs	1381 1322	COPD in general and specialist clinic	-	Cross-sectional	66.00 66.00	0.29 0.31	66.00 71.00	-	-	-	-	
Rutten- van Molken et al [221]	Multi	1235	UPLIFT trial & spirometry	-	RCT	64.50	8.40	73.00	-	-	48.77	12.19	Pharmaceutical

2006													
Decramer M et al [222] 2005	Multi Eu	256 (a) 267 (b)	COPD patients-Clinic	-	RCT	62 62	8 8	79 79	-	-	57 57	9 9	Pharmaceutical
Brazier, et al [223] 2004	UK	225 230	COPD outpatient clinic & spirometry test	-	Cross-sectional	67.00	10.40		-	-	-	-	-
Monninkhof et al, [224] 2004	The Netherlands	127 121	Outpatient clinic & spirometry test	-	RCT	65 65	-	85 84	-	-	56.1 58.4	-	Self-management program

HR: high resource group; **Co**: control group; **EU**: European countries; **In**: Intervention group; **RCT**: randomised Control Trial; **Multi**: multicounty; **FEV1% pred:** predicted amount as a percentage of the forced expiratory lung volume in one second;
* value before randomization,

Table 2-2 Utility values estimated in included studies

First author (year)	Health quality of life measure Instrument (number of patients)	Disease Severity	Average estimated health-related quality of life (Utility value)		Data collection method	Inclusion & exclusion criteria
			Mean	*SD/SE*		
Wu et al, [197] 2015	EQ-5D Index EQ VAS	I, II, III, IV	0.726 66.6	0.150 16.2	Interview	
Wilson et al, [172] 2015	EQ-5D Index In Co	I, II, III, IV	0.6 0.7	0.3 0.2	Interview	>35 yrs, physician Labelled diagnosis of COPD, emphysema or chronic bronchitis, >20 pack-year smoking history, FEV1of <80%.
Sundh et al, [198] 2015	EQ-5D Index EQ VAS	III, IV	0.6887 56.5137	0.2749 23.0107	Interview	
Stoddart et al, [199] 2015	EQ-5D Index In Co	I, II, III, IV	0.4454 0.4868	0.0301 (SE) 0.0211 (SE)	Interview	No other lung disease
McDowell et al [200] 2015	EQ-5D Index In Co EQ VAS In Co	II, III	0.49 0.52 50.1 45.5	0.35 0.30 18.0 23.1	Interview	diagnosis of moderate to severe COPD (GOLD stage 2 or 3 & at least two admissions in past 12, months, not having any other respiratory disease
Donohue et al, [201] 2014	EQ-5D Index Trial1 In Co Trial2 In Co	II, III	0.70 0.68 0.70 0.70	0.228 0.243 0.229 0.225	Interview	
Lin et al, [202] 2014	EQ-5D Index EQ VAS	I, II, III, IV	0.79 70.6	0.15 19.6	Interview	Diagnosed as COPD – GOLD guideline), Spirometry test data, completion of questionnaires
Ferreira et al, [203] 2014	EQ-5D Index SF-6D	Not specified	0.86 0.81	0.17 0.12	Self-administered	-

Chen et al, [204] 2014	EQ-5D Index SF-6D (UK) EQ-VAS	III, IV	0.644 0.629 55.28	0.306 0.133 20.42	Interview	FEV1 30-49 % & < 30%
Gillespie et al. [205] 2013	EQ-5D Index	II, III	0.762 0.801	0.252 0.232	-	FEV1 ≥ 30% and ≤ 80%, FEV1/FVC < 70%
Browne, et al, [206] 2013	EQ-5D Index	Not specified	0.6 0.7	0.3 0.2	Interview	> 35 yrs, FEV1 <80%, no significant comorbidities, participated in at least 60% of the session of the initial PR programme
Kruis et al, [207] 2013	EQ-5D Index EQ VAS	I, II, III, IV	0.74 67.0	0.26 17.4	Interview	Exclusion criteria: terminally ill. dementia, cognitive impairment, alcohol or drug abusers, not understanding Dutch
Taylor et al, [208] 2012	EQ-5D Index In Co	II, III, IV	0.73 0.76	0.04 0.04	Self-administered	>35 yrs, FEV1/FVC <0.7, FEV1 <80%, Exclusion criteria: life-threatening comorbidity, psychological impairment, involvement in the previous self-management, lacking English fluency
Garcia-Polo , et al [209] 2012	Global EQ-5D Index EQ VAS High resource EQ-5D Index EQ VAS Control EQ-5D Index EQ VAS	I, II, III, IV	0.72 58.6 0.64 56 0.82 61.9	±0.31 ±20.1 ±0.35 ±0.22 ±0.19 ±21.2	Interview	General (>40 yrs, Diagnosed COPD Stable COPD, Current or former smoker ≥10 pack-yrs) High RU (history of admission, 2 ER visits, 2 clinic visits in last year)
Naberan, et al [210] 2012	EQ-5D Index EQ VAS	I, II, III, IV	0.7 59.3 9.4	0.3 16.5 4.7	Interview	>40 yrs, Diagnosed COPD, stable No comorbidity
Egan, et al [211] 2012	EQ-5D Index	Not specified	0.7	±0.3	Not specified	Diagnosed COPD, stable, no Exacerbation in last month, no comorbidity
Starkie et al [109] 2011	EQ-5D Index	II, III, IV	0.73	0.23	Not specified	Confirmed COPD

Utility-based quality of life

Fletcher, et al [187] 2011	EQ-5D Index	I, II, III	0.636	0.007 (SE)	Face to face or telephone Interview	45-67 yrs, diagnosed COPD, Current or former smoker ≥10 pack-yrs) or biomass exposure, under prescription
Janssen, et al [212] 2011	EQ-5D Index EQ VAS AQoL	III, IV	0.51 62.9 0.46	0.33 14.0 0.28	Not specified	Diagnosed COPD, no hospitalization 4 weeks, later on, no nursing home
Khdour, et al [213] 2011	EQ-5D Index In Co	I II, III, IV	 0.465 0.485	 0.301 0.330	Not specified	>45 yrs, Diagnosed COPD (>1 yr), FEV1 <30–80%, no CHF, no learning difficulty, no severe mobility problem, terminal illness
Pickard, et al [214] 2011	EQ-5D Index EQ VAS	I, II, III, IV	0.63 65.3	0.27 18.9	Not specified	Diagnosed COPD
Agh T, et al [215] 2011	EQ-5D Index	I, II, III, IV	0.55	0.21	Not specified	>40 yrs, Diagnosed COPD No asthma, allergic rhinitis, lung operation, heart failure, liver failure, renal failure
Heyworth, et al [216] 2009	EQ-5D Index EQ VAS	Not specified	0.53 57.5	0.35 19.8	Self-administered Postal survey	
Miravitlles, et al [217] 2009	EQ-5D Index EQ VAS	I, II, III, IV	0.64 55.81	0.23 16.83	Interview face to face	>40 yrs, after exacerbation, Current or former smoker ≥10 pack-yrs), not admitted, excluding asthma, no significant cognitive problems
Skoupá J. et al [218] 2009	EQ-5D Index Co In EQ VAS Co In	II, III, IV	0.582 0.377 71.5 37.1	0.176 0.229 18.7 17.7	Interview	-
Ringback, et al [196] 2008	EQ-5D Index EQ VAS	II, III, IV	0.759 58.6	0.174 16.6	Not specified	Stable COPD patients, FEV1 <80% no significant cardiac or cognitive problems
Stellefson M, et al [219] 2008	EQ-5D Index EQ VAS	Not specified	0.68 46.07	0.57 17.83	Not specified	> 50 yrs, Clinical diagnosis of COPD Presence of dyspnea, No formal COPD self-management education exposure within the last 6 months

Punekar, et al [220] 2007	EQ-5D Index (a) (b)	I, II, III, IV	0.70 0.68	0.68-0.71 0.66-0.69	Not specified	40-75 yrs, FEV1 40-70% ,
Rutten- van Molken et al [221] 2006	EQ VAS EQ-5D Index	I, II, III, IV	45.00 0.76	16.98 0.21	Not specified	>40 yrs , Current or former smoker ≥10 pack-yrs, Diagnosed COPD
Decramer M et al [222] 2005	EQ-5D Index (a) (b)	II, III	0.76 0.79	0.22 0.19	Interview face to face	
Brazier, et al [223] 2004	EQ-5D Index SF-6D	I, II, III, IV	0.540 0.572	0.309 0.112	Not specified	Exclusion criteria: Other diseases like asthma, fibrosis, and cancer FEV1 >80%
Monninkhof et al, [224] 2004	EQ-5D Index (a) (b)	II, III, IV	0.81 0.82	0.017 0.017	Not specified	40-75 yrs, FEV1 ≤ 80%

COPDSS: COPD Severity Score; **PCS** & **MCS**: Physical (PCS) and Mental (MCS) component; **Co**: control group; **In**: intervention group; **SD**: Standard Deviation; **SE**: Standard Deviation;

Seventeen studies reported utility values for some COPD stages (including ten studies which only reported utility values for stages of COPD)Table 2-3). One study [187] used British Thoracic Society (BTS) staging system based on Medical Research Council (MRC) dyspnoea scale. Because of similarity in the definition of stages I, II and III in this scaling with stages II, III, and IV of GOLD staging system respectively, the equivalent utility values were incorporated in the meta-analysis. One study [225] used American Thoracic Society staging system (ATS) 1987. Due to the similarity in the definition of stages II (moderate) and III (severe) in this scaling with stages III and IV of GOLD staging system respectively, the equivalent utility values were incorporated in the meta-analysis. One study [109] followed the GOLD staging definition but it merged stages I and II of COPD patients into one single moderate (II) stage and attributed one single utility value for these groups. The utility value of stage II of this study was omitted from meta-analysis. In one study [220] the 'severe' (GOLD-stage III) and 'very severe' (GOLD-stage IV) subsets were merged into one single 'severe' (stage III) subset. The utility value of stage III of this study was omitted from meta-analysis.

2.4.2 Approaches and measures in COPD

Three studies (four observations) were omitted [195, 226, 227] from the final analysis due to reporting very extreme EQ-5D elicited utility values (<0.008 & >0.96). Attempts were made to contact these authors but the explanations provided did not fully clarify the reasons for the extreme values. The number of participants for general utility scores ranged from 41 to 4803, with an average of 779. Of these, 63.62% were male and the weighted average age was 66.0 years. The weighted average FEV1% predicted was 45.61 (95% CI 49.518 to 50.103) which indicated severe airflow obstruction according to GOLD guidelines (2011) [228]. Mean pack per year smoking cigarette was 44.90. Identifying specific COPD comorbidities were not possible. Five studies reported Charlson comorbidity index.

Table 2-3: Values of utility according to the Spirometry staging and COPD severity staging system in included studies

First Author (year)	Utility Instrument	COPD severity staging system	GOLD stages (SD) [range] "SE"			
			Stage I	Stage II	Stage III	Stage IV
Wu et al, [197] 2015	EQ-5D Index EQ VAS	GOLD	0.786 (0.085)	0.734 (0.158)	0.691 (0.155)	0.655 (0.151)
Kim SH et al, [229] 2014	EQ-5D Index EQ VAS	GOLD	0.83 "0.04"	0.88 "0.02"	0.81 "0.03"	0.60 "0.04"
Kim ES et al, [230] 2014	EQ-5D Index	GOLD	0.906 "0.006"	0.912 "0.005"	0.857 "0.018"	0.780 "0.071"
Jodar-Sanchez et al, [231] 2014	EQ-5D Index EQ VAS	GOLD	-	-	-	0.55 (0.33)
Samyshkin, et al,[131] 2013	EQ-5D Index	GOLD	-	-	0.751 [0.738-0.765]	0.657 [0.635-0.678]
Solem, et al [232] 2012	EQ-5D Index	GOLD	-	-	0.701 (0.182)	0.593 (0.236)
Asukai, et al [194] 2012	EQ-5D Index	GOLD	0.82 [0.8-0.84]	0.801 [0.794-0.809]	0.774 [0.767-0.782]	0.743 [0.730-0.756]
Fletcher, et al [187] 2011	EQ-5D Index	BTS	0.836 (0.007)	0.579 (0.009)	0.409 (0.015)	-
Pickard, et al [214] 2011	EQ-5D Index *(UK* value *set)* *(US value set)*	GOLD	0.73 (0.19) 0.80 (0.13)	0.59 (0.32) 0.70 (0.21)	0.63 (0.25) 0.72 (0.19)	0.63 (0.24) 0.72 (0.16)
Starkie, et al [109] 2011	EQ-5D Index	GOLD	-	0.752(0.22)	0.708(0.23)	0.672(0.22)
Menn, et al [233] 2010	EQ-5D Index SF-6D	GOLD	-	-	0.62 (0.26) 0.61 (0.13)	0.60 (0.26) 0.54 (0.08)

Utility-based quality of life

Punekar, et al [220] 2007	EQ-5D Index (a) (b)	GOLD	0.77 [0.73-0.81] 0.68 [0.64-0.72]	0.68 [0.626-0.72] 0.72 [0.69-0.75]	0.62 [0.56-0.68] 0.64 [0.61-0.67]	-
Rutten-van Molken, et al, 2007 *(The European journal of health economics)*[221]	EQ-5D Index	GOLD	-	0.809 “0.008”	0.762 “0.009”	0.655 ”0.024”
Rutten-van Molken, et al, 2006 *(Chest Journal)*[221]	EQ-5D Index *(UK* value *set)* *(US* value *set)*	GOLD	-	0.787 [0.771-0.802] 0.832 [0.821–0.843]	0.750 [0.731-0.768] 0.803 [0.790–0.816]	0.647[0.598-0.695] 0.731 [0.699–0.762]
Stahl, et al [234] 2003	EQ-5D Index	GOLD	0.84 (0.15)	0.73 (0.23)	0.74 (025)	0.52 (0.26)
Spencer, et al, [225] 2005	EQ-5D Index	ATS	0.81 “{0.02”	0.72 “0.03”	0.67 “0.05”	-
Borg, et al,[235] 2004	EQ-5D Index	GOLD	0.8971 (0.1117)	0.7551 (0.2747)	0.7481 (0.2991)	0.5493 (0.3129)

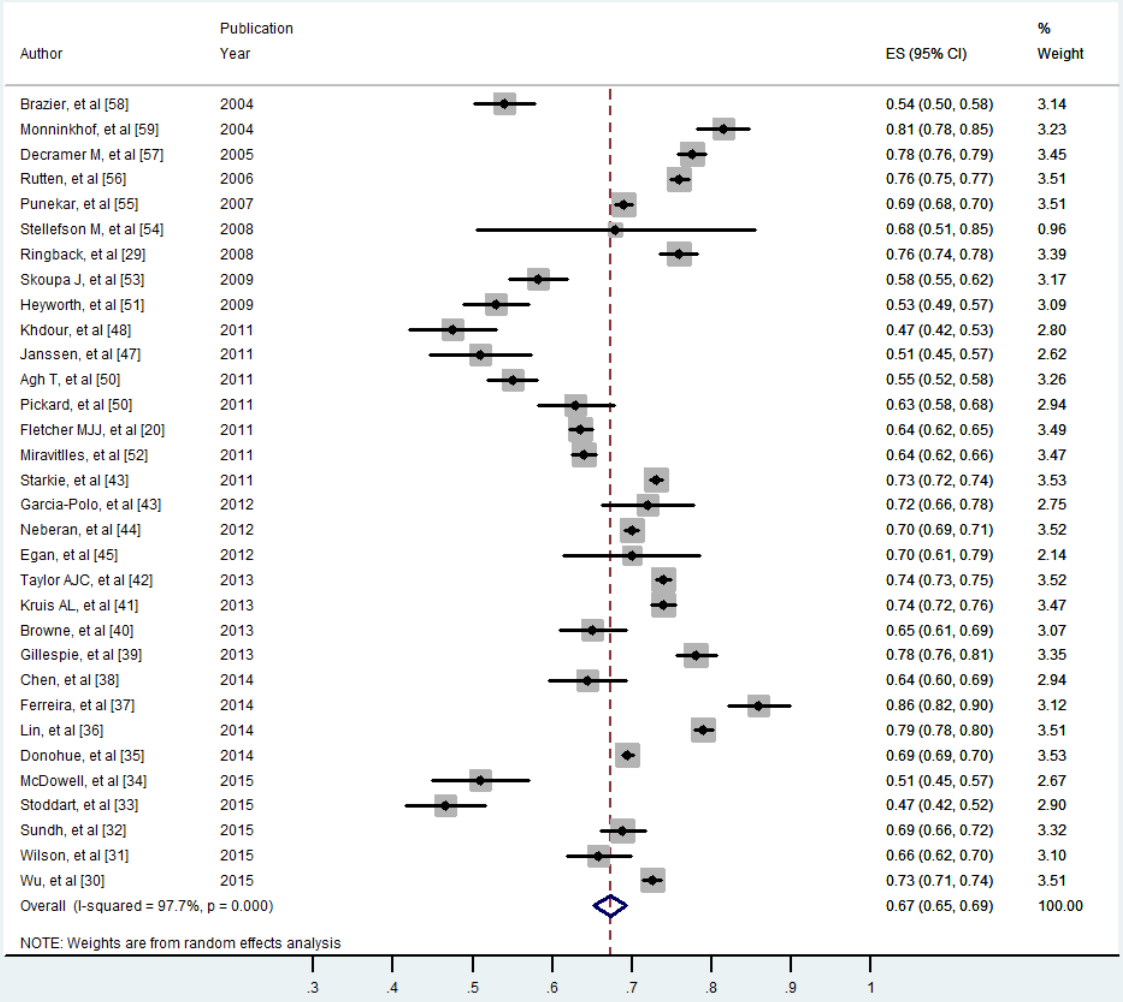
EQ-5D, EuroQol 5D: European Quality of Life questionnaire; **SF-12:** Short-Form Health Survey-12; **SF-36**: Short-Form Health Survey-36; **VAS**: visual analogue scale; **GOLD:** Global Initiative for Chronic Obstructive Pulmonary Disease**; ATS:** American Thoracic Society staging system**; ERS:** European Respiratory Society**; BTS:** British Thoracic Society

2.4.3 Meta-analysis

Forest plot: Figure 2-2 represents 32 utility values ordered by date of publication. The mean utility value estimated from random effect meta-analysis was 0.673 (95% CI 0.653 to 0.693). There was substantial heterogeneity in the utility values: I2 (variation in ES attributable to heterogeneity) = 97.7%, heterogeneity chi-square = 1348.12, degree of freedom = 31, p <0.001 and estimate of between-study variance Tau-squared = 0.0029.

Funnel plot: There was evidence of potential publication bias in this meta-analysis based on

Figure 2-2 Forest plot (random effect) of utility values for COPD patients, general utility values, effect size



Begg's funnel plot (Figure B1) and on Egger's test (p-value <0.001) but it should be noted that when between-study heterogeneity is large, none of the bias detection tests work well [236]. In addition, as health utilities are often secondary outcomes in the individual studies, result of the funnel plot is not relevant. Test of influence of an individual study on the overall meta-analysis estimate, "metaninf", did not show significant outliers

2.4.4 Subgroup analyses -interaction tests

The mean utility values for each state of COPD disease estimated from random effect meta-analysis are presented in Table 2-4 & Figure 2-3. The estimated utility value for stage I was 0.820 (95% CI 0.767 to 0.872) and the value constantly declined by increasing the severity of disease; 0.782, 0.721 and 0.624 for stages II, III, and IV respectively. Tests of difference between estimated utility means (Table 2-5) rejected the hypothesis of equality of means between stages of COPD, especially between stages II against III and stages III against IV.

Table 2-4 Estimated mean utility values in general and four stages of COPD (%95 confidence interval)

	Utility value /effect size (95% CI)	Heterogeneity chi-squared /Cochran's Q test			I^2 Heterogeneity statistics	Tau - squared
		χ^2	df	P value		
General utility value *	0.673 (0.653 - 0.693)	1348.12	31	<0.001	97.7%	0.0029
Stage I	0.820 (0.767 - 0.872)	254.29	7	<0.001	97.2%	0.0041
Stage II	0.782 (0.741 - 0.823)	563.78	10	<0.001	92.9%	0.0013
Stage III	0.721 (0.688 - 0.753)	639.18	14	<0.001	97.9%	0.0035
Stage IV	0.624 (0.571 - 0.677)	516.10	14	<0.001	97.9%	0.0099
Overall stages †	*0.724 (0.700 – 0.749)*	*3481.83*	*48*	*<0.001*	*98.6%*	*0.0067*

* the value that was measured in the general population of COPD patients irrespective of their stages
† the overall stages utility value is the result of pooled effect sizes of meta-analyses of utility scores in stages

Figure 2-3 Forest plot (random effect) of utility values for COPD, stages utility, effect size

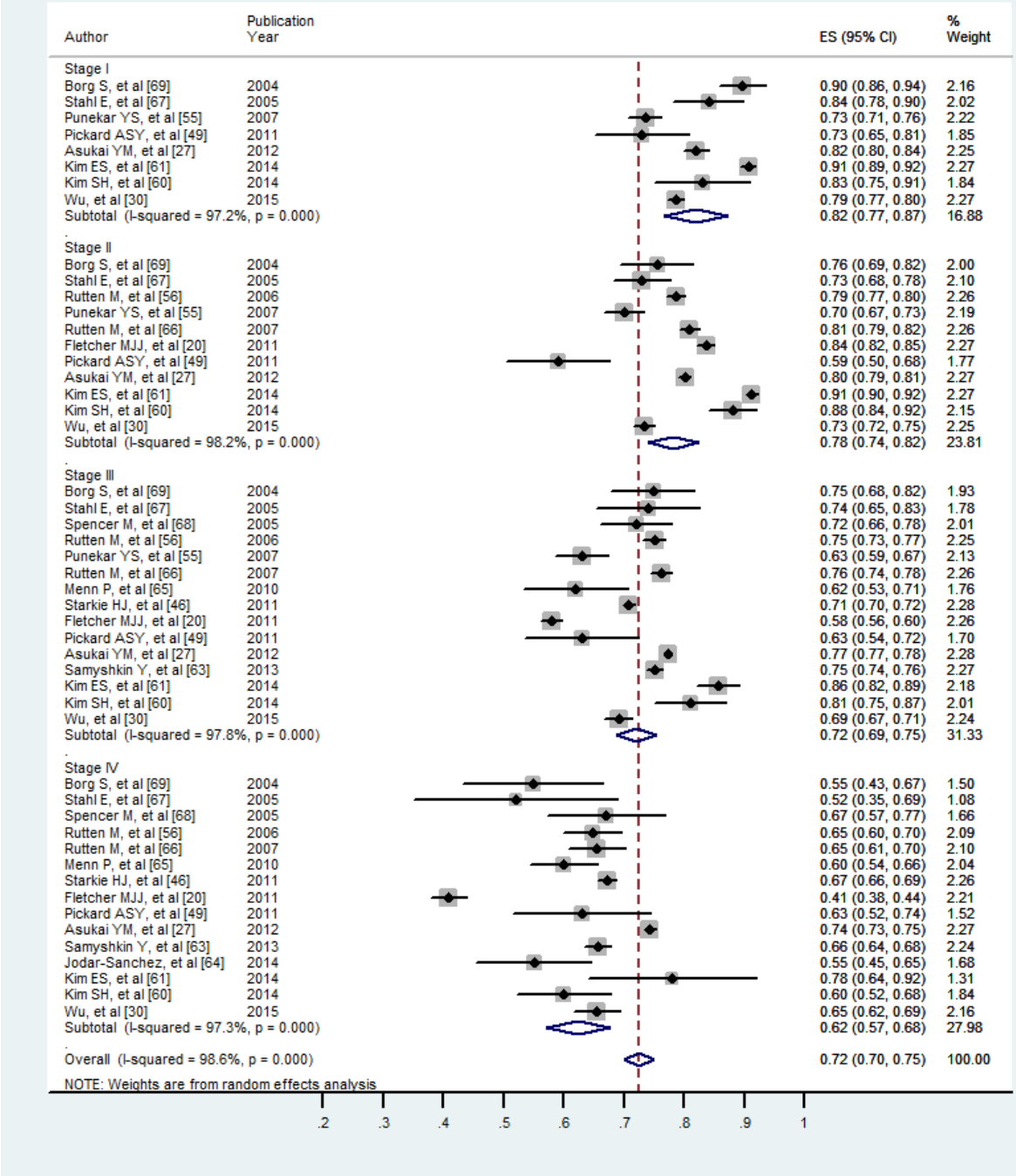


Table 2-5 Difference between estimated utility value means in subgroups

One-way ANOVA analysis of variance for mean estimated utility by COPD stages	SS	df	MS	F statistics	P value
Between groups	0.2537	3	0.0846	12.40	<0.001
Bartlett's test for equal variances: chi2(3) = 1.1370 Prob>chi2 = 0.768					

Two-sample t test with equal variances	diff	SE	P value Ha: diff <0	P value Ha: diff !=0	P value Ha: diff >0
Stage I / Stage II	0.042	0.0373141	0.862	0.276	0.138
Stage II / Stage III	0.058	0.032487	0.956	0.088	**0.044**
Stage III / Stage IV	0.10	0.0306422	0.998	**0.004**	**0.002**
Study type: RCT / cross-sectional	0.07	0.0451579	0.931	0.138	0.069
Cigarette: 35-45 Pack yr / 46-55 Pack yr	0.06	0.0457979	0.906	0.188	0.094
FEV1 30-49% / FEV1 50-80%	0 006	0.0505905	0.456	0.912	0.544
Age: < 64 / 65-69	0.016	0.0485167	0.704	0.740	0.297
Year-of-publication					
<2008 / 2008-2011	0.130	0.0427302	0.996	**0.0088**	0.0044
2008-2011/ 2012-2014	0.142	0.031917	**0.0002**	**0.0003**	0.9998
2012/2014 / >2014	0.119	0.0439269	0.9916	**0.0168**	**0.0084**

df: degree of freedom; **SS**: Sum of the Squares; **SE:** Standard Error; **MS:** Mean Squire; **FEV1% pred:** predicted amount as a percentage of the forced expiratory lung volume in one second;

Characteristics of study populations. After performing pre-specified subgroup analysis (conditional on the availability of data), there was no evidence of a difference in the heterogeneity of estimated utility value with age groups of the patients, which was available for all the included studies (Table 2-5). Some evidence in favour of the effect of study type and cigarette pack-per-year on estimated utility mean were captured (one-tailed T-test, Table 2-5).

Table 2-6 Results of interaction tests for subgroup analyses

Group		Utility value /effect size (95% CI)	Heterogeneity chi-squared /Cochran's Q test			I^2 Heterogeneity statistics	Tau-squared
			χ^2	df	P value		
Study type	RCT	0.681 (0.654-0.707)	429.11	12	<0.001	97.2%	0.0020
	Cross sectional	0.669 (0.638-0.700)	873.45	18	<0.001	97.9%	0.0044
Pack yrs	35-45 Pack yr	0.711 (0.672-0.751)	344.46	5	<0.001	98.5%	0.0024
	46-55 Pack yr	0.651 (0.698-0.703)	306.75	6	<0.001	98.0%	0.0046
	Not reported	0.665 (0.634-0.696)	681.17	18	<0.001	97.4%	0.0043
FEV1 % pred	FEV1 30-49%	0.658 (0.629-0.687)	293.19	11	<0.001	96.2%	0.0022
	FEV1 50-80%	0.658 (0.592-0.725)	350.79	6	<0.001	98.3%	0.0078
	Not reported	0.693 (0.661-0.725)	661.61	12	<0.001	98.2%	0.0031
Stages included in the studies	I, II, III, IV	0.682 (0.641-0.723)	435.77	8	<0.001	98.2%	0.0037
	I, II, III	0.663 (0.610-0.716)	37.53	1	<0.001	97.3%	0.0014
	II, III	0.655 (0.585-0.724)	212.10	4	<0.001	98.1%	0.0058
	II, III, IV	0.698 (0.657-0.738)	196.50	5	<0.001	97.5%	0.0023
	III, IV	0.618 (0.524-0.712)	26.07	2	<0.001	92.3%	0.0063
	Not specified	0.670 (0.584-0.757)	242.13	6	<0.001	97.5%	0.0124
Age	< 64	0.692 (0.654-0.731)	381.02	6	<0.001	98.4%	0.0023
	65-69	0.678 (0.647-0.708)	814.64	17	<0.001	97.9%	0.0040
	> 70	0.613 (0.516-0.709)	28.44	2	<0.001	93.0%	0.0067
Charlson Index	< 2.49	0.693 (0.645-0.741)	80.92	2	<0.001	97.5%	0.0018
	> 2.5	0.615 (0.410-0.821)	23.38	1	<0.001	95.7%	0.0211
	Not reported	0.673 (0.650-0.696)	1200.20	26	<0.001	97.8%	0.0032
Gender	> 85% male	0.718 (0.633-0.804)	176.50	5	<0.001	97.22%	0.0109
	85-50% male	0.717 (0.697-0.738)	483.91	12	<0.001	97.5%	0.0013
	< 50% male	0.606 (0.551-0.661)	244.85	9	<0.001	96.3%	0.0071
	Not reported	0.579 (0.505-0.652)	12.92	2	<0.001	84.5%	0.0034

df: degree of freedom; **RCT**: Randomized control trial; **FEV1% pred**: predicted amount as a percentage of the forced expiratory lung volume in one second
Subgroup analyses were done only when at least two studies were in each subgroup

Other study characteristics. The interaction tests did not suggest any evidence of a difference in utility value and heterogeneity index between the subgroups for the country of origin. Interestingly, the general utility value showed a quadratic distribution across year-of-publication (Figure 2-2). Interaction tests revealed a significant change in utility value among groups of year-of-publication but the heterogeneity remained constant. Utility value was high in studies before 2008, followed by a decline in 2009 to 2011 and a raise in 2012 to 2015. T-test and ANOVA tests confirmed this trend and the differences.

2.5 Discussion

This study aimed to summarize utility measures used in COPD and estimate mean utility value for these patients taking the sources of heterogeneity of included studies into account. Thirty-two studies were captured. They reported utility values of COPD based on patient level data. Cross-sectional studies were the dominant type of published studies (nineteen studies). There were in addition, thirteen Randomized Control Trial studies. A meta-analysis, controlled for between-study variation, random effect model, calculated mean utility value of 0.673 (95% CI 0.653 to 0.693) for COPD patients. This systematic review has revealed substantial diversity in the measuring instrument of HSUV used, and a wide range of utility values in COPD. The utility values ranged from 0.820 (95% CI 0.767 to 0.872) for stage I to 0.624 (95% CI 0.571 to 0.677) for stage IV. The meta-analysis indicated a high degree of heterogeneity in utility that was not explained by other factors. The utility score observed in this study is considerably lower than utility score in a general population-based sample, which suggests a major impact of COPD on HSUV. For example, a US population-based survey reported a mean utility value of 0.87 [237] on the EQ-5D scale. Another representing study from Alberta, Canada, reported a mean utility of 0.91 for individual with no medical problems in a general population survey [238]. Similarly, a study presented value set of general population norm of EQ-5D-3L utility value in Queensland, Australia, reported a value of 0.87 (0.86–0.87) [239].

It is well-known that there is inter-instrument variation in the estimation of health utility [240]. For this study, in order to reduce diversity and make a precise estimation of utility score, a meta-analysis was confined only to EQ-5D Index measure. Nevertheless, there was significant utility value diversity between studies which utilized EQ-5D measure (I^2 = 97.7%).

Clinical and study methodological diversity can both produce heterogeneity, though disaggregation of effects between the two is sometimes very difficult. Patients may be more willing to express the severity of impairment in self-administered than in interviewer-administered questionnaire [241] but the current study did not find evidence against the null hypothesis of similarity between two study subgroups.

Although some included studies did not report spirometry results (40.6%), almost all of them clearly mentioned that COPD diagnostic guidelines were considered and spirometry tests were performed, not only through the registrationon process (when COPD patient samples were recruited from registry databases) but also by investigators as part of inclusion criteria. For two studies [187, 216] it was based on General Practitioner diagnosis. An interaction test was performed with subgroup analysis of studies which reported and not reported FEV1% preb value (Table 6). The test result could not reject the null hypothesis of similarity between the two groups. In both groups heterogeneity was very significant and estimated mean utility value were similar.

This study did not show any association between degree of airflow obstruction (FEV1% pred) and general utility score. This may be explained by the chronic nature of COPD that leads many patients to adjust their lifestyle in accordance with their daily living ability and minimizes their sense of functional impairment [242]. Another possible reason is related to the limitation of preference-based measures in measuring HSUV in COPD disease. It has been shown that these measures have some limitations in tracing the impact of a disease over time, due to the floor

effects with the SF-6D and ceiling effects with the EQ-5D [243]. Guyatt *et al* [244] pointed out that responsiveness of generic measures to treatment effects in randomized trials in chronic respiratory disease is likely to be limited and may not be valid for measuring longitudinal differences over time. Hesselink *et al* [245] reported that changes in FEV1 % pred were weakly correlated with HSUV changes during a two-year follow-up of COPD patients. These findings were consistent with the results of previous studies [246-248]; which implied clinical measures such as FEV1% pred provided limited information about a health condition and were not well correlated with the health status of COPD patients. Consistent with these evidence, the new approach of the updated 2014 GOLD report suggests that progression and severity of the COPD disease cannot be drawn in a single-shot picture using only one diagnostic criterion and a combined COPD assessment is needed for prognosis of the disease [34]. The combined assessment approach takes three elements into consideration: spirometric test, the risk of exacerbations and one of the following disease-specific HR-QoL measures: COPD Assessment Test (CAT) or COPD Control Questionnaire (CCQ). This method, in conjunction with an assessment of potential comorbidities, provides a better approach for COPD staging and individualization of the disease management.

Given the current state of knowledge three systematic literature reviews of utility values for COPD disease were published. [214, 242, 249]. The aim of these studies was to summarize utility/disutility values in COPD by the severity of the disease. Due to the following methodological variations, their estimations were different from the current study: 1) In two of these studies, estimated mean utility values for stages of disease were derived from simple mean calculation without incorporating variances around utility values in each included study; in other word, meta-analysis was not statistical approach. 2) The current study performed a more comprehensive and, up-to-date systematic literature review and captured more valuable studies for the general and stage-specific utility values. 3) In the current study, appropriate statistical tests were used to demonstrate sources of heterogeneity and differences in estimated utility

values by sub-group analyses. 4) The current study tried to adhere to general recommendations of Peasgood et al [176] in the selection of included studies and running meta-analysis.

Another five literature reviews were captured that focused mainly on QoL and outcomes considering a variety of interventions in COPD [247, 250-253]. The most recent literature review [253] was a qualitative study covering humanistic and economic burden of COPD. In the humanistic section, the study focused on 32 non-RCT studies which almost thirty percent of them were conference abstracts. Different types of HR-QoL measures were included. No quantitative analyses were carried out by this study. Some suggested associations between study characteristics and patient conditions such as demographic, disease symptoms, comorbidities, resource use and cost were proposed. This study recommended that a comprehensive quantitative study is needed for a reliable conclusion.

In comparison with the findings from the past, a current systematic literature review has significant clinical and research implications. In reference to the Peasgood's critical paper [176], this study tried to overcome major concerns related to a meta-analysis of utility estimates in chronic diseases. Very restricted inclusion and exclusion criteria (such as excluding values that were not the appropriate utilities) were applied to capture unbiased study population. Especial attempted were made to generate a pool of utility values elicited from similar health state of COPD patient's population. Adopting EQ-5D as the only elicitation method ensured consistency in the methodological estimation of utility. All available study characteristics were reported transparently and justifications for choosing data from studies were clearly explained. So, modellers can choose the most appropriate estimated value.

There are a few limitations applied to this research. First, the form of aggregated data (study level not individual information) assembled in this study meant that it was not possible to do a more comprehensive meta-regression analysis in order to investigate correlation of study

characteristics [213], demographic diversity [210, 216, 217], clinical staging [50, 193, 218] or health condition differences such as comorbidities with heterogeneity. Secondly, COPD patients have a higher prevalence of osteoporosis, anxiety/panic attacks, heart trouble, heart attack, and heart failure, than smokers or non-smokers general population [60, 254]. Comorbidity measured by Charlson Index was only considered by five studies that were included [207, 209, 210, 212, 255]. Thirdly, the review did not include non-English language publications unless English versions of their abstracts were available. Fourthly, no quality assessment was carried out. It is possible that study quality may be a source of heterogeneity? For instance, studies with larger proportion of missing data, suggesting a potential bias towards healthier patients more likely to return their questionnaire, may be more likely to over-estimate health utilities.

For the future research, consideration of specific limitations of some HSUV measure instruments (e.g. ceiling effect and limited sensitivity in EQ-5D) are essential; using EQ-5D-5L instead of EQ-5D-3L may overcome this limitation. In addition, Individual Participant Data (IPD) meta-analyses as a 'gold standard' of systematic review which can improve the quality of data and the type of analyses is also recommended as a solution to the source of heterogeneity. This method which rely on the original research data sought directly from the researchers responsible for each study rather than extracting summary (aggregate) data from study publications or from investigators.

In conclusion, this study shows considerable inconsistency in utility measures among COPD-related published literature. It confirms that the utility value in COPD is considerably lower than the general population. However, the effects of contributing factors such as spirometry assessment and comorbidities on utility value remain largely unclear. This paper suggests that careful consideration should be taken into account when using systematic method (meta-analysis) for calculation of input parameters in health economic analysis. In the case of high

level of heterogeneity, appropriate sensitivity analyses are recommended for more accurate health economic appraisals.

3 Chapter 3 – Literature review of COPD progression modelling studies

Disease Progression Modelling (DPM) [256], the modelling of the progression of a target disease with computational methods, is an important technique that can help with the early detection and management of chronic diseases. By characterizing the entire disease progression trajectory, DPM also facilitates disease prognosis improvement, drug development, and clinical trial design. Modelling disease progression based on real-world evidence is a very challenging task due to the incompleteness and irregularity of the observations, as well as the heterogeneity of the patient conditions.

Projection of the future burden of COPD and the requirement for economic evaluations of existing and emerging technologies have resulted in multiple COPD models. Understanding the general characteristics of such models, such as the target population, model structure, and type of questions answered, can provide future investigators with a systematic and broad view of the COPD modelling landscape. In addition, characterizing the COPD-specific assumptions made in such models can support future model development and decision analysis in terms of comprehensiveness. This literature review of modelling studies comprised studies that used or developed a kind of COPD disease progression model. As a definition:

"Obstructive pulmonary disease model is an analytic methodology (i.e. a sequence of logical-mathematical computations) that links together evidence on obstructive lung disease from many sources to generate estimates of all phenotypes of COPD disease. It is essentially a mechanistic representative of disease progression [257]".

This review considered adherence to the best practice modelling guidelines as well as the assumptions made in COPD models relating to specific aspects of the disease. The point of interest is to find the areas of similarity as well as differences across published COPD models in search of opportunities for potential improvement in decision-analytic modelling in the field of COPD. In order to further illustrate the chronological evolution of the COPD progress models and main points of each model, a narrative summary of selected modelling studies was presented.

3.1 Methods

The following electronic databases were searched for relevant articles: MEDLINE, Web of Science, BIOSIS Citation Index, and CABI: CAB Abstracts. A search strategy was employed for MEDLINE database (Appendix B Table 1) and was adapted for other databases. A hand search and citation-tracking were conducted. The literature review has been conducted for English articles which 1) used, developed or conducted a mathematical simulation model for 2) describing the progress of any phenotype of COPD disease as a first outcome. The model was indicated as Markov model, simulation model, prediction model, disease simulation, progression model, mathematical model, regression model, dynamic population model, decision analytic model, life table model and state transition model. All abstracts were reviewed based on the above-mentioned criteria. Full texts of included articles were reviewed. Other types of studies and reports such as letters, editorials, conference abstracts and posters because of lack of enough detailed information were excluded. A detailed description of the process of study selection has been presented in Chapter 4.

3.1.1 General Characteristics of disease progression models

The types of progression models can be summarised and defined as follows, (models were classified according to published taxonomies [258]):

1. **Decision Tree** is a simulation technique in which an individual or a cohort of individuals can move to different states, or different events might occur with different probabilities [91]. Decision Trees are intrinsically close to Markov models with the difference that unlike Markov models they are untimed. Although the implementation of a Decision Tree model is straightforward, the fact that time is essentially ignored in a Decision Tree model is its biggest drawback.
2. **Markov model** consist of a set of mutually exclusive states that patients can transition between at a cycle. Markov models are mostly used to project the trajectory of a cohort of individuals over time, through which between-individual variation (i.e., heterogeneity) is usually forgone. Markov models are very popular for disease modelling because of their simplicity of implementation. Nevertheless, two disadvantages attached to Markov models are 1) the Markovian assumption underlying models that expresses that the future states depend only on present states and 2) Markov models are not fully capable of reflecting an individual's trajectory over time (even if they are used to model individuals rather than a cohort, they give the probability of an individual being at different states at a cycle rather than a specific state for that individual to be at that cycle).
3. **Discrete-event simulation** is a simulation technique in which the agent of a model is an individual rather than a cohort, with possible interaction between agents of the model [258]. Discrete-event simulation is a capable framework for reflecting between-individual variation (i.e., heterogeneity) and modelling the trajectory of an individual over time. Nevertheless, probabilistic implementation of such models requires a high computational capacity.

4. **Individual sampling model** is similar to discrete-event simulation when the agent of a model is an individual; nevertheless, unlike discrete-event simulation, there is no interaction between the model's agents in individual sampling model [258].
5. **System Dynamics** is another simulation technique for modelling a cohort, through which differential equations inform the present states within the model [258]. System dynamics are not capable of modelling heterogeneity and their probabilistic implementation requires high computational capacity.
6. **Time-in-state modelling** has a similar concept as an Markov model because there are some mutually exclusive states that at each cycle contain a proportion of the cohort [259]. The difference between Time-in-state modelling and Markov model is that there are no transition probabilities in Time-in-state modelling, which simply relaxes the underlying Markovian assumption of Markov models.

3.2 Result

3.2.1 Study characteristics

Of 1831 non-duplicated abstracts, 65 citations met inclusion criteria and were reviewed in depth full text. 27 articles were excluded. Three of 38 included studies were improved versions of previously reported models. They were included in this review because they had different structural characteristics which affected the prediction of the disease progression.

In this study, we described COPD progression models from five aspects: 1) model types and structures, 2) clinical and economic assumptions, 3) data sources and inputs, 4) model validations, 5) treatment of uncertainty.

Table 3-1 presents a summary of the 38 models. A wide range of simulation modelling approaches had been applied: 41 studies were Markov models, 2 were decision trees, 2 used an

individual sampling modelling approach [57,58], 1 was a discrete-event simulation [59], and 2 were system dynamics models [60,61].

Most of the models (n = 35) were developed for the purpose of economic evaluation, either of alterative COPD treatments or of a COPD management program. One models [260] were developed to project the future burden of COPD; one model [261] represented a case study for methodological work; and one model [112] were developed as a generic modelling framework (multipurpose and not an ad hoc model).

In general, the majority of models were cohort Markovian, but other types of simulation approaches such as, decision trees, system-wide dynamic population and micro-simulation were introduced. More delicate and system based simulation tools, adapted from economic and mathematical sciences became more popular in healthcare literature in recent years.

In terms of modelling COPD progression, 35 studies modelled transition across GOLD stages, whereas only one study [112] modelled progression through FEV1 decline. Two Markov models [124, 262] used exacerbation status in defining model states, and one study modelled COPD through states defined by the maintenance therapy usage [125].

For the most part, treatment effect was modelled as a direct reduction in exacerbation rate without any impact on lung function [113, 116, 124, 125, 129, 131, 262-265]. Several other studies, however, modelled the impact of treatment in improving lung function either without [115, 120, 123, 129, 233, 266] or with [112, 114, 117, 119, 121, 131, 225, 235, 261, 267] a simultaneous impact on reducing the rate of exacerbation. The impact on lung function, however, was mostly modelled through a one-time jump in lung function at the beginning of therapy. One study [130] did not clearly mention how the effect of treatments was modelled.

Most studies incorporated at least some aspects of disease heterogeneity into their main analysis through subgroup-level stratification. The most popular subgroup variables were baseline disease severity, sex, and age. Nevertheless, only eight studies [123, 131, 233, 260, 266] clearly reported results of subgroup specific analyses.

Only one models, those by Lock et al. [120][14], explicitly incorporated the impact of comorbidities. It evaluated the cost-effectiveness of smoking cessation and the authors acknowledged the importance of comorbid conditions in the context of their evaluation. Some other models indirectly considered the impact of comorbidity. Price et al. [119] mentioned comorbidity as a predictor for calculating utility values.

3.2.2 Selected simulation models

3.2.2.1 Sin DD, et al (2004)

Sin, et al [263] developed the first Markov model in 2004, to assess the cost-effectiveness of four different treatment strategies involving inhaled corticosteroids: no use regardless of COPD severity, use in all disease stages, use in patients with stage II or III, and use in patients with stage III. The time horizon of three years was divided into 3-month window increments. The disease severity was based on the recommendation from the American Thoracic Society that relies on Forced Expiratory Volume in 1 second (FEV_1). Exacerbation severity sub-classified into three mutually exclusive categories, mild, moderate and severe. Estimation of QALYs was done using the EQ-5D Index questionnaire. QALYs during exacerbation period have been estimated from the responses of the respiratory physicians who completed the questionnaires from the perspective of patients. Annual discount rate assumed to be 5%.

Table 3-1 Characteristics of Model-based studies

	First author (year)	Country	Purpose	Time Horizon	Prevalence/ Incidence	Patient Severity	Interventions incorporated	Type of model	Perspective	Outcome measure	Software
1	Jubran, et al [130]1993	USA	CEA	1 year	Incidence	II, III	Theophylline, Ipratropium bromide	Markov Cohort	Third party payer	Cost, Toxic effects of drugs	-
2	Rutten-van Molken, et al [268] 1999	The Netherland	Cost estimation	1999-2010	Prevalance	-	-	Dynamic multistate life table model	-	Cost	-
3	Feenstra, et al, [269] 2001	The Netherland	Future COPD burden estimation	1994-2015	Prevalance	-	-	Dynamic multistate life table model	-	DALY, Cost, COPD prevalence	-
4	Sin, et al [263] 2004	Canada	CEA	3 years	Prevalence	I, II, III, IV	Inhaled CS in various COPD severity stages	Markov	Societal	QALYs, All-cause mortality	-
5	Borg et al [235] 2004	Sweden	Future EE	Lifetime	Prevalence	-	Two hypothetical interventions, one having lung function decline and one reducing exacerbations by 25%	Markov	Societal & health care provider	LY, QALY, Exacerbation free day, No of Exacerbations	-
6	Feenstra, et al, [270] 2005	The Netherland	CEA	75 years	Incidence	-	Face to face smoking cessation	a dynamic population model	Societal	Cost, ICER	
7	Spencer M [225] 2005	Canada	CEA	25 years	Prevalence	II, III, IV	Salmeterol/ fluticasone vs. usual care	Markov	healthcare payers	Reduction in exacerbations, Mortality	-
8	Hoogendoorn, et al [266] 2005	The Netherland	Future EE	2000-2015	Incidence	-	Minimal counselling and intensive counselling + bupropion vs. current practice	Dynamic population-based Markov	Health Care System	ICER	-
9	Oostenbrink et al, [261] 2005	The Netherland Canada	CEA	1 year	Prevalence	II, III	Ipratropium, Tiotropium, Salmeterol	Stochastic Probabilistic Markov	Health Care System	No of exacerbation, QALYs	-

10	Lee, et al [271] 2006	Singapore	Cost saving	1 year	Prevalence	-	Tiotropium bromide	-	Health Care System	ICER	
11	Maniadakis, et al [267] 2006	Greece	CEA	1 year	Prevalence	II, III, IV	Tiotropium, Salmeterol	Probabilistic Markov (Oostenbrink, 2005)	Health Care System	Reduction in exacerbations, QALYs	-
12	van der Palen, et al [262] 2006	The Netherlands	CEA	6 months	Prevalence		Inhaled steroid withdrawal	Decision tree	Health Care Payer, direct cost	Cost per exacerbation prevented & cost per admission prevented	-
13	Rutten-van Molken, et al [272] 2007	The Netherlands	CEA	5 years	Prevalence		Tiotropium, Salmeterol or Ipratropium	Probabilistic Markov	National Health System & Societal perspectives	ICER	Microsoft Excel
14	Dal Negro, et al [265] 2007	Italy	CEA	1, 5, 10, lifetime	Prevalence		Five alternative therapeutic strategies	Markov	Societal, Health Care System & patient	No of exacerbation & symptom-free days	Microsoft Excel
15	Chuck, et al [264] 2008	Canada	CEA	3 years & lifetime	Prevalence		Combination therapy	Markov	Health Care System	QALY, ICER, Cost	TreeAge
16	Earnshaw, et al [273] 2009	USA	CEA	Lifetime	Prevalence		Fluticasone propionate/Salmeterol versus no treatment	Markov	Third party payer, direct costs	Cost, ICER, QALYs,	Microsoft Excel
17	Nielsen, et al [260] 2009	Norway	Not applicable	20 years	Prevalence		Present and future cost of COPD in Norway and Iceland	Markov	Payer, direct costs	Cost	Microsoft Excel
18	Oba [129] 2009	USA	CEA	3 years	Prevalence		Salmeterol, Fluticasone, combination therapy & placebo	Markov	Third party payer, direct costs	ICER	TreeAge Pro & Excell
19	Oba [110] 2009	USA	CEA	5 years	Prevalence		Long-term continuous oxygen therapy	Markov	Third party payer, direct costs	ICER	TreeAge Pro
20	Rutten-van Molken, et al [188] 2009		-	5 & 20 years	Incidence			Markov			
21	Wildman, et al [128] 2009	UK	Not applicable	180 days	Incidence		Predicting mortality in patients with exacerbations COPD and Asthma (development an	Multivariable Logistic Regression with	Not applicable	Mortality	-

						outcome prediction model)	bootstrapping			
22	Gani, et al [127] 2010	UK	CEA	1 year	Prevalence	Tiotropium with Ipratropium or Salmeterol	Markov (Oostenbrink, 2005)	Health Care System	QALYS, Cost	-
23	Mapel, et al [126] 2010	USA	CEA		Prevalence	Salmeterol, Ipratropium, Salbutamol	Monte Carlo simulation	Payer	Cost per exacerbation avoided	-
24	Naik, et al [274] 2010	USA	CEA	1 year	Prevalence	Tiotropium, Salmeterol versus no treatment for moderate COPD	Markov Cohort & Decision tree	Third party payer, direct costs	Cost per exacerbation avoided	Data TreeAge Pro
25	Neyt, et al [124] 2010	Belgium	CUA	1 year	Incidence	Tiotropium compared with placebo	Decision tree	Health Care payer	QALY	Microsoft Excel with @Risk add-in program
26	Atsou, et al [123] 2011	France	CEA	Lifetime	Incidence	Estimate the burden of continuous smoking & smoking cessation interventions	Cohort Markov & Monte Carlo	Society	LYs & QALY	TreeAge Pro
27	Casanova, et al [122] 2011	USA		10 years	-	Longitudinal study evaluating FEV_1 in COPD	Regression model	-	FEV_1	-
28	Hoogendoorn M. [121] 2011	The Netherland	CEA	1 year to Lifetime	Incidence	Five scenarios: Baseline, Pharmacotherapies, Smoking cessation & Pulmonary rehabilitation	Stochastic dynamic population Markov	Health Care System		-
29	Lock, et al [120] 2011	UK	CEA	Lifetime	Prevalence	Varenicline versus placebo	Markov	Health Care System (six EU countries)	LYs & QALY	Microsoft Excel
30	Price et al, [119] 2011	UK	CUA	3 years	Prevalence	Indacaterol maintenance therapy for moderate to severe COPD	Markov	Health Care System	Number of exacerbation	Microsoft Excel
31	Sun et al, [118] 2011	USA	CEA	5 & 30 years		Roflumilast/tiotropium therapy versus tiotropium monotherapy for severe and very severe COPD	Markov	The US payer, Direct costs	FEV_1 & QALY	-
32	Chandra, et al [117] 2012	Canada	CUA	Lifetime	Prevalence	Smoking cessation, multidisciplinary care, pulmonary rehabilitation, long-term oxygen therapy and ventilation care	Markov	Health Care System	Utility	-
33	Hertel et al [116]	UK	CEA	Lifetime		Cost-effectiveness of	Markov Cohort	The UK	Cost, LYs &	TreeAge

	2012						available treatments options for severe and very severe COPD	Model	National Health Service	QALYs	Pro Suite 2009 & Excel
34	Petra Menn et al [115] 2012	Germany	CUA	10, 40 years and lifetime	Incidence	I	Smoking cessation program of Lung Health Study	Markov	Societal perspective	QALYs	TreeAge Pro 2007
35	Najafzadeh, et al [114] 2012	Canada	CEA	25 years	Prevalence	I, II, (III, IV)	Hypothetical prevention molecular screening test intervention. Hypothetical pharmacogenomics intervention. Hypothetical molecular predictive test for exacerbation	System-wide dynamic population model	Societal perspective (direct and indirect cost)	QALYs	Vensim PLE Plus -Version 5.10e
36	Zaniolo, et al [113] 2012	Italy	CEA	Lifetime	Prevalence	II, III, IV	Tiotropium bromide versus placebo	(Stochastic) Probabilistic Markov	Health Care System	LYs, QALY & No of exacerbation	TreeAge Pro
37	Asukai, et al [112] 2013	UK		Lifetime		II, III, IV	Any treatment compared with the alternative, placebo or "no treatment".	Micro-simulation (Individual Sampling Model)	Health Care System	Expected cost, QALYs, LTs, Exacerbations, Threshold analysis	Microsoft Excel
38	Samyshkin [131] 2013	Switzerland	CEA	Lifetime		II, III, IV	Roflumilast in combination with bronchodilator therapies for severe and very severe COPD	Markov Cohort [a]	Health care, payer	Reduction in exacerbations, In-hospital mortality, QALY	-

CEA: Cost Effectiveness Analysis, CUE: Cost Utility Analysis, EE: Economic Evaluation, $FEV_{1:}$ forced expiratory volume in 1 second, QALY: Quality Adjusted Life Years, LY: Life Year,
Note: [a] The model is the same as Hertel, 2012

3.2.2.2 Sixten Borg, et al (2004)

Borg, et al [235] developed next Markov model that was based on the Global initiative for Chronic Lung Disease (GOLD) guidelines. It was assumed that the disease severity and COPD-related exacerbations influenced the probability of moving to either milder or worse disease and of death, generating a two-dimensional Markov model. Each dimension was in itself a Markov chain, with a separate state space. Each state for the severity of disease was updated mid-yearly. Within each state, the exacerbation status chain was located and updated weekly. The possibility of regressing one-step back to a milder stage has been assumed. Transitional probabilities for health status and exacerbations were determined by epidemiological data. Two variables by which exacerbations influence disease progression and mortality have been defined. One-year cycle for the disease progression and 1-week cycle for the exacerbation status Markov chain were used. Moreover, the discount rate of 3% has been set for the lifetime period.

3.2.2.3 Spencer et al, (2005)

Another study was conducted by Spencer et al (2005) [225], used four disease states (mild, moderate, severe disease and death), in order to compare the cost-effectiveness of a combination drug treatment to usual care (base case scenario) over a 25-yr time horizon. The cycle length for the model was set to 3 months and disease progression was unidirectional. The discount rate was set to 5% per annual.

3.2.2.4 Oostenbrink et al, (2005)

Oostenbrink et al, [261] developed a stochastic Markov model with the period of one year to compare the cost-effectiveness of three bronchodilators for COPD patients across two countries, Canada, and Netherland. Resource utilization during exacerbations and maintenance treatment was derived from previously done clinical trials and a countrywide observational study. The utility values for disease states were based on data from an observational study using EQ-5D

index scores for moderate, severe, and very severe COPD. The outcomes of the model were based on specific trial designs on Tiotropium studies and other relevant evidence related to the efficacy of bronchodilator medications. Therefore, the model may not provide sufficient information for decision makers. On the other hand, the model is a short-term model without the capability to reflect the smoking and mortality impacts and it cannot demonstrate the lifetime disease progression. The length of the first cycle was set at eight days but the length of subsequent cycles was one month. Time horizon of the model was one year. The transition between status was assumed to take place halfway the cycle. Discounting was not applied for this one-year model. In order to address the uncertainty around the point estimates of the model inputs, this study adopted Dirichlet distribution for transitions between disease states, beta distribution for exacerbations and utilities and a gamma distribution for estimation of resource use. Second-order Monte Carlo simulations were undertaken. The uncertainty around costs and effects addressed by means of incremental cost-effectiveness plans and separate acceptability curves per treatment based on the net benefit approach. Ten separate sensitivity analyses were performed. The robustness of the model for alternative transition and exacerbation probabilities, baseline distribution of patients over disease state, alternative utility values and new input parameter were investigated.

3.2.2.5 Rutten-van Molken et al, (2007):

This was a fully probabilistic Markov model [272], allowing COPD patients moved between disease severity states with varying risk of exacerbation and death. The built on Oostenbrink study and extended the time horizon from 1 year to 5 years and aimed to assess the cost-effectiveness of three bronchodilators for COPD patients in Spain. In this study, both societal and NHS perspective had been utilized. Varying degrees of discount rate between 6-0% according to adopted assumptions for each scenario were applied. During the first year, both forward and backward transitions were possible but in the base-case and third scenario, backward transitions during 2 to 5 year were not allowed. The sensitivity analysis of the study

has been performed through scenario analysis. A fully probabilistic design was adopted to address the uncertainty around the probabilities to move between disease states, to experience exacerbations, utilities, and healthcare utilization. It was performed by defining a probability distribution for each input parameter. The results were propagated by conducting second-ordered Monte Carlo simulation. The final results were based on 5,000 iterations.

3.2.2.6 Hoogendoorn et al, (2011):

This is stochastic, dynamic, population multistate model [121], including the effects COPD exacerbations and capturing the uncertainty around main parameters. It was based on the life table method. Exacerbations in the model were observed according to an event-based definition, which was an increase in health care use. Exacerbations were populated to affect disease progression (decline in lung function in FEV1% pred), mortality, QoL, and costs based on literature reviews. By making the model stochastic, the main parameters entered as distribution and Monte Carlo simulation captured the uncertainty. The length of a Markov cycle was one year. Case fatality rate of exacerbation was calculated as 1 minus the backward extrapolated survival during the stable time back to the time of exacerbation inception. The utility values for the COPD severity stages were based on EQ-5D and adopted from the previous study. In order to estimate the impact of exacerbations on the number of QYLYs loss, results of two relevant studies were consumed. Annual exacerbation rate and its relation between lung function in the populations of reviewed studies was estimated applying weight log-linear regression with random effects. The prevalence, incidence, smoking prevalence, smoking transition rates and relative risks of smokers were updated by using Statistics Netherland, STIVORO, and VTV-2010 study. The last one utilized five general practice datasets. Uncertainty around the estimates of incidence, prevalence and case fatality was assessed by using the observed variation between and within the different GP registries. Two types of sensitivity analysis were utilized. First, one-way sensitivity analysis for key model assumptions and key parameters including parameters that for which probabilistic approach is not appropriate such as discount rates. Second,

probabilistic sensitivity analysis, using Monte Carlo simulation, for most input parameters. To address the uncertainty around the cost-effectiveness of the scenarios, 1000 model simulations were used. The model was a dynamic population that includes changes in birth and smoking patterns. Therefore, under observed population was composed of old and newly entered groups, and at the end there would be some patients that have been followed for the whole-time period and other patients have been observed for shorter periods of time. In this case, unified long-term effects cannot be captured.

3.2.2.7 Najafzadeh, et al, 2012

This study [114] was conducted to predict the future (25 years) burden of COPD disease in Canada and the impact of various hypothetical interventions. It was based on a dynamic population model and incorporating input data from the previous study. The interventions targeted different COPD management policies comprising, primary prevention (risk assessment for developing COPD disease in patients starting smoking (incident cases), secondary prevention (early detection and pharmaceutical approach reducing the progress of the disease) and tertiary prevention (reducing deteriorating impact of established disease through predicting major medical events).

In this model, the flow of general population (over 40 years old) and COPD cases into different disease states (no COPD, mild, moderate and severe) was simulated. The very severe cases treated as severe ones.

The model argued that the most cost-effective strategy for reducing the cost of COPD diseases is to target exacerbations. Smoking cessation interventions had a modest effect and the reasons could be related to the following evidence:

(i) The long lag time between exposure and initiation of COPD disease.

(ii) The incidence rate of COPD, independently of smoking, increases with the increase in average age of the population.

(iii) Progression of COPD disease proceeds even after smoking cessation.

This was the case for interventions that aimed to reduce the decline of FEV1. Evidence showed that cost bearing events in COPD diseases such as exacerbations, clinical symptoms, and mortality were not purely related to FEV1 and other playing factors were involved.

Major assumptions of the model were:

(i) The study assumed that estimated COPD prevalence in Vancouver is representative of rates across Canada.

(ii) The background mortality rates were related to age and smoking status.

(iii) Any COPD mortality was related to a major exacerbation. So the impact of smoking status, age and disease severity on COPD-related mortality were considered indirectly from their effects on exacerbations.

(iv) The subgroup-specific (sex, age, and smoking status) incident rates calculated based on their specific prevalence rates and a number of individuals in each subgroup.

(v) It was considered that the indirect costs related to COPD account approximately 20%, 33% and 45% of total costs of mild, moderate and severe COPD patients respectively.

(vi) In order to consider the long-standing effect of asthma as a risk factor for COPD, the study also modelled the possible impact of the rising rates of asthma on the costs of COPD over time.

3.2.2.8 Asukai et al (2013)

The model [112] was a micro-simulation (individual sampling model (ISM)), describing each individual through discrete time periods (cycle) the length of them adjustable by the user. There was no defined health state. Lung function levels was modelled as a continuous variable. A

Monte Carlo simulation method was used to explain patient progress through the model. A correlation matrix based on pooled data of patients of previous RCTs was developed to describe the lung function of patients through the model. The model allowed changes of intervention according to the pre-specified events in COPD progress. Time horizon and discount rate were adjustable.

3.3 Discussion

This chapter was a prelude for the next chapter. It demonstrated a chronological evolution of the COPD progression models from simple disease state Markov models designed for cost-effectiveness analysis in a specific population [263] to more complex simulation models incorporating COPD risk factors (such as smoking habit and exacerbation rates) and some comorbidities with dynamic stochastic structures for whole population [121] and further into micro-simulation individual sampling models [112].

Ongoing effort on COPD progression models are directed to incorporating more elements of the disease and in contrary to the older Markov models that use FEV1% predicted as measure of disease severity the newer models tried to include more patient characteristics to define severity. Key priorities in future models include better input parameters, better definition of outcome measures and with special consideration of COPD progression risk assessment. New approach in disease progression microsimulation modelling using characteristics at individual level of patients can provide more flexible tool for predicting more accurate measures of outcomes. This can be achieved by incorporating the updated COPD assessment tool introduced in the 2014 GOLD report. This combined assessment approach takes three elements into consideration: spirometric test, exacerbations risk and one of the following disease-specific HR-QoL measures: COPD Assessment Test (CAT) or COPD Control Questionnaire (CCQ).

In cohort models (e.g., Markov models), violation of the homogeneity principle can cause bias in the estimated outcomes, even when the outcome of interest is cost effectiveness for the whole population [275]. Cohort models should be stratified on subgroups such that each subgroup can be considered a homogeneous population. If the creation of many subgroups is required to account for heterogeneity, then cohort models can become unwieldy. In such instances, the use of microsimulation (individual-level modelling) is recommended [258]. In addition to this technical requirement, we think there are other reasons to encourage the use of microsimulations.

4 Chapter 4 – Do modelling studies in Chronic Obstructive Pulmonary Disease (COPD) measure correct values of utility? A meta-analysis

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4.1 Abstract

Background. Chronic obstructive pulmonary disease (COPD) is a progressive chronic disease that has a considerable impact on utility-based, health-related quality of life. The utility is a key input of many decision analytic models used for economic evaluations.

Purpose. To systematically review COPD-related utilities and to compare these with comparable values used in decision models.

Methods**.** The literature review comprised studies that generated utilities for COPD-related stages based on EQ-5D surveys of patients and of decision models of COPD progression that have been used for economic evaluations. The utility values used in modelling studies and those from the meta-analysis of actual patient-level studies were compared and differences quantified.

Results**.** Twenty COPD decision modelling studies used utility value as an input parameter were found. Within the same span of publication period, thirteen studies involving patient-level utility data were identified and included in the meta-analysis. The estimated mean utility values ranged from 0.806 (95% CI 0.747 to 0.866) for stage I to 0.616 (95% CI 0.556 to 0.676) for stage IV. The utility scores for comparable stages in modelling studies were significantly different from the mean utility values derived for stage III meta-analysis (difference 0.045 (95%

CI 0.041 to 0.052)). Modelling studies consistently used higher utility values than average reporting patient-level data.

Conclusions. COPD decision analytic models are based on a limited range of utility values that are systematically different from average values estimated using a meta-analysis. A more systematic approach in the application of utility measures in economic evaluation is required to appropriately reflect current literature.

4.2 Key Points for Decision Makers

- Decision model studies relied on a diverse range of published utility values in each stage of COPD that does not necessary follow good modelling practice recommendations
- There is scarcity of representative and valid data about utility values in exacerbations and different states of COPD for decision modelling studies
- Input parameters in modelling studies should be considered with caution especially when the sensitivity of the instrument (such as EQ-5D) for detecting small changes is not satisfactory

4.3 Introduction

Economic models of chronic obstructive pulmonary disease (COPD) are intended to simulate disease progression and quantify the impact of interventions on outcomes primarily in terms of quality-adjusted life years (QALYs). An important aspect of these models is Health State Utility Value (HSUV) (commonly referred to as utilities) which, associated with major stages of COPD, or disutility related to the major events such as exacerbations form the basis of QALY outcomes. A systematic search of the health economic literature located a large number of studies reporting progression models [112-121, 123, 125, 127, 129, 131, 225, 235, 263, 264, 267, 272, 273, 276, 277] that included utility values for one or more stages of COPD.

The utility values employed in all models were based on information from a single study, which has been standard practice in the health economic literature. Utilities employed in COPD models to date have come from summary measures derived from EQ-5D Index, a generic instrument of HSUV, and show variation in utility assumption across models. This variation is likely to impact on the generalizability of the model outputs and raises the question as to whether the model would have produced outcomes that were sufficiently different to impact on cost-effectiveness decisions.

In recent years, meta-analyses have begun to be conducted to generate overall utility values for common health states. This has included studies of utility values for HIV/AIDS [183], chronic kidney disease [184], diabetes [180] and various types of cancer [181, 278]. To date, there have been only one meta-analysis of utility values of COPD stages [214], which is surprising given a large number of evaluations of therapies for COPD that are now routinely undertaken. The results of the meta-analyses have not been used as inputs to COPD modelling studies.

Chapter 4

The aim of this study is to conduct a systematic review of utilities for the stages of COPD used in modelling studies and to compare these with summary measures from meta-analyses of available utility studies within the publication period of modelling studies derived from patients with COPD. We also examine the implications of differences between utility used in past models and estimates of the average utility for health states that are derived from a meta-analysis of the available literature of patient-derived values for utility associated with COPD states.

4.4 Methods

4.4.1 Study selection

Two different systematic literature reviews were conducted.

1. Patient-reported outcome studies

The first literature review covered HSUV studies in COPD that used EQ-5D Index to estimate utility value for patient level research in COPD; simulation-based studies were not included.

Studies matched with the following criteria were included:

- health utility studies published up to 2014 (the publication date of the last COPD model included in this study; this studies are a subset of included studies in chapter 2)
- utility scores based on UK tariff value because of consistency and availability of data
- studies in which their sample population was specifically categorized as COPD as defined by standard criteria for COPD diagnosis and spirometric confirmation (should clearly be addressed in the methodology of included studies),

- English language studies; non-English language studies were included if they accommodated English abstracts.

Exclusion was applied for the following criteria:

- editorials/opinion pieces, letters, systematic reviews, and meta-analyses
- studies that reported utilities from proxies (e.g. reported by a family member or doctor)
- studies that obtained utility estimates from the literature, if there was not enough information on the derivation of utility, or if utility values were not reported
- studies that did not distinguish COPD with other types of obstructive pulmonary disease such as asthma or cystic fibrosis
- papers using utility values mapped from other reported quality-of-life studies.

In order to minimize within-study correlation, a special effort was made to exclude studies utilizing the same population and report multiple HSUV measures.

This study covers different COPD severity staging guidelines: Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) [4], American Thoracic Society (ATS) [279], European Respiratory Society (ERS) [280, 281] and British Thoracic Society (BTS) [282, 283] staging systems. All of them are based on the severity of airflow obstruction captured by spirometric examination, but with different cut-off points evolved over time. An attempt was made to match similar levels of COPD severity of above-mentioned staging systems with each other.

2. Modelling studies

A second literature review captured reported EQ-5D derived HSUV use as input in COPD Markov modelling studies. The literature review has been conducted for articles that use,

develop or conduct a mathematical simulation model for describing the progress of COPD as a first outcome.

Studies matching the following criteria were included:

- Model-based studies in COPD
- English language studies;
- input values for utility scores of COPD stages reported or the reference articles cited.

In order to make an evaluation of reference citations of COPD modelling research studies, all available modelling articles were reviewed. A hand search and citation tracking were also conducted.

These systematic reviews follow MOOSE guidelines for observational studies [284]. A search strategy was employed for MEDLINE database (Appendix 1) and was adapted for other databases. Endnote X7.0 was used to download citations, and to identify and extract duplicate studies.

4.4.2 Search Methods

The systematic review of the literature on utility values for COPD in each stage was part of a wider systematic review of economic evidence on COPD disease, related pharmacological and psychological interventions and progression modelling for patients with COPD. The following electronic databases were searched for relevant articles: MEDLINE, EMBASE (for prior to 2014), Web of Science, CINAHL, ProQuest (including PsycINFO and 61 other databases), the Cochran Library Database (which includes NHS Economic Evaluation Database, Health Technology Assessment Database, Cochrane Database of Systematic Reviews and other three

databases), International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and Google Scholar. An attempt was made to find unpublished literature and to decrease the likelihood of publication bias [190], using dissertation abstracts, authors and websites of key academic institutions such as NICE (National Institute for Clinical Excellence), CCOHTA (Canadian Cooperating Office for Health Technology Assessment), SBU (The Swedish Council on Technology Assessment in Health Care), Health Economic Evaluations Database (HEED) and the Cost-Effectiveness Analysis Registry at Tufts-New England Medical Centre.

The same electronic databases were searched for modelling studies.

4.4.3 Data extraction and management

The following variables were obtained from each citation: principal author, year of publication, clinical characteristics and demographic of patients, number and country of patients, study design, HSUV measure and its estimate (mean and standard deviation). In intervention studies – for example, randomized control trials – baseline characteristics were used to avoid the potential effect of the intervention on the quality-of-life estimates. When a demographic or clinical factor split intervention groups, the entire number of the group was adopted where possible. For the modeling studies, results of sensitivity analysis for utility values were captured.

Assessment of study eligibility and extract of information from each study were carried out by two independent reviewers.

4.4.4 Data analysis

In order to estimate a single utility score value for each stage of COPD, a meta-analysis was conducted. Point estimates and 95% Confidence Intervals (CI) for utility scores were calculated and displayed in forest plots.

Meta-analysis was conducted with the command “metan” [191] to conduct a meta-analysis and graph the result in a funnel plot, using Stata version 13.1. In order to account for anticipated study heterogeneity, random-effects models were used [285]. Heterogeneity among the studies was measured using I^2 statistics and 95% CI. If any study did not present enough data for measuring standard error, it was excluded.

Differences between the utility scores used in modelling studies and the utility values exploited in the meta-analysis were evaluated using unpaired T-test. Statistical significance was accepted at the $P < 0.05$ level.

In order to investigate the impact of the estimated utility values derived from the meta-analysis on the output of the COPD model, we estimated the relationship between changes in utility values and changes in the incremental cost-effectiveness ratios based on reported results of sensitivity analyses form included modelling studies. The underlying relative relationship was used to make estimates of the potential impact of basing modelling analyses on literature-based meta-analysis results.

4.5 Results

4.5.1 Study characteristics

Patient-reported outcomes

The utility values extracted from the literature were based on patient-reported information (Figure D1). The initial pool of studies for utility values comprised 15,682 entries, of which 15,677 were from various databases, three citations captured through hand search [194-196] and two theses. After scanning of abstracts, 15,368 citations were excluded. Full-text examination of 314 studies was carried on using the inclusion and exclusion criteria, 49 studies were selected

for review and 13 studies were included for conducting the meta-analysis of utility values at COPD stages. Table D2 summarizes study characteristics of the articles included in the final analysis. The number of participants ranged from 117 to 11,066, with an average of 2,016. Of these, 65.45% were male and the average age was 64.9 years. Cross-sectional studies were the dominant type of published studies (eight studies).

Table D3 summarizes values of utility. Countries of origin of the studies were European and North American. Studies were published between 2004 and 2013 and reported utility values ranging from 0.8971 [235] to 0.409 [187]. Differences of minimum and maximum values of estimated mean utility for stages I to IV were 0.2171, 0.253, 0.394 and 0.223 respectively.

The following considerations were applied for selecting studies in meta-analysis:

- Reported utility values of one study [195] were omitted from the final analysis due to reporting very extreme EQ-5D Index elicited utility values (<0.008). Attempts were made to contact the author but the explanation received was not clear.
- One study [187] used British Thoracic Society (BTS) staging system based on Medical Research Council (MRC) dyspnoea scale. Because of similarity in the definition of stages I, II and III in this scaling with stages II, III, and IV of GOLD staging system respectively, the equivalent utility values were incorporated in the meta-analysis.
- One study [225] used American Thoracic Society staging system (ATS) 1987. Due to the similarity in the definition of stages II (moderate) and III (severe) in this scaling with stages III and IV of GOLD staging system respectively, the equivalent utility values were incorporated in the meta-analysis.
- One study [109] followed the GOLD staging definition but it merged stages I and II of COPD patients into one single moderate (II) stage and attributed one single utility value

for these groups. The utility value of stage II of this study was omitted from meta-analysis.

- In one study [220] the 'severe' (GOLD-stage III) and 'very severe' (GOLD-stage IV) subsets were merged into one single 'severe' (stage III) subset. The utility value of stage III of this study was omitted from meta-analysis.

Modelling studies

Flow diagram for the derivation of studies included in the modelling review is presented in Figure D2. The initial pool of citations for modelling studies comprised 2,884 abstracts. Sixty-five citations met inclusion criteria and the full texts were reviewed in depth. If the reference source of utility score as an input parameter in modelling studies was reported it was included in this analysis. Four modelling studies were excluded because the utility was not one of their input parameters [125, 277]. In spite of the fact that utility estimates of the two modelling studies [116, 131] were referred to an excluded study [194], they were included in modelling utility analysis. According to their clarification, their utility values were derived from pooled raw data of two clinical trials M2-124 and M2-125 [195].

Characteristics of 20 included modelling studies were summarized in Table 4-1. Markovian model was the dominant structure. The models were designed for economic evaluation of clinical trials. All of them used single study reported utility value. Included 20 modelling studies were categorized into seven groups, based on their reference utility value studies (Table 4-2). Utility values used by included modeling studies showed ranges of scores (e.g. 0.67 to 0.751 for stage III of COPD) depending on their single reference study.

Table 4-1 Characteristics of included modelling studies

First author, year	Country	Purpose	Time horizon	COPD severity staging system	Interventions incorporated	Type of model	Perspective	Outcome measure	Software
Sin, et al [263] 2004	Canada	CEA	3 years	ATS	Inhaled CS in various COPD severity stages	Markov model	Societal	QALYs, All-cause mortality	-
Borg, et al [235] 2004	Sweden	Futur e EE	Lifetime	GOLD	Two hypothetical interventions, one having lung function decline and one reducing exacerbations by 25%	Markov model	-	LY, QALY, Exacerbation free day, No of Exacerbations	-
Spencer M. et al [225] 2005	UK	CEA	25 years	ATS	Salmeterol/ fluticasone vs. usual care	Markov model	-	Reduction in exacerbations, Mortality	-
Oostenbrink JB, et al [261] 2005	The Netherland & Canada	CEA	1 year	GOLD	Ipratropium, Tiotropium, Salmeterol	Stochastic Probabilistic Markov model	Health Care System	No of exacerbation, QALYs	-
Maniadakis, et al [267] 2006	Greece	CEA	1 year	-	Tiotropium, Salmeterol	Probabilistic Markov model (Oostenbrink, 2005)	Health Care System	Reduction in exacerbations, QALYs	
Rutten-van Molken, et al [272] 2007	The Netherland	CEA	5 years	GOLD	Tiotropium, salmeterol and ipratropium	probabilistic Markov model	Societal	ICER cost,	Microsoft Excel
Chuck A, et al, [264] 2008	Canada	CEA	3 years & lifetime	ATS	Combination therapy	Markov model	Health Care System	ICER, cost, QALYs	TreeAge
Earnshaw, et al [273] 2009	USA	CEA	Lifetime	GOLD	Fluticasone propionate/Salmeterol versus no treatment	Markov model	Third party payer, direct costs	Cost, ICER, QALYs,	Microsoft Excel
Oba [129] 2009	USA	CEA	5 years	GOLD	Long-term continuous oxygen therapy	Markov model	Third party payer, direct costs	ICER	TreeAge pro
Gani, et al [127] 2010	UK	CEA	1 year	GOLD	Tiotropium with Ipratropium or Salmeterol	Markov model (Oostenbrink, 2005)	Health Care System	QALYS, Cost	-
Atsou K, et al, [123] 2011	France	CEA	Lifetime	GOLD	Estimate the burden of continuous smoking & smoking cessation interventions	Cohort Markov model	Society	ICER & LYs & QALY & Cost	TreeAge pro

Hoogendoorn M, et al.[121] 2011	The Netherland	CEA	1 year & lifetime	GOLD	Five scenarios: Baseline, Pharmacotherapies, Smoking cessation & Pulmonary rehabilitation	Stochastic dynamic population Markov model	Health Care System	-	Mathematica
Lock K, et al, [120] 2011	UK	CEA	Lifetime	GOLD	Smoking cessation based on a randomised controlled trial of varenicline versus placebo	Markov model	Health Care System (six EU countries)	LYs & QALY	Microsoft Excel
Price D, et al, [119] 2011	UK	CUA	3 years	GOLD	Indacaterol maintenance therapy for moderate to severe COPD	Markov model	Health Care System	Number of exacerbation	Microsoft Excel
Sun SX, et al, [118] 2011	USA	CEA	5 & 30 years	ATS	Roflumilast/tiotropium therapy versus tiotropium monotherapy for severe and very severe COPD	Markov model	The US payer, Direct costs	FEV_1 & QALY	-
Chandra K, et al [117] 2012	Canada	CUA	Lifetime	GOLD	Smoking cessation, multidisciplinary care, pulmonary rehabilitation, long-term oxygen therapy and ventilation care	Markov probabilistic model	Health Care System	Utility	-
Menn P, et al [115] 2012	Germany	CUA	10, 40 years and lifetime	GOLD	Smoking cessation program of Lung Health Study	Markov model	Societal perspective	QALY	TreeAge Pro 2007
Najafzadeh M, et al [114] 2012	Canada	CEA	25 years	ATS	Hypothetical prevention molecular screening test intervention. Hypothetical pharmacogenomics intervention. Hypothetical molecular predictive test for exacerbation	System-wide dynamic population model	Societal perspective (direct and indirect cost)	QALY	Vensim PLE Plus - Version 5.10e
Hertel NRW, et al [116] 2012	UK	CEA	Lifetime	GOLD	Cost-effectiveness of available treatments options for severe and very severe COPD	Markov Cohort Model	National Health Service	Cost, LYs & QALY	TreeAge Pro Suite 2009 & Excel
Samyshkin Y, et al, [131] 2013	Switzerland	CEA	Lifetime	GOLD	Roflumilast in combination with bronchodilator therapies for severe and very severe COPD	Markov Cohort model	Health care, payer	Reduction in exacerbations, In-hospital mortality, QALY	-

CEA: Cost effectiveness analysis; **CUA**: Cost-utility analysis; **LY**: life years; **ICER**: Incremental Cost Effectiveness Ratio; **GOLD**: Global Initiative for Chronic Obstructive Pulmonary Disease; **ATS**: American Thoracic Society staging system; **ERS**: European Respiratory Society; **BTS**: British Thoracic Society

Table 4-2 Reference sources of utility scores in COPD modelling studies

group	Reference articles	Utility values in references	Modelling studies	Utility values in modelling studies
1	Prescott-Clarck P, et al, 1998 [47] *(National Health Survey)*	• Stage I: 0.81 (0.02) * • Stage II: 0.72 (0.03) * • Stage III: 0.67 (0.05) *	• Spencer M, et al, [19] 2005 • Sun SX, et al, [20] 2011 *(incorrect utility values were adapted from reference article)* • Najafzadeh M, et al, [12] 2012	• Stage I: 0.81 (0.02) * • Stage II: 0.72 (0.03) * • Stage III: 0.67 (0.05) *
2	McBride A, et al, [48] 1999	• Stage I: 1 • Stage II: 0.92 • Stage III: 0.84	• Sin DD, et al, [18] 2004	• Stage I: 1 • Stage II: 0.92 • Stage III: 0.84
3	Borg S, et al, [2] 2004 *(cost-of-illness study, Jansson SA et al 2002)*	• Stage I: 0.8971 (0.1117) † • Stage II: 0.7551 (0.2747) † • Stage III: 0.7481 (0.2991) † • Stage IV: 0.5493 (0.3129) †	• Hoogendoorn M, et al, [8] 2011 • Atsou A, et al, [1] 2011 • Lock K, et al, [9] 2011 • Earnshaw SR, et al, [5] 2009 • Chuck A, et al, [4] 2008 *(incorrect utility values were adapted from reference article)* • Maniadakis N, et al, [10] 2006 • Oostenbrink JB, et al, [14] 2005 • Borg S, et al, [2] 2004	• Stage I: 0.8971 (0.1117) † • Stage II: 0.7551 (0.2747) † • Stage III: 0.7481 (0.2991) † • Stage IV: 0.5493 (0.3129) †
4	Rutten-van MPMH, Oostenbrink, et al, [55] 2006 (Chest) *(Multinational UPLIFT clinical trial)*	Overall utility values: 0.76 (0.21) * • Stage II: 0.787 (0.771-0.802) ‡ • Stage III: 0.750 (0.731-0.768) ‡ • Stage IV: 0.647 (0.598-0.695) ‡	• Menn P, et al, [11] 2012	Overall utility values: 0.76 (0.21) * • Stage II: 0.787 • Stage III: 0.750 • Stage IV: 0.647
			• Gani R, et al, [6] 2010 *(incorrect utility values were adapted from reference article)*	• Stage I: 0.787 • Stage II: 0.750 • Stage III: 0.647
			• Oba Y, [13] 2009 *(US set of utility were adapted and incorrectly allocated to the wrong COPD stages)*	• Stage II: 0.832 • Stage III: 0.803 • Stage IV: 0.731
5	Rutten-van M, et al, [16] 2007 *(The European journal of health economics)*	• Stage II: 0.809 (0.008) * • Stage III: 0.762 (0.009) * • Stage IV: 0.655 (0.024) *	• Chandra K, et al, [3] 2012 • Rutten-van M, et al, [16] 2007	• Stage I: 0.84 • Stage II: 0.81 • Stage III: 0.76 • Stage IV: 0.66
6	Calverley PM, et al, [42] 2009	Intervention group: 0.0072 Control group: 0.0049	• Samyshkin Y, et al, [17] 2013 • Hertel N, et al, [7] 2012	• Stage III: 0.751 • Stage IV: 0.657
7	Donohue J, et al, [49] 2010 & Kornmann et al, [50] 2009 & Stahl [56] et al, 2005	Drived from pooled clinical trials	• Price D, et al, [15] 2011 *(Reference articles didn't report utility values)*	• Stage I: 0.82 (0.8–0.84) ‡ • Stage II: 0.80 (0.79–0.81) ‡ • Stage III: 0.77 (0.77–0.78) ‡ • Stage IV: 0.74 (0.73–0.76) ‡

* Standard Error; † Standard Deviation; ‡ Confidence Interval

Only three studies measured disutility around exacerbation state [225, 226, 235], Table D4. In one study [225], utilities were estimated from the physician perspective. Due to the scarcity of patient-level data, a meta-analysis was not carried out for exacerbation states.

4.5.2 Meta-analysis

Meta-analysis was performed on aggregated data reported in individual studies captured from 10 included studies.

Forest plots: Figures 1a–1d represent forest plots for utility values at each stage of COPD, ordered by date of publication. Meta-analysis was performed for each stage, with utility values reported score on that stage. According to the guidelines recommendation in a meta-analysis [285], a random-effect meta-analysis was used to estimate mean utility values for each stage of COPD. The results are presented in Table 4-3 & Figure 4-1. Heterogeneity was substantial in all stages. The estimated utility

Figure 4-1 Forest plot (random effect) of utility values elicited by EQ-5D Index at different stages of COPD

Fig. 1 (a) Stage I

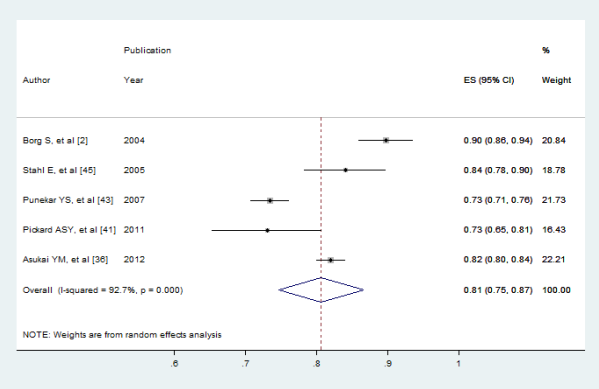


Fig. 1 (b) Stage II

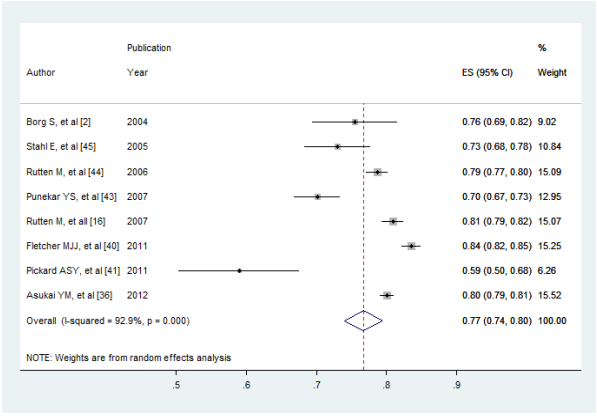


Fig. 1 (c) Stage III

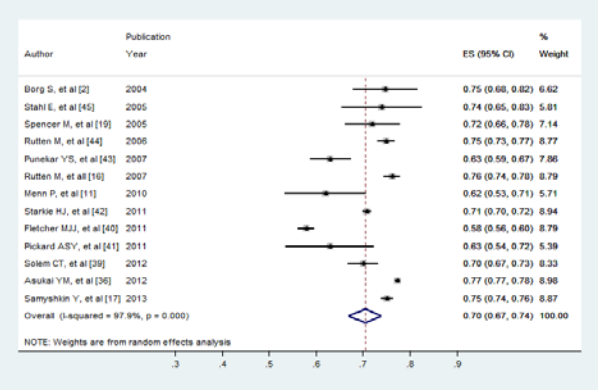
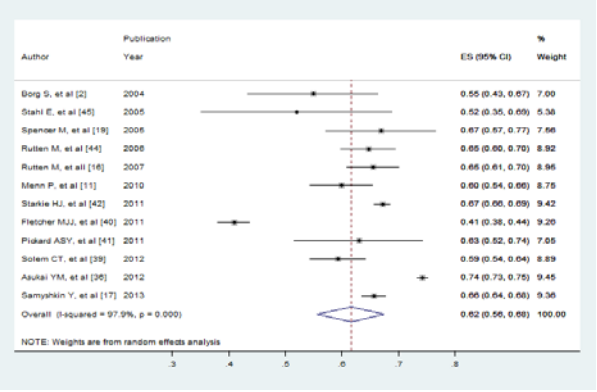


Fig. 1 (d) Stage IV



declined at higher stages of COPD, with utility values ranging from 0.806 (95% CI 0.747 to 0.866) in stage I to 0.616 (95% CI 0.556 to 0.676) at stage IV.

Table 4-3 Estimated mean utility values at four stages of COPD

	Utility Estimate (95% CI)	I^2 Heterogeneity statistics	Tau-squared	Heterogeneity chi-squared /Cochrane's Q test		
				χ^2	df	P value
Stage I	0.806 (0.747– 0.866)	92.7%	0.0041	54.91	4	<0.001
Stage II	0.767 (0.740 – 0.795)	92.9%	0.0013	98.53	7	<0.001
Stage III	0.704 (0.670 – 0.739)	97.9%	0.0035	581.65	12	<0.001
Stage IV	0.616 (0.556 – 0.676)	97.9%	0.0099	512.85	11	<0.001

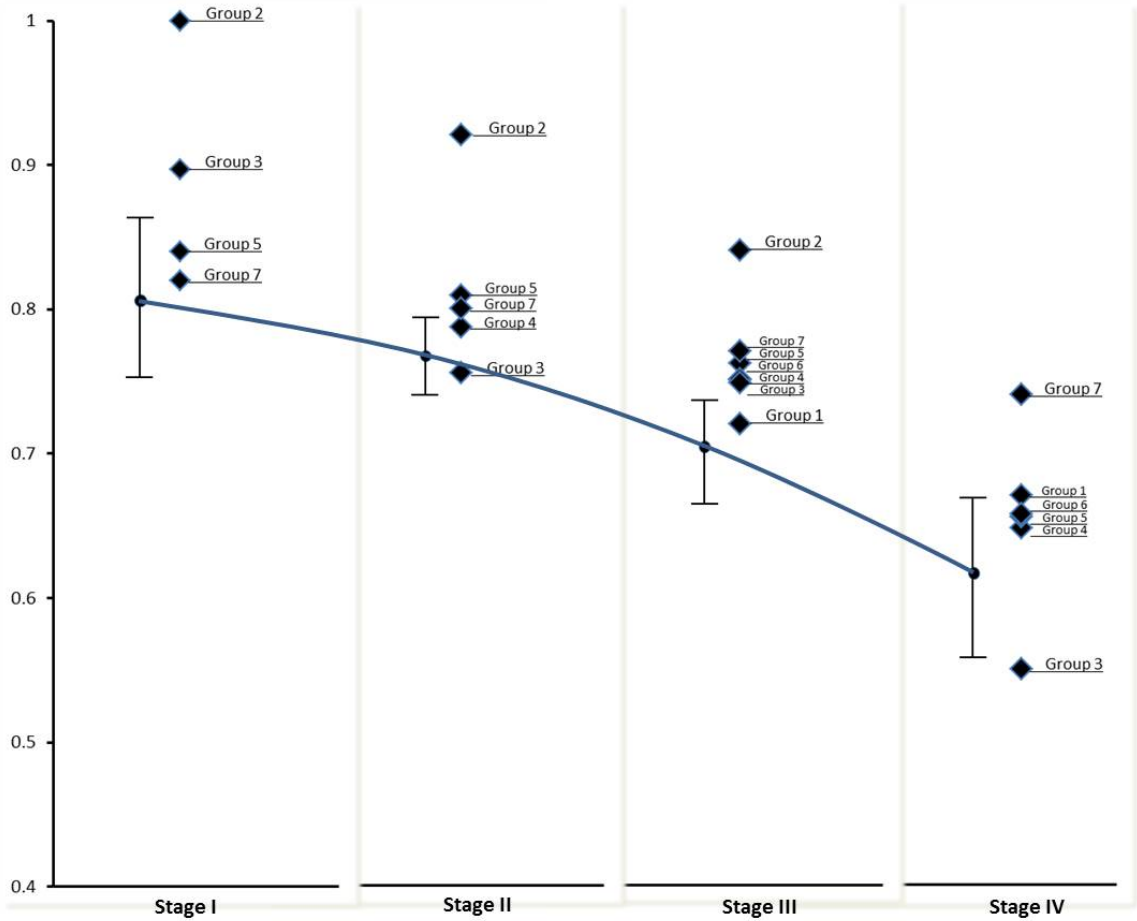
df: degree of freedom; **CI**: confidence interval

Figure 4-2 compares utility values used by modelling studies with meta-analysis mean utility estimates by stages of COPD. Confidence intervals around the means are highlighted. Mean utility values used by modelling studies were above the confidence intervals of mean utility values derived from the meta-analysis in 50%, 60%, 86% and 20% of cases in COPD stages I to IV respectively. Major deviations were captured in group 2 of modelling studies (in stages I, II and III), followed by group 7 (in stages II, III, and IV), group 5 (in stages II and III) and group 3 (in stages I, II and IV). Results of T-test (Table 4-4) showed that the mean utility value used in modelling studies for stage III is significantly different (p-value 0.0266) from mean utility value derived from meta-analysis. Although the differences of utility values in other stages were not statistically significant, modelling studies reportedly used higher utility values than those derived from patient-level data meta-analysis. The percentages of differences between meta-analysis derived mean utility values and mean utility values used by modelling studies were measured, 5.8% to 9.3% at different stages of COPD.

Table 4-4 The differences between utility values used in modelling studies and meta-analysis derived utility values; t-test (95% CI) and simple percentage

	Mean utility value modelling studies	**Mean utility value Meta-analysis**	***P* value**	**% difference in means**
Stage I	0.889 (0.761 –1.018)	0.806 (0.747– 0.866)	0.1311	- 9.3
Stage II	0.814 (0.737 – 0.892)	0.767 (0.740 – 0.795)	0.1652	- 5.8
Stage III	0.751 (0.711 – 0.791)	0.704 (0.670 – 0.739)	0.0266	- 6.3
Stage IV	0.654 (0.590- 0.718)	0.616 (0.556 – 0.676)	0.1897	- 5.8

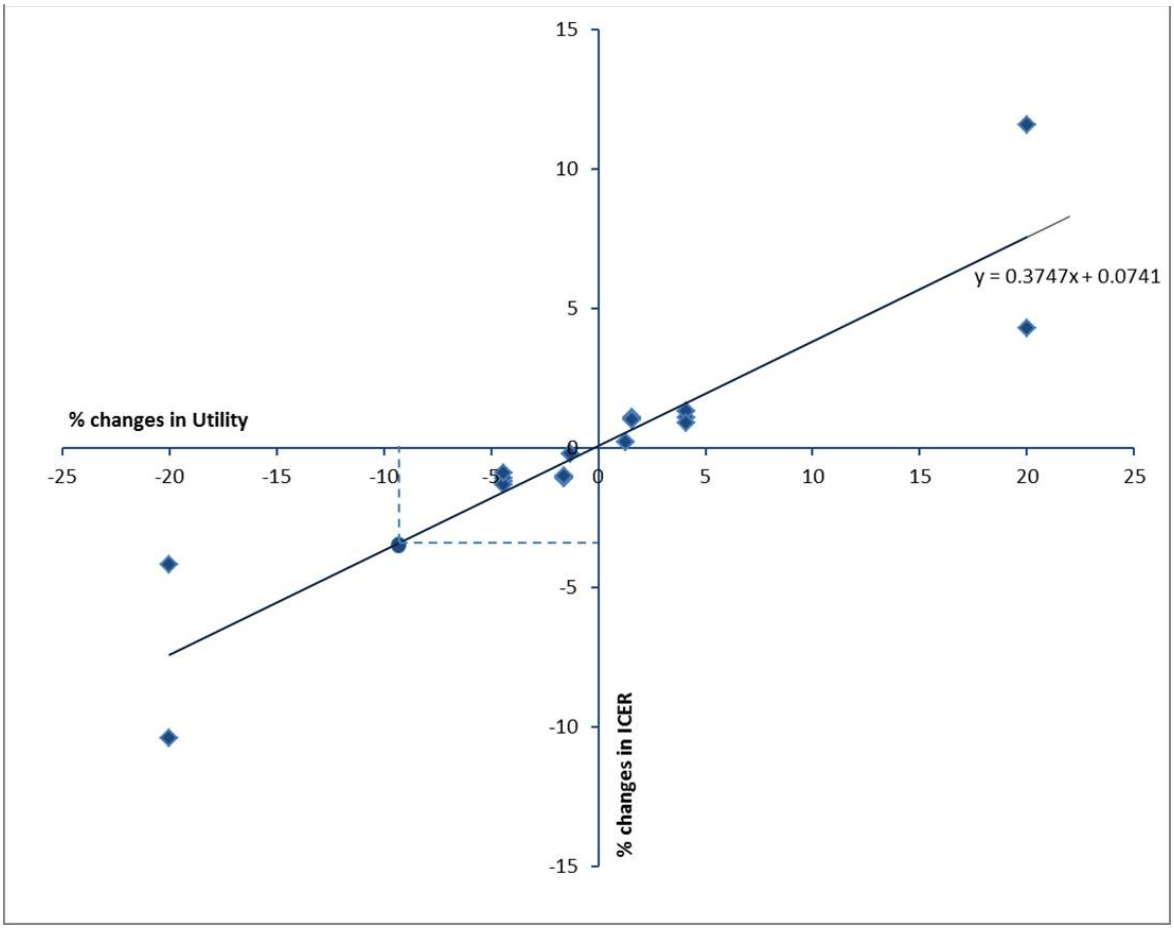
Figure 4-2 Utility scores used in the modelling study groups at each stage of COPD and the meta-analysis estimated mean utility values



Group1: Spencer M et al,[19] 2005; Sun SX et al, [20] 2011; Najafzadeh M et al,[12] 2012
Group2: Sin DD et al, [18] 2004
Group3: Borg S et al, [2] 2004; Oostenbrink J, et al, [14] 2005; Maniadakis, N et al, [10] 2006; Earnshaw SR et al, [5] 2009; Hoogendoorn M et al, [8] 2011
Group4: Oba Y et al, [13] 2009; Gani R et al, [6] 2010; Menn P et al, [11] 2012
Group5: Chandra K et al, [3] 2012
Group6 : Samyshkin Y et al, [17] 2013; Hertel N et al, [7] 2012
Group7: Price D et al, [15] 2011

Estimated mean utility values used by modelling studies at each stage of COPD
Meta-analysis means utility values, surrounded by 95% confidence interval lines

Figure 4-3 Percentage of changes in model output (%Δ ICER) according to percentage of changes in utility values (%Δ Utility) as an input parameter, linear regression model with prediction line



The linear regression model was defined as: %Δ ICER = 0.37 %Δ Utility + 0.08

◆ Observed value derived from sensitivity analysis of two studies, Earnshaw et al [273] & Oba [129]

● Predicted value for ICER based on % difference between meta-analysis mean utility and modelling studies mean utility values

Prediction of %Δ ICER (-3.5%) after -9.3% change in utility is demonstrated as the cross point of dotted lines on the prediction line.

We then examined the association between changes in utility and changes in Incremental Cost Effectiveness Ratio (ICER) as the output of modelling studies in sensitivity analyses (Table D5). Only two studies reported the detailed result of sensitivity analyses on utility values [129, 273]. Oba [129] ran SAs for three and five-year' time horizons for two clinical trials. The range of utility values used in the SAs reported ICER and percentages of change were summarized in Table D6 & D. A linear regression model was defined (Figure 4-3). It showed that there was a significant evidence of a positive association between utility and ICER (*p*-value <0.001); one percentage change in utility value was associated with 0.37% (95% CI 0.30 – 0.45) change in ICER. Figure 3 shows the observed and predicted values of the linear regression model. Prediction of % change ICER (-3.5%) after -9.3% change (Table 4-4) in utility is demonstrated as the cross point of dotted lines. It can be interpreted that if the meta-analysis means utility values are incorporated in the modelling studies the mean % of changes in ICER will be between -2.2% to -3.5% at different stages of COPD.

4.6 Discussion

COPD is a disease of considerable interest to health economists, in part due to the need to evaluate an expanded range of treatment options. For example, there have been four reported evaluations [116, 118, 131, 286] of the drug Roflumilast, all of which have used various simulation models, with a range of values for utility (e.g. 0.67 to 0.751 for stage III of COPD). An important element of evaluations was the utility value assigned to the stages of COPD, as this would influence the estimate of QALYs associated with treatment options. The current study has demonstrated that modelling studies use on average higher values than estimated mean utility from the meta-analysis of the patient-level data. This deviation was significant in stage III of COPD Table 4-4. Furthermore, depending on the stages of COPD, up to six modelling groups (at stage III) used utility scores that were outside the meta-analysis derived CIs.

What impact does the difference between utility values used in COPD models and patient-based utility values have on economic evaluations of COPD therapies? To examine this issue we estimated the relationship between the change in utility and the impact on the ICER, based on a limited number of studies (see Figure 4-3). According to a regression analysis of all available studies, the higher utility values reported in the modelling studies are likely to have a relatively modest effect on the ICER of around 3.5%. However, it should be noted that our analysis of sensitivity is based on only two of the nine modelling studies that reported the effect of utility value as a factor in their SAs (Table D5). Given the wide variation in patient-based utility values, it would be appropriate for all COPD models to include a variation in utility for key health states in their sensitivity analysis in future. If we consider the maximum difference between utility values measured through meta-analysis with mean utility used by modelling studies, we can suggest that our estimated mean utility values may reduce the mean QALYs produced by the COPD model by up to 3.5%. It should be noted that some modelling studies used much higher values than the mean estimate, especially in stage II and III. This is inconsistent with some evidence regarding the modest to the high impact of utility value on the output of modelling studies [118, 121, 129]. This highlights the need for a more systematic approach to be taken when incorporating utility values into COPD models [287].

This study revealed a high level of heterogeneity in utility values derived from patient-level data for all stages of COPD, with the I^2 statistic ranging from 92.7% to 97.9%. This range of diversity has been reported in a previous systematic literature review in COPD [214, 249, 253]. Health economic decision models currently do not account for this degree of variation, as most rely on a single value taken from one patient-level data study. We found that one study [194] used aggregated data from three RCTs and another [288] from six RCTs.

In addition, modelling studies may not align with patient-level data in that they do not fully follow COPD stages. Two studies [109, 220] used merged utility values of adjacent stages in their COPD models and one study [225] used a previous version of COPD severity staging system, ATS 1987. Such variation would be eliminated through the development of a COPD reference simulation model

that used a common set of stages and utility values which were aligned with international staging guidelines [4].

To the best of our knowledge, this is the first study to systematically compare the input assumptions of modelling studies with systematic literature review. This approach can be undertaken for other modelling parameters and it is surprising that despite the trend to use meta-analyses to inform clinical decisions, their use in informing decision analytic modelling studies has been limited. The current review followed the MOOSE 2000 guideline and included a comprehensive and reproducible literature search to capture relevant studies from different perspectives. Included studies and the results were properly documented and visualized in tables and figures, by countries, design, and population of studies.

Our study focused on utility values in COPD stages under stable conditions, but in order to develop a comprehensive COPD model, valid estimations of utility values in exacerbation-affected health states are required. Our literature review has shown that limited studies (Table D4) tried to highlight the effect of mild to severe COPD exacerbations on utility values. This precluded an extension of the analysis from including exacerbation as a state in our meta-analysis, making it difficult to evaluate this aspect of the modelling studies. Measuring health status during exacerbation is a challenging issue due to the difficulty of taking valid HSUV questionnaire responses at the point of exacerbation and later follow-up [225]. In addition, there is controversy around the appropriateness of the EQ-5D Index measure in COPD. Some authors believe that preference-based measures have a limited discriminating ability, especially between moderate and severe COPD [242]. It is claimed that generic HSUV measures (such as EQ-5D Index) are too general and not sensitive enough for COPD.

There are a few limitations applied to this research. First, articles in languages other than English have not considered effectively and only the English version of their abstract, if available, was reviewed. These constraints should be considered when making inferences. Secondly, due to limited resources, this study did not evaluate the quality of the included studies. The same weight was applied to all the

studies, irrespective of sample size or quality of utility measurement. Our recommendation for future study is to investigate and apply appropriate weight based on the quality of included studies. Thirdly, no attempt was made to develop a meta-regression model to investigate the effect of different confounding factors such as sex, education, comorbidity, socioeconomic status or ethnicity on utility values, as the collected studies rarely reported such information and the study sample size was small (ten studies). Fourthly, this literature review was confined to studies that measured utility scores directly from COPD patients, so studies that reported utilities from proxies or through mapping process were not included.

A new approach in disease progression microsimulation modelling using characteristics at the individual level of patients [112] can provide a more flexible tool for predicting accurate measures of outcomes. This can be achieved by incorporating the updated COPD assessment tool introduced in the 2014 GOLD report [4]. This combined assessment approach takes three elements into consideration: spirometric test, exacerbations risk and one of the following disease-specific HR-QoL measures: COPD Assessment Test (CAT) or COPD Control Questionnaire (CCQ). Future meta-analyses will need to take account of these developments and provide appropriate comparisons with the patient-level utilities to determine the applicability of utility values used in more recent COPD models.

As a general recommendation, utility values for decision-analytical modelling studies should fit health states predetermined by the model structure, be elicited from the same population as the model specifies, be up to date, and be derived from a representative sample size. In practice, health economic researchers should justify their assumptions regarding the quality of model parameter inputs and the consistency with published utility values. The advantage of this study is to provide a reference value for each COPD stage that can be used in future economic evaluations and simulation modelling; including estimates of confidence intervals around these summary values which are valuable statistics for sensitivity analysis in COPD progression models [289]. However, there is also a need to try to understand the factors that lead to high levels of heterogeneity across studies involving patient-reported outcomes that rely on the EQ-5D and thereby improve the reliability of health economic

decision models. Regression-based studies such as Rutten et al 2006 [221] tried to explain the factors associated with EQ-5D derived utility values in COPD patient. While this study has focused on utility differences by stage, the technique of comparing model assumption to a meta-analysis of published results can be extended to other factors as more studies report regression based results to explain the variation in utility across COPD patient groups. Especial attention in measuring, reporting and incorporating covariates such as gender, number of hospitals and emergency department visits in the year before baseline measurement, measurement of comorbidity, country of origin and considering different utility value set and tariffs is recommended.

In conclusion, this study is one of the first meta-analyses of HSUV at different stages of COPD. It showed that there were systematic differences between utility values used as inputs in COPD models and results derived from a systematic literature review. This paper suggests that improvement in the consistency of modelling studies may be achieved if published recommendations on good modelling practices [290, 291], especially the data identification, are followed closely as suggested. In this case, if secondary data (meta-analysis) is going to be used, the recommendation is to follow appropriate inclusion and exclusion criteria to meet the relevant of patient characteristics and the clinical situation to the purpose of the model structure.

5 Chapter 5 – Efficiency and cost effectiveness of Cognitive Behaviour Therapy (CBT)-based interventions against psychological illnesses accompanied with chronic Obstructive Pulmonary disease (COPD): Review of literature

5.1 Introduction

Chronic Obstructive Pulmonary Disease (COPD) is an important cause of disability and mortality globally [4]. According to the latest World Health Organization (WHO) estimates [167, 292], currently 64 million people have suffered from COPD and 3 million people died of COPD in 2012. WHO predicts that COPD will become the third leading cause of death worldwide by 2030. Whilst it has been demonstrated that the prevalence of mental health problems is very high in COPD; with a prevalence rate of 8% - 80% for depression and 6% - 75% for anxiety [293-295]; and their impact on health, wellbeing and quality of life are prominent, there has been insufficient attention to the management of this problem in guidelines and clinical literature [296]. The most likely reason is the paucity of evidence regarding the efficiency and effectiveness of the treatment of these problems in COPD patients. Depression may impair patients' ability to adhere the medical regimens (diet, physical activity, quitting smoking, and taking medication regularly), worsening the course of chronic comorbidities, increased avoidance of potentially therapeutic activities that require exertion, poorer outcomes following emergency treatment and may also lead to greater healthcare utilization and related costs [297-301]. Even relatively mild depressive symptoms might reduce patient's quality of life [302]. Presence and persistence of depressive symptoms in old age seem to be associated with future direct costs even after adjustment for comorbidity. The most relevant cost drivers are costs for inpatient care, pharmaceuticals, and home care [303].

Previous studies have revealed impaired cognitive function among COPD patients. Even mildly hypoxic (mean Pao^2 = 66.3 ± 7.0) COPD patients suffer from decrements on tests of abstract

reasoning, psychomotor speed, and memory when compared to gender- and age-matched controls. [304]. Cognitive ability may be damaged in concern with memory, learning ability, attention/concentration, abstract thinking and problem solving. It can reduce the level of daily functioning [305, 306] and consequently can affect compliance with both medication and oxygen therapy that itself increases the risk of acute exacerbation [307, 308]. In a recent literature review of 15 studies, it has concluded that although the cognitive function is impaired in COPD as compared to healthy controls, but the level of impairment is not as severe as in Alzheimer's disease [309]. Moreover, the association between the level of dysfunction and severity of COPD disease is much more significant in severe to very severe COPD. From the methodological point of view, it is interesting to mention that some aspect of cognitive function (e.g. verbal fluency task) may be important to include in models of adherence among patients with COPD. This is the case for interventions that may be mediated by perceived self-efficacy [310].

Female patients have higher levels of anxiety and depression and worse symptom-related QoL. Female patients reported a higher level of dyspnea than males for the same level of ventilatory impairment [294]. Dyspnea is more strongly correlated with depression in women than in men. Anxiety and depressive symptoms are common in patients affected by COPD, even when their disease is mild in terms of FEV1 and respiratory symptoms. Female patients appear to be more exposed to psychological impairment, which correlates well with some specific symptomatic aspects of the disease, such as dyspnea. The recommendation is the psychological aspects need to be carefully assessed in COPD patients, particularly in females.

Cognitive behavior therapy (CBT) is one of the non-pharmacological approaches to the treatment of the anxiety and depression. Its effects are not confined to treating psychological illnesses; it has been effectively used in the management of patients with chronic physical disabilities and reduction of depression in elderly depressed adults [311]. CBT is a structured, psychological intervention in which patient works collaboratively with the therapist to identify the types and effects of thoughts, beliefs and interpretations of current symptoms, feeling states and/or problem areas [312]. Low-intensity

CBT-based psychological interventions (e.g. computerized CBT, online CBT, telephone CBT, or a structured group physical activity program using principles of CBT) are recommended for patients with mild to moderate anxiety and/or depression. High-intensity psychological intervention using CBT in combination with medication is recommended for people with moderate to severe depression [313, 314]. Several meta-analyses have shown that psychological treatments, including CBT, are effective in the treatment of depression in older adults [315, 316]. Furthermore, somatic comorbidity does not adversely affect the positive response of CBT [317]. On the other hand, CBT may alleviate somatic symptoms such as breathing difficulty in elderly patients with COPD [318]. The effect size of evidence favoring the CBT-based treatments, such as Internet CBT, is high in the treatment of depression, anxiety disorders, and severe anxiety [319]. In this case, Cost-effectiveness data were relatively scarce but suggested that CBT has more than 50% probability of being cost-effective compared with no treatment or to conventional CBT when willingness to pay for an additional improvement is zero [319].

This review is intended to formulate an in-depth picture of the CBT-based intervention for anxiety and/or depression problems in patients with COPD, and to reveal some negotiable aspect of applying of this treatment modality in chronic diseases. Due to lack of evidence on the economic efficiency of CBT treatment in COPD, there is an absolute recommendation about conducting economic evaluation studies on different programs for the treatment of psychological problems in COPD patients [296].

5.2 Method

The literature review has been conducted for studies that examined the efficiency of CBT-based interventions on psychological problems and economic evaluation of this approach in COPD patients. The MEDLINE, Web of Science, Scopus, PsyclNFO and PubMed databases were searched. Essential keywords were chronic obstructive pulmonary disease, COPD, elderly population, cognitive behavior therapy, CBT, psychological therapy, depression, anxiety, cost effective, cost benefit, cost utility,

economic evaluation, computer simulation, and economic model. Supplemented articles were selected from articles' reference list.

Studies for inclusion in this review were required to be in the English language, published between before the year 2012. We included studies that were experimental or quasi-experimental of controlled comparative design. Participants were defined as adults (men and women aged 18 years and above) with a confirmed diagnosis of COPD, treated for symptoms of anxiety and depression. The primary COPD diagnosis and severity of the disease was to be determined by spirometry as defined by the GOLD standard. In the absence of spirometry confirmed COPD, studies that provided sufficient clinical documentation of COPD were also considered. Studies including individuals with psychiatric illnesses other than anxiety and/or depression, or other physical comorbidities were excluded.

The Standardized Mean Difference (SMD) and corresponding 95% CI were calculated for continuous data that measured the same outcome utilising different assessment scales. The SMD is a useful indicator of an intervention's effect size, relative to the variability present in the study. Individual trial SMDs were calculated by subtracting the post-treatment mean of the control group from the post-treatment mean of the intervention group, divided by the pooled SD.

RCT studies were assessed according to the following criteria: clear aims, randomization techniques, concealment of treatment allocation, comparability of groups at baseline, blinding of interventionists and participants, eligibility for intervention assessed, description of intervention provided to allow replication, attrition, effect size, details of long term follow-up and sustained change, analysis of confounding variables, power analysis, definition of all outcomes, measured with reliable measurement tools and results provided for each, appropriate statistical analysis and inclusion criteria.

5.2.1 Quality of studies

In order to assess the quality of the studies a comprehensive list of indicators is utilized in this review (adopted from Olivo, 2008 [320]) (Table 5-3). These criteria can be classified under the following headings: patient selection, blinding, interventions, outcomes, statistics.

5.3 Results

Ten RCT articles closely related to the CBT-based treatment in COPD have been captured. Included articles are tabulated in Table 5-1. Overall, the studies made a measurement of anxiety; but in one study the anxiety data was not presented [321]. In all the studies depression and quality of life were measured either using a disease specific or a generic scale. Two studies measured health care utilization or cost [322, 323]. Self-efficacy was the outcome measure in two studies [139, 324].

All the studies utilized standard diagnostic criteria of COPD included spirometry test and covered mild to severe cases; one study included only severe cases [323]. The mean age of the participant ranged from 53.8 years to 71.44 years. The recruitment process consisted of selecting hospital or medical clinic patients, one study relied on patients from primary care practices, and Pulmonary Rehabilitation Programs (PRP). The advertisement was another recruitment tool in some studies [310].

Table 5-1 Characteristics of the included studies on CBT effect in COPD patients

Principal Author	Study design, *Sampling, dropout*	Intervention *(What, duration, group or individual, who delivered)*	No. of Participants, (intervention group) *Inclusion criteria (details of control group)*	Characteristics of Participants	Instruments	Result
Catharina C. M. Jonkers (2012) [324] Netherland	RCT, recruited from primary care practice, 38% in intervention group and 30% in control group,	MPI, nurse-led home provision, 2 to 10 visits in less than 3 months, CBT-based treatment consist of 5 phases, mean visits= 4, the mean duration of visit=61 minutes.	N=361 (183), 180 DM type II and 176 COPD, age>60; minor, mild to moderate depression and dysthymia, (usual care)	Mean age 70.8, male 53.6%,	MINI (Inclusion test), HDRS (Inclusion Test for depression), SCL-90 (Anxiety), GARS (Activity), IPA (Social Participation), Self-efficacy scale	• At nine months after treatment, the MPI was associated with less anxiety (mean difference 2.5; 95%CI 0.7–4.2) • better self-efficacy skills (mean difference 1.8; 95% CI 3.4–0.2), daily functioning (mean difference 1.7; 95% CI 0.6–2.7) • Social participation (mean difference 1.3; 95% CI 0.4–2.2). • Effect sizes for these outcomes were small to medium (0.29–0.40) • No major differences were observed between DM and COPD patients.
Femke Lamers; Catharina C. M. Jonkers; et al (2010) [325] Netherland	RCT recruited from primary care practice, 38% in intervention group and 30% in control group	MPI, nurse-led home provision, 2 to 10 visits in less than 3 months, CBT-based treatment consist of 5 phases, mean visits= 4, the mean duration of visit=61 minutes.	N=361 (183). 180 DM type II and 176 COPD, age>60; mild to moderate depression and dysthymia, (usual care)	Mean age 70.8, male 53.6%,	SF-36 (Quality of life), BDI (depression),	• Less depressive symptoms in interventional group: partially caused by a decrease in depressive symptoms in the intervention group and an increase in depressive symptoms in the control group over time. • 6 50% reduction in depressive symptoms relative to baseline values • No significant difference in quality of life overall but diabetic MPI patients had a better quality of life than diabetic controls
Claire Howard (2010) [323] The UK	CT (within-subject design), hospital patients, 10.5%	4 weekly 2-hour group training sessions (up to 10 people), CBT designed for panic and anxiety, self-control design, six-week telephone follow-up, provided by multidisciplinary team	N=48 (48), COPD stage III or above, Age>71(within-subject design)	Mean age 71, male 60%,	SGRQ (Disease-specific QoL), HADS (Anxiety, depression), satisfaction, Respiratory test, hospital cost data, hospital admission data	• Overall health status and perceived impact of COPD on daily life significantly improved • Non-significant reduction in anxiety • Significant reduction of depression
Cully, Jeffrey A (2010) [326] The USA	Open Clinical Trial, veteran database, 26.1%	tailored CBT (ACCESS), Six 50 min sessions face to face; three 10-15 min telephone sessions, delivered by psychologists	N=23 (23) veteran; COPD and CHF (no comparative)	Mean age 71.44, male 95.7%	BDI-II (Depression), STAI (Anxiety), CRQ (COPD specific QoL), KCCQ (CHF disease-specific outcome), CSQ (Satisfactory)	• Symptoms of depression (effect size = 0.97) and anxiety (effect size = 0.57) were improved at 8 weeks and maintained at 3-month follow-up
Minna J. Hynninen,	RCT, outpatient	7 weekly 2 hr group	N=51 (25) age >40,	Mean age	BAI (Anxiety); BDI-II	• CBT resulted in improvement in symptoms of

et al (2010) [139]	hospital clinic, 10%	sessions CBT, led by master-level psychology student , followed by encouraging telephone call	FEV1<80%, FEV1/FVC<0.7, BAI>15, BDI-II>13, (Standard care of COPD + telephone calls to monitor their psychological wellbeing)	59.4 in CBT, Male 50%,	(Depression); SGRQ (Disease-specific QoL), PSQI (sleep quality); actigraphy (self-efficiency)	anxiety and depression, with effect sizes of 1.1 and 0.9 at post-treatment. • The improvement was maintained at the 8-month follow-up, with effect sizes of 1.4 and 0.9. In the control group, there was no significant change.
Rossane Frizzo. de Godoy (2009) [327] Brazil	RCT, patients from PRP,	12-week treatment; 24 sessions of physical exercise, 24 sessions of physiotherapy, 12 psychological sessions, and 3 educational sessions. Assessment after 24 months	N=30	Mean age 60.3, male 73%	BAI (Anxiety), BDI (Depression), 6MWD (Walking competency),	• The benefits provided by the PRP in terms of the indices of anxiety, depression and quality of life, as well as the improved 6MWT performance, persisted throughout the 24-month study period.
Kunik ME, et al (2008) [293] The USA	RCT, hospital patients,	8 1-h sessions of group CBT, led by interns and fellows + home practice, vs COPD education intervention	N=238 (118), FVC<70%, FEV1<70%, BAI≤16, BDI-II>14, treatment by a GP (education only)	Mean age 66.3, male 96.2%, mild anxiety, and depression	CRQ (COPD specific QoL), SF-36 (QoL), BAI (Anxiety), BDI-II (Depression); 6MWD (Functional status); Service use by diary	• No significant difference between two study groups in: - QoL, anxiety and depression, at 8 weeks and during follow-ups - Pre and post treatment health care utilization • The effects maintained during follow-ups 44 weeks
Stanley, M. A; Kunik ME, et al (2005) [300] The USA	Case Study	CBT-RADAR: eight (1 hr) weekly group sessions, up to 10 people. Final session assessment, 12 months assessment. led by psychology intern and post-doctoral fellows	N=5, moderate depression, and anxiety		CRQ (COPD specific QoL), SF-36 (QoL), BAI (Anxiety), BDI-II (Depression)	• CBT is effective but Individual tailored CBT intervention is preferable
Dagoberto V. de Godoy (2003) [137] Brazil	RCT, patients from PRP	12-week treatment; 24 sessions of physical exercise, 24 sessions of physiotherapy, 12 psychological sessions, and 3 educational sessions. Group 2 did not participate in psychotherapy sessions. Last assessment after 12 months.	N=30 (14) confirmed COPD spirometry (PR and education)	Mean age 60.3, male 73%,	BAI (Anxiety), BDI (Depression), 6MWD (Walking competency), SGRQ (Disease-specific QoL)	• Including psychotherapy in a pulmonary rehabilitation program for COPD reduced patients' anxiety and depression levels but did not modify 6MWD performance.
Emery, et al (1998) [310] The USA	RCT, advertisement, 7.6%	EXESM: 4 hr per day for 5 weeks intensive exercise; Followed by 5 weeks, 3	N=79 (29), age >50, (two control groups: education and stress	Mean age 66.6, male 37%,	Pulmonary functions test; Bicycle ergometry testing; CES-D;	• Greater COPD knowledge was associated with increased anxiety • EXESM leads to significant change in pulmonary

	times per week exercise; 37 exercise sessions, 16 educational sessions, 10 stress management sessions ESM: no exercise WL group: no interventions. small group (1-5) therapy conducted by psychologist	management group (ESM group, 25) & waiting list (WL group, 25) not to alter their behaviour up to 10 weeks)	Bradburn Affect-Balance Scale; STAI (Anxiety); SCL-90-R (Depression and Anxiety), MHLC (QoL). SIP (QoL), DVT & FTT & TMT & WAIS (cognition) ….	function, reduced anxiety, and improved cognitive performance

PRP: Pulmonary rehabilitation program; **RCT**: Randomised control trial; **QoL**: Quality of life; **DM:** Diabetes mellitus; **BDI–II**: Beck Depression Inventory II; **STAI**: State/Trait Anxiety Inventory (T: Trait; S: State); **CRQ**: Chronic Respiratory Questionnaire; Kansas City Cardiomyopathy Questionnaire; **SF-36**: Medical Outcomes Survey Short Form-36 (**PCS**: Physical Health; **MCS**: Mental Health); **FEV1**: forced expiratory value in 1 second; **FEC**: forced vital capacity; **FEV1 %**: predicted, forced expiratory value; **TD6MW**: Total Distance in the 6-Minute Walk, measured in feet; **SGRQ**: St. George Respiratory Questionnaire; **EXESM**: exercise, education, and stress management; **ESM**: education, and stress management; **WL**: waiting list; SCL-GSI: summary score of psychological distress from the Hopkins Symptom Checklist-90-Revised;

Table 5-2 Effect of psychological interventions for COPD on symptoms of anxiety and depression at post-treatment

Principle Author	Intervention	Outcome	Post treatment mean (SD)		SMD (95% CI)	Outcome summary
			Intervention	Control		
Catharina C. M. Jonkers (2012) [324]	Minimal Psychological Intervention	Anxiety (SCL-A)	20.4 (6.8) 114	22.8 (6.5) 122	-0.36 (-0.62 to -0.10)	The intervention was effective in chronically ill old patients.
Femke Lamers; Catharina C. M. Jonkers; et al (2010) [325]	Minimal psychological intervention vs Usual care	Anxiety (SCL-A) Depression (BDI)	19.85 (0.87) 15.04 (1.00)	23.54 (0.84) 17.96 (0.96)	-0.12 (-0.46 to 0.23) -0.29 (-0.64 to 0.06)	Intervention group showed lower symptoms of anxiety and depression compared to control group. Intervention group also improved QoL measures
Claire Howard (2010) [323]	group cognitive-behavioural breathlessness intervention	HADS (Anxiety, depression)	9.6 7.5	-	-	Significant improvements in depression and health status. There was a non-significant improvement in anxiety.
Cully, Jeffrey A (2010) [326]	CBT, open trial	Anxiety (STAI) Depression (BDI-II)	36.77 (13.37) 10.47 (7.77)	-	-	Symptoms of depression (effect size = 0.97) and anxiety (effect size = 0.57) were improved at 8 weeks.
Minna J. Hynninen, et al (2010) [139]	CBT vs Enhanced standard care	Anxiety (BAI) Depression (BDI-II)	11.0 (6.1) 13.4 (5.9)	18.7 (10.1) 19.7 (8.9)	-0.53 (-1.08 to 0.03) -0.54 (-1.10 to 0.02)	CBT intervention group significantly reduced symptoms of anxiety and depression. No significant changes in control group
Rossane Frizzo. de Godoy (2009) [327]	pulmonary rehabilitation program (PRP)	Anxiety (BAI) Depression (BDI-II)	5.5 ± 4.4 6.0 ± 5.8	-	-	The benefits provided by the PRP in terms of the indices of anxiety, depression, persisted throughout the 24-month study period.
Kunik ME, et al (2008) [293]	CBT vs COPD education	Anxiety (BAI) Depression (BDI-II)	15.89 (14.87) 14.19 (13.69)	17.46 (14.54) 14.54 (13.47)	-0.11 (-0.46 to 0.25) -0.03 (-0.38 to 0.33)	Both intervention and control groups significantly improved anxiety and depression and QoL, with no significant difference between intervention groups
Stanley, M. A; Kunik ME, et al (2005) [300]	-	-	-	-	-	-
Dagoberto V. de Godoy (2003) [137]	PR with Psychotherapy vs PR without Psychotherapy	Anxiety (BAI) Depression (BDI)	4.2 (3.8) 5.0 (4.5)	9.2 (8.6) 12.3 (11.8)	-0.73 (-1.48 to 0.01) -0.08 (-1.54 to -0.05)	Intervention group showed significant reduction in anxiety and depression levels; however, it did not modify physical performance

Emery, et al (1998) [310]	Education and stress management	Anxiety (STAI), depression (CES-D)	36.7 (7.9) 11.9 (9.3)	37.0 (8.7) 12.5 (7.9)	-0.04 (-0.76 to 0.69) -0.07 (-0.8 to 0.66)	No observed change in reduced anxiety,

SMD: Standardized Mean Difference, **SCL-A:** Anxiety subscale of the Symptom Checklist-90**; STAI:** The State-Trait Anxiety Inventor**; BDI-II**: Beck Depression Inventory 1996 revision; **HADS**: Hospital Anxiety and Depression Scale; **CES-D**: Centre for Epidemiologic Studies Depression Scale

The main purpose of the studies was to evaluate the efficacy of CBT-based interventions in reducing psychological problems in COPD patients. Two studies examined the effectiveness of the intervention on other chronic diseases, Diabetes Mellitus type II [324] and Congestive Heart Failure [326], and compared the results with COPD. Three studies investigated the efficacy of the CBT-based intervention on physical activity of COPD patients [137, 293, 310, 327]. Hynninen et al, 2010 [139] examined the effects of age and sex on the change in symptoms of anxiety and depression. The unique feature of this study was its focus on the quality of sleep in COPD patients before and after the intervention. de Godoy, 2009 [327] assessed the long-term, 12-months, effect of CBT-based therapy.

The objectives of Kunik, et al, 2008 study [293] went beyond the efficacy of CBT therapy on anxiety and depression. This study tried to disclose changes in use of health services after incorporating CBT intervention within usual educational courses in COPD patients. Howard et al, 2010 [323], tried to explore the CBT breathlessness therapy for severe COPD patients on their health status, accident & emergency attendance and length of stay in the hospital. The patient level data of two studies were the same, DELTA project; Jonkers et al, 2012 [324] investigated the benefit of a kind of CBT-based therapy, Minimal Psychological Intervention (MPI) on self-efficacy, anxiety, daily functioning and social participation of COPD and diabetic type II patients and Lamers et al, 2010 [321], described the effect of this therapy on depression symptoms.

Altogether 860 participants were included in these ten different studies, 470 were received a psychological intervention. All studies have mentioned their own exclusion and inclusion criteria. Some of the exclusion criteria were in common: treatment with antidepressant, major psychiatric problems (bipolar disorder, schizophrenia, alcohol or non-nicotinic substance abuse or dependence), current psychological/psychiatric treatment (to prevent contamination from other treatment), serious cognitive problems (a score of 23 or less on the Mini-Mental State

Examination), on a waiting list for a nursing home, bedridden, loss of spouse within the previous three months, not fluent in current language and coexistence of other overwhelming diseases such as myocardial infarction and cancer or Tuberculosis that limit their participation in exercises. The nature of inclusion criteria depended on the study. Some of the inclusion criteria were as follows: confirmed COPD patients, having at least two symptoms of depression present for more than half of the days, one of them being lost of interest or depressed mood [324], Beck Anxiety Inventory (BAI) score of ≥ 16 and/or BDI-II score of > 14 [293].

Six studies were designed as RCT; while one study was a case report about implementation of a CBT-based therapy that used as a pilot exercise [300] for another RCT study [293]. One study utilized methodology of "within subject design" for assessing the effects of CBT intervention and "retrospective between subject design" for measuring hospital admission and related costs for participants [323]. Cully's study, 2010 [326] has been described as an open clinical trial.

Seven studies were designed to have a control group. Control intervention in two studies was usual treatment according to COPD protocol [324, 325], one study added telephone calls to usual care to monitor the psychological wellbeing of the control group [139], two studies provided additional educational material to usual care [137, 293], one study used within-subject control design (Howard, 2010) and one study accommodated two control groups one education and stress management group (ESM) and the other waiting list group (WL) not to alter their behavior up to 10 weeks. The last three studies did not have any comparative group [137, 300, 328].

Seven studies assessed CBT-based interventions. Three of them provided individual tailored CBT based therapy [321, 324, 328] and the others delivered group sessions of CBT interventions. One study utilized psychotherapy [137, 327] and one study used stress management sessions [310]. The cognitive behavioural interventions delivered in varying time

and formats, from 2 sessions [324] up to 12 sessions [137] and highly structured with five phases [324] to simple stress management sessions [310]. Three studies provided individual tailored CBT intervention [321, 324, 328], the number of visit and content of the CBT module depended on condition and progress of patients. The psychological therapy offered over 12 weekly psychotherapy sessions [137] or as 16 stress management sessions [310].

Nurse delivered intervention in two studies [321, 324] and psychologist in three others [137, 310, 328]; psychology intern, post-doctoral fellows or master level psychology student conducted an intervention in three studies [139, 293, 300]. And one study utilized a multidisciplinary team [323]. All the studies offered the interventions through face to face contact at the hospital, clinic or home. Encouraging telephone follow up utilized by Hynninen, 2010 and Howard, 2010 [139, 323]. Only in one study, telephone sessions, three 10-15 minutes, as part of CBT therapy were offered [328].

A summary of outcomes and individual SMDs for each study is shown in table 5-3. Overall, the individually calculated SMDs appear to suggest that the treatment effect direction favors psychological interventions for anxiety and depression; however, it is critical to note that the SMD values represent the separate effects of each study, and it is not possible to assert conclusions about the interventions' summary effect. The size of the separate treatment effects and their significance are varied, with most values found within the small 0.2 to medium 0.5 effect.

Quality of the studies was assessed in four domains, Table 5-2. Patient selection: different types of randomization have been utilized; satisfactory randomization methods were utilized in studies, using SAS PLAN procedure, flipping a coin [293], random number table [310], block randomization [321, 324] or it was not completely described [137, 139, 327], and one study used within-subjects-design method for outcomes [323]. The study of Cully, 2010 [328], was

not RCT and Stanley's study was a case study. Baseline comparability was mentioned between control and intervention groups in six studies [137, 310, 321, 324, 327], except for mean education years, CBT>Control [139].

Blinding: Treatment allocation group concealment was treated in one study [310]. Participant blindness about the other group intervention was described in de Godoy, 2009 & 2003 [137, 327] research and study personnel performing assessments were blinded to a treatment condition in Kunik, 2008 [293] research. In other studies, due to the nature of the intervention, group assignment was not blinded for participants and therapists [139, 321, 324], but Data entry was performed by researchers blinded to the allocation [324, 325].

Table 5-2 Quality of included studies in CBT trial in COPD patients

Quality Criteria	Studies, first author, year of publication									
	Jonkers 2012	Lamers 2010	Howard 2010	Cully 2010	Hynninen 2010	De Godoy 2009	Kunik 2008	Stanley 2005	De Godoy 2003	Emery 1998
Clear definition of aims	2	2	2	2	2	2	2	2	2	2
Patient selection										
Clearly defined inclusion and exclusion	2	2	2	2	2	2	2	2	2	2
Method of Randomization described	2	2	0	0	2	1	2	0	1	2
Randomization concealed	2	2	0	0	2	0	2	0	0	2
Treatment allocation concealed	0	0	0	0	2	0	0	0	0	2
Baseline comparability analysed	2	2	0	0	2	2	2	0	2	2
Blinding										
Blinding of participants	0	0	0	0	0	2	0	0	2	0
Blinding of assessor	0	0	0	0	0	0	2	0	0	2
Blinding of investigationists	0	0	0	0	0	?	0	0	?	0
Intervention										
Adequately described protocol	2	2	2	1	2	2	2	2	2	2
Control group utilized	2	2	2	0	2	2	2	0	2	2
Detail of treatment of control group	2	2	1	0	2	2	2	0	2	2
Comparability of groups	2	2	2	0	2	2	2	0	2	2
Attrition rate	2	2	2	2	2	2	2	0	0	2
analysis of attritions	2	2	0	2	0	0	2	0	0	2
Description of withdrawals	2	2	0	0	2	0	2	0	0	2
Reasons for attrition	2	2	2	2	2	2	2	0	0	2
Long term follow up time	0	0	1	0	0	2	1	2	1	0
Outcomes										
Clear definition of outcomes	2	2	2	2	2	2	2	2	2	2
Reliable measure of outcomes	2	2	2	2	2	2	2	2	2	2
Statistics										
Power of analysis done	2	2	0	0	2	0	2	0	0	0
Effect size reported	2	2	0	2	2	0	2	0	0	0
Missing values dealt with	2	2	0	0	2	0	2	0	0	0
Appropriate statistical analysis	2	2	2	0	2	1	2	0	1	2
Adequate sample size	2	2	0	0	1	0	2	0	0	0
Intention to treat analysis	2	2	2	0	2	0	2	0	0	0
Total score / 52	42	42	24	17	41	28	41	12	23	36

Interventions: Reasons for withdrawal to participate in a study such as a problem with transportation, does not feel anxiety/depression is a problem, no time, feeling too seek or fatigued, and lower educational level of the population was stated in two studies [139, 293]. Attrition rate and report of analysis about the differences between groups have been described in five studies [139, 310, 321, 324, 328]. There was no dropout in studies except in Howard's study which was attributed to the death of the patients.

Statistics: Two studies performed a Priori Power Analysis in order to estimate sample size [293] but the number of participants estimated in the power analysis was not reached by the end of the study period in one of them [139].

Generally, the studies utilized similar statistical methods specifically t-tests and χ^2 for comparability of groups, ANOVA, MAONVA, Poisson regression to estimate the event rate and rate ratios between groups and random coefficient model, ANCOVA, to test differences between groups at different points in time.

Anxiety measured in seven studies. Improvement in anxiety scores was reported in six studies. One study revealed that the condition of control group deteriorated, while the intervention group remained stable. The difference reached significance at the last follow-up, nine months. [324]. In one study, the difference between pre- and post-intervention anxiety level was not significant [323]. One study did not demonstrate any difference in improvement between intervention and control arms [293].

Depression measures were used in seven studies. Improvement in depressive symptoms was showed in seven studies. One study revealed that the intervention group had significantly less depressive symptoms than the control group after the second follow-up, three months [321]. And depression was significantly lower in the post-intervention period [323]. In contrary,

Hynninen, 2010 [139] showed this improvement was not persistent during 2 and 8 months follow-up after the intervention. In addition, there was a negative covariance between intercept and slope (rate of change) implying that individuals with lower scores at baseline changed less compared to individuals with higher baseline scores. One study did not show a significant difference in improvement between intervention and control groups [293].

Long-term follow-up of changes after the intervention was reported in one study, a sustained positive effect of the intervention on reducing anxiety and depression over 24 months and improvement of the quality of life [327]. In addition, 44 weeks follow up that performed by Kunik et al (2008) [293] showed persistent significant improvement in anxiety, depression, and QoL but still no significant differences in changes between groups.

The self-efficacy measures reported in one study, demonstrating the difference between control and intervention groups, more self-efficacy skills in the intervention group after first and second follow-ups but not in a strong significance [324].

Daily functioning, as one of the first outcomes, was poor in the control group and it was consistent across all follow-ups and reached significance after the second one [324]. Overall health status and perceived impact of COPD on daily life after intervention improved but the questionnaires did not generate a consistent response in all aspects, indicating that the used scale (SGRQ) may not be sensitive enough for assessing heath status in this disease [323]. Physical activity was measured by Kunik, 2008 [293], and de Godoy, 2003 [327], and both showed significant improvement in intervention group over the control group.

For social participation, the control group experienced significantly less participation than the control group after third follow-up, nine months [324].

CBT clinical trials in COPD

Only two studies performed quality of life analysis, producing mixed results. One study measured both generic and disease-specific QoL, although the significant improvement was traced in disease-specific QoL (Chronic Respiratory Questionnaires, CRQ) and generic QoL (SF-36) subcategory mental health and emotional composite scores, but the change did not differ significantly between groups [293]. Cully 2010, revealed that CRQ emotional and fatigue subscales improved at 8 weeks but declined by the 3 months follow-up and no changes obtained for the dyspnoea subscale.

Disease-specific alteration on the effects of intervention was not traced; except that the effect of COPD on daily functioning is much profound than DM-II [324].

Health care service utilization, as the secondary outcome, measured in different ways in two studies. Using hospital admission data showed that Accident and Emergency unit admission and length of stay are much better in the intervention group but it is only significant when considering the length of stay [323]. Kunik, 2008 [293] showed that ratios of post-treatment to the pre-treatment number of visits (outpatient, mental health and emergency visits and hospital admission) in the intervention and control groups were equal.

in one study, the CBT therapy improvement effect on psychological problems was shown for both COPD and CHF patients but it cannot be specifically attributed to COPD alone [328].

Jonkers C.M. et al 2009 [329] did not find any significant difference in the annual cost and effects of the usual care provided by physicians at their offices with the CBT-based Minimal Psychological Intervention (MPI) for mild to moderate depression of COPD and Diabetes Mellitus (DM) type II delivered by trained nurse at home.

Two studies assessed the satisfaction of the participants and/or carers. Howard, et al, 2010, [323] showed that more than 90% of patients and carers accepted the intervention as a tool for understanding the problem and condition of the COPD disease and were less distressed when breathless, were more able to relax. Additionally, Cully, 2009, [328] standardized satisfaction data from the Client Satisfactory Questionnaire (CSQ) suggest that patients experienced the intervention to be both highly satisfying and effective for helping them cope with their emotional and physical health difficulties.

5.4 Discussion

This study identified ten recent research studies between 1995-2012 years; with various qualities, focusing on CBT-based interventions to improve the psychological problem and quality of life of patients suffering from COPD. It compares in accordance with previous reviews: Baraniak et al, 2011 (n=9) [135]; Coventry, 2008 (n=4) [330]; Cafarella, et al, 2012 (n=12) [296]. In addition, this study reviewed two Economic Analysis research studies, dealing with the cost of COPD and cost utility of CBT intervention. The study populations predominantly were patients with moderate to severe COPD disease with comorbidity of mild to moderate anxiety and/or depression. Two studies included other chronic diseases and tried to compare the effect of CBT-based therapy on their psychological wellbeing with COPD patients. Eight studies utilized CBT-based interventions, one intervention was based on psychotherapy and one study examined the exercise rehabilitation and stress management.

In the case of the outcomes, unlike the previous literature reviews and older studies (later than 1995), fortunately, the reviewed studies are very comparable. Almost all the studies reported all relevant outcomes using the same measurement tools. The quality of life was considered as the first outcome in one study and as the second outcome in seven other studies. Although both generic and disease-specific scales were used; the tendency was to divert from disease specific

to generic during past years. This may be due to the generalizability and more accuracy of the results of the generic scales. The same trend can be traced in utilizing measurement tools for depression and anxiety; this chronological change is in favour of comparability and a higher standard of new research studies. This is true in regard to the criteria describing the severity of COPD disease. Consistency in use the GOLD guidelines should be considered as well as evaluation of the long-term benefits of intervention in terms of health outcomes and cost-effectiveness [135].

The majority of studies showed the improvement in depression symptoms of patients in intervention arm but the effect was not persisting a long time after the intervention. Mixed results reported for the effect of interventions on anxiety comorbidity. Two studies did not show any improvement and another study reported a positive effect after nine-month follow-up. The controversy ineffectiveness of interventions, that have been shown to be effective in alleviating anxiety and depression in the general population, may be explained by the fact that the some symptoms of COPD disease are overlapping with the items used to measure these psychological outcomes, for example, fatigue symptom and depression. In addition, it is possible that some techniques (e.g. voluntary hyperventilation) that are used in this kind of therapies may not be feasible for use in COPD patients [135]. The other explanation is insufficient powered studies due to small sample sizes ($n<50$) that leaded failure in detection of significant differences on outcome measures. Power calculation was done in four studies and the number of estimated participants in one of them was not reached by the end of study period [139]. Additionally, the validity of nonrandomized clinical trial study [328] may be compromised by methodological bias and uncontrolled confounding factors. The other important issue is most of the studies treated depression not independently from anxiety, which might lead to biased results and less optimal treatment of the depression in COPD patients. The reason is that recovery of patients with depression and comorbid anxiety is much longer than depressive alone patients and have a higher risk of chronicity of depression and resistance to treatment [311].

Another concern about the efficacy of CBT-based interventions, related to the isolating treatment effect of CBT from concomitant treatments in control or intervention groups, such as pulmonary rehabilitation, education or exercise. Emery, 1998, [310] suggested that improvement in the psychological problem of the patients in EXESM arm is the effect of the intensive exercise program not the stress management component of the intervention. In fact, patients in ESM arm experienced increased psychological distress that suggested behavioral education program might not by itself sufficient to alleviate anxiety and depression in COPD patients. By contrast, de Godoy, 2003, indicated that exercise alone could not reduce the depression and anxiety symptoms of patients in his intervention group. This study showed that both the intervention and control groups improved their exercise capacity but only patients who received both exercise training and psychotherapy, experienced a reduction of anxiety and depression.

It has been reported that dyspnea and lower health-related quality of life are more prevalent in women with CPOD than men are, regardless of lung function and burden of smoking (Martinez, 2007). Women seem to be more susceptible to some of the systematic complication of COPD, such as muscle dysfunction or fat-free body mass depletion [331, 332]. Women may also have a tendency to cope with the illness in unfavorable ways, which might elevate emotional distress [333]. The high prevalence of psychological comorbidity in women may contribute to both dyspnea and lower health-related QoL. Hynninen et al, 2010 [139] showed that female sex and younger age were associated with higher BAI and BDI-II scores at baseline, and age had a differential effect on change over time, younger patient tended to get worse in due course. These evidences underline the importance of considering the female and younger age groups among COPD patients. It is worthy to consider that younger adult may be more adept than older adults in learning the skills and tools associated with CBT and have a higher cognitive functioning, so they may response to CBT- based treatment more than older adults.

CBT clinical trials in COPD

Cully et al, 2010, [328] in their study found that over 50% of enrolled patients were experiencing co-occurring clinically significant levels of depression and anxiety symptoms. The fact that patients with chronically ill patients (Congestive Heart Failure and COPD) frequently encounter both depression and anxiety suggests the importance of screening for both conditions and offering clinical services that address these overlapping but unique patient needs. Some trials using conventional CBT approaches for medically ill patients did not show a significant effect on depression and anxiety symptoms outcomes [293]. Changes to the current CBT intervention such as an integration of physical and emotional health concerns and use of individual appointments, shorter treatment duration, incorporation of telephone sessions, and increased patient choice are likely reasons for the apparent increase in engagement and treatment effects. Cully, 2010, [328] suggested that tailored, focused, and flexible CBT interventions have the potential to address the multifaceted physical and emotional health needs of multi-morbid patients with chronic disease such as CHF and COPD.

Consideration should also be given to the content and structure of the CBT psychological sessions most appropriate for the COPD patients. Most of the studies reviewed in this report, utilized face-to-face, group-based therapy delivered by a single therapist; and given that fact that most of them found not very significant positive results, other format and delivery methods of CBT-based treatment may be more effective and suitable for COPD patients. Considering the significant effect of recent studies [324, 325, 328], patient-tailored sessions or protocols based on elective modules appropriate for the patients' most pressing needs, are recommended. It is suggested that group based CBT may be too inflexible to meet the needs of a heterogeneous group of COPD patients [330]. Additionally, the sessions may be offered conveniently by telephone, face-to-face or even computerized internet, based on patients' preference. Incorporating CBT based therapies for COPD patients, who are usually disabled and socially deprived, within primary care facilities settings, should be investigated. In this context, nurse-

led CBT including short-term home visits may be effective in mild to moderate depression or anxiety in COPD patients [321, 324].

Disparities in socioeconomic and educational levels may affect the outcomes of self-management interventions alleviating depression and anxiety symptoms [334]. Patients with a lower level of education who have a diminished sense of control and poorer health outcomes may have a lower outcome in terms of adherence to treatment, daily activities, and emotional consequences. Thus, differences in education should be taken into account when self-management interventions are implemented; otherwise, self-management support might widen rather than narrow the differences in health outcomes between patients with chronic general medical conditions who have different levels of education [334].

It can be concluded that CBT-based therapy may be an efficient treatment modality for elderly people with COPD disease. This conclusion may be reinforced by the fact that, compliance with and feasibility of medical treatment of psychological disorders in elderly people because of fear of side effects, frustration with taking many medications and denial of psychological symptoms is very low. In contrast, the compliance and satisfaction with CBT based treatments in this group of patients seem to be very good.

6 Chapter 6 – Cost-utility analysis of telephone-based cognitive behaviour therapy in Chronic Obstructive Pulmonary Disease (COPD) patients with anxiety and depression comorbidities: a randomized control trial

This chapter is going to be submitted for publication.

6.1 Abstract

Depression and anxiety as a prevalent comorbidity in Chronic Obstructive Pulmonary Disease (COPD) are associated with the high volume of health services utilization and deterioration of the quality of life. This study evaluated the cost-effectiveness of telephone-based cognitive behavioural therapy (TB-CBT) in comparison with a usual care plus befriending program in COPD outpatients with mild to severe depression and/or anxiety.

Alongside a clinical trial, the cost-utility analysis was performed to measure cost and quality-adjusted life years gained based on the Assessment of Quality of Life (AQoL-4D) measure. Multiple imputation for missing data, baseline correction of outcomes and non-parametric bootstrapping were applied.

TB-CBT group was associated with a significantly negative incremental total health care cost of AUS -$352.3 (p-value <0.001, SE: 39.64) per patient and slightly negative incremental quality-adjusted life year (QALY)-gained of -0.0071 (p-value 0.542, SE: 0.011) per patient within the trial time horizon. Incremental cost-utility ratio (ICUR) was a positive ratio resulted from cost saving and QALY sacrificed: AUS $49,868.7 (95% CI -26,407 to 11,636) reduction per QALY loss (located in the South West quadrant of the ICUR plane).

TB-CBT can be considered as a cost saving approach. With consideration of AUS $64,000 ceiling/flooring ratio of societal willingness-to-accept (WTA) for an additional QALY sacrificed and after applying the WTA/willingness-to-pay ratio of 1.9, this study showed that the probability of TB-CBT being a cost-effective option over control was less than 0.36. Clinical trials identifier: ACTRN12612000254897. Available from www.anzctr.org.au/ACTRN12612000254897.aspx.

6.2 Highlights

- Depression and anxiety comorbidities are major influential factors in lowering health state in COPD
- Telephone-based cognitive behavioural therapy can be considered as a cost saving approach
- This study provides a distinctive interpretation of the incremental cost-utility ratio

6.3 Introduction

Depression and anxiety are common and widespread comorbidities in patients with chronic diseases such as Chronic Obstructive Pulmonary Disease (COPD) and diabetes [295, 335-339]. The reported prevalence rates were between 8% – 80% for depression and 6% – 75% for anxiety in COPD patients [293-295, 337]. Untreated and undetected anxiety and depression symptoms may increase physical disability, health-care utilization, in compliance with medical treatment and mortality following hospitalization after exacerbations [337, 340, 341]. Whilst it has been demonstrated that the prevalence of mental health comorbidities is very high in COPD and their impacts on health, wellbeing and quality of life are significant [342-345], there has been insufficient attention to the management of these problems in guidelines and clinical literature [346]. The most likely reason is the paucity of evidence regarding the efficiency and effectiveness of the treatment of these problems in COPD patients.

Cognitive Behavioural Therapy (CBT) is a structured, minimal psychological intervention in which patient works collaboratively with a therapist to identify the types and effects of thoughts, beliefs and interpretations of current symptoms, feeling states and/or problem areas (for the definition refer to the chapter 5) [347]. CBT is one of the non-pharmacological approaches for the treatment of anxiety and depression. Its effects are not confined to treating psychological illnesses. It has been effectively used in the management of patients with chronic physical disabilities and reduction of depression in elderly depressed adults [311]. New ways to administer CBT such as self-help, telephone- based (TB-CBT) and internet-based CBT can improve access, increase compliance to the treatment and reduce costs [348, 349]. While there is strong evidence that behavioural treatments are in general cost-saving and reduce unnecessary medical usage [350], cost-effectiveness evidence on non-pharmacological intervention for psychological problems in COPD patients is rare. The clinical effectiveness of CBT in COPD patients has been investigated in a few studies [137, 139, 293, 300, 310, 323, 324, 326, 327].

But the lack of evidence in the economic evaluation of this intervention in COPD is prominent [329]. A robust evaluation and economic investigation is justified. Therefore, a randomised control trial (RCT) was developed to measure effectiveness as well as cost-effectiveness of TB-CBT on the level of anxiety and depression in a sample of outpatient COPD older patients (January 2012 until January 2014) [351]. The aim of the current study was to assess, from a health service payer perspective, the cost-utility of the TB-CBT compared with a standard care without CBT.

6.4 Methods

6.4.1 Study design

This economic evaluation used data from the TB-CBT clinical trial which has been described in detail elsewhere [351]. The study was designed as a pragmatic, two-armed RCT with a baseline measurement (before randomization) and two follow-up measurements at post-intervention and eight weeks after the TB-CBT/Befriending intervention period, using structured questionnaire. Because of the nature of the study, blinding of patients and therapists was not possible but researchers undertaking the baseline and follow-up assessments, and the data analysis were blinded. It was assumed that the use of structured and self-reported questionnaires for the outcome variables might reduce the possibility of observed bias (such as interviewer bias). Diagnosis of COPD was confirmed by participants' general physicians and lung function test results. Data entry was performed by the researchers blinded to the allocation. The intervention group received the TB-CBT with an initial getting-to-know-you session, followed by eight scheduled weekly telephone calls of approximately 30 minutes in length. For participants from remote rural and regional areas, the initial getting-to-know-you session was also conducted over the telephone. The control group received a befriending program delivered by trained volunteers. It is a non-directive emotional social support provided predominately by volunteers and often over the telephone has been found to affect a small but significant reduction in

depressive symptoms in carers, those with a chronic illness, and the socially isolated. It constituted a minimum program beyond 'usual care' and avoided bias associated with the placebo effect if 'usual care' alone had been used as the control group. After the application of inclusion and exclusion criteria and completing a baseline questionnaire, patients were randomly allocated to the TB-CBT (n=54) or befriending care arms (n=56).

Incremental cost-utility ratio (ICUR) was the main decision algorithm of the cost-utility analysis. A cost-effectiveness plane and cost-effectiveness acceptability curve (CEAC) were generated to show a range of societal willingness-to-pay (WTP) thresholds per QALY gained indicating the probability that TB-CBT has an ICUR below this threshold. To estimate the effectiveness of the interventions on participants, Health State Utility Value (HSUV) was adapted as the main outcome. This study followed Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guideline [352, 353].

6.4.2 Economic appraisal cost and outcome measures

6.4.2.1 Health care utilization and costs

The study perspectives were intended to include both that of societal and health service payer. However, since almost all the participants (106 out of 110) were retired so the concept of productivity loss (societal point of view) was not applicable, hence only direct costs to the health service were included in the analyses. The time horizon was limited to the study period of 17 weeks, so costs and effects were not discounted.

Relevant cost items were identified and the volume of resources used for each item was measured. Resource use was captured via structured questionnaires and cost diaries at baseline and the two follow-up data collection sessions: post-intervention and eight weeks after the TB-CBT/Befriending intervention period. The validity of self-reported health services utilization in

COPD patients has been evaluated [354]. A comprehensive list of services, treatments and equipment used by COPD patients was developed and incorporated into the participants' cost diaries and questionnaires before the study started. The cost diary consisted of questions that addressed the following items and answered weekly: working status, allied health care services, GP visit, specialist visit, hospital utilization and emergency visit. Daily usage of medications and average utilization of health care services were used to extrapolate baseline cost to annual cost for the purpose of adjusting the difference in cost at the baseline between control and intervention groups. Utilization of health care services such as medication (including type, power, and daily dosage), allied health care, oxygen therapy and purchasing or renting equipment separately were measured and related questions were embedded into the baseline, 9 and 17-week measurements. A blinded researcher retrieved the data at the end of the first and second follow-ups.

Details of the specific resource related to the above-mentioned cost components and their assigned unit cost are listed in Appendix, Table E1, E2 & E3 [22, 74, 355]. Unit costs were obtained from sources congruent with the Manual of Resource Items for use in Major Submissions to the Australian Pharmaceutical Benefits Advisory Committee involving Economic Analyses [355]. The Manual recognises sources that include the Medicare Benefits Schedule book [74], the Schedule of Pharmaceutical Benefits [22], the Department of Veterans' Affairs Schedule of Fees [128]. Other sources included Australian Institute of Health and Welfare [33], National Hospital Cost Data Collection, Round 17 [126], Australian Prudential Regulation Authority [8] and market values. Australian national level unit cost in mid-2013 prices was used to calculate the total cost; the annual discount rate of 5% and an inflation rate of 2% were applied for adjustment of the unit prices (Table E1) to 2013 values.

Two groups of cost items were categorized: downstream healthcare costs and intervention cost. Health care related costs were all costs attributed to one of these six components: 1) general

practitioner visit, 2) specialist visit, 3) hospital (inpatient and outpatient) and emergency services including ambulance transfer, 4) allied health care including pulmonary rehabilitation, 5) medical aid, spirometry tests, and assistant devices, 6) prescribed medicines including antidepressive, anxiolytic and COPD-specific therapies. Hospital costs were based on data from 68 public hospitals in the state of Victoria. For acute hospital admission and emergency department visit an overall figure of $4,251 and $667 per admission and visit were adapted respectively. For subacute hospital admission, a flat rate of $752 per day was applied.

Intervention costs comprised of the costs attributed to the process of intervention administration and included telephone counselling, telephone charges, stationery and publishing self-help materials (Table E2). Specific items related to the research such as payment to statistician were not included. The hourly cost of telephone counselling was based on the initial counselling fee for social workers paid by the Australian Federal Government [355]. The befriending approach was delivered by volunteer staff without any cost. In order to consider this approach as a real routine practice, a payment schedule for telephone counsellor was set in the cost analysis of the intervention arm. Payroll information was used to calculate the hourly wages of trainers.

The final estimation of the cost of health care utilization was based on the cost diaries and questionnaires information. Baseline cost including medication, allied health care, GP visit, oxygen therapy and purchasing or renting equipment was used for comparability of two groups and as a proxy for baseline adjustment in cost-effectiveness analysis. Total health care cost was computed by summation of the individual components costs.

6.4.2.2 Health outcome

The main outcome of the trial, HSUV was measured by the Assessment of Quality of Life (AQoL-4D) scale. AQoL-4D has 12 items and measures the following four dimensions:

independent living, mental health, relationships, and senses. Each item is rated on a 4-point scale, and utility weightings are applied to each item to make the resulting score suitable for calculation of quality adjusted life years and therefore useful for cost-utility analyses. The minimum AQoL score (-0.04) represents the worst possible HSUV (health state worse than death). The maximum score (1.00) represents full health. The self-administered questionnaire of AQoL was used together with the cost diaries at the baseline and post-intervention and eight weeks after the TB-CBT/Befriending intervention period. The estimated utility values were used to calculate quality-adjusted life years (QALY) by using the area under the curve method [356].

6.4.3 Missing data handling

GP visit and medication were used to calculate missing-ness in economic evaluation. The assumption was that each patient should have had at least one medication and one GP visit during the study period. Multiple Imputation (MI) with chain equations was undertaken to estimate missing values, using “mi estimate” command in Stata. The MI was performed at the individual cost component and utility. The imputation models included all the known covariates supposed to be associated with the missingness mechanism and interrelationships between cost components. The observed covariates considered were age, sex, marital status and baseline utility value. MI was carried out for each arm of the trial separately. A general guideline for handling missing data in RCTs proposed by Faria et al [357] was followed.

6.4.4 Cost-utility analysis

The within-trial economic analysis was accomplished by estimating mean utility gained and mean cost per patient calculated for the study period of 17 weeks post-randomization in each of two groups. All analyses were carried out on the basis of intention to treat (ITT) (all participants after randomization were included in the final analyses) using Stata 13.1.

Estimation of adjusted health care costs and utility carried out by using linear regression models. The models were controlled by baseline cost and utility [358-361] to take account of potential bias inherent in the study as a result of differences between study arms. The analysis was undertaken using the “mi estimate” and “mi predict” commands in Stata, which estimate regression parameters on the imputed dataset and generate coefficients of interest through Rubin’s rules [362-364].

The adjusted cost and utility (predicted cost and utility) were used in cost-utility analyses and calculating QALY. Incremental cost-utility ratio (ICUR) was calculated as ICUR = (Ci - Cc) / (Ei - Ec), where Ci was the adjusted annual total cost of the intervention group, Cc was the adjusted annual total cost of the control group, Ei was the adjusted effect (QALY) for the intervention group and Ec was the adjusted effect for the control group. To account for the skewed nature of the data, non-parametric bootstrap estimation with 1,000 replications was performed to get means and standard deviations of incremental cost and effect data. The results were plotted in the form of a cost-utility plane and cost-effectiveness acceptability curve (CEAC) which presented more information on uncertainty around the cost-effectiveness of a health-care intervention and showed acceptability of the intervention according to a range of potential societal WTP per QALY gained [365-367]. It was used as an alternative to confidence intervals around ICUR. Since the majority ICUR ratios fell in the south-west quadrant of the ICUR plane, we have used the willingness-to-accept (WTA) health loss to address the concept that the ‘selling price’ of a unit of QALY is greater than the ‘buying price’ [368].

Furthermore, two sensitivity analyses were conducted on the total cost by excluding cost outliers (outside of two standard deviations) and hospital cost item.

6.4.5 Willingness to accept versus willingness to pay

The value of health care, its calculation and implications for the distribution of economic resources, is a constantly debating subject [369]. To place a value on the service the user receives in the health system is complicated [370], there is no market mechanism that enables this. In economics, willingness to pay (WTP) is the maximum amount an individual is willing to sacrifice to purchase a good or avoid something undesirable [371]. The price of any goods transaction will thus be any point between a buyer's willingness to pay and a seller's willingness to accept [372, 373]. On the other hand, willingness to accept compensation (WTA) is the minimum amount of money that a person is willing to accept to abandon a good or to tolerate something negative, such as pollution. It is equivalent to the minimum monetary amount required for sale of a good or acquisition of something undesirable to be accepted by an individual [374, 375]. Unlike WTP, WTA is not restricted by an individual's wealth. For example, the willingness to pay to stop the ending of one's own life can only be as high as one's wealth, while the willingness to accept compensation to accept the loss of one's life would be an extremely high number (or maybe infinite, meaning that there would be no finite acceptable payment amount)[376, 377]. The concept of the WTP–WTA disparity is that, in theory, the value of consumer surplus measured by WTP and WTA should be the same. In practice, they differ, with WTA exceeding WTP by quite a margin depending upon the program or commodity being valued [368].

One of the implication of this concept is that how to determine the cost-effectiveness threshold. Current routine practice is that any accept–rejection criterion is symmetric; graphically, a straight line through the origin of the cost-effectiveness plane. The WTA–WTP evidence suggests a downward ‘kink’ through the origin for the south-west quadrant, such that the ‘selling price’ of a QALY is greater than the ‘buying price’ [368].

6.5 Results

Of the 110 participants who entered the study, 54 were assigned to the telephone-based CBT intervention and 56 to the control group (Table 6-1). Fifteen participants (14%) did not finish the intervention and three other participants did not finish the second follow-up. In accordance with ITT methodology, all of them were included in the final analysis. The rate of missing values in cost data ranged from 10.9% at baseline for medicine to 46.36% for GP visit at the end of the trial. For the raw data, the control group had a slightly higher baseline cost than the intervention group but this difference was not statistically significant. Age, sex, educational level and smoking habit were comparable between groups. Mean utility value for the whole participants at baseline was 0.325 (95% CI, 0.284 to 0.366).

Patients had different patterns of missing data for cost and utility outcome. Twenty patients did not complete cost diaries with the major reasons for withdrawal being ill-health or deceased and the intervention not appropriate to their needs. Complete cases were attained for 90 of the 110 participants (81.8%). The AQoL-4D questionnaire was fully completed at baseline. The missing rates for utility data at the first and second follow-ups were 16.4% (18 cases) and 17.3% (19 cases) respectively. Demographic characteristics of the complete patients were comparable with incomplete participants.

Two participants died during the trial. Utility value and cost data of 0.00 were applied for the current and next follow-up of these participants.

Table 6-1 Descriptive analysis of TB-CBT and control interventions in terms of socio-demographic variables and baseline values of costs (AUS$ in 2013) and outcomes

	TB-CBT (n=54)	Control (n=56)	P value
Age, mean years (SD)	68.5 (9.4)	67.0 (9.1)	0.38
Sex, No. (%)			
Male	19 (35.2)	19 (33.9)	0.89
Female	35 (64.8)	37 (66.1)	
Education level, No. (%)			
Low	32 (59.3)	36 (66.7)	0.44
Medium	13 (24.1)	11 (20.4)	
High	9 (16.7)	7 (13.0)	
Smoking, No. (%)			
Non-smoker	3 (5.6)	7 (12.5)	0.69
Ex-smoker	40 (74.7)	36 (64.3)	
Smoker	11 (20.7)	13 (23.2)	
Comorbidity score, No. (%)	7 (13.0)	13 (23.2)	0.85
<3	13 (24.1)	14 (25.0)	
4	21 (38.9)	12 (21.4)	
5	13 (24.1)	17 (30.4)	
>6			
Utility – AQoL, Mean (CI)	0.318 (0.262 - 0.374)	0.333 (0.273 - 0.393)	0.72
Annual baseline Medicine Cost, Mean (SD)			
Total medicines	617.9 (436.7)	604.8 (384.5)	0.87
Anxiolytic and antidepressant medication	124.1 (124.1)	107.8 (203.9)	0.68
Annual total baseline cost, Mean (SD) *	4543.6 (447.4)	5115.6 (419.0)	0.35

*** Total baseline cost included**: medication, allied health care, GP visit and oxygen therapy and purchasing or renting equipment
SD: standard deviation, **CI:** Confidence Interval; **AQoL**: Assessment of Quality of Life; **TB-CBT**: Telephone-Based Cognitive Behaviour Therapy; **Control**: usual care plus befriending intervention

6.5.1 Cost analysis

The mean cost of implementing the TB-CBT telephone counselling per patient was AUS $827.6 for the whole trial (Table 6-2), compared to AUS $596.4 for the befriending group. The extra cost was calculated as AUS $231.2 per person and was attributed to the difference between a

professional counsellor and volunteer befriender in the two groups. Intervention cost was incorporated in all cost-utility analyses.

Table 6-2 Predicted mean costs (AUS$ in 2013) and health outcome for TB-CBT and control groups at 17 weeks, derived from multiple imputation linear regression models controlled for baseline cost and effect

	Mean (SE)			
	TB-CBT	Control	Difference	P value
Healthcare related costs				
GP visit	419.9 (1.0)	276.8 (1.0)	143.1 (1.4)	<0.001
Specialist visit †	529.7 (2.1)	218.6 (1.8)	313.7 (2.1)	<0.001
Allied health care	400.1 (7.3)	310.2 (6.2)	83.4 (7.4)	<0.001
Medical aid and assistant devices	255.6 (7.8)	237.2 (6.6)	25.2 (7.9)	0.002
Prescribed and OTC medicine	204.0 (1.4)	190.6 (1.2)	13.4 (1.6)	<0.001
Hospital & Emergency visit	348.4 (26.7)	1512.4 (25.2)	-1164.0 (36.7)	<0.001
Total	2158.2 (27.1)	2743.4 (27.1)	-585.2 (39.5)	<0.001
Intervention cost per patient †				
Telephone counsellor	-	460.4	- 460.4	
Self-help materials	20.0	20.0	0.0	
Medical Practitioner counsellor	691.6	-	691.6	
Stationary & recording of counselling	100.0	100.0	0.0	
Telephone charges	16.0	16.0	0.0	
Total	827.6	596.4	231.2	
Total cost ‡	**2985.8 (28.8)**	**3339.8 (27.1)**	**-354.0 (39.5)**	**<0.001**
Utility – AQoL				
Utility at the first follow up	0.359 (0.021)	0.385 (0.023)	-0.204 (0.032)	0.528
Utility at the second follow up	0.324 (0.018)	0.362 (0.020)	-0.025 (0.027)	0.346
QALY	0.115 (0.008)	0.122 (0.008)	-0.007 (0.011)	0.542

SE: standard error, **AQoL**: Assessment of Quality of Life; **QALY**: Quality Adjusted Life Year; **TB-CBT**: Telephone-Based Cognitive Behaviour Therapy; **Control**: usual care plus befriending intervention

* Any kind of subspecialty physician related to the COPD disease

† The value of intervention cost is deterministic

‡ Because of the effect of multiple imputation and rounding errors, total cost are not exactly equal to the sum of included cost items

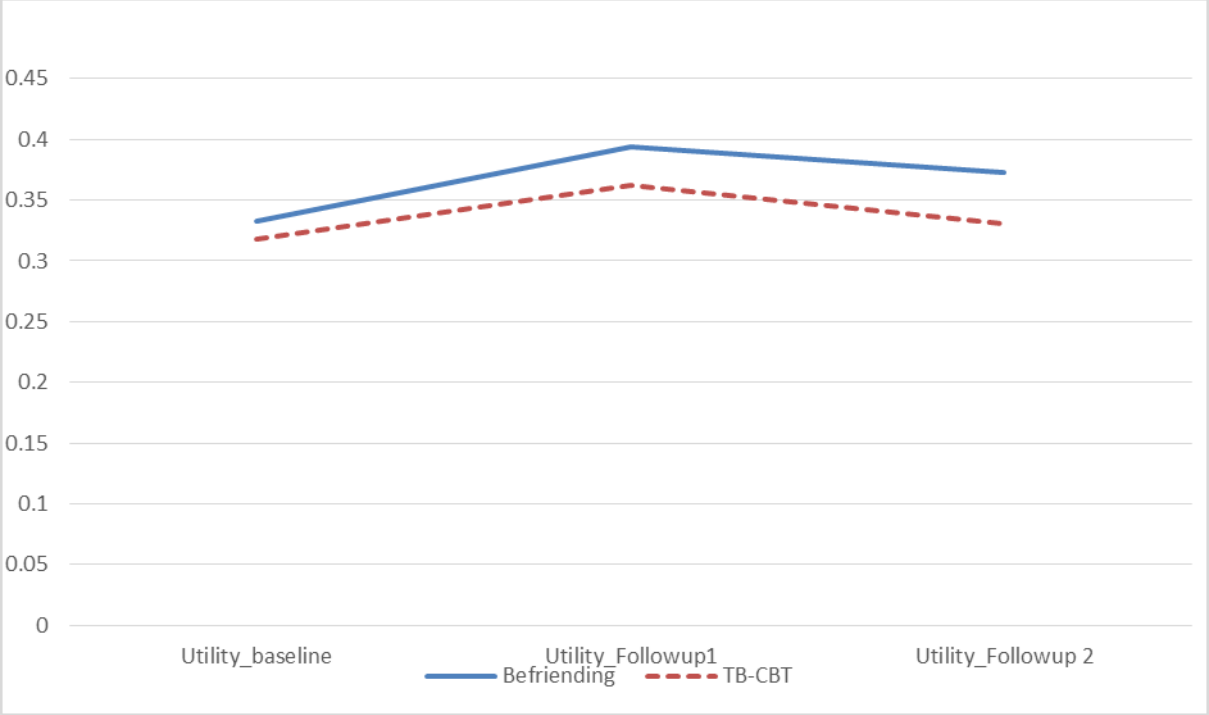
Predicted costs by different categories per patient for the time horizon of the trial after incorporating multiple imputation and baseline corrections are presented in Table 6-2. The

values of cost items were significantly different between two arms of RCT. The main difference was found in hospital and emergency services in favour of TB-CBT arm of the study ($348.4 for TB-CBT versus $1512.4 for befriending; p <0.001). It was due to higher emergency events in the control group (ten emergency events in befriending versus three in TB-CBT group). Total costs for TB-CBT and control arms were $2985.8 (SE 28.8) and $3339.8 (SE 27.1) respectively that showed a significant difference, p-value <0.001.

6.5.2 Health outcomes

The point estimate of mean utility values in both control and intervention groups showed relatively small increases in the first follow-up relative to the baseline values (0.318 to 0.359 in the intervention group and 0.333 to 0.385 in the control group). These changes followed by decreases in utility values in the second follow-up. No statistically significant differences were found in mean utility-AQoL between control and intervention groups at the baseline, first and second follow-ups. The trend in utility is presented in Figure 1.

Figure 6-1Utility trend for intervention and control group over the 17 weeks of the study period



6.5.3 Cost-utility analysis

Incremental cost-utility analysis revealed that TB-CBT group was associated with a negative incremental cost of -$354.0 (SE 39.5) and a negative incremental QALY gain of -0.007 (SE 0.011) per patient. This indicated that TB-CBT group experienced lower utility gained (i.e. a health loss) and lower total cost than the control group within a trial. The outputs of non-parametric bootstrap replication analysis corrected for baseline outcome values are presented in Table 6-3 and Figure 6-2. The results were confirmatory of the point estimates of the incremental cost-utility ratio (ICUR). The summary probabilities of incremental cost-utility are presented in Table 6-4. The results showed that with a probability of 0.74, TB-CBT would be less costly but also have lower utility (i.e. in the south-west, SW, quadrant of the cost-effectiveness plane). There was a probability of 0.26 that TB-CBT would be dominant due to having higher utility with lower cost (south-east quadrant, SE). The chances of being costlier with higher utility (north-east quadrant, NE) or being an inferior treatment, costlier with lower utility (north-west quadrant, NW) alternatives were zero. The ICUR was AUS $49,868.7 per QALY sacrificed (for the SW quadrant).

Table 6-3 Non-parametric bootstrapping incremental cost and utility analyses, predicted values derived from multiple imputation linear regression models controlled for baseline cost and effect

Analysis		SE	95% CI
Cost-analyses			
Incremental cost	-352.3	39.64	-275.7 to -432.3
Utility analysis			
Incremental QALY	-0.0071	0.011	-0.0287 to 0.0152

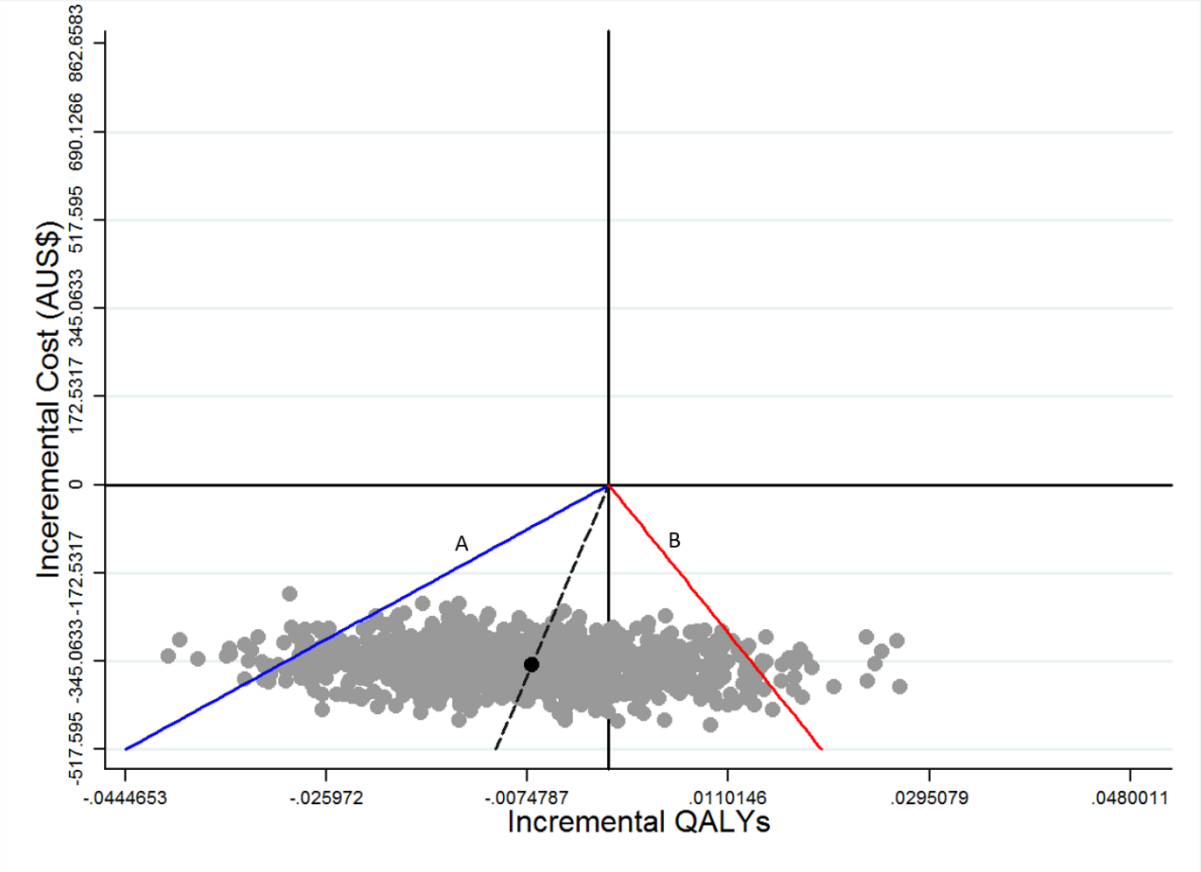
Incremental: intervention - control; **SE**: Standard Error

Table 6-4 Non-parametric bootstrapping incremental cost-utility ratio and probabilities of dominance or inferiority of TB-CBT

Analysis	ICUR (95% CI)	More effect Higher cost	inferior	Less effect Lower costs	Dominant
	49,868.7 (- 26,407 to 11,636)	0	0	0.74	0.26

To further represent the uncertainty around ICUR per QALY sacrificed, the CEAC is plotted in Figure 6-3. The probability of the intervention being superior to the control for varying ratios for societal WTA for each QALY loss is demonstrated. In this special case, the CEAC did not intersect the y-axis because the intervention was less costly, less effective and ICURs mainly fell into the SW quadrant. On the other hand, the CEAC started at one because the entire density of the ICUR involved cost-savings (south to the x-axis) but was asymptotic horizontally to a value less than one because not all ICUR involved health gain (west to the y-axis). Hence, the CEAC was a descending function of λ ($\Delta C/\Delta E=\lambda$). The λ is a parameter external to the cost-effectiveness analysis and defines the threshold monetary value accepted for a unit of effect loss.

Figure 6-2 Incremental cost-effectiveness plane. Cost and QALY were estimated with linear regression with 1,000 bootstrap replications. The dashed line indicates the point estimate of ICUR.



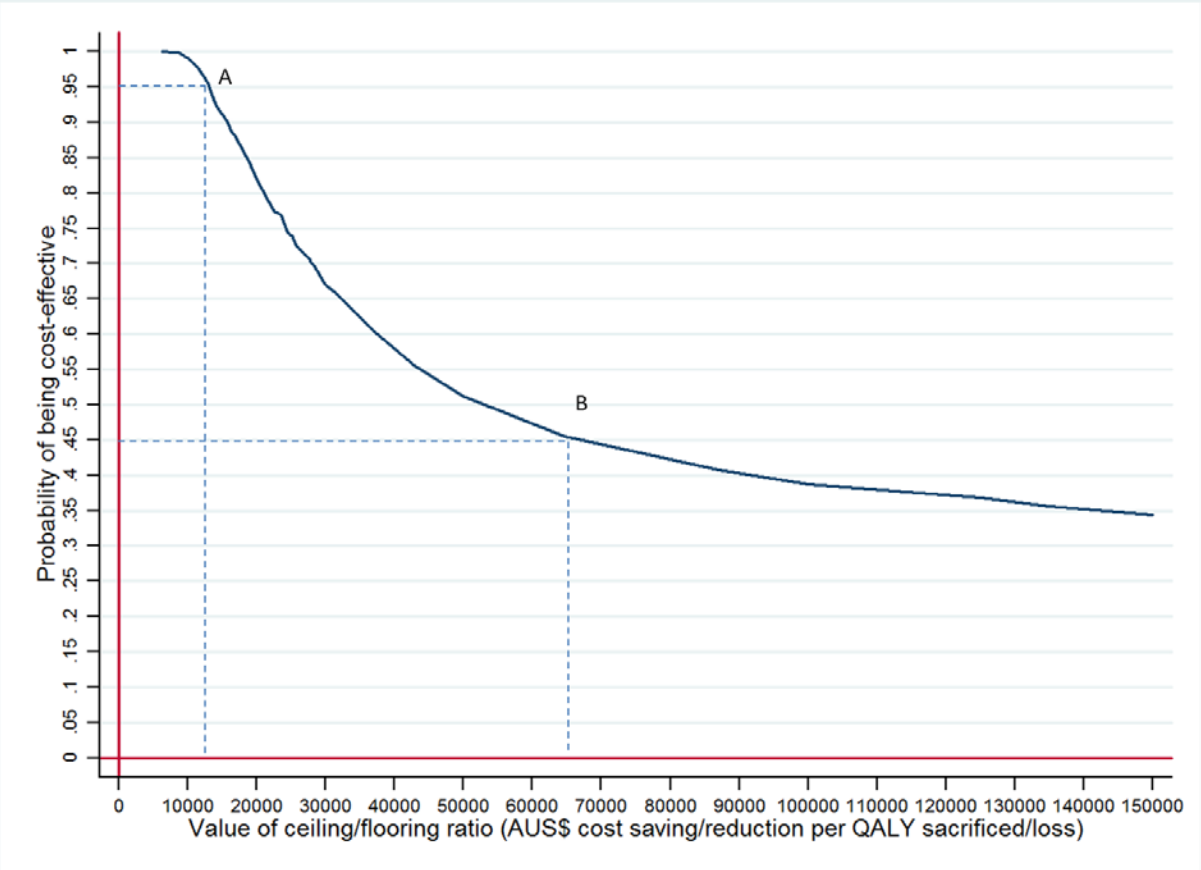
Line A represents the lower limit of the confidence interval for ICUR, point estimate of AUS $11,636 per QALY loss (in SW quadrant), equivalent to point A in Figure 3.

Line B represents the upper limit of the confidence interval for ICUR, point estimate of AUS -$26,407 per QALY gain (in SE quadrant), equivalent to a straight line parallel to the horizontal axis in CEAC at the probability of one to being cost-effective.

If we set the threshold of ICUR of cost reduction per QALY loss as low as AUS $11,636, there was 0.95 probability of TB-CBT being cost-effective option (point A Figure 6-2). In another word, it was acceptable to lose one QALY if the minimum cost saving could be less than AUS $11,636. There was, however, an increased adverse health outcome associated with TB-CBT, resulting in a decrease of the probability of it being a cost-effective option above this threshold. In order to provide a meaningful interpretation of the measured ICURs, we needed to compare them with an accepted ICUR threshold in Australia. ICUR threshold was defined as the minimum value of money per additional health outcome (QALY gained) [366, 378] should be

turned into the floor of the threshold that a minimum saving/reduction in cost must be achieved for one standard unit of health (ie, QALY) sacrificed (specifically in SW quadrant) that a jurisdiction decides to accept for adapting a technology or an intervention for replacing the current practice. With a proposed acceptable cost-effectiveness threshold for the ICUA located at SW quadrant (flooring ratio λ) of at least AUS $64,000 reduced per QALY loss by previous researches [379, 380], TB-CBT was superior to the befriending intervention with a probability of 0.45, as shown in Figure 3 at the point of B. The probability would increase if flooring ratio per QALY sacrificed reduced. The probability would be one if the societal WTA approached the value as low as AUS $11,636 saved per QALY sacrificed.

Figure 6-3 Cost-effectiveness acceptability curve for TB-CBT intervention; the thresholds of minimum amount of monetary value that society is willing to accept to sacrifice a unit of health (QALY)



Sensitivity analysis by removing outliers did not show significant changes (Appendix II). On the other hand, sensitivity analysis by the exclusion of hospital cost from final analysis had a significant effect on the results (Tables E4, E5 & Figure E2). The incremental total cost and QALY were $809.9 (SE 2.8) and -0.0068 (SE 0.0111) per patient respectively. The ICUR was -$119.714.6 per QALY gained. The results showed that with a probability of 0.73 percent, TB-CBT would be inferior (north-west quadrant, NW). There was a probability of 0.27 percent that TB-CBT would be more costly and effective (north-east quadrant, NE).

Under loss aversion from prospect theory which is based on individual preference [381], the values that people are willing to accept (WTA) compensation for the health loss are expected to be greater than WTP for an equivalent health gain, (WTA>WTP) [382, 383]. Based on this assumption, the slope of the ceiling ratio line is steeper in the SW quadrant with a downward kink through the origin in cost-effectiveness plane. Giving the high probability for ICUR being in SW quadrant and WTA-WTP disparity, the probability that TB-CBT would be cost-effective would be reduced at any level of λ. After applying the suggested WTA/WTP ratio of 1.9 to 6.4 for health care studies [368], the new cost-effectiveness flooring threshold of minimum cost saving per QALY sacrificed could be calculated as AUS $121,600 to $409,600. By this inference, the probability of TB-CBT being dominant decreased to less than 0.36.

6.6 Discussion

This study performed an incremental cost-utility analysis of TB-CBT treatment for depression and anxiety in elderly COPD patients in a two-arm RCT. The main finding of this study is that the ICUR of TB-CBT compared to the control is located in the south-west quadrant of the cost-

effectiveness plane. This finding requires different decision rule compared to the ICUR located in the north-east quadrant of the cost-effectiveness plane. The traditional threshold of willingness-to-pay per QALY gained is no longer applicable to this result. Thus, we have to re-define the decision rule as the threshold of the willingness to accept (ie, a minimum flooring ratio) of the cost saving must be achieved for a QALY sacrificed. There was a probability of less than 0.45 that TB-CBT was a superior treatment modality at the Australian proposed cost-effectiveness WTP ceiling threshold turned into WTA flooring threshold. This probability decreased when the WTA for compensation for QALY loss increased (about 0.36 at $121,600 per QALY sacrificed) [384]. This study, therefore, indicates that TB-CBT has a slight probability of demonstrating cost-utility if added to usual care of anxiety/depression comorbidity in COPD patients. The threshold analyses aimed to indicate a lower confidence limit for cost-effectiveness, meaning there is a high probability that TB-CBT would be reimbursed no more than an additional AUS $11,636 per QALY sacrificed.

Furthermore, since TB-CBT was significantly less costly than the befriending intervention (control) and a slightly non-significant negative impact of TB-CBT on incremental utility, these findings indicate that TB-CBT with a probability of 100% can be considered as a cost saving approach alleviating anxiety and depression in COPD.

The intervention cost did not include the cost of initial counsellor training; it was assumed that it should be part of routine education. This study showed that TB-CBT can reduce health care utilization. This finding is in accordance with the published literature [385, 386]. McCrae et al [387] have demonstrated that a brief CBT for insomnia can decrease in a number of medications and medical visits after six months. In patients diagnosed with rheumatoid arthritis, introducing CBT significantly reduced the number of inpatients nights, physiological referral, total injection and total health care use [388, 389].

There are some limitations to this study. The time horizon of the intervention and follow-ups were too short (17-week) to allow for TB-CBT treatment to have its effect on main (anxiety and depression) and secondary (HSUV and costs) outcomes. Previous studies revealed that measuring at least three months or two weeks in every two months (12 times) of a year in chronic diseases can give reasonable estimates of annual costs [390]. The natural progression of COPD involves exacerbation states which can rapidly change a patient's condition and increase health service utilization and pharmaceutical consumption significantly. Depending on the severity of exacerbation, this period of flare up may last from two to four weeks. After this period, medical utilization does not necessary return to pre-exacerbation levels. Due to the short time horizon of the study, one-time high resource health care services such as inpatient hospital stay, ambulance, and specialist visit might have been missed or overestimated.

The second limitation includes participants blinding. They were randomized to control and intervention arms following a collection of baseline data, which indicate they were well matched. However, there was no way to blind the intervention group to participants or to those facilitating the programme and the study was open to a risk of performance bias. The third limitation is the effect of befriending modality itself on anxiety and depression. There is evidence that this approach has modest anti-depressive effects and it could be used as a treatment for depressive symptom and loneliness in the elderly population [391]. In addition, it bore some costs to provide this program. The use of this comparator made it more difficult to reveal the superiority of TB-CBT in cost-utility analysis. The fourth limitation is related to sample size calculation that was based on clinical outcomes alone. As a consequence, the economic comparison can be underpowered, which lead to the wide confidence interval for incremental cost and effect [361, 392].

This study used a cost diary as an accurate cost data collection method because of its prospective methodology. As a complementary measure, MI was applied to overcome missing

values in cost and utility data. This study employed robust statistical methods for balancing cost and effect to account for the baseline cost and utility. This study might be a unique example of analysis and interpretation of an economic evaluation with ICER in SW quadrant of cost effective plane enriched by incorporation of WTA concept.

This study adds to the limited literature on the cost-utility analysis of Minimal Psychological Intervention (MPI) such as TB-CBT in chronic somatic patients suffering from depression or anxiety. Jonkers et al's study [329] revealed limited probability that MPI was a cost-effective intervention over usual care in COPD and diabetic patients. Annual cost and utility were not significantly different between MPI and control groups after a 12-month follow-up. Holman et al's [393] analysis of CBT versus talking and usual care for depressed older people in primary care setting found that CBT was more costly and more effective. Two recently published articles [394, 395] showed that internet-delivered CBT slightly increased utility values after 12-month follow-up but incurred higher costs in older adults whose anxiety and depression were not related to somatic diseases. Conversely, Tyrer et al's [396] multicentre RCT to investigating the effect of TB-CBT group therapy for patients admitted to secondary care with somatic diseases suffering from health anxiety found that although the TB-CBT was effective in reducing anxiety after two-year follow-up, the incremental cost and utility were not significantly different from control group receiving usual care.

An interesting finding of the current study was related to the estimated utility value in COPD patients with depression and/or anxiety comorbidities. A recent study [397] showed that mean utility value for depressed COPD patients was estimated to be 0.62 (SD 0.24). From a multivariate analysis, this study revealed that utility value, measured by EQ-5D, was independently and significantly associated with the presence of depression in COPD. The utility value measured by AQoL-4D, for all of the participants in the current study at baseline, was

0.325 (SD 0.217), significantly different from the above-mentioned study finding. Further study for evaluating the comparability of EQ-5D and AQoL utility scales in COPD is recommended.

In conclusion, this study does not support using TB-CBT treatment for COPD in its current form as a cost-effective modality than control approach (befriending care), assuming a WTA threshold of more than AUS $121,600 per QALY sacrificed. This study shows that TB-CBT can be recommended as a cost-saving approach to usual care plus befriending if a relatively less health gain is acceptable. However, findings of this study emphasised that depression and anxiety comorbidities are major influential factors in lowering HSUV in COPD patients and should be addressed in usual practice.

7 Chapter 7 – Outcome of smoking cessation; Piecewise two-way fixed effect linear regression models, using Australian population panel data; a close step to the notion of causality

This chapter is going to be submitted for publication.

7.1 Abstract

Aims: to explore the effect of the transition from “Smoker” to “Ex-smoker” status (smoking cessation) on Health-Related Quality of Life (HRQoL) in an Australian general population sample using a large prospective cohort study (HILDA).

Methods: Panel data from thirteen waves (2001 to 2013) of a nationally representative longitudinal survey of Household Income and Labour Dynamics of Australia was used to model HRQoL (measured by SF-36) trajectories before and after cessation events. 1,858 respondent persons (5% of total HILDA sample) who experienced only one cessation event in their HILDA life were selected. Piecewise two-way fixed effect linear regression models were adapted to capture within-person differences in HRQoL trajectories. This process enabled us to measure discontinuities in outcomes and change of regression slopes by controlling all time-invariant characteristics.

Results: A significant effect of smoking cessation was discovered for role physical, bodily pain and general health domains and Physical Component Summary (PCS) of SF-36 measure. An annual increase of 0.708 [95% Confidence Interval (CI) = 0.109-1.308] in role physical and 0.227 [95% CI= 0.058-0.396] in PCS scores after cessation were estimated.

Conclusions: Relation of smoking cessation and Health Related Quality of Life, irrespective of other factors, was likely to involve a strong association between quitting and improved physical aspects of Health-Related Quality of Life.

7.2 Introduction

Despite considerable decline in the prevalence of tobacco consumption in several countries, smoking is still the most harmful health risk behaviour associated with early stage disease and death [398, 399]. Several studies have investigated the association of smoking behaviour and quality of life (QoL), indicating that cigarette consumption is related to lower QoL/mental wellbeing [150, 158, 400-406]. The academic literature suggested that smoking cessation therapy may improve QoL [108, 162, 167, 407], but opposite results or insignificant change in QoL have been reported by other studies [405, 408, 409].Time since smoking quitting and a number of cigarettes consumed before quitting having shown a dose-response relationship with mortality, morbidity and QoL [154, 403, 410, 411] but studies from USA, France, Spain, Japan and the Netherland reported mixed results [403, 412-415].

This controversy around the effect of smoking transition may be related to the process of smoking cessation which is complicated and dependent on multiple factors (such as the number of quit attempts, the number of cigarettes, age, education and major health event leading to quitting) [274, 416-418]. In addition, it takes several years of abstinence for QoL to be the same as non-smokers [419]. Because of confounding effect of time (the effect of time-modified cofounder such as time after cessation) [420], cohort effects (the effect of time-varying cofounder such as age in cross-sectional studies) and focusing on a specific group of population, interpretation of findings of cross-sectional studies is inconsistent and inconclusive and cannot be extrapolated to the general population. We found very few studies have used longitudinal data (more than a year) with repeated measurements of smoking habit and comprehensive dimensions of QoL to examine within-person changes. We are aware of only one study that included a large nationally representative sample (n=7,484) of an adult over 40 to describe the trajectories of QoL in relation to smoking status [419]. This Canadian study found that among former daily smoker men, QoL at 20 years of cessation was similar to that of non-smokers; this

figure was after 10 years among former smoker women. Australian longitudinal studies on this research question are, till this day, altogether missing.

The central research question is whether or not smoking exerts an association with QoL. In the current paper, we examined the role of smoking status in QoL value in an Australian general population using a large prospective cohort study with 13-years annual follow-ups of measurements. We exploited panel design of the surveys to look at the change of QoL within the same individuals over time as smoking behaviour change. The main aim was to explore the effect of the transition from “Smoker” to “Ex-smoker” status (smoking cessation) on QoL This aim implies the following assumptions: a change in smoking status from smoker to ex-smoker is in accordance with the improvement of QoL.

7.3 Methods

7.3.1 Study design

We used a piecewise regression / interrupted time series (ITS) (as a quasi-experimental research) design to test statistically for a change in the HRQoL value in the time periods before and after smoking cessation event in an Australian general population sample using a large prospective cohort study (HILDA). In order to control for all time-invariant unobserved components / unmeasured confounding, we used two-way fixed effect regression. We compared a smoker’s HRQoL at the estimated of time of smoking with the same individual’s HRQoL after quitting during another suitable time period. Because the individuals are their own controls, this methodology controls for all time-invariant / confounding characteristics of the respondent persons which may affect the outcome value. As it is important that time-invariant unobserved components before and after smoking transition are similar, we compared HRQoL during control interval (time before cessation), with HRQoL during intervention interval (time after cessation).

7.3.1.1 Data

We used data from waves 1 (2001) to 13 (2013) of the Household Income and Labour Dynamics in Australia (HILDA) yearly survey, which is a national longitudinal study based on a multi-stage area sample of households and collects information about economic status, health and well-being, labour market dynamics, family dynamics, persistence and recurrence of various life events and experiences [421]. HILDA survey has a complex multi-staged sampling survey design. At the first stage, a sample of 488 Census Collection Districts (CDs) was selected comprising 200–250 households. Then, within each CD, a sample of approximately 22–34 dwellings were selected based upon on occupancy and expected response rates of the area. Finally, within each dwelling, up to three households were chosen for the sample. Members of each household are traced over time [422]. HILDA includes a face-to-face and phone interview and a self-completion questionnaire for over 15-years old RPs. Data collection in Wave 1 had an overall response rate of 66% with an interviewed sample size of 13,696 Responding Person (ResPers) (7,682 households). The retention rate for the wave 2 was about 86.8% and after that, it was more than 90%, up to 96.5% in wave 11. The number of observations (person-year) in the thirteen waves was a total of 247,826 (37,426 RPs). Methodological details about HILDA are described elsewhere [422].

7.3.1.2 Sample population and inclusion criteria

In order to capture smokers in all ages, the sample was restricted to responding persons (ResPers) aged more than 15 years old. All person-years from ResPers for whom data on all interested variables (QoL and smoking state) in at least one cycle (panel) were available, were included in the main sample (171,439 observations out of 247,826, 69% of the main sample). The temporal and smoking transition analysis was assessed in survey participants who responded to at least two consecutive waves and with at least one event of cessation in their

HILDA life (subsample of cessation, as illustrated in Figure 7-1). The effect of cessation event on QoL was measured in a restricted group of participants (12,117 observations, 46.8% of cessation subsample) in cessation subsample who had only one cessation event in their HILDA life without any succeeding relapse.

7.3.1.3 Exposure variables

Smoking status was defined on the basis of a series of questions in HILDA questionnaires (see appendix F1). The exposure was a transition from smoker to ex-smoker, cessation. For the smoking cessation analysis, we defined transitional coding of exposure variable; respondents who were a current smoker in a given wave and reported to be an ex-smoker in subsequent wave were considered to have quit smoking. The wave (t-1) of "Smoker" status was coded 0 (reference), and a wave (t0) spent in "Ex-smoker" status following a wave in "Smoker" status was coded 1 (exposure), (Table F2, model A).

7.3.1.4 Outcome variables

QoL was represented as the outcome variables and is measured by using SF-36. this is one of the widely used self-completion generic measures for quantifying health status [423]. It has been validated for use in research, examining Australian population health characteristics and for detection of within-person change over time. In previous studies [424-426], it was shown that the eight scales of SF-36 measure are psychometrically sound, with good internal consistency, discriminant validity, and high reliability.

SF-36 questionnaire produces eight health domains, namely physical functioning (PF), role limitations due to physical functioning (RP), bodily pain (BP), general health (GH), social functioning (SF), role limitations due to emotional problems (RE), general mental health (MH) and vitality (VT) and are derived using 36 questions. Each of these domains ranges from a score

of 0 (worst health) to 100 (best health). In addition, two summary scores, Mental Component Summary (MCS) and Physical Component Summary (PCS) are derived through factor analysis of weighted combinations of the eight domains by using method set out in the Australian Bureau of Statistics' publication National Health Survey [422]. Both PCS and MCS are standardized to Australian population norm in HILDA sample and vary between 3.6–71.9 and 4.5–73.9 with a mean score of 49.2 and 49.9, respectively [424].

Another derived variable from the SF-36 is the preference-based measure of health, SF-6D (as outlined by [427]). This measure reflects the subjective value assigned to specific health related condition. It is derived by using seven of the eight domains covered by SF-36 [94]. It comes with a set of preference weights obtained from a sample of the general population using the recognised valuation technique of standard gamble. The resulting SF-6D index scored from 0.0 (worst health status) to 1.0 (best health status), allows the analyst to obtain utility values from the SF-36 for use in economic evaluation studies. A difference (or change) of 0.010 to 0.048, with a weighted mean estimate of 0.033 (95% CI: 0.029 to 0.037) SF-6D in utility score is considered as minimal meaningful clinical importance [428].

All above-mentioned outcomes were modelled as continuous outcomes in regression analyses.

7.3.1.5 Other outcome variables

HILDA included an SF-36 question on health transition, which records the rate of the health of ResPers relative to one year earlier. The optional responses are "Much better now", "Somewhat better now", "About the same", "Somewhat worse now", "Much worse now"; the rating is in reverse order. Meanwhile, a self-assessed health scale is included in HILDA questionnaire. The optional responses are "Excellent", "Very good", "Good", "Fair" and "Poor", in reverse order. In addition, a health satisfaction rating scale ranged from 0 to 10 is also used to get a self-health

image. These three additional self-reported outcome measures were used to test the validity of the regression models.

7.3.2 Methodological aspect of panel data analysis

7.3.2.1 General characteristics of panel data

Panel data have a set of repeated observations on individual units. Instead of one observation per individual, it has a set of observations for each individual. Examples of panel data are the Terman Study of the Gifted or Genetic Studies of Genius (GSG), the Panel Study of Income Dynamics (PSID), the National Longitudinal Survey of Youth (NLSY), the Medical Expenditure Panel Survey (MEPS) and HILDA.

Panel data have elements of cross-sectional data, which contain one observation point for many units, and time-series data, which contain repeated observations for one unit. The repeated nature of the observations enable researchers to understand the causal relationship and how the variables they are analysing change over time. In other words, panel data allow us to study dynamic relationships.

The theoretical framework for analysing panel data assumes there are a large number of units and a small number of observations per unit. This framework excludes theoretical arguments from time series that assume there is an arbitrarily large number of time periods, but it is an accurate description of panel datasets commonly used by researchers. For instance, in the MEPS and HILDA, where the number of units is much larger than the number of time periods for which they are surveyed. In contrast with cross-sectional data, panel data allow us to look at individual-level means. It can also be studied how a variable changes over time for each individual.

The other defining characteristic of panel data is unobserved time-invariant individual heterogeneity. Each individual has inherent characteristics which remain constant over time and affect individuals. It is important to note that individual heterogeneity is not a characteristic of models for cross-sectional and univariate time-series data. Also, for the cross-sectional case, it is not possible to conceive the unobserved component as changing or remaining constant over time.

These characteristics of panel data can be illustrated using the following relationship:

$$y_{it} = x_{it}'\beta + \alpha_i + \varepsilon_{it} \qquad i=1,\ldots,N, \quad t=1\ldots T \qquad (1\text{-}1)$$

Equation (1-1) describes a linear panel-data model. For expository purposes, the i and t subscripts as individual and time. xit are the regressors for individual at time. (If the regressors are for individual for all time periods, it will be by Xi).

Another important characteristic of equation (1-1) is that there are two unobserved random components, α_i and ε_{it}. $\alpha_i$is the individual heterogeneity. The other unobserved component, ε_{it}, changes over time and can be understood as an extension of the random unobserved component in a cross-section. The behaviour of this random component is important in dynamic models.

7.3.2.2 The random-effects (RE) estimator

The random-effects (RE) estimator is a particular case of the generalized least squares (GLS) estimator. Apart from the concept of variance–covariance matrix to obtain a more efficient estimator, the other key component of the RE estimator is the assumption that the unobserved

time-invariant random component of the model is unrelated to the regressors. This, of course, is not different from the regression assumption that the unobserved random disturbance is unrelated to the regressors that yielded consistency. Thus, as was the case for GLS, there is a consistent and efficient estimator.

The RE model can be written as:

$$y_{it} = x_{it}'\beta + \alpha_i + \varepsilon_{it}$$

$$= x_{it}'\beta + v_{it} \qquad (1\text{-}2)$$

$$v_{it} \equiv a_i + \varepsilon_{it}$$

which denotes a linear panel-data model. The expressions emphasize that the unobserved random disturbance vit has a time-varying and a time-invariant component. This way of modelling unobserved random disturbances highlights the idea that there are elements in our model that change with time and elements that do not. This implies that panel data allow us to think about unobserved individual heterogeneity and dynamic relationships.

The following conditions describe the first moments of the RE model:

$$E(\varepsilon_{it} \mid x_{i1},\ldots,x_{iT},a_i) = 0 \qquad t=1,\ldots,T \qquad (1\text{-}3)$$

$$E(a_i \mid x_{i1},\ldots,x_{iT}) = E(a_i) = 0 \qquad (1\text{-}4)$$

(1.3) says that the time-varying random disturbance on average provides no information once we account for the regressors and the unobserved time-invariant component of the model. There are two relevant differences between (1.3) and the expectation of the random disturbances conditional on the regressors in simple regression models. The first difference is that it was conditioned not only on the regressors for the current time period but also on the past and future

values of the regressors χi1, …, χiT. This is what is called strict exogeneity. A case where this assumption is implausible, for instance, is if our dependent variable is wages and one of our regressors is marital status. In this context, (1.2) implies that a past divorce has no relationship with unobserved random variables that affect current wages. More importantly, it excludes the possibility of using lagged variables in our models. In dynamic models, this restriction can be dropped.

The second difference between (1.3) and the regression conditional mean independence is that it is now conditioned on the time-invariant component, αi. This means that the two random disturbances, αi and εit are mean independent or uncorrelated.

The second condition, (1.4), is the defining characteristic of the RE model. It states that the unobserved time-invariant component is unrelated to the regressors.

7.3.2.3 Fixed-effects model

It is difficult to claim that time-invariant unobserved components are unrelated to regressors. The fixed-effects model is used to address this matter, given by

$$y_{it} = x_{it}'\beta + \alpha_i + \varepsilon_{it}$$

$$= x_{it}'\beta + v_{it} \qquad (1\text{-}2)$$

$$v_{it} \equiv a_i + \varepsilon_{it}$$

Once more, the assumption is strict exogeneity:

$$E(\varepsilon_{it} \mid x_{i1},\ldots,x_{iT},a_i) = 0 \quad t=1,\ldots,T \qquad (1\text{-}3)$$

The big difference between RE and fixed effects is that now the unobserved random component is allowed to be related to the regressors. In other words, $E(\varepsilon_{it} \mid x_{i1},\ldots,x_{iT},a_i)$ could be an arbitrary function of xi. As mentioned before, if an unobserved component is related to the regressors, the estimators are not consistent. To overcome this difficulty, the time invariance of the random disturbance is exploit to estimate a transformed version of the model. In other words, fixed effect model cannot estimate the effect of covariates that do not vary over time.

7.3.2.4 Deciding between random and fixed effects

The Hausman test exploits the fact that under the assumption of the random disturbance is unrelated to the regressors, the within (FE) and the RE estimators are consistent but RE are more efficient. If this is true, the distance between the RE and the within estimates should be close to zero. Hausman (1978) defined this distance to be a square distance normalized by the variances of both estimators. This yields a chi-squared statistic that, under the null, assumes that the difference between the coefficients is not statistically significant.

However, the Hausman test has important limitations. First, the test assumes homoscedasticity which is difficult to maintain. Second, the difference between the variances is not guaranteed to be positive definite. If this occurs, the test can't be computed. Finally, it does not allow for serial correlation.

7.3.3 Statistical analysis

The analysis was conditional on ResPers being alive, so no record was assigned as the age at the time of death. The death report was used to verify the final observation of the dead participants. For respondents who died during follow-up, a final record was created to include age at the time of death and a QoL score of 0.00. No further records were included for these respondents. In

longitudinal studies, usually appropriate sampling weights are applied to include an adjustment for attrition and benchmarking back to the initial wave characteristics. But there were no appropriate longitudinal sampling weights for the analysis used in the present study which contained unbalanced panel database, so all models were fitted without sampling weights [429].

To deal with the aim of this study, two regression equations were used: a) single linear regressions and b) segmented regressions with one-knot point. QoL value before and after smoking transitions served as the outcome variable. Two models types that were considered in this paper are:

a) Two-way fixed-effect longitudinal linear regression models were used to investigate whether there were within-person differences in QoL between smoking trajectories by controlling all time-invariant characteristics. This model has an overall constant as well as "individual effect" for each individual and a "time effect" for each period. This is shown in Eq. (1)

$$y_{it} = \beta_0 + \gamma_i + \delta_t + \beta_1 x_{it} + \varepsilon_{it} \quad (1)$$

where x_{it} is a n × k matrix of time-varying explanatory variables for period t. γ is a n × 1 vector representing the individual fixed effects, while δ represents the time effects in period t.

Cluster-robust standard errors (asymptotic variance) were calculated to account for within-panel correlation (heteroscedasticity and serial correlation). Likelihood ratio tests were used to test their significance of statistical analysis. Hausman test is used to determine whether a fixed or random effect model is most appropriate.

b) Piecewise linear regression models were adopted to allow for discontinuities in outcomes and varying slopes of regression lines. It allows jumps at change point values. This procedure, however, should yield support for association smoking with QoL. In

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this part, we restricted regression models to one-knot point regression equation, where the outcome is modelled in Eq. (2)

$$y_{it} = \begin{cases} \beta_0^{(1)} + \beta_1^{(1)} x_{it} + \varepsilon_{it1} & if \quad x_{it} \leq r \\ \beta_0^{(2)} + \beta_1^{(2)} x_{it} + \varepsilon_{it2} & if \quad x_{it} > r \end{cases} \qquad (2)$$

where r is the knot point at the smoking transitional year, and $\beta_0^{(1)}$, $\beta_1^{(1)}$and $\beta_0^{(2)}$, $\beta_1^{(2)}$are the intercept and slope for equations on the left and right side of the knot point, respectively.

The final integrated models were defined by using two-way fixed-effect regression models in each arm of the picewise regression models. Cluster-robust standard errors (asymptotic variance) were calculated to account for within-panel correlation (heteroscedasticity and serial correlation). We investigated QoL changes associated with a (hypothetically upward) trajectory from at least one wave (t_{-1}) "Smoker" status towards the second wave in which a transition to "Ex-smoker" status (t_0) occurred (cessation analysis) and onward waves in ex-smoker status. Because the focus of this analysis was not on the associations between QoL and smoking habit in general, ResPers who remained in the same smoking status over time were not included in this part of analysis. Moreover, in order to get the net effects, the models were restricted to ResPers who had experienced only one smoking transition in HILDA survey. The estimated effects were then used to predict values that can be deployed as QoL value attached to each smoking status in order to inform future economic evaluations of tobacco-related interventions/policies.

A sensitivity analysis was performed to validate the impacts of smoking habit on QoL. For this analysis (Appendix F2 Table F2, model D), it was assumed that the effect of smoking transition on QoL may require at least two-year constant exposure to the new smoking status. It has been proposed that at least in some specific group of population (men 25-44 years old), an association of smoking and QoL was time-dependent and the positive effects of smoking

cessation being seemingly perceived after two years and especially between 2 and 5 years after quitting [403]. In addition, in this way we avoid unnecessary data noisiness due to short-term exposure to a new smoking status. For example, a person who had been in the status of current smoker for 3 years and then moved to ex-smoker status for 4 years, would contribute two person-years of smoking (last two years of smoking status) and 3 person-years of non-smoking (last three years of non-smoking status) (It is demonstrated in Appendix F2 Table F2, model D).

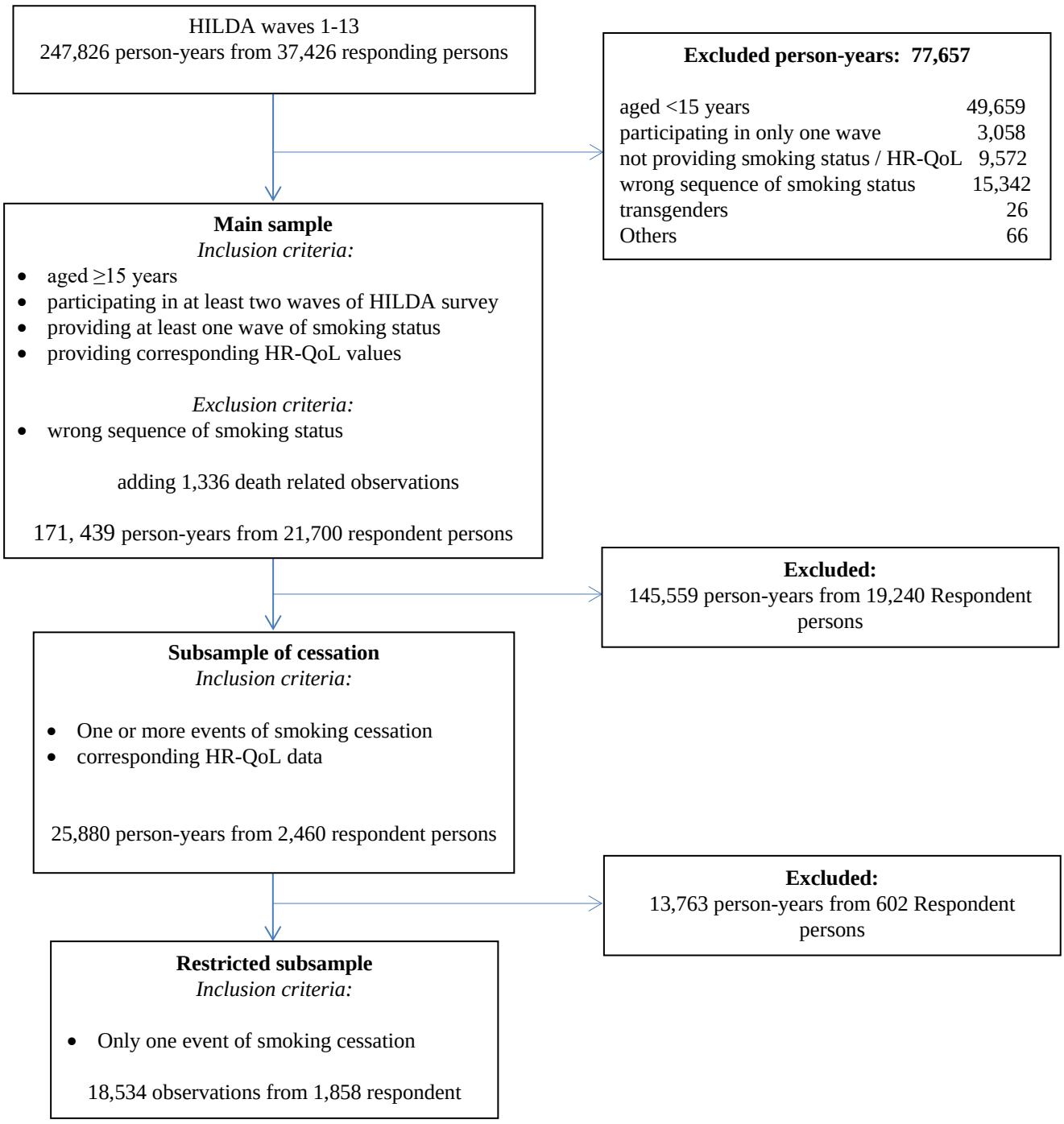
Stata IC version 14.1 was used in all analyses.

7.3.4 Handling missing data

In order to handle the potential biases and loss of precision due to the complete-case analysis, we conducted Multiple Imputation (MI) using Chained Equations (MICE) to impute missing values for the outcome and exposure variables [430-432]. Truncated linear regression models for each of the interested continuous variable, multinomial logistic regression models for each nominal variable and ordered logistic regression model for an ordinal variable were fitted and 20 imputations were generated, considering the percentage of incomplete cases for each imputed variable [432]. The imputed datasets were combined by using Rubin's combination rules. The imputation followed published recommendations and was carried out in the long format datasets [433, 434], using internal Stata command "mi impute".

Smoking status was imputed for 14.7% of person-years, at least one wave for 47% of ResPers (50.4% for one cycle, 20.2% for two cycles, and 29.4% for three or more cycles). Missing patterns of the main interested variables are presented in Appendix F2 Table F3.

Figure 7-1 Selection process of sample population



Descriptive statistics (Table 7-1) were based on the non-imputed database.

7.4 Results

The flow diagram (Figure 7-1) summarises the selection process of articles to be included. Of 247,826 observations in combined data set at wave thirteen, 49,659 were deleted to confine the dataset to ResPers aged 15 and over. In addition, 9,572 observations (PYs) were excluded because of missing values for smoking status at all cycles (a drop of 4,557 panels). The incorrect coding sequence of smoking status in proceeding waves (non-smoker to ex-smoker; ex-smoker to non-smoker and smoker to a non-smoker) were detected (19,443 observations). Of them, 4,011 were changed into correct smoking statuses based on adjacent wave's values and information derived from other relevant variables. The rest, 15,432 observations with incorrect sequences were deleted. An additional 3,058 observations were excluded because of no successive pair of cycles. Two cases of transgender (26 observations) were excluded from the main analysis to keep gender as a time-invariant variable. After adding valid death related observations (1,336 cases), the remaining 171,439 observations from 21,700 unique persons who contributed at least two observations across 13-year follow-up period constructed the main sample. Of the total number of ResPers, 52.0% contributed to all thirteen possible waves, 5.1% to eleven and 4.0% to ten waves, with the mean of 10.4 observations in each panel. The total number of individual-year observations in the restricted subsample smoking cessation analysis was 18,534 representing 1,858 unique individuals across all survey waves who experienced only one event of smoking cessation in their HILDA life.

Relevant descriptive statistics regarding restricted subsample are summarized in Table 7-1 a&b. In addition, key statistics regarding main sample are presented in 0Appendix F2, Table 1, 2, 3 & 4.

Table 7-1a Descriptive statistics (time-invariant covariates) of the 18,534 Person-Years (observations) from 1,858 Respondent Persons, Annual Data Collection Waves in the Household Income and Labour Dynamics in Australia (HILDA), 2001-2013, Restricted sub-sample

Covariates	No of Observation	No of ResPers	% in ResPers
Sex			
Male	9,246	941	50.7
Female	9,288	917	49.3
Country of birth			
Australia	14,894	1,487	80.3
Main English Speaking	1,979	197	10.7
Other	1,661	174	9.0
How often you smoke cigarettes*			
Every day		634	86.9
At least weekly (but not daily)		57	7.8
Less often than weekly		39	5.3

ResPers: Respondent Person; **Obs**: observations;
* This question is asked only in wave 7.

Table 7-2b Descriptive statistics (time-variant covariates) of the 18,534 Person-Years (observations) from 1,858 Respondent Persons, Annual Data Collection Waves in the Household Income and Labour Dynamics in Australia (HILDA), 2001-2013, Restricted sub-sample at entrance wave

Covariates	Mean (SD)
Age, years	35.3 (15.0)
HR-QoL	
Physical functioning (PF)	85.0 (21.5)
Role limitations due to Physical Functioning (RP)	81.3 (33.2)
Bodily pain (BP)	74.2 (24.9)
General health (GH)	68.3 (21.0)
General mental health (MH)	71.6 (18.1)
Role limitations due to Emotional problems (RE)	81.3 (33.6)
Vitality (VT)	58.7 (20.0)
Social functioning (SF)	80.5 (23.9)
Mental Component Summary (MCS)	47.1 (10.9)
Physical Component Summary (PCS)	50.6 (9.5)
Short Form-6 Dimension (SF-6D)	0.76 (0.12)
Self-assessed health	2.60 (0.95)
Reported health transitions	2.82 (0.79)
Satisfaction - Your health	7.18 (2.15)
Age at starting smoking regularly*	17.10 (2.59)
Number of cigarettes each week*	73.84 (63.80)

SF-36: Medical Outcomes Study Short Form;
* This question is asked only in wave 7.

The Hausman test clearly rejected the random-effects assumptions (p-values < 0.001). In other words, there were correlations between QoL and un-observed individual specific characteristics. Results of piecewise two-way fixed effect models showed that for most of the SF-36 scores there was a positive association effect between cessation transition and some SF-36 domain scores (Table 7-3 & Figure 7-2). The p-values reported on Figure 7-2 have been adapted from Table 7-3. This effect was significant for role physical, bodily pain, general health domains and PCS component. In addition, jumps of QoL values (intercept change, β3) at knot point were significant for these measures. In fact, the results indicate that the association between smoking trajectories and the PCS score is driven primarily by the effect on the role physical, bodily pain, and general health scales and to a lesser extent on the physical function scale. The impact of cessation transition on the increase of QoL each year differs by domain with, for example, a 0.708 increase in role physical score and 0.227 increase in PCS score each year. It was interesting that the effect for role emotional, mental health domains and MCS component was negative and deterioration of QoL after cessation was much worse than pre-transition over time. The predicted utility scores (SF-6D measure) before and after cessation showed positive but not statistically significant association.

7.4.1 Sensitivity and validity tests

Results were not appreciably affected significantly in the sensitivity (D) and validity analyses conducted, as detailed in Table F2. The result of validity tests revealed consistent results. Transitional effects of smoking cessation on “self-assessed health”, “health transition” and “satisfaction with one’s health” were shown by improvement in post cessation slope coefficients (predicted change per year, -0.021, -0.0132 and 0.031, respectively), of them self-assessed health improvement was statistically significant. Change of intercept (jump) after quitting for these outcome variables was mainly significant and in line with a decrease of QoL right after cessation event (Table 7-3).

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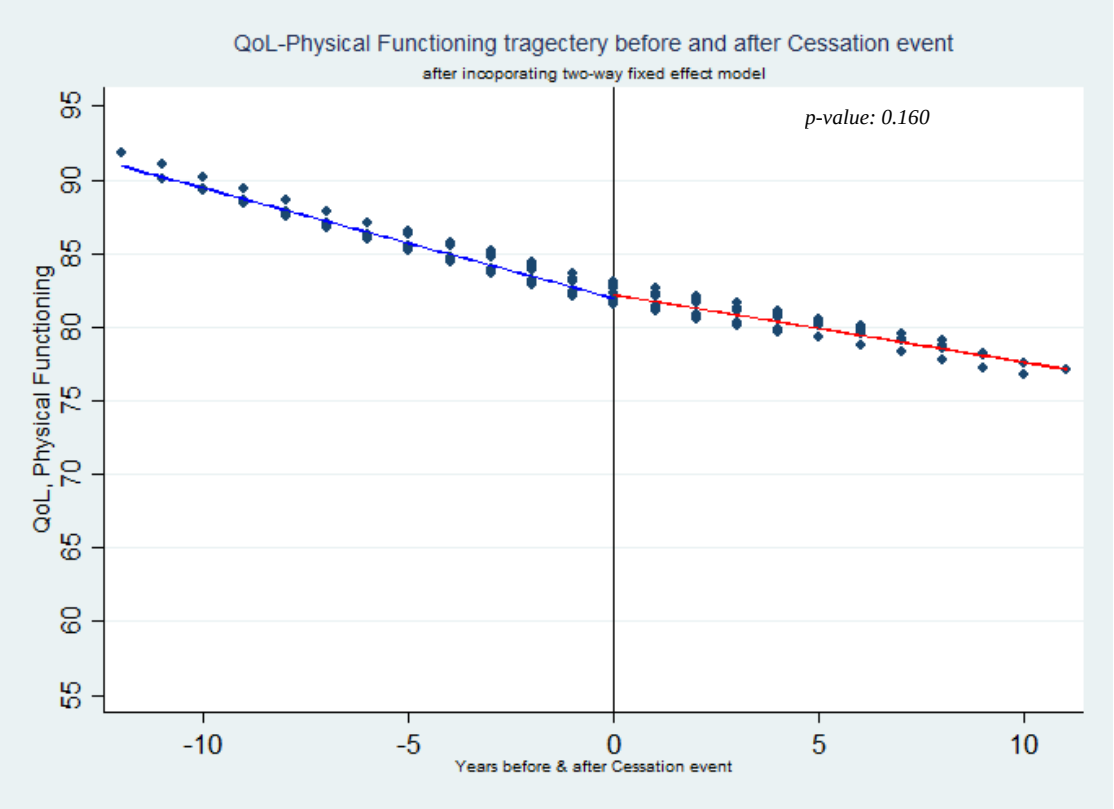
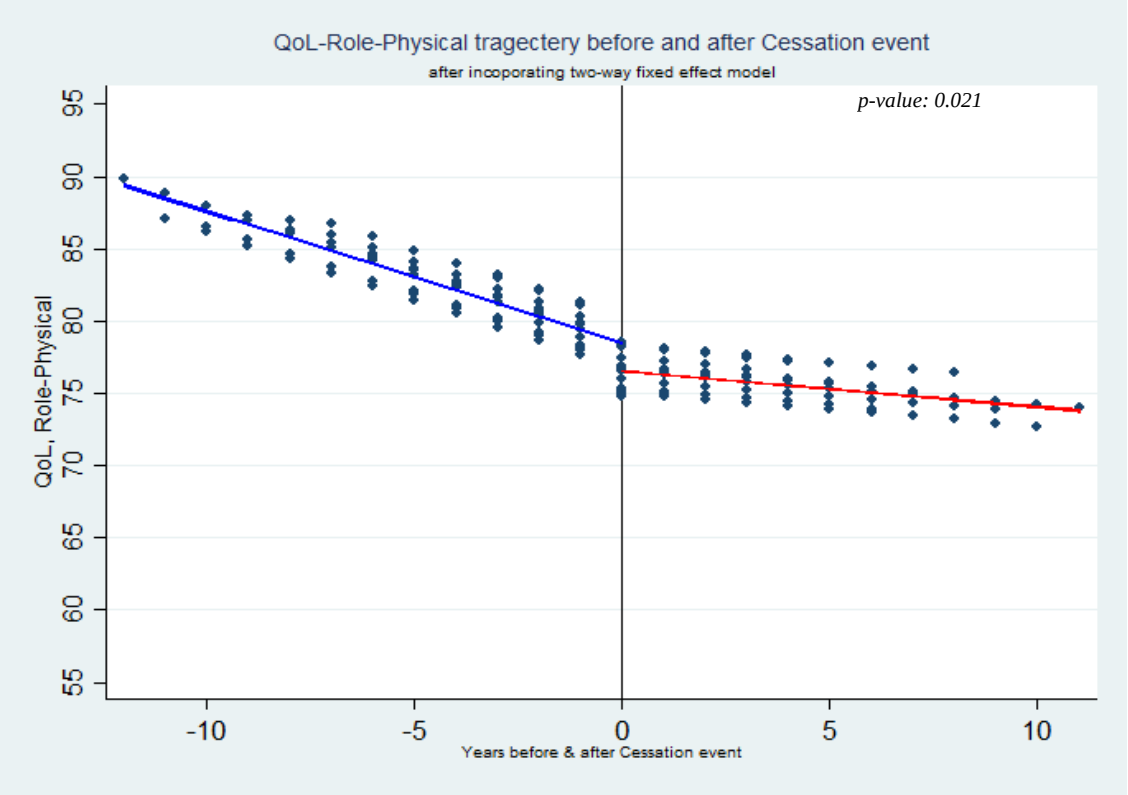
Table 7-3 Piecewise two-way fixed effect regression model outputs for outcome variables, in Cessation analysis (SE), pre/post cessation

	Intercept $\beta_0^{(1)}$	Slope pre $\beta_1^{(1)}$	Slope post $\beta_1^{(2)}$	Pre-post slopes difference test	Change of intercept pre to post (jump) β_2	rho
Physical Functioning	82.33 (0.74)	-0.79 *** (0.16)	-0.51 *** (0.13)	0.28 (0.20)	0.31 (0.52)	0.64
Role-Physical	78.54 (1.16)	-0.94 *** (0.24)	-0.23 (0.21)	0.71 ** (0.31)	-2.01** (0.82)	0.56
Bodily Pain	71.50 (0.78)	-0.74 *** (0.16)	-0.22 * (0.13)	0.52 ** (0.19)	-1.8 *** (0.53)	0.61
General Health	64.41 (0.60)	-0.84 *** (0.12)	-0.29 ** (0.11)	0.55 *** (0.16)	1.60 *** (0.41)	0.72
Social Functioning	81.97 (0.78)	-0.05 (0.16)	0.09 (0.13)	0.14 (0.20)	-0.94 (0.55)	0.58
Role-Emotional	82.20 (1.11)	-0.29 (0.23)	-0.38 (0.19)	-0.09 (0.29)	1.13 (0.81)	0.52
Mental Health	72.55 (0.55)	0.02 (0.11)	-0.04 (0.10)	-0.06 (0.14)	0.21 (0.36)	0.62
Vitality	58.90 (0.91)	-0.17 (0.12)	-0.12 (0.11)	0.05 (0.16)	-0.59 (0.42)	0.64
Physical Component Summary (PCS)	48.95 (0.32)	-0.43 *** (0.07)	-0.21 *** (0.06)	0.23 ** (0.09)	-0.44 ** (0.23)	0.65
Mental Component Summary (MCS)	48.15 (0.34)	0.08 (0.07)	-0.02 (0.06)	-0.10 (0.09)	0.11 (0.24)	0.60
SF-6D	0.756 (0.004)	-0.002* * (0.0008)	-0.002 ** (0.0007)	0.000 (0.000)	-0.003 (0.003)	0.62
Self-assessed health	2.75 (0.03)	0.04 *** (0.01)	0.01 (0.01)	-0.02 ** (0.01)	-0.04 ** (0.02)	0.66
Reported health transition	3.00 (0.03)	0.030 *** (0.01)	0.02** (0.01)	-0.01 * (0.01)	-0.16 *** (0.02)	0.35
Satisfaction – your health	6.82 (0.07)	-0.07 *** (0.01)	-0.04 ** (0.01)	0.03 * (0.02)	0.04 * (0.05)	0.62

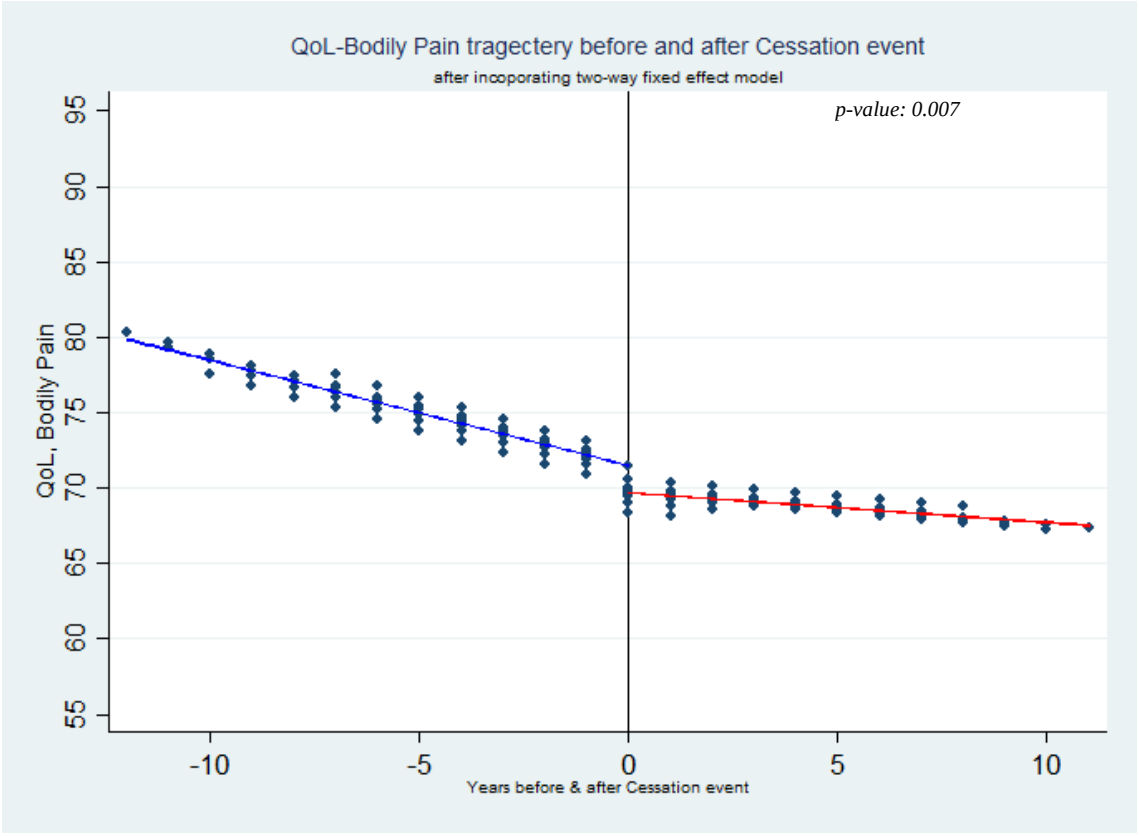
*p<0.10, **p < 0.05, *** p < 0.001
SE: Standard Error; **SF-36**: Medical Outcomes Study Short Form; **SF-6D**: Short Form-6 Dimension

Figure 7-2 Quality of Life trajectories before and after smoking cessation event after incorporating piecewise two-way fixed effect models, p-value of pre-post slope difference test





Before cessation ——— After cessation ———


QoL-Bodily Pain tragectery before and after Cessation event
after incoporating two-way fixed effect model
p-value: 0.007
QoL, Bodily Pain
55
60
65
70
75
80
85
90
95
-10
-5
0
5
10
Years before & after Cessation event

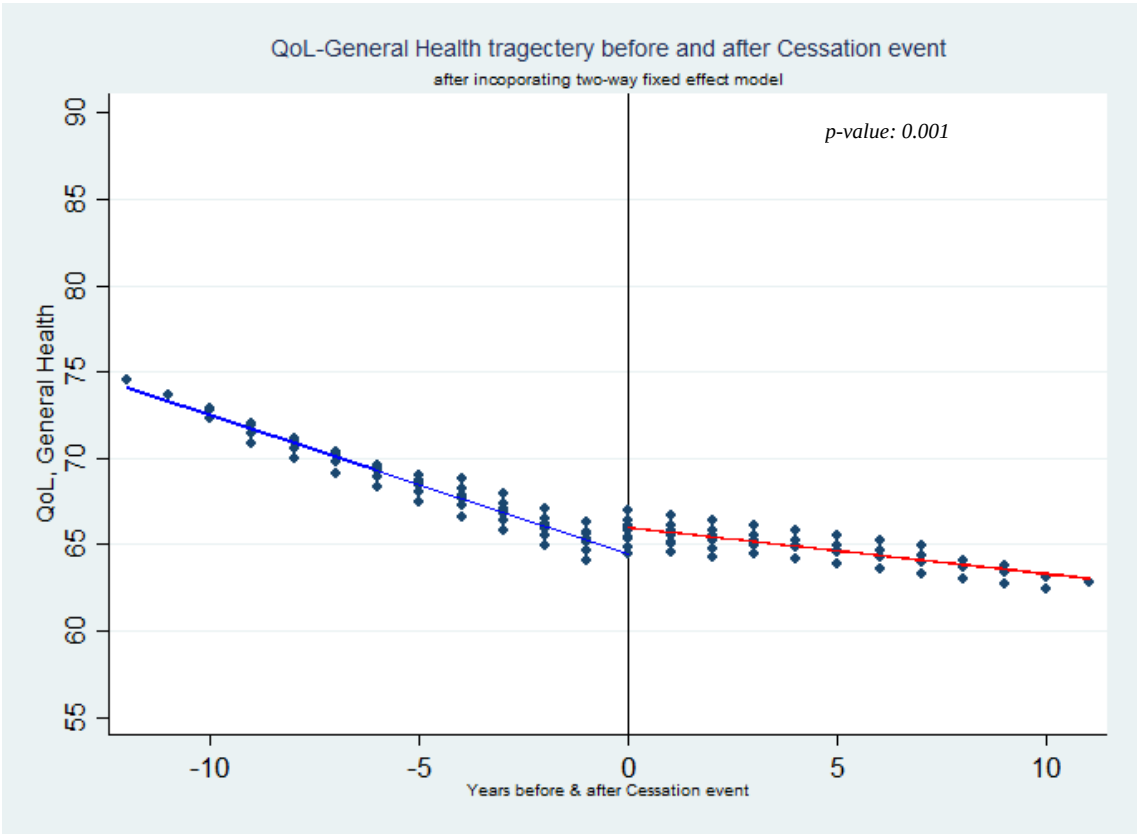
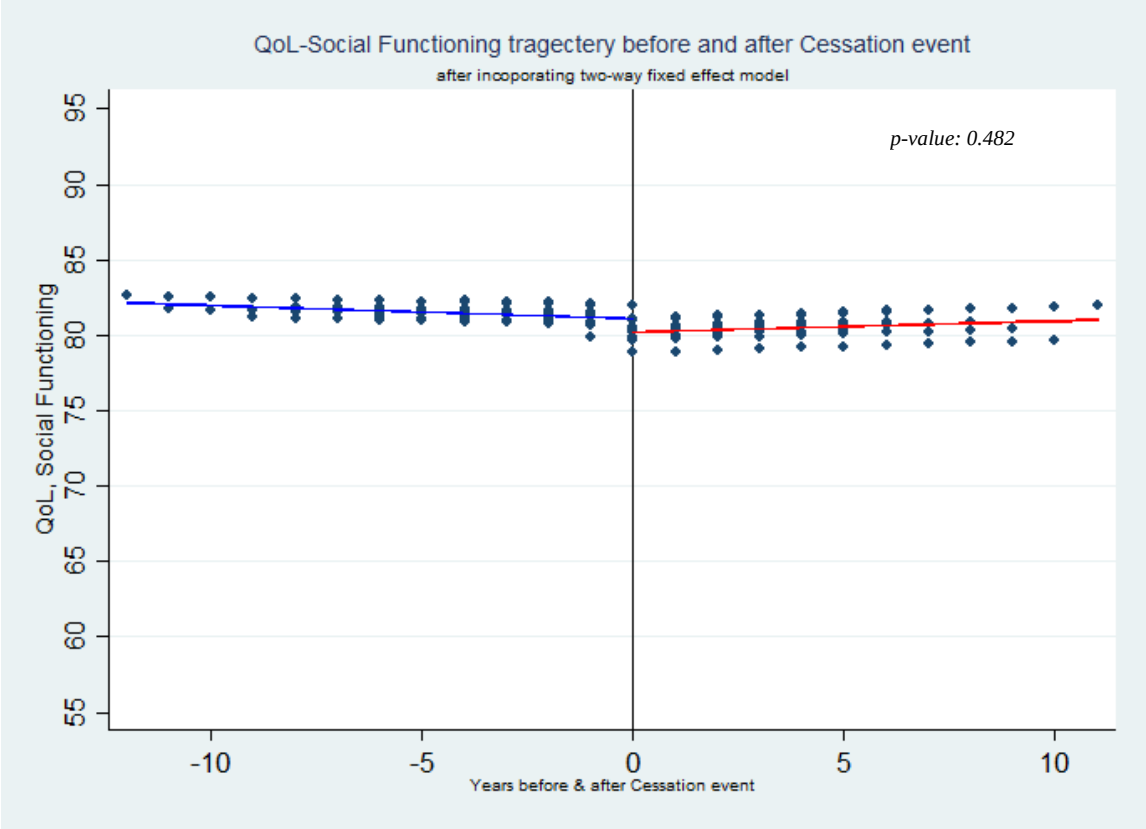
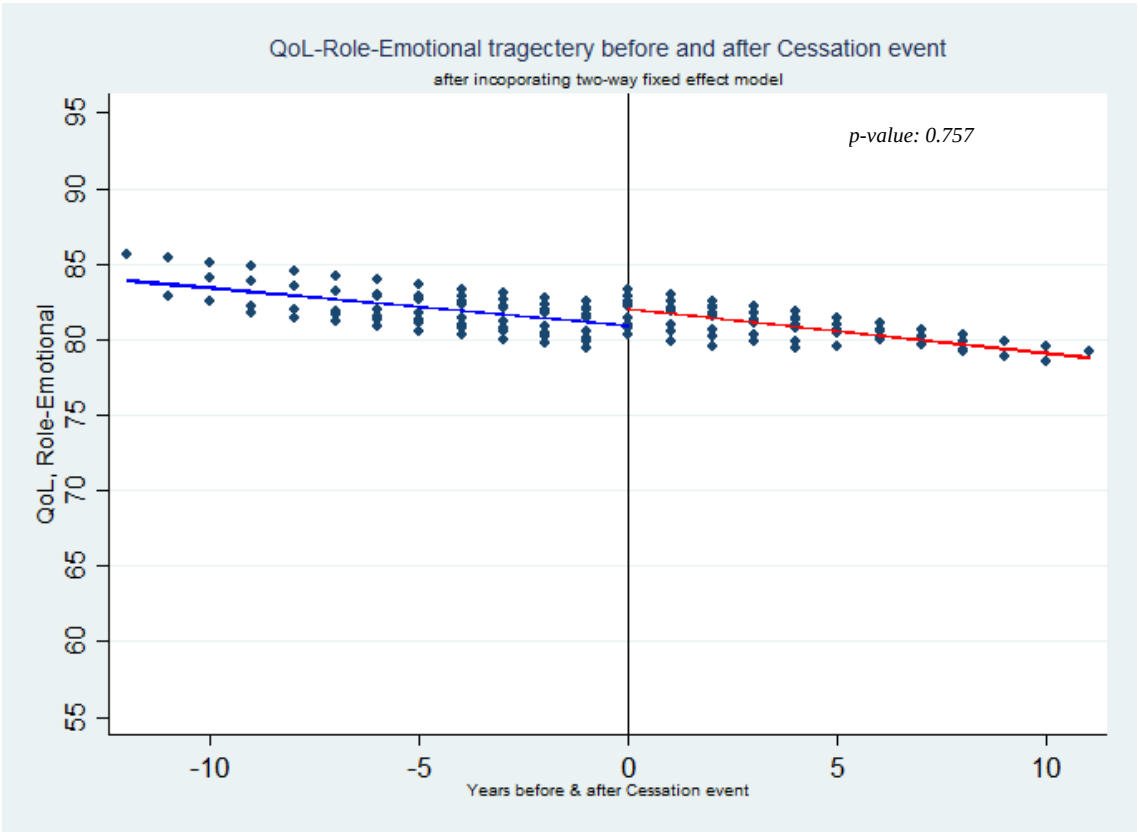
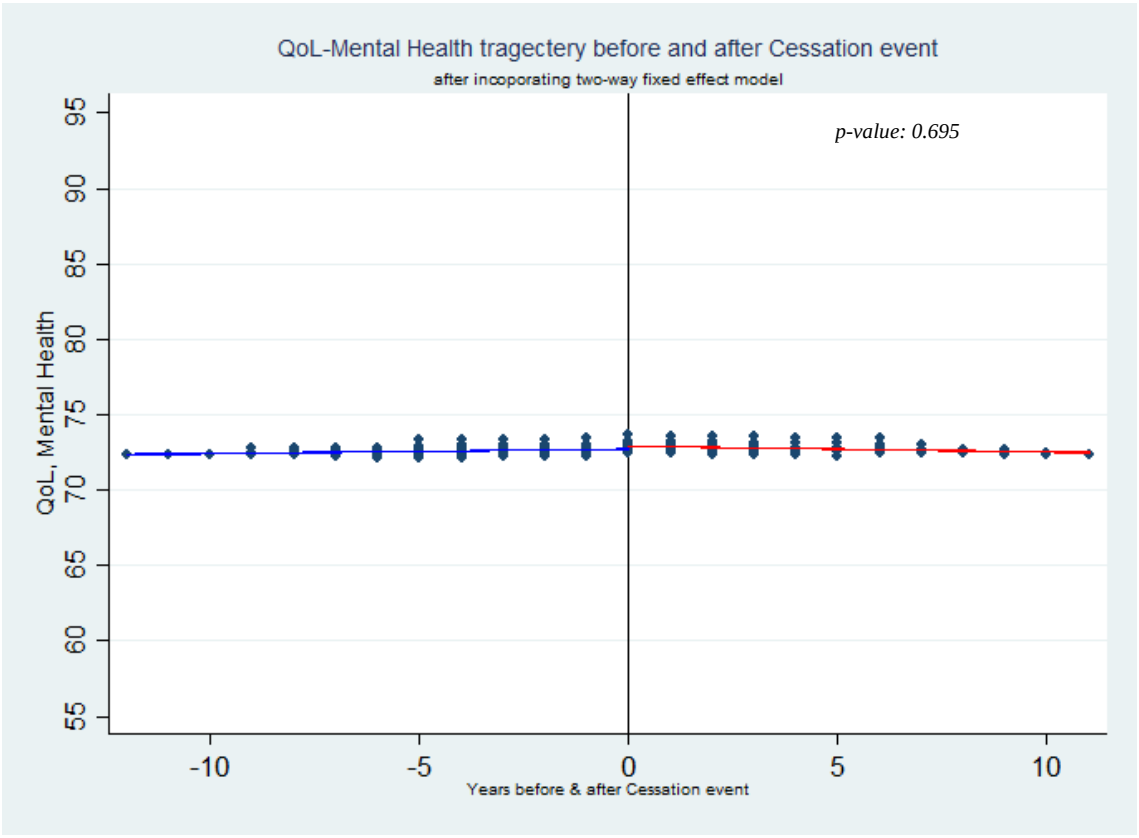

QoL-General Health tragectery before and after Cessation event
after incoporating two-way fixed effect model
p-value: 0.001
QoL, General Health
55
60
65
70
75
80
85
90
-10
-5
0
5
10
Years before & after Cessation event

Figure 7-3 Quality of Life trajectories before and after smoking cessation event after incorporating piecewise two-way fixed effect models, p-value of pre-post slope difference test, continue .






QoL-Mental Health tragectery before and after Cessation event
after incoporating two-way fixed effect model
p-value: 0.695
QoL, Mental Health
55
60
65
70
75
80
85
90
95
-10
-5
0
5
10
Years before & after Cessation event

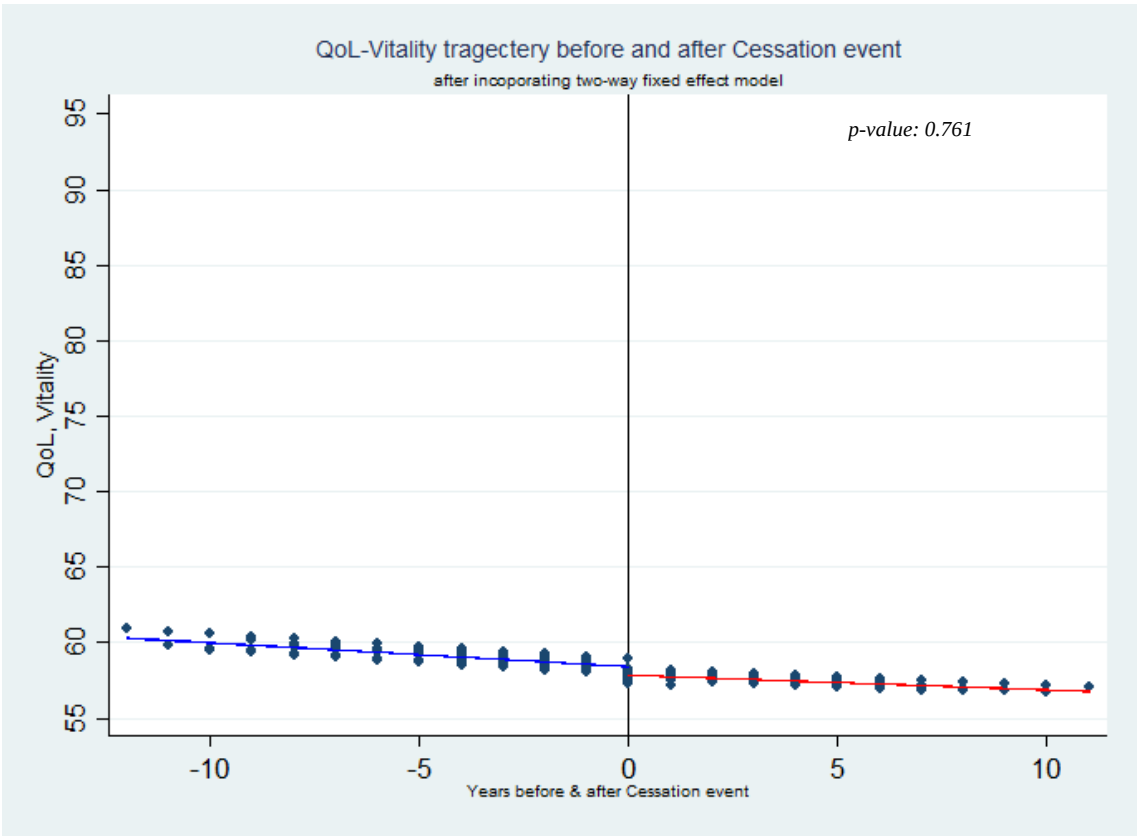
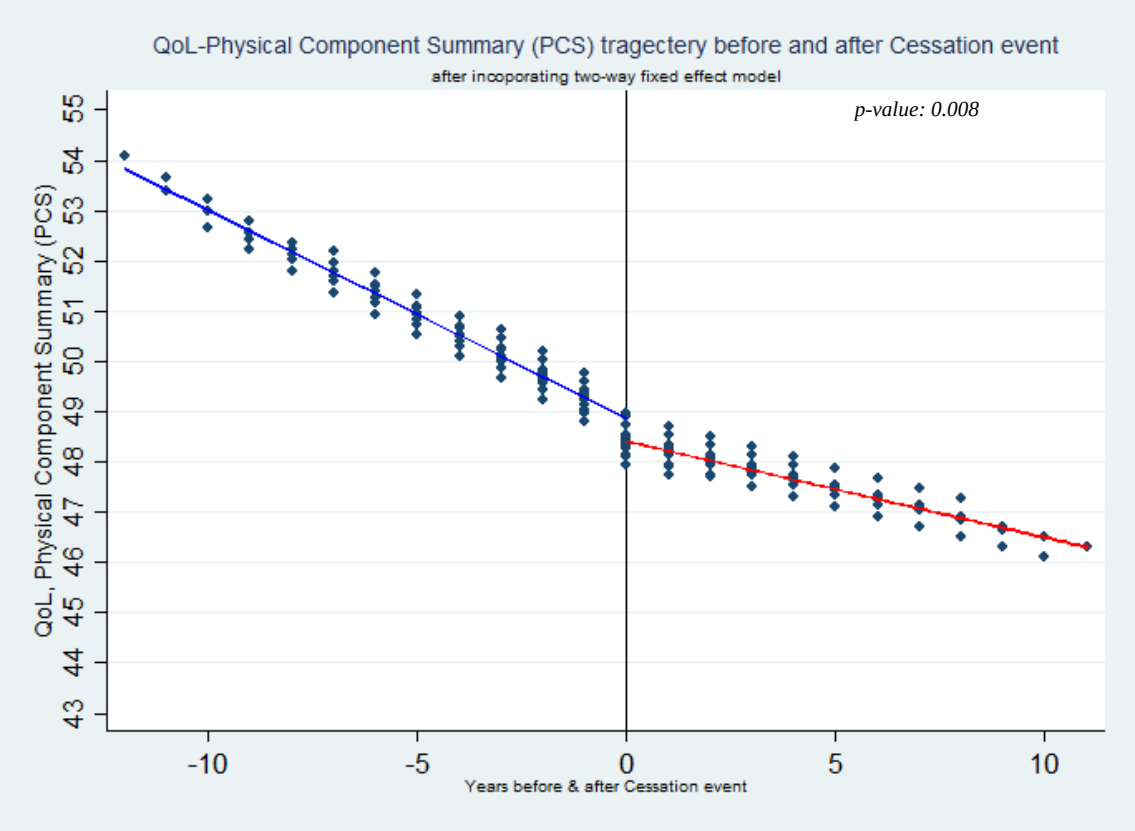
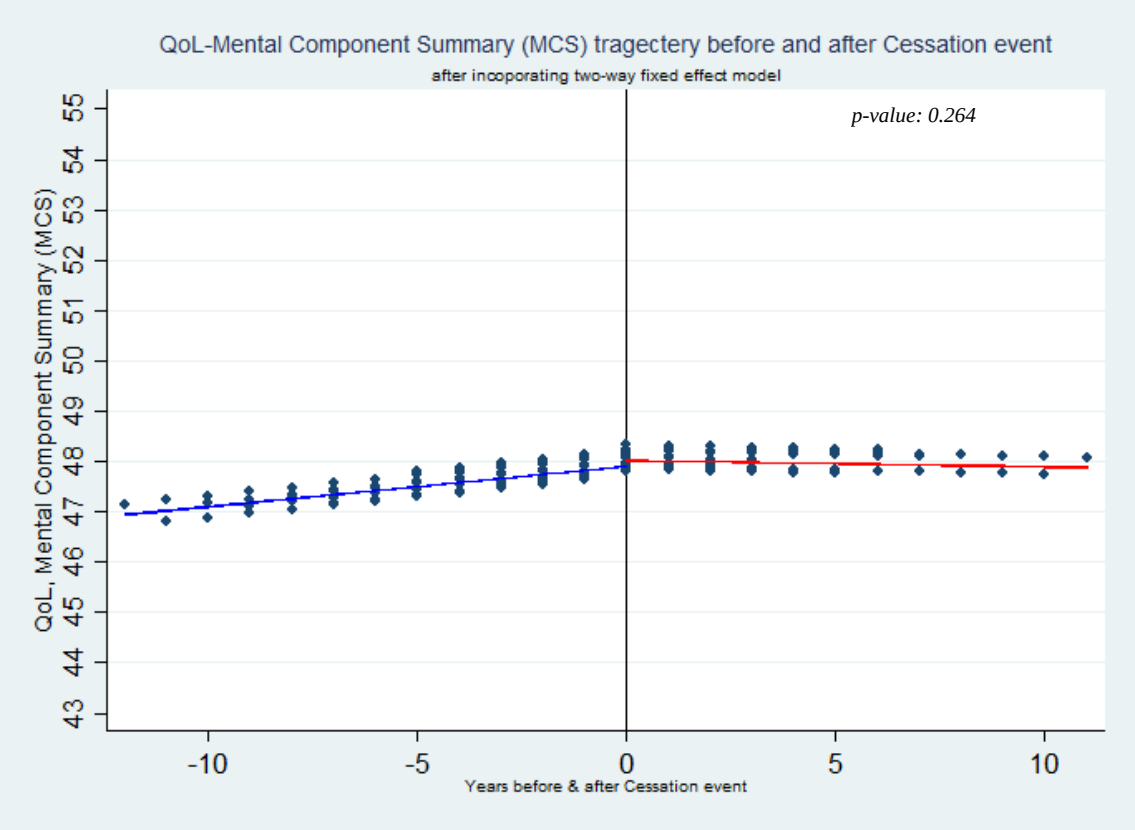

QoL-Vitality tragectery before and after Cessation event
after incoporating two-way fixed effect model
p-value: 0.761
QoL, Vitality
55
60
65
70
75
80
85
90
95
-10
-5
0
5
10
Years before & after Cessation event

Figure 7-4 Quality of Life trajectories before and after smoking cessation event after incorporating piecewise two-way fixed effect models, a p-value of pre-post slope difference test, continue …





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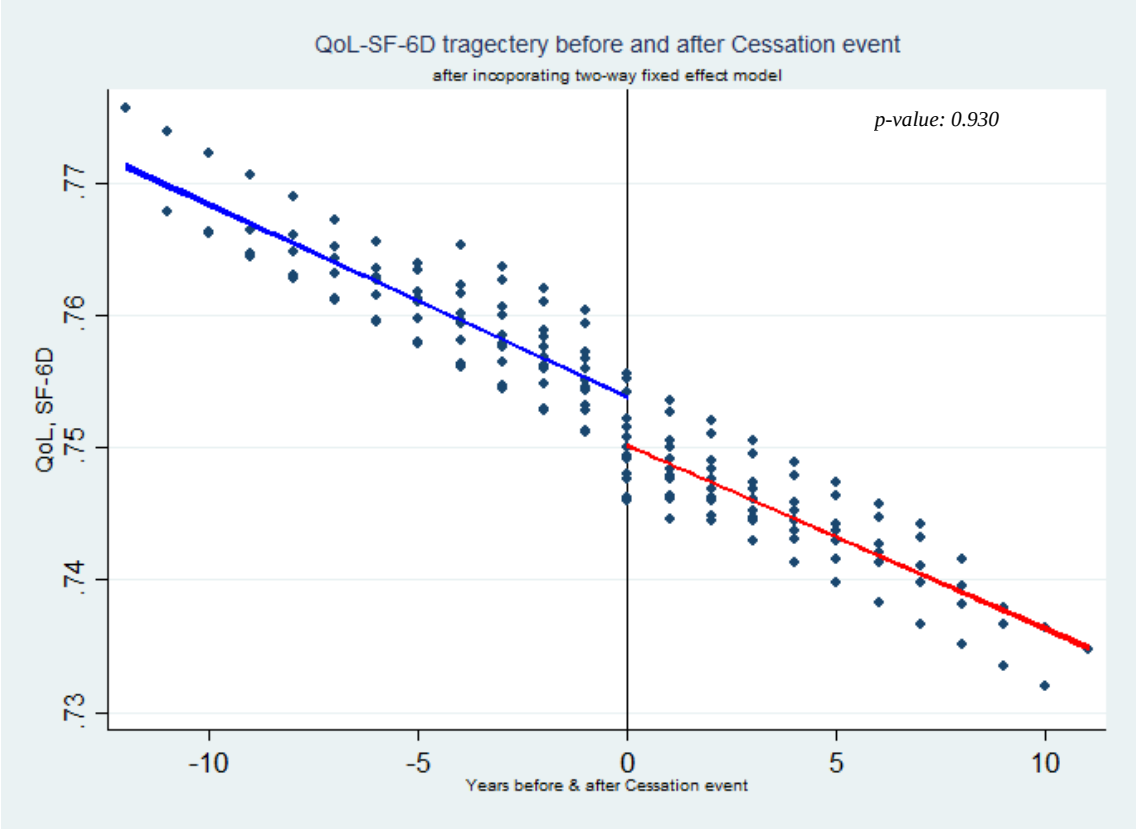

7.5 Discussion

To elucidate trends in quality of life after smoking cessation, panel data were analysed by piecewise two-way fixed effect linear regression models. The results indicated that performance in role physical, bodily pain, general health dimensions and PCS component of SF-36 QoL measure improved very substantially and continued improving thereafter as the effect of smoking cessation, irrespective of age and sex and other related time-invariant covariates. Of the eight SF-36 dimensions, only physical health factors showed pervasively and significant improvements after the smoking transition (estimated changes per year, 0.71, 0.52 and 0.55 for Role Physical, Bodily Pain and General Health respectively). The same figure was captured for PCS (estimated change per year, 0.23). However, improvement in Physical Functioning dimension is positive but it was not statistically significant (estimated change per year, 0.28). These findings consolidate the effect of smoking on physical health and wellbeing impairment. Interestingly, smoking cessation has a deteriorating effect on mental dimensions of QoL but not on a statistically significant scale.

Quitting associated with a negative jump in QoL in Role Physical and Bodily Pain dimensions and PCS component. These relatively low QoL scores might be expected as quitting is a common response to the event of new illness; for example, a recent diagnosis of vascular disease is predictive of smoking cessation. If it is the case, individuals with better health will remain in the smoker status, diminishing the health differences between these two smoker groups [435]. Another explanation for the lower value of QoL in recent years after quitting is the observed higher risk of death among recent quitter compared with those who never smoked. Hence, a considerable number of recent ex-smokers did not survive to realize the benefits of long-term cessation [419]. Another observation favouring lower QoL maybe the negative effects of smoking have already had their effect, and it could be too late for the quitters to improve their QoL [415]. lower Other sociocultural, neuropsychological or occupational factors entangled

with smoking may have simultaneous and conflicting effects on change of QoL and obscure the net short-term effect of smoking transition [436]. The same figure was traced for utility score after smoking cessation. Positive but not statistically significant improvement in SF-6D score (estimated change, 0.00) and a negative jump of 0.001 has been estimated. There are a few biological evidences which support the association of lower QoL after quitting attempt. A recent study based on nationally representative birth cohort data using fixed effect structural equation modelling showed that the best-fitting causal model was one in which nicotine dependence led to increased risk of depression [437]. They also suggested that common or correlated risk factors might be another route for an explanation of comorbidity between smoking cessation and depression [437]. On the contrary, it has been shown that self-administered nicotine appears to uplift depression-prone smokers' emotional response to a pleasant stimulus [438]. It was also claimed that relief from negative mood due to smoking depends on the situation [439], smokers' expectation [440] or nicotine withdrawal [441] rather than cigarette consumption itself.

Additional interesting findings revealed by this study were the association of smoking cessation and other QoL measures such as "health transition" and "satisfaction with one's health" though less pronounced. This association ran primarily through improvements in QoL brought about by smoking cessation, but there was also evidence of a small independent effect of smoking cessation on overall wellbeing. This means that the benefits of quitting on global assessments of well-being go beyond any health improvements and might be related to other mechanisms such as perceived self-efficacy, physical self-esteem or affect.

The very substantial improvement in physical dimetions of SF-36 QoL measure is consistent with other prior studies [442, 443]. Some biological evidence make this relationship plausible; smoking may lead to osteoporosis through a complex mechanism such as estrogenic inefficiency [444]; in addition, smoking may cause losses in pulmonary function [445, 446]. There are evidence in favour of association of smoking cessation with increased muscle and fat

mass, muscle strength and bone density [447]. The causal relationship between smoking and mental health is well documented but the nature of which is still debated.

In line with these observations, provision of psychological support such as access to mental health services in conjunction with other cessation interventions may reduce emotional and mental barriers and enhance psychological functioning which may have an additive effect on overall HR-QoL and eventually increase succeed rate of the interventions.

Some limitations are applied to this study. All smoking information was based on self-reported data, so potential reporting biases related to smoking status, a number of cigarette and length of abstinence might have confounded the results. Another limitation is that we did not access to data on reasons for quitting, especially whether transitions were due to a recent cardiovascular disease. This study was not aimed to explore the effect of time-invariant covariates (such as country of birth, sex …), which has been fixed by defining the appropriate regression models, on HRQoL after smoking transition. The other limitation is related to our piecewise regression simplicity approach that is limited to only one cessation event in the HILDA life. It would be worth to model more than one knot points to show the effects of more than one quitting attempts on HRQoL. This study did not aimed to explore the effect of transition from non-smoker to smoker (take-up) or ex-smoker to smoker (relapse) on HRQoL.

The current study is one of the first nationally representative studies analysing the relationship between smoking and QoL measures. This enables to extrapolate research findings to the Australian population as a whole. This study overcomes some of the data and methodological limitations of previous studies by 1) using longitudinal data with thirteen years of follow-up 2) reducing bias from loss to follow-up using unbalanced data [448, 449]. These features stand in mark contrast to nearly all relevant studies. Panel data as a longitudinal or cross-sectional time-series data provides unique opportunity to account for individual heterogeneity and focus on within-person changes in QoL as smoking status change while controlling for unobserved time-

invariant individual characteristics fixed effects on observed covariates. Both the values of QoL and its proxies (for example self-assessed health) and the methods of which are estimated in current paper are deemed more robust.

This study suggests several avenues for future research to improve our understanding of the nexus between smoking and QoL. From the methodological point of view, panel data provides a valuable base for applying another statistical approach within the field of smoking such as time-varying effect models for capturing the effects of covariates over time. In addition, the relationships between smoking cessation and QoL may be different across population groups with varying characteristics. For example, gender and age diversity have a considerable impact on the final dynamic model of smoking progression and cessation [403, 419, 450-455]. Future research can explore the dose-response relationship of smoking with QoL and discovering the underlying mechanisms associated with the decline in smoking QoL over time.

We found that there is strong and sizable evidence that smoking cessation has significant effect on QoL and reinforces the body of literature demonstrating the benefits of quitting. Our conclusion has important consequences for the health of Australians. In order to intensify mental wellbeing gain during cessation process, the inclusion of psychological support sessions under the Australian Medicare and optimizing the design of smoking cessation interventions are recommended.

Appendix F2, Table 1, 2, 3 & to this chapter was developed with the aim to estimate the values of health-related quality of life, as measured by SF-36 and Short Form-6 dimension (SF-6D), in different smoking status in the Australian general population. A second aim was to find out which dimensions of QoL are affected by smoking, and if so, to which degree they were affected.

8 Chapter 8 Conclusion

The main goal of this dissertation was to analyse the health state utility value around Chronic Obstructive Pulmonary Disease and its main risk factor, smoking. This thesis was based on three sources of data bases generated through systematic literature reviews, a primary data from a clinical trial and the secondary data, the Household, Income and Labour Dynamics in Australia (HILDA) Survey, provided by the Melbourne Institute of Applied Economic and Social Research.

8.1 Summary of research questions

This thesis addressed the following question in four areas:

- What is the mean HSUV for COPD in general and for each stage of the disease? What is the main sources of heterogeneity in the mean HSUV across a variety of clinical and study characteristics in published literature in COPD?
- What is the trend of evolution of COPD progression models? Did they use correct values of HSUV for stages of COPD? Did they follow the recommended guidelines of good practice, especially in data identification of HSUV?
- Do the minimal physiological interventions such as cognitive behavioural therapy (CBT) are effective measure tacking the mental comorbidities in COPD as a chronic disease? What is the probability for telephone-based-CBT to be of cost-effective approach against depression and anxiety comorbidities in COPD compared with a standard care without CBT, from a health service payer perspective?
- Does smoking cessation exert an effect on QoL? What is the transitional probability of staying in the same smoking status or moving between take-up, cessation and relapse states in general Australian population? How much are the net values of health-related quality of life in different smoking status in the Australian general population?

8.2 Summary of results, recommendations and policy implications

This thesis was comprised of eight chapters including four studies. The chapter two reviewed published researches on the valuation of the HSUV in COPD patients, and performed a meta-analysis to estimate general and stage level HSUV. The chapter three was a chronological review of existing COPD decision models and their main advantages. This study was a prelude to the next study (the chapter four) which investigated how decision model COPD researches followed good modelling practice recommendations specifically the HSUV data identification. The chapter five was a systematic literature review of CBT-based intervention for anxiety and depression problem in patients with COPD. This study provided some inputs for the next study (the chapter six) which was an economic evaluation of TB-CBT in COPD patients and tried to assess the impact of this intervention on HSUV. The chapter seven appraised the effect of the smoking behaviour on HSUV of the Australian population and within this context assessed impact of smoking state transitions on HSUV. The main outcomes of the above-mentioned studies are summarized accordingly in the current chapter.

8.2.1 Health state utility value in COPD patients

The study summarized comprehensively the HSUV of COPD based on patient-level data measured by using the EQ-5D index. The estimated mean general utility value was 0.673 (95% CI 0.653 to 0.693), derived from a random effect meta-analysis. This systematic review has revealed substantial diversity in the measuring instruments of HSUV used, and a wide range of utility values in COPD. The utility values ranged from 0.820 (95% CI 0.767 to 0.872) for stage I to 0.624 (95% CI 0.571 to 0.677) for stage IV. Tests of difference between estimated utility means rejected the hypothesis of equality of means between stages of COPD.

Conclusion

The meta-analysis indicated a high degree of heterogeneity in utility that was not explained by other factors (I^2 statistic ranging from 92.7% to 97.9%). The subgroup analysis did not show evidence of a difference in the heterogeneity of estimated utility value with available study and patients' characteristics.

In comparison with the findings from the past, a current systematic literature review has significant clinical and research implications. This study was one of the first meta-analyses of HSUV at different stages of COPD. This study tried to adhere to general recommendations in the selection of included studies and running meta-analysis in chronic diseases. In the current study appropriate statistical tests were used to demonstrate sources of heterogeneity and differences in estimated utility values by sub-group analyses.

This study showed considerable inconsistency in utility measures among COPD-related published literature. It confirms that the utility value in COPD was considerably lower than the general population. However, the effects of contributing factors such as spirometry assessment and comorbidities on utility value remained largely unclear. This paper suggested that careful consideration should be taken into account when using systematic method (meta-analysis) for calculation of input parameters in health economic analysis. In the case of high level of heterogeneity, appropriate sensitivity analyses were recommended for more accurate health economic appraisals.

Recommendations of this study for the future research were:

(i) consideration specific limitations of some HSUV measure instruments (e.g. ceiling effect and limited sensitivity in EQ-5D) and

(ii) using EQ-5D-5L instead of EQ-5D-3L may overcome this limitation.

8.2.2 Chronological review of COPD decision models

A systematic literature review was conducted to provide a narrative summary of exciting COPD decision models highlighting their main features. Thirty-eight studies were captured. They were analysed according to five main aspects: 1) model types and structures, 2) clinical and economic assumptions, 3) data sources and inputs, 4) model validations, 5) treatment of uncertainty. This study was a prelude to the third study of my thesis and provided extended information related to the next chapter.

8.2.3 Health state utility values in COPD modelling studies

This study demonstrated that there were systematic differences been utility values used as input parameters in COPD decision models and results derived from a systematic review of the literature; on average, modelling studies used higher values than estimated mean utility from the meta-analysis of the patient-level data. This deviation was significant in stage III of COPD. Furthermore, depending on the stages of COPD, up to six modelling groups (at stage III) used utility scores that were outside the meta-analysis derived CIs.

This study found that in spite of the high level of heterogeneity in utility values derived from patient-level data for all stages of COPD, related health economic decision models currently did not account for this degree of variation, as most rely on a single value taken from one patient-level data study. In addition, modelling studies may not align with patient-level data in that they do not fully follow COPD stages.

This was the first study to systematically compare the input assumptions of modelling studies with a systematic literature review using meta-analysis. This review included a comprehensive and reproducible literature search to capture relevant studies from different perspectives. Included studies and the results were properly documented and visualized in tables and figures,

by countries, design, and population of studies. The advantage of this study is to provide a reference value for each COPD stage that can be used in future economic evaluations and simulation modelling; including estimates of confidence intervals around these summary values which are valuable statistics for sensitivity analysis in COPD progression models.

This study has recommended:

(i) improvement in the consistency of modelling studies may be achieved if published recommendations on good modelling practice, especially the data identification, are followed closely as suggested.

(ii) the development of a COPD reference simulation model that use a common set of stages and utility values which are aligned with international staging guidelines is required,

(iii) health state utility values for decision-analytical modelling studies should fit health states predetermined by the model structure, be elicited from the same population as the model specifies, be up to date, and be derived from a representative sample size

8.2.4 Review of CBT interventions against COPD psychological comorbidities

This study was a systematic literature review of the efficiency of CBT-based interventions on psychological problems in COPD patients and economic evaluation of this approach. Altogether ten clinical trials and two economic evaluations were captured. The quality of the studies were assessed according to the following criteria: clear aims, randomization techniques, concealment of treatment allocation, comparability of groups at baseline, blinding of interventionists and participants, eligibility for intervention assessed, description of intervention provided to allow replication, attrition, effect size, details of long term follow-up and sustained change, analysis of confounding variables, power analysis, definition of all outcomes, measured with reliable

measurement tools and results provided for each, appropriate statistical analysis and inclusion criteria.

8.2.5 Cost-utility analysis of TB-CBT in COPD

The main finding of this study was that Telephone-based cognitive behavioural therapy (TB-CBT) group was associated with a significantly negative incremental total health care cost of AUS -$352.3 (p-value <0.001, SE: 39.64) per patient and slightly negative incremental quality-adjusted life year (QALY)-gained of -0.0071 (p-value 0.542, SE: 0.011) per patient within the trial time horizon. Incremental cost-utility ratio (ICUR) was a positive ratio resulted from cost saving and QALY sacrificed: AUS $49,868.7 (95% CI -26,407 to 11,636) reduction per QALY loss (located in the South West quadrant of the ICUR plane).

This study did not support using TB-CBT treatment for COPD in its current form as a cost-effective modality than control approach (befriending care), assuming a WTA threshold of more than AUS $121,600 per QALY sacrificed. This study shows that TB-CBT can be recommended as a cost-saving approach to usual care plus befriending if a relatively less health gain is acceptable.

This study added to the limited literature on the cost-utility analysis of Minimal Psychological Intervention (MPI) such as TB-CBT in chronic somatic patients suffering from depression or anxiety. This study followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guideline, using multiple imputation for missing data, baseline correction of outcomes and non-parametric bootstrapping.

A key strength of this study was that it provided a distinctive interpretation of the incremental cost-utility ratio. This finding required different decision rule compared to the ICUR located in the north-east quadrant of the cost-effectiveness plane. The traditional threshold of willingness-

to-pay per QALY gained was no longer applicable to this result. Thus, the study re-defined the decision rule as “the threshold of the willingness to accept (ie, a minimum flooring ratio) of the cost saving must be achieved for a QALY sacrificed”. This was in accordance with the economic concept that the ‘selling price’ of a unit of QALY is greater than the ‘buying price’.

Findings of this study emphasised that depression and anxiety comorbidities are major influential factors in lowering HSUV in COPD patients and should be addressed in clinical guidelines and usual practice. This study revealed that COPD patients suffering from psychological comorbidities had very low values of HSUV, 0.325 (SD 0.217). Further study for evaluating the comparability of EQ-5D and AQoL utility scales in COPD is recommended.

8.2.6 Outcome of smoking on QoL and HSUV

Results of piecewise two-way fixed effect models showed that for most of the SF-36 scores there was a positive association between cessation transition and some SF-36 domain scores (Table 7-4 & Figure 7-2). This effect was significant for role physical, bodily pain, general health domains and PCS component. In addition, jumps of QoL values (intercept change, β3) at knot point were significant for these measures. In fact, the results indicated that the association between smoking trajectories and the PCS score was driven primarily by the effect on the role physical, bodily pain, and general health scales and to a lesser extent on the physical function scale. The impact of cessation transition on the increase of QoL each year differs by domain with, for example, a 0.650 increase in role physical score and 0.225 increase in PCS score each year. It was interesting that the effect for role emotional, mental health domains and MCS component was negative but not statistically significant. The predicted utility scores (SF-6D measure) before and after cessation showed positive but not statistically significant association.

The results of the study indicated that performance in role physical, bodily pain, general health dimensions and PCS component of SF-36 QoL measure improved remarkably and continued

improving thereafter as the effect of smoking cessation, irrespective of age and sex and other related time-invariant covariates.

The current study is one of the first nationally representative studies analysing the relationship between smoking and QoL measures. This study overcomes some of the data and methodological limitations of previous studies by 1) using longitudinal data with thirteen years of follow-up 2) reducing bias from loss to follow-up using unbalanced data [207, 287]. These features stand in mark contrast to nearly all relevant studies.

This study has recommended:

(i) provision of psychological support such as access to mental health services in conjunction with other cessation interventions may reduce emotional and mental barriers and enhance psychological functioning which may have an additive effect on overall HR-QoL and eventually increase succeed rate of the interventions.

The appendices of this chapter provided additional information regarding smoking habit in Australian population and the related QoL. The information presented in these appendices can be summarized as:

- The mean values for SF-36 scores in ever smokers, ex-smoker, and non-smoker over the HILDA life showed enough indication that smoking is significantly associated with QoL. Mean SF-36 domain scores were ranged from 84.82 (22.73 SD) for Physical Functioning to 61.45 (19.67 SD) for Vitality in non-smokers. This figure was lower in ever ex-smokers and much lower in ever smokers with consideration of slight higher values for Physical Function, Role-physical, Bodily Pain and PCS component in smokers than ex-smokers. Domain wise, heavy smokers were much more likely to

report a problem in all QoL domains compared to moderate and light smokers. These differences were relatively systematically observed across the eight domains of SF-36, PCS and MCS components and SF-6D scores for all smoking status and smoker sub-classes.

- The same figure was captured for HSUV. Overall, mean observed HSUV value was declined from non-smoker to ex-smoker and then to smoker status. The same decreasing slope for HSUV was detected through subgroups of smokers, a decline from light smoker to moderate and then heavy smokers.

8.3 Implication for future studies

There are a number of questions that could be explored in this area to further shed light on issues related to the HSUV measurements in chronic diseases, comparability of the results,

(i) This thesis tried to investigate the challenges around valuating HSUV in a chronic somatic disease, COPD. The results showed considerable inconsistency in utility measures among COPD-related published literature. It was evident that relevant literature was poor in capturing disease specific conditions that could affect the HUSVs such as comorbidities, severity of disease and risk factors of the disease (smoking and exacerbation risk and rate) at patient's level investigation. This major pitfall would affect the outcome, interpretation of the results and generalizability of the studies. In addition, lack of some key input such as valid estimations of utility values in exacerbation-affected health states, is required to be addressed in the future studies. Chapter two did not find any tangible factor that can explain the heterogeneity in HUSV in COPD because aforementioned reasons. For the future studies, more in depth investigations by using meta-analysis of patient-level databases from included studies is recommended.

(ii) Chapter four revealed that despite the trend to use meta-analyses to inform clinical decisions, their use in informing decision analytic modelling studies has been limited. Not using the recommended good modelling practices in HSUV input parameter, had statistically significant effect on the output of COPD progression models. For the future studies, validity of other model input parameters can be investigated.

(iii) Given the growing popularity of disease progression model in decision making and economic appraisal researches, this thesis recommends that future studies will need to take into account of using new approach in disease progression microsimulation modelling and incorporating the updated COPD assessment tool. They should provide appropriate comparisons with the patient-level utilities to determine the applicability of utility values used in more recent COPD models.

(iv) Chapter six focused on an economic evaluation of a minimal psychological intervention for treatment of depression and anxiety in elderly COPD patients in a two-arm RCT. HSUV, as the outcome of this economic evaluation, did not show very significant improvement. It was suggested that the time horizon of the intervention and follow-ups were too short (17-week) to allow for the treatment to have its effect on main (anxiety and depression) and secondary (HSUV and costs) outcomes. For the future studies a longer follow-up at least three months or two weeks in every two months (12 times) of a year in chronic diseases is recommended. Especially in cases such as COPD which its natural progression involves exacerbation states which can rapidly change a patient's condition and increase health service utilization and pharmaceutical consumption significantly. Depending on the severity of exacerbation, this period of flare up may last from two to four weeks. Due to the short time horizon of the study, one-time high

resource health care services such as inpatient hospital stay, ambulance and specialist visit might have been missed or overestimated.

(v) Chapter seven paid particular attention to the impact of smoking, as the main risk factor of the leading causes of death in the world; ischemic heart disease, stroke, COPD and lung cancer, on HRQoL. It used a piecewise regression / interrupted time series (ITS) (as a quasi-experimental research) design to test statistically for a change in the HRQoL value in the time periods before and after smoking cessation event in an Australian general population sample using a large prospective cohort study (HILDA). And revealed significant improvement in physical dimensions of QoL. For future studies, it is recommended to investigate underlying reasons for smoking cessation, their effects on QoL and incorporating them into the appropriate statistical models such as survival analysis. In addition, future researches can focus on the effect of time-invariant covariates (such as country of birth, sex …), which has been fixed by defining the appropriate regression models in this study, on HRQoL after smoking transition. More complicated piecewise regressions which model more than one cessation event is also suggested. Further studies can aim to explore the effect of transition from non-smoker to smoker (take-up) or ex-smoker to smoker (relapse) on HRQoL. Meanwhile, future researches can explore the dose-response relationship of smoking with QoL and discovering the underlying mechanisms associated with the decline in smoking QoL over time.

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Appendix A to Introduction

Table A0-1 Characteristics of utility and quality of life measures used in COPD studies

Instrument	Number of Items	Response Option	Completion time (min)	Administration
Disease specific				
AQ20/30	20/30	Yes, no, not applicable	1-3	Self-administered
AQ 20 R	20	Yes, unable, no, not applicable	1-3	Self-administered
CAT	8	5-point Likert scale	1-3	Self-administered
CCQ	10	7-point Likert scale	1-3	Self-administered
CRQ	20	7-point modified Likert scale	10 15-25	Interview Self-administered
EXACT & EXACT-RS	14			Self-administered
LAS/VAS-8	8	Horizontal line 10cm with extremes in words on end	3	Self-administered
LCOPD	22	Dichotomous true/not true	10	Self-administered
McGill COPD	29	5-point Likert scale	10-15	Self-administered
MRF-28	28	Dichotomous true/false	10	Self-administered
QoL-RIQ	55	7-point Likert-type	5-10	Self-administered
RQLQ	20	5-point Likert scale	10-15	Self-administered
SOLQ	29	5 & 7-point Likert scales	5-10	Self-administered
SGRQ	76	5-point Likert and dichotomous (yes.no)	10	Supervised self-administered
SRI	49	5-point Likert scale	20	Self-administered
VSRQ	8	Horizontal numerical scale 0-10 grades/1 cm	3	Interview
Generic				
DartmCoop	9	5-point ordinal scale (words and graphically)	5	Interview / Self-administered
FACIT	27	5-point Likert-type scale	15	Interview / Self-administered
Hyland Scale	1	1 scale extremes on end (0-100)	<5	Interview / Self-administered
MYMOP	3	Choosing problematic symptom and ADL/7-ponit scale	<10	Interview / Self-administered
MOS-6A		5/6-point Likert scale	<2	Self-administered
NHP	45	Dichotomous yes/no	10-15	Self-administered
QLICD-GM	30	5-point Likert scale		Self-administered
MOS-6A		5/6-point Likert scale	<2	Self-administered
NHP	45	Dichotomous yes/no	10-15	Self-administered
SIP	136	Dichotomous yes/no	20-30	Interview / Self-administered
Utility measures				
15D	15	5 ordinal levels	5-10	Self-administered
EQ-5D Index	15	3 levels: no problem, some problems and severe problems	8	Self-administered
EQ-5D VAS	-	20 cm vertical visual analogue scale		Self-administered
HUI	8	5 or 6 point scale	3	Self-administered
QWBSA	10	Preference weighted 0-1	12-20	Self-administered
SF-36	36	5-point response choices	10-15	Interview / Self-administered
SF-12	12	5-point response choices	5	Interview / Self-administered
SF-6D	11	six multi-level dimensions		Self-administered
SG				Interview
TTO				Interview
WHOQOL-BREF	26	5-point Likert scale	10	Self-administered

Adopted and expanded from Weldam et al, 2013. **AQ-20/30**, Airway Questionnaire 20/30; **AQ-20R**, Airway Questionnaire 20 Revised; **CAT**, COPD assessment Test; **CCQ**, Clinical COPD Questionnaire; **CRQ**, Chronic Respiratory Questionnaire;

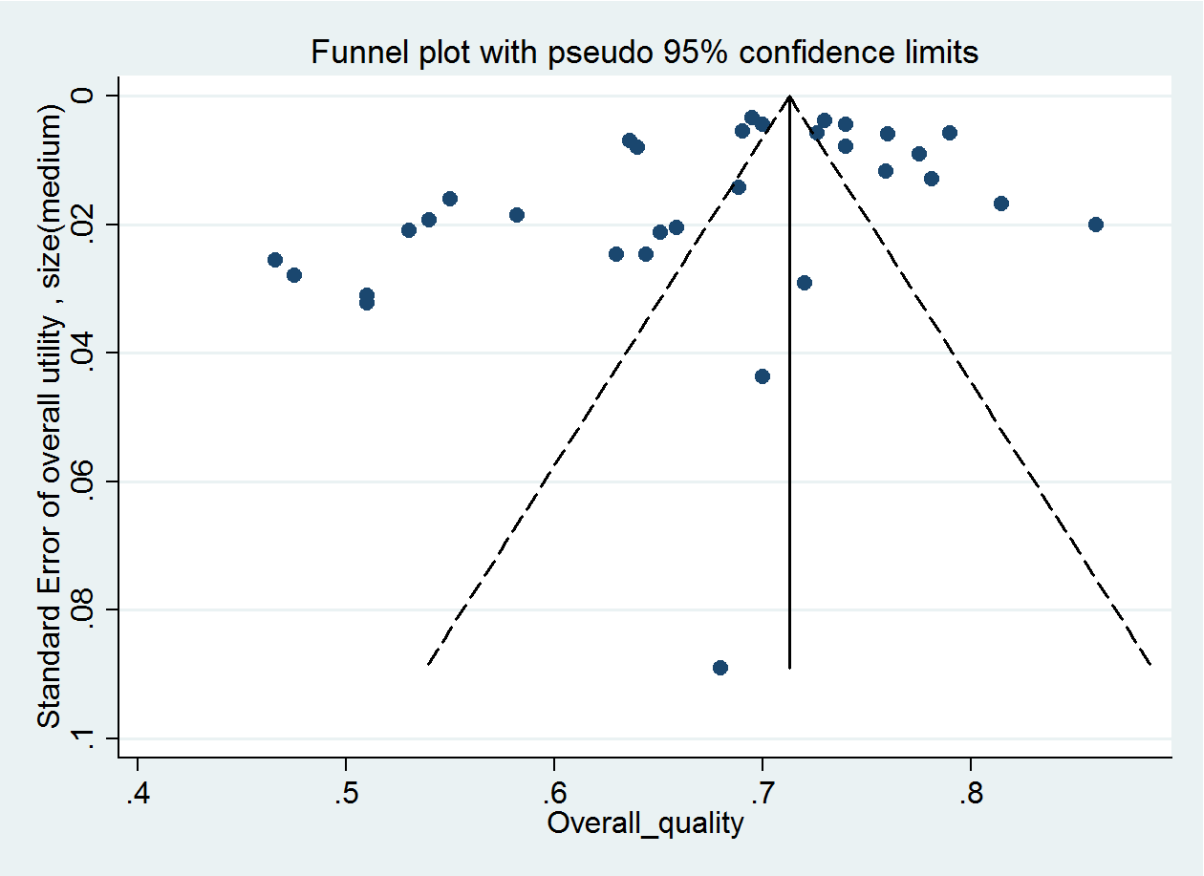
DartmCoop, The Dartmouth Northern New England Primary Care Cooperative Information Project chart system; **EQ-5D**, **EuroQol 5D:** European Quality of Life questionnaire; **EXACT**: EXAcerbation of Chronic Pulmonary Disease Tool; **EXACT-RS:** EXACT Respiratory Symptoms **;** **FACIT**: Functional Impairment of Chronic Illness Therapy; **HUI**: Health Utility Index; **LAS/VAS-8**, Linear Analogue Scale/Visual Analogue Scale; **LCOPD**, Living with Chronic Obstructive pulmonary disease questionnaire; **McGill COPD**, McGill COPD Quality of Life Questionnaire; **MOS-6A:** medical outcomes study 6-item general health survey; **MRF-28**, Maugeri Respiratory Failure Questionnare-28; **MYMOP**, Measure Yourself Medical Outcome Profile; **NHP**, Nottingham Health Profile; **QLICD-GM**, Life Instruments for chronic Diseases-General Module, **QoL-RIQ**: Quality of Life in Respiratory Illness Questionnaire; **QWBSA**, Quality of Well Being Self-Administered; **RQLQ**, Respiratory Quality of Life Questionnaire; **SF-12**, Short-Form Health Survey-12; **SF-36**, Short-Form Health Survey-36; **SG**, standard Gambling; **SGRQ**, St. George Respiratory Questionnaire; **SIP**, Sickness Impact Profile; **SOLQ:** Seattle Obstructive Lung Disease Questionnaire; **SRI**, Severe Respiratory Insufficiency; **TTO**, Time Trade Off; **VSRQ**, Visual Simplified Respiratory Questionnaire; **WHOQOL-BREF**, World Health Organization Quality of Life short version list.

Appendix B to Chapter 2

Table B1 Summery of MEDLINE search strategy

1	COPD
2	Chronic obstructive pulmonary disease
3	Chronic obstructive lung disease
4	Emphysema
5	Chronic bronchitis
6	1 or 2 or 3 or 4 or 5
7	"quality of life"
8	CUA
9	Euroqol-5d
10	eq-5d
11	eq5d
12	Qaly
13	"Quality -adjusted life year"
14	Health state
15	QoL
16	Utility
17	7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16
18	6 AND 17

Figure B1 Funnel plot of general utility values, included studies of COPD



A funnel plot is a scatter plot of the intervention effect estimates (Quality of life) from individual studies against some measure of each study's size or precision (Standard Error) (Cochran handbook, Chapter 10). Assessment of symmetry in the funnel plot is often subjective. Inspection of the funnel plot in the example above suggest asymmetry because the estimated utility values are unevenly scattered outside the superimposed limits.

The reason can be [456]:

1. Poor methodological design. This will lead to an absence of studies on the left-hand side at the base of the funnel plot.
2. Publication bias / selective outcome reporting bias. If there is bias, for example because smaller studies without statistically significant effects remain unpublished, this will lead to an asymmetrical appearance of the funnel plot with a gap in a bottom corner of the graph.
3. Although the included studies are large enough to lead to high precision (low variance of point estimates), they have high variance among the point estimates. High degree of heterogeneity (I^2 = %98.6), maybe is the reason of this unusual pattern studies' distribution in this funnel plot.

In our case, there are two distinctive features. Firstly, the range of changes in utility are very subtle (between 1 to 0) which makes the value of standard error very small. Secondly, as health utilities are often secondary outcomes in the individual studies, result of the funnel plot is not quite relevant.

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Table B1 Longitudinal data for COPD interventions/exacerbation utility-based quality of life

Six citations reported longitudinal data on mean values of utilities after incorporating a kind of interventional procedures such as Lung transplantation, rehabilitation or pharmaceutical intervention, Table B1. One study [457] reported change of utility during progression of COPD disease for a period of 12 months. Inconsistency in detecting longitudinal changes in utility value during one year was detected. The study disclosed that agreement in HR-QoL change direction between disease-specific and generic measures existed only in 45% of patients during 4 months period. They concluded both disease-specific and generic HR-QoL measures should be used to gain insight into the impact of the disease on health status of patients and progression of disease. Two studies [217, 458] captured the change in utility score after experiencing an exacerbation. Both studies included exacerbation type I, II and III, but they didn't measure pre-exacerbation utility values. Therefore it is not possible to investigate time laps returning to baseline value of utility score after exacerbation. Other studies revealed that Lung transplantation (LTx) and rehabilitation intervention have significant effect on utility of patients in general.

Appendix

Table B1: Longitudinal data for COPD interventions/exacerbation utility-based quality of life, (SD)

Study	Utility Elicitation Instrument	Type of intervention	Number of Patients	Utility				
				Pre-intervention	Post-intervention			
					2 mo	4 mo	8 mo	12 mo
Wilke, et al 2012 [457]	$EQ\text{-}5D_{index}$ $EQ\text{-}5D_{VAS}$ AQoL	-	105	0.55 (0.30) 64.1 (13.2) 0.50 (0.27)		0.57 (0.31) 61.7 (15.1) 0.48 (0.26)	0.52 (0.32) 61.9 (14.5) 0.44 (0.26)	0.51 (0.31) 60.6 (13.4) 0.45 (0.24)
Egan et al, 2012 [211]	EQ-5D	Rehab	47	0.77 (0.1)	0.82 (0.1)	0.79 (0.2)	-	0.8 (0.1)
Santana et al 2010 [459]	HUI EQ-5D	LTx		0.56 (0.26) 0.71 (0.17)		0.69 (0.25) 0.81 (0.15)		
Goossen et al 2011 [458]	$EQ\text{-}5D_{index}$ $EQ\text{-}5D_{VAS}$	Exacer	59	0.683 (0.209) 34.75 (25.244)	***1 week*** 0.726(0.216) 36.68(25.24)	***2 week*** 0.768 (0.169) 48.03 (32.787)	***6 week*** 0.760 (0.181) 50.25 (31.19)	
Miravitlles et al, 2011 [217]	$EQ\text{-}5D_{index}$ $EQ\text{-}5D_{VAS}$	Exacer	346	0.54 (0.23) 34.4 (27.4)	***1 mon*** 0.61 (0.21) 41.8 (31.2)			
Ringback et al, 2008 [407]	$EQ\text{-}5D_{index}$ $EQ\text{-}5D_{VAS}$	Rehab	90	0.759(0.174) 58.6 (16.6)	***0 mo*** 0.778(0.18) 60.7 (19.0)	***1 mo*** 0.771(0.192) 59.2 (17.8)		

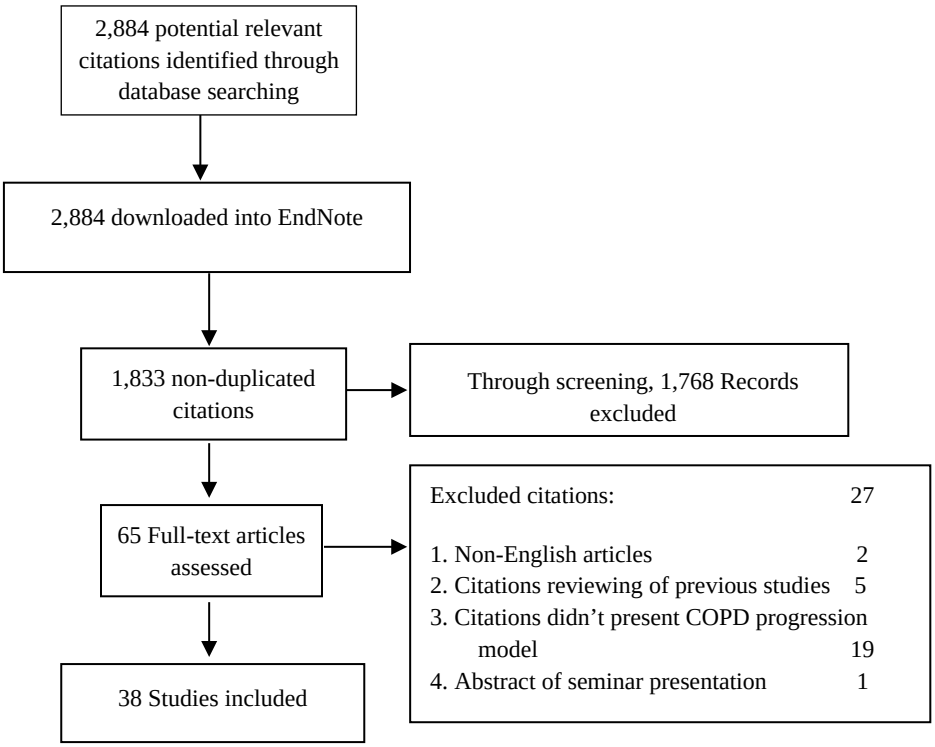
LTx: lung transplantation, **Rehab**: Lung rehabilitation, **Exacer**: Exacerbation

Appendix C to Chapter 3

Table C1 Summery of MEDLINE search strategy

Table 00-1 Summery of MEDLINE search strategy	
1	COPD
2	Chronic obstructive pulmonary disease*
3	Chronic obstructive lung disease*
4	Emphysema
5	Chronic bronchitis
6	1 or 2 or 3 or 4 or 5
7	Simulation
8	Modelling
9	Prediction or Predictor
10	7 or 8 or 9
11	Economic*
12	Cost
13	Quality
14	11 or 12 or 13
15	6 and 10 and 14

Figure C1 Flow diagram for derivation of studies included in modelling literature review *



* Last search was performed in November 2015

Appendix D to Chapter 4

Figure D1 Flow diagram for derivation of studies included in meta-analysis literature review *

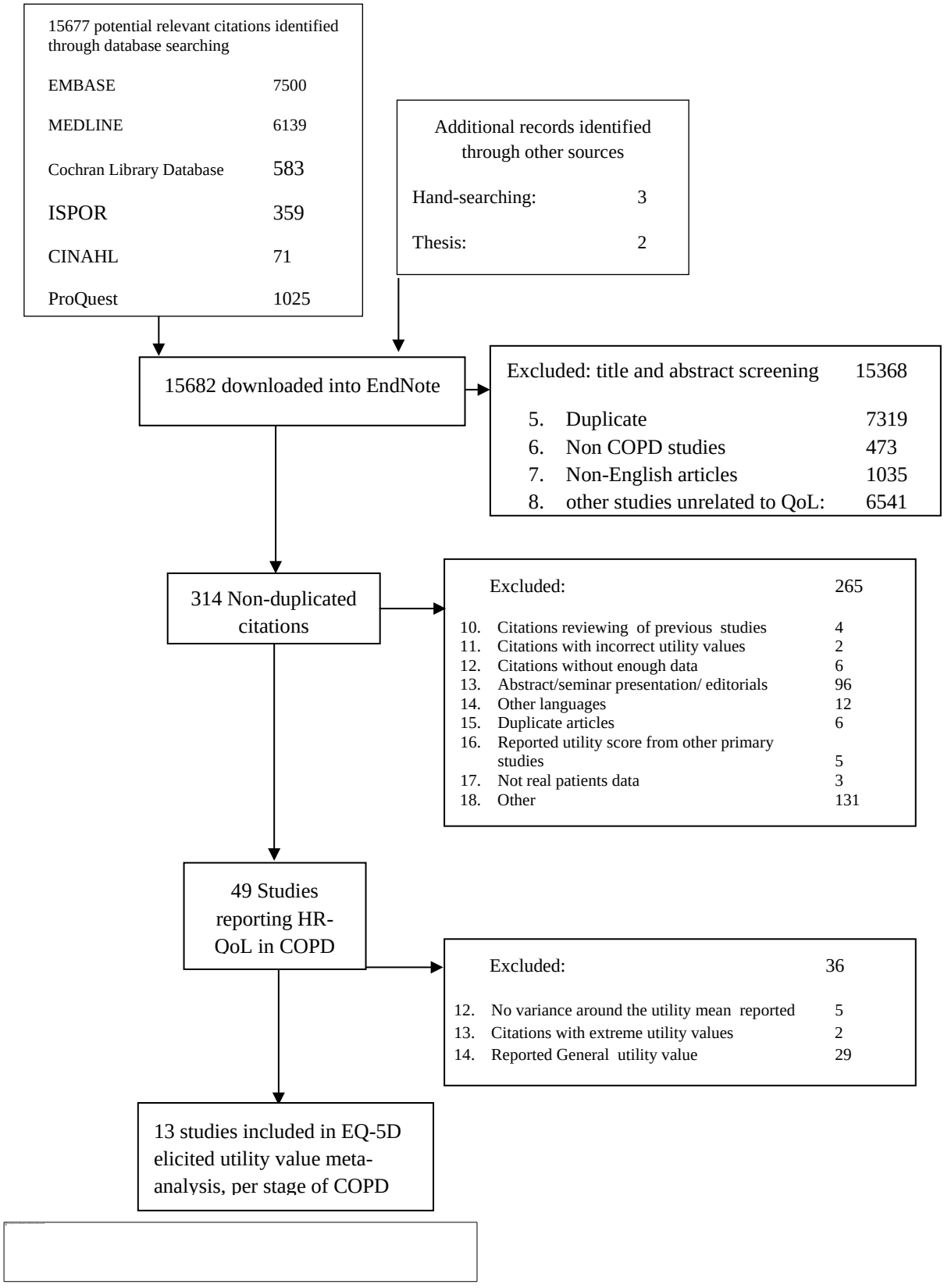
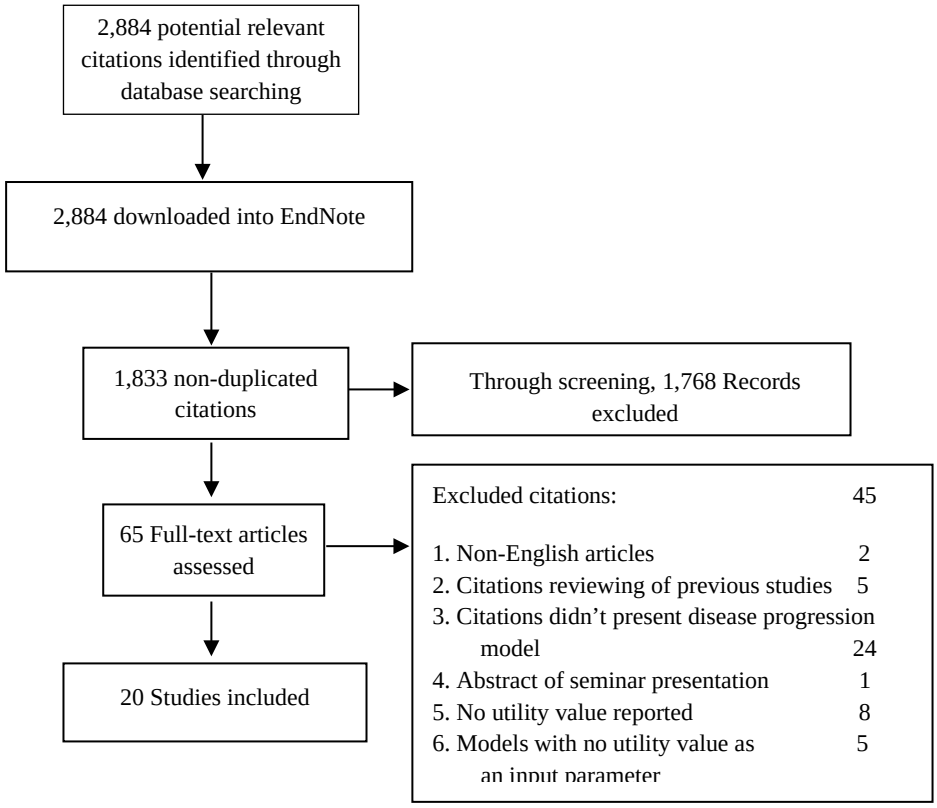


Figure D2 Flow diagram for derivation of studies included in modelling literature review *



* Last search was performed in November 2013

Table D1 Summery of MEDLINE search strategy

1	COPD
2	Chronic obstructive pulmonary disease
3	Chronic obstructive lung disease
4	Emphysema
5	Chronic bronchitis
6	1 or 2 or 3 or 4 or 5
7	"quality of life"
8	CUA
9	Euroqol-5d
10	eq-5d
11	eq5d
12	Qaly
13	"Quality -adjusted life year"
14	Health state
15	QoL
16	sf6d
17	sf-6d
18	"time-trade-off"
19	TTO
20	“standard gamble”
21	"COPD assessment Test "
22	"utility score"
23	SGRQ
24	“St. George's Respiratory Questionnaires”
25	CRQ
26	"Chronic Respiratory Questionnaire"
27	Utility
28	7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27
29	6 AND 28

Table D2 Characteristics of the patients-based studies included in the meta-analysis

Characteristics of the patients-based studies included in the meta-analysis

	First author, year	Country	Number of patients	Population	COPD severity staging system	Study design	Age		Male (%)	FEV1 % pred		Intervention
							Mean	SD or range		Mean	SD or range	
1	Samyshkin, et al, [17] 2013	Switzerland			GOLD							
2	Solem, et al, [53] 2012	USA	206	Exacerbated COPD	GOLD	Cross-sectional	67.7	10.2	52	-	-	-
3	Asukai, et al [41] 2012	UK	11066	-	GOLD	Three RCTs	-	-	-	-	-	Pharmaceutical
4	Fletcher, et al [44] 2011	6 countries	2426	-	BTS	Cross-sectional	56.4	-	49.00	-	-	-
5	Pickard, et al [54] 2011	USA	120	-	GOLD	Cross-sectional	71.20	10.30	98.30	58.40	24.80	-
6	Starkie, et al [45] 2011	UK	3640	-	GOLD	RCT - TORCH	64.70	8.40	-	-	-	Self-Management
7	Menn, et al [11] 2010	Germany	117	Exacerbated COPD	GOLD	Cross-sectional		-	-	-	-	-
8	Punekar, et al [46] 2007	5 European countries	2703	COPD in general practice	GOLD	Cross-sectional	66.00	-	-	-	-	-
9	Rutten-van Molken, et al, 2007	Spain	-	Pooled COPD	GOLD	Six RCTs	-	-	-	-	-	Pharmaceutical

	(The European journal of health economics)[16]			patients								
10	Rutten-van Molken, et al, 2006 *(Chest Journal)* [55]	Multi-national	1235	UPLIFT trial	GOLD	RCT	64.50	8.40	73.00	48.77	12.19	Pharmaceutical
11	Stahl, et al [56] 2003	Sweden	-	COPD from General population	GOLD	Cross-sectional	64.3	(28-80)	58.3	62	(18-118)	-
12	Spencer, et al [19] 2005	UK	283	COPD from general population	ATS	Cross-sectional	-	-	-	-	-	-
13	Borg, et al, [2] 2004	Sweden	212	COPD patients from longitudinal study	GOLD	Cohort studies	64.4	-	56.6	-	-	-

RCT: Randomized Control Trials; **TORCH**: Towards a Revolution in COPD Health trial; **UPLIFT**; the Understanding Potential Long-term Impacts on Function with Tiotropium trial; **FEV1% pred:** predicted amount as a percentage of the forced expiratory lung volume in one second; **GOLD:** Global Initiative for Chronic Obstructive Pulmonary Disease**; ATS:** American Thoracic Society staging system**; ERS:** European Respiratory Society**; BTS:** British Thoracic Society

Table D3 Utility values and measure instrument in the included studies for the meta-analysis, stratified according to the GOLD Spirometric staging

First Author (year)	Utility Instrument	COPD severity staging system	GOLD stages (SD) [range] "SE"			
			Stage I	Stage II	Stage III	Stage IV
Wu et al, [197] 2015	EQ-5D Index EQ VAS	GOLD	0.786 (0.085)	0.734 (0.158)	0.691 (0.155)	0.655 (0.151)
Kim SH et al, [229] 2014	EQ-5D Index EQ VAS	GOLD	0.83 "0.04"	0.88 "0.02"	0.81 "0.03"	0.60 "0.04"
Kim ES et al, [230] 2014	EQ-5D Index	GOLD	0.906 "0.006"	0.912 "0.005"	0.857 "0.018"	0.780 "0.071"
Jodar-Sanchez et al, [231] 2014	EQ-5D Index EQ VAS	GOLD	-	-	-	0.55 (0.33)
Samyshkin, et al,[131] 2013	EQ-5D Index	GOLD	-	-	0.751 [0.738-0.765]	0.657 [0.635-0.678]
Solem, et al [232] 2012	EQ-5D Index	GOLD	-	-	0.701 (0.182)	0.593 (0.236)
Asukai, et al [194] 2012	EQ-5D Index	GOLD	0.82 [0.8-0.84]	0.801 [0.794-0.809]	0.774 [0.767-0.782]	0.743 [0.730-0.756]
Fletcher, et al [187] 2011	EQ-5D Index	BTS	0.836 (0.007)	0.579 (0.009)	0.409 (0.015)	-
Pickard, et al [214] 2011	EQ-5D Index *(UK* value *set)* *(US value set)*	GOLD	0.73 (0.19) 0.80 (0.13)	0.59 (0.32) 0.70 (0.21)	0.63 (0.25) 0.72 (0.19)	0.63 (0.24) 0.72 (0.16)
Starkie, et al [109] 2011	EQ-5D Index	GOLD	-	0.752(0.22)	0.708(0.23)	0.672(0.22)
Menn, et al [233] 2010	EQ-5D Index SF-6D	GOLD	-	-	0.62 (0.26) 0.61 (0.13)	0.60 (0.26) 0.54 (0.08)

Punekar, et al [220] 2007	EQ-5D Index (a) (b)	GOLD	0.77 [0.73-0.81] 0.68 [0.64-0.72]	0.68 [0.626-0.72] 0.72 [0.69-0.75]	0.62 [0.56-0.68] 0.64 [0.61-0.67]	-
Rutten-van Molken, et al, 2007 *(The European journal of health economics)*[221]	EQ-5D Index	GOLD	-	0.809 “0.008”	0.762 “0.009”	0.655 ”0.024”
Rutten-van Molken, et al, 2006 *(Chest Journal)*[221]	EQ-5D Index *(UK* value *set)* *(US* value *set)*	GOLD	-	0.787 [0.771-0.802] 0.832 [0.821–0.843]	0.750 [0.731-0.768] 0.803 [0.790–0.816]	0.647[0.598-0.695] 0.731 [0.699–0.762]
Stahl, et al [234] 2003	EQ-5D Index	GOLD	0.84 (0.15)	0.73 (0.23)	0.74 (025)	0.52 (0.26)
Spencer, et al, [225] 2005	EQ-5D Index	ATS	0.81 “{0.02”	0.72 “0.03”	0.67 “0.05”	-
Borg, et al,[235] 2004	EQ-5D Index	GOLD	0.8971 (0.1117)	0.7551 (0.2747)	0.7481 (0.2991)	0.5493 (0.3129)

EQ-5D, EuroQol 5D: European Quality of Life questionnaire; **SF-12:** Short-Form Health Survey-12; **SF-36**: Short-Form Health Survey-36; **VAS**: visual analogue scale; **GOLD:** Global Initiative for Chronic Obstructive Pulmonary Disease**; ATS:** American Thoracic Society staging system**; ERS:** European Respiratory Society**; BTS:** British Thoracic Society

Table D4 Reference sources of utility and disutility estimate in exacerbation state in COPD modelling studies

Reference articles	Utility values	Modelling studies
O'Reilly JF, et al, [51] 2007	After exacerbation: • In admission= - 0.120 (0.366) † • 3 days after discharge: 0.635 (0.243) † • 3 days follow up = 0.389 (0.313) †	Hoogendoorn M, et al, [8] 2011 Neyt M, et al, [52] 2010
Borg S, et al [2], 2004 & Oostenbrink et al, [14] 2005	• Mild exacerbation = stage utility score × 0.95 • Moderate exacerbation = stage utility score × 0.85 • severe exacerbation = stage utility score × 0.30	Earnshaw SR, et al, [5] 2009
Spencer M, et al, [19] 2005 *(proxy patients, physicien perspective)*	Minor exacerbation • Stage I: 0.72 (0.02) * • Stage II: 0.475 (0.05) * • Stage III: 0.658 (0.03) * Major exacerbation • Stage I: 0.519 (0.02) * • Stage II: 0.447 (0.07) * • Stage III: 0.408 (0.05) *	Najafzadeh, et al, [12] 2012 Spencer M, et al, [19] 2005

* Standard Error; † Confidence Interval

Table D5 Effects of sensitivity analyses (SA) around utility values input used in modelling studies

	First author, year	Type of SA	Intervetion on utility	Result of SA
1	Sin DD et al [18] 2004	Multivariate SA	No detail	No report on utility
2	Borg S et al [2] 2004	Univariate SA	No detail	Not for utility
3	Spencer M et al [19] 2005	Probabilistic SA	No detail	No report on SA
4	Oostenbrink et al [14] 2005	Univariate SA	Stage II: 0.81 Stage III: 0.72 Stage IV: 0.67	Alternative utility values did not change the cost-effectiveness frontier
5	Rutten-van Molken, et al [16] 2007	Probabilistic SA	-	No report on utility
6	Maniadakis, N et al [10] 2006	One-way SA, Probabilistic SA	-	No report on utility
7	Chuck A, et al [4] 2008	Multivariate Probabilistic SA	-	No report on utility
8	Earnshaw, et al [5] 2009	One-way SA *(tornado diagram)*, Probabilistic SA	±20% utility value	The incremental cost per QALY is somewhat sensitive to changes in utility for moderate COPD stage
9	Oba Y et al [13] 2009	One-way SA, Probabilistic SA	Stage I: 0.821 – 0.843 Stage II: 0.790 – 0.816 Stage III: 0.699 – 0.762	Alternative utility values did not have significant effect. US set of utility were adopted and incorrectly allocated to the wrong COPD stages
10	Gani R et al [6] 2010	Multivariate Probabilistic SA	No detail	No report on utility
11	Atsou K, et al [1] 2011	One-wapy SE *(tornado diagram)*	No detail	When health utilities and costs were not discounted and or when a discounting rate of 5% was applied, the changes in the corresponding ICERs were also modest
12	Hoogendoorn M et al [8] 2011	One-wapy SE *(tornado diagram)*, Probabilistic SA	No detail	Utility values do not have much impact on the model outputs. For the scenario on pulmonary rehabilitation a 10% reduction or increase in intervention costs or changes in utility values for the COPD severity stages had the

				greatest influence on the cost per QALY.
13	Lock K, et al [9] 2011	Univariate SA *(tornado diagram)*, Probabilistic SA	Ranges used for SA Stage I: 0.72-1 Stage II: 0.60-0.91 Stage III: 0.60-0.90 Stage IV: 0.44-0.66	Uncertainty around the utilility decrement associated with each state were modelled. ICER was insensitive to changes in utility (from tornado diagram).
14	Price D et al [15] 2011	Univariate SA *(tornado diagram)*, Probabilistic SA	CIs used for SA Stage I: 0.8-0.84 Stage II: 0.79-0.81 Stage III: 0.77-0.78 Stage IV: 0.74-0.76	Utility values do not have much impact on the model outputs (from tornado diagram).
15	Sun SX et al [20] 2011	One-way SA *(tornado diagram)*, Probabilistic SA	CIs used for SA Stage III: 0.6480-0.7920 Stage IV: 0.6030-0.7370	Utility values have moderate impact on the model outputs (from tornado diagram).
16	Chandra K et al [3] 2012	One-way SA, Probabilistic SA	-	Not for utility
17	Menn P et al [11] 2012	Univariate SA, *(tornado diagram)* Multivariate Probabilistic SA	-	Not for utility
18	Najafzadeh M et al [12] 2012	One-way SA *(tornado diagram)*	-	No report on utility
19	Hertel N et al [7] 2012	One-way SA *(tornado diagram)*, Multivariate Probabilistic SA	No detailed result	Utility values do not have much impact on the model outputs
20	Samyshkin Y et al [17] 2013	Multivariate Probabilistic SA	-	No report on utility

SA: sensitivity analysis; **CI**: confidence interval;

Table D6 - Effects of one-way sensitivity analysis of utility value on ICER in two modelling studies

Study `	Time horizon	ICER ($/HSUV)					
		Group 1			Group 2		
		Base-Case analysis	Net value of ICER after SA	% of change	Base-Case analysis	Net value of ICER after SA	% of change
Oba Y et al [13], 2009	Three-year	23,807	Stage II: 23,540 – 24,080 Stage III: 23,509 – 24,123	±1.1% ±1.3%	477,929	Stage I: 476,966 – 478,895 Stage II: 473,016 – 482,945 Stage III: 473,795 – 482,273	±0.2% ±1.0% ±0.9%
	Five-year	16,124	Stage II: 15,942 – 16,310 Stage III: 15,924 – 16,335	±1.1% -1.2 – 1.3%	306,356	Stage I: 305,750 – 306,964 Stage II: 303,406 – 309,365 Stage III:303,149 – 309,738	±0.2% ±1.0% ±1.1%
Earnshaw et al [5], 2009	Five-year	33,865	Stage II: 30,347 - 38,307 Stage IV: 32,456 - 35,402	-10.4 – 11.6% -4.2 – 4.3%			

ICER: icremental cost effective ratio; **HSUV**: health State utility value; **SA**: sensitivity analysis;

Table D7 - Utiliy values used in sensitivity analysis by two modelling studies

Study	Base-Case	Utility ranges used in SA	% changes
Oba Y et al [13], 2009	Stage I: 0.832	0.821 – 0.843	±1.3%
	Stage II: 0.803	0.790 – 0.816	±1.6%
	Stage III: 0.731	0.699 – 0.762	-4.4 – 4.1%
Earnshaw, et al [5] 2009	Stage II: 0.755	± 20%	± 20%
	Stage III: 0.748	± 20%	± 20%
	Stage IV: 0.549	± 20%	± 20%

SA: Sensitivity Analysis

Appendix E to Chapter 6

Table E1 Sources and unit price list of health care services (AUS$ in 2013)

Service S	Source	unit	Unit price
Oxygen LOLT	Australian Institute of Health and Welfare (2005) [441]	Annual	1,794
Oxygen Cylinder + regulator	Market value (rental + refill) http://oxygensolutions.com.au/cylinders-and-accessories/	weekly	35.00
Hospital stay			
Admitted acute (AR-DRG 6.0x) Per weighted separation	National Hospital Cost Data Collection. Round 17 [455]		4,251
Non-admitted (Tier 2 clinic) Per weighted service event	National Hospital Cost Data Collection. Round 17 [455]		292.00
Emergency department (URG v1.3) Per admitted weighted presentation	National Hospital Cost Data Collection. Round 17 [455]		667.00
Per non-admitted weighted presentation	National Hospital Cost Data Collection. Round 17 [455]		540.77
Subacute (per day)			752.77
Ambulance	Australian Prudential Regulation Authority (2013) http://www.apra.gov.au/PHI/PHIAC-Archive/Pages/PHIAC-Archive-Statistical-Trends.aspx [460]		1241.78
GP	MBS [448]	<20	37.05
		20-40	70.30
		>40	105.55
GP at home	MBS [448]	<20	63.00
Specialist	MBS [448]	First	85.55
		Next	43.00
Specialist at home	MBS [448]	First	125.50
		Next	79.45
Psychologist	MBS [448]	<15	43.35
		15-30	86.45
		30-45	133.10
		45-75	183.65
		>75	213.15
Psychologist at home	MBS [448]	<15	79.55
		15-30	124.65
		30-45	181.65
		45-70	219.75
		>75	249.55
Physiotherapy	MBS [448]		62.25
Nurse at home	MBS [448]	hourly	76 .00
Spirometry test	MBS [448]		20.55
X-ray	MBS [448]		35.35

Counselling	Department of Veteran Affairs 2013 [454]	63.30
COPD group therapy	Department of Veteran Affairs 2013 [454]	25.95
Pulmonary rehabilitation	Department of Veteran Affairs 2013 [454]	63.30
Exercise	Department of Veteran Affairs 2013 [454]	63.30
Smoking cessation	Department of Veteran Affairs 2013 [454]	
20 - 50 minutes counselling		71.85
Group therapy 60 min		25.95

MBS: Medicare Benefits Schedule

Table E2 Sources and unit price list of intervention cost (AUS$ in 2013)

Service	Source	No	Unit price:
Telephone counsellor	Department of Veteran Affairs 2013 [454]	8	57.55
Self-help materials			20.00
Medical Practitioner counsellor	MBS [448]	8	86.45
Stationary & recording of counselling			100.00
Telephone charges	Cost of a local call	8	2.00

MBS: Medicare Benefits Schedule

Table E3 List of medicines have been used by COPD patients in the study (AUS$ in 2013)

Oral Medicine in Non-flare up	Generic name and class of drug	Strength	Qty	Price *
Theophylline	Nuelin-SR 200	200 mg	100	13.37
		250 mg	100	14.53
		300 mg	100	15.90
133.3 mg/25 mL oral liquid	Nuelin Syrup	133.3	1	13.52
Alprazolam	Xanax - Benzodiazepines	1 mg	50	13.68
	Kalma - Alprax	2 mg	50	17.00
Diazepam	Antenex - Benzodiazepines	2 mg	50	8.93
	Valium	5 mg	50	9.06
Mirtazapine	Avanza - Antidepressant	45 mg	30	26.09
	Axit	30 mg	30	24.59
		15 mg	30	20.35
Citalopram	Citalopram - Antidepressants	20 mg	28	14.67
Dothiepin hydrochloride	Dothep - Antidepressant	25 mg	50	10.59
Fluvoxamine	Fluvoxine - Antidepressant	50 mg	30	17.01
		100 mg	30	21.84
Escitalopram	Lexapro - Antidepressant	20 mg	28	16.95
		10 mg	28	16.86
Prednizolone	Panafcortelone - Corticosteroids	5 mg	60	9.68
	Solon	25 mg	30	11.34
		1 mg	100	9.54
Desvenlafaxine	Pristiq - Antidepressant	50 mg	28	36.10
Tiotropium bromide	Tiotropium - Bronchodilator		30	36.10
Sertraline	Zoloft/Setrona - Antidepressant	100 mg	30	17.12
	Xydep - Antidepressant	50 mg	30	17.12
Nicotine Patches	-	21 mg	28	36.10
Quetiapine	Seroquel – Antianxiety	100 mg	90	36.10
		200 mg	60	36.10
		25 mg	60	36.10
Doxepin	Antidepressant	25 mg	50	11.26
Oxazepam	Serapax	30 mg	50	10.11
		15 mg	50	10.11
Paroxetine	Aropax - Antidepressant	20 mg	30	18.31
Esipram	Escitaloram - Antidepressant	20 mg	28	16.95
		10 mg	28	16.86
Duloxetine	Cymbalta - Antidepressant	30 mg	28	34.33
		60 mg	28	36.10
Effexor	Venlafaxine - Antidepressant	75 mg	28	36.10
		150 mg	28	36.10
Xolair (injectable)	Omalizumab	150 mg	1	425
Fluoxetine	Lovan - Antidepressant	20 mg	28	18.75
Doxepin		25 mg	50	11.26

** Maximum Recordable Value for Safety Net*

Table E4 Non-parametric bootstrapping incremental cost and utility analyses, predicted values derived from multiple imputation linear regression models controlled for baseline cost and effect (AUS$ in 2013)

Exclusion of outliers		SE	95% CI
Cost-analyses			
Incremental cost	-294.8	39.4	-219.0 to -373.1
Utility analysis			
Incremental QALY	-0.0088	0.0121	-0.0150 to 0.0317
Without hospital costs		SE	95% CI
Cost-analyses			
Incremental cost	809.9	2.8	815.5 to 804.4
Utility analysis			
Incremental QALY	-0.0068	0.0111	-0.0287 to 0.0152

Incremental: intervention - control; **SE**: Standard Error

Table E5 Incremental cost-utility ratio and probabilities of dominance or inferiority of TB-CBT treatment

Analysis	ICUR (95% CI)	More effect Higher cost	inferior	Less effect Lower costs	Dominant
Exclusion of outliers	33,561.5 (-19,739 to 8,450)	0	0	0.78	0.22
Without hospital costs	-119.714.6 (51,517 to -28,978)	0.27	0.73	0	0

Figure E1 Incremental cost-effectiveness plane, sensitivity analysis through exclusion of outliers. Cost and QALY were estimated with linear regression with 1,000 bootstrap replications. The dashed line indicates the point estimate of ICUR

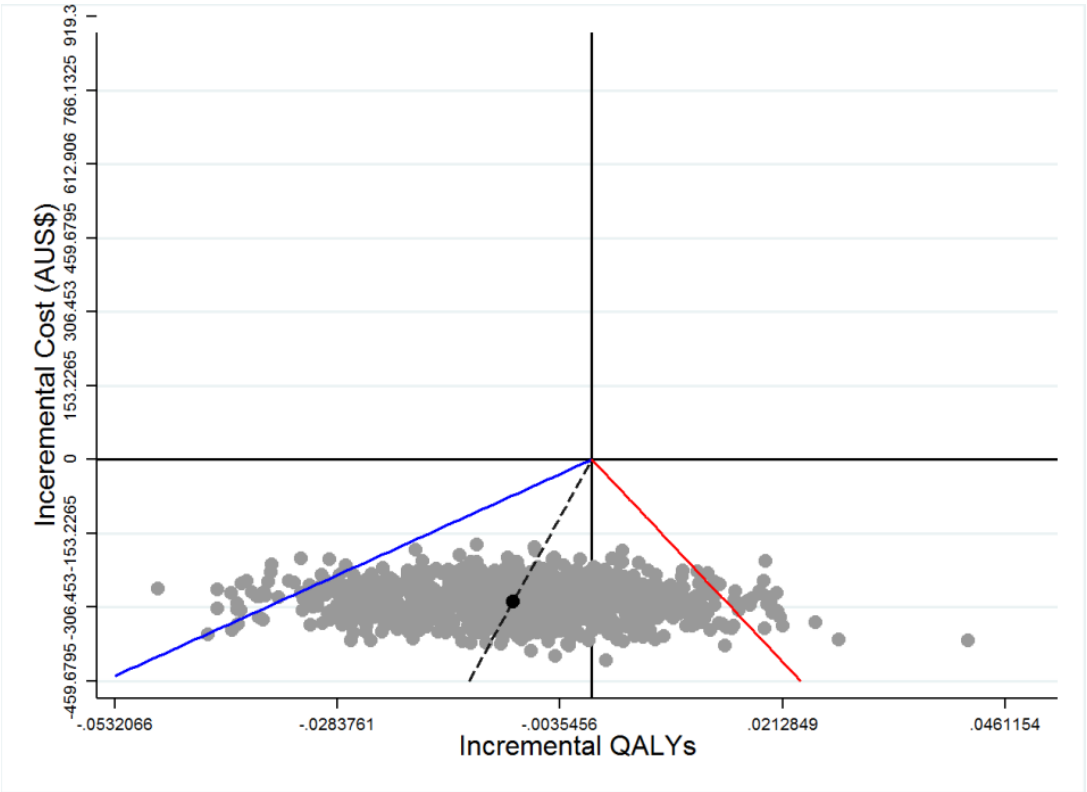
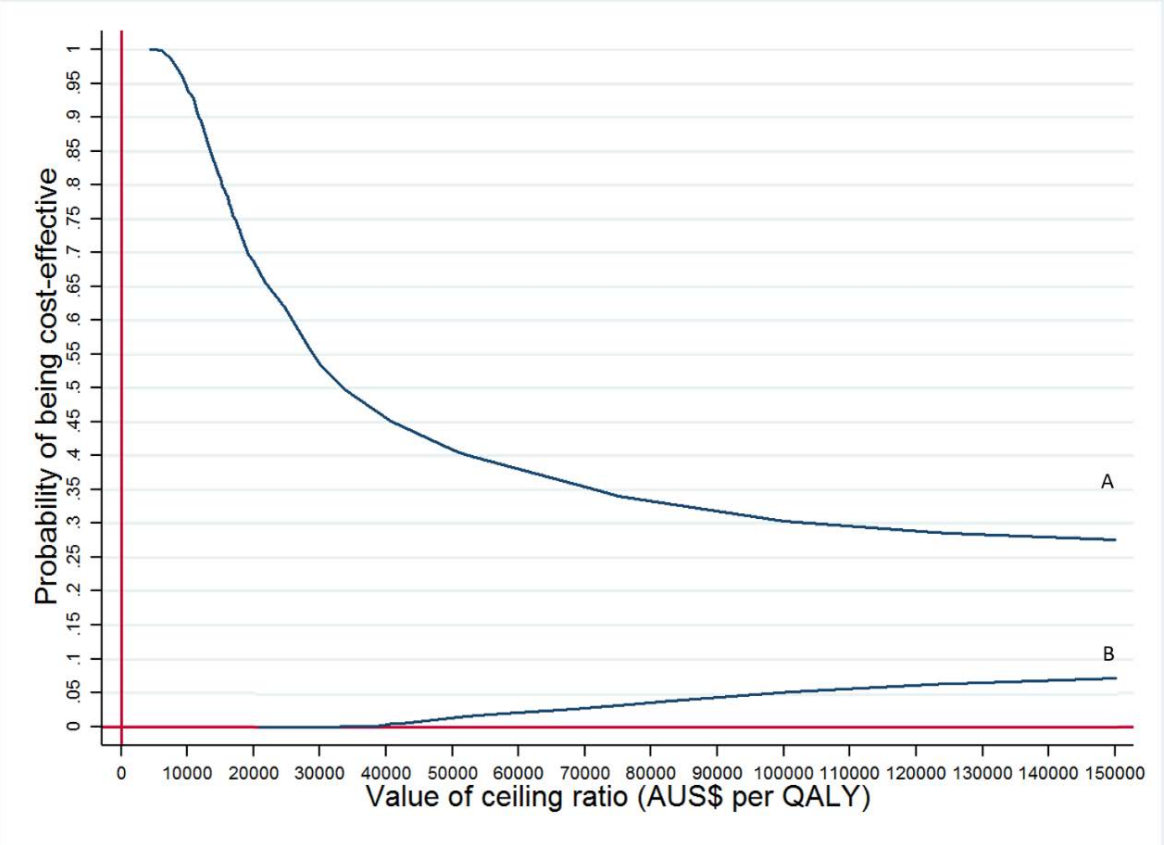


Figure E2 Cost-effectiveness acceptability curve (CEAC) for TB-CBT intervention, sensitivity analyses through exclusion of outliers.



Line A, CEAC for sensitivity analysis without outliers, the horizontal axis would be the ceiling ration for AUS$ cost saving/reduction per QALY sacrificed/loss

Line B, CEAC for sensitivity analysis without hospital cost item, the horizontal axis would be the ceiling ration for AUS$ cost per QALY gain

Figure E3 Incremental cost-effectiveness plane, sensitivity analysis through exclusion of befriending cost. Cost and QALY were estimated with linear regression with 1,000 bootstrap replications. The dashed line indicates the point estimate of ICUR

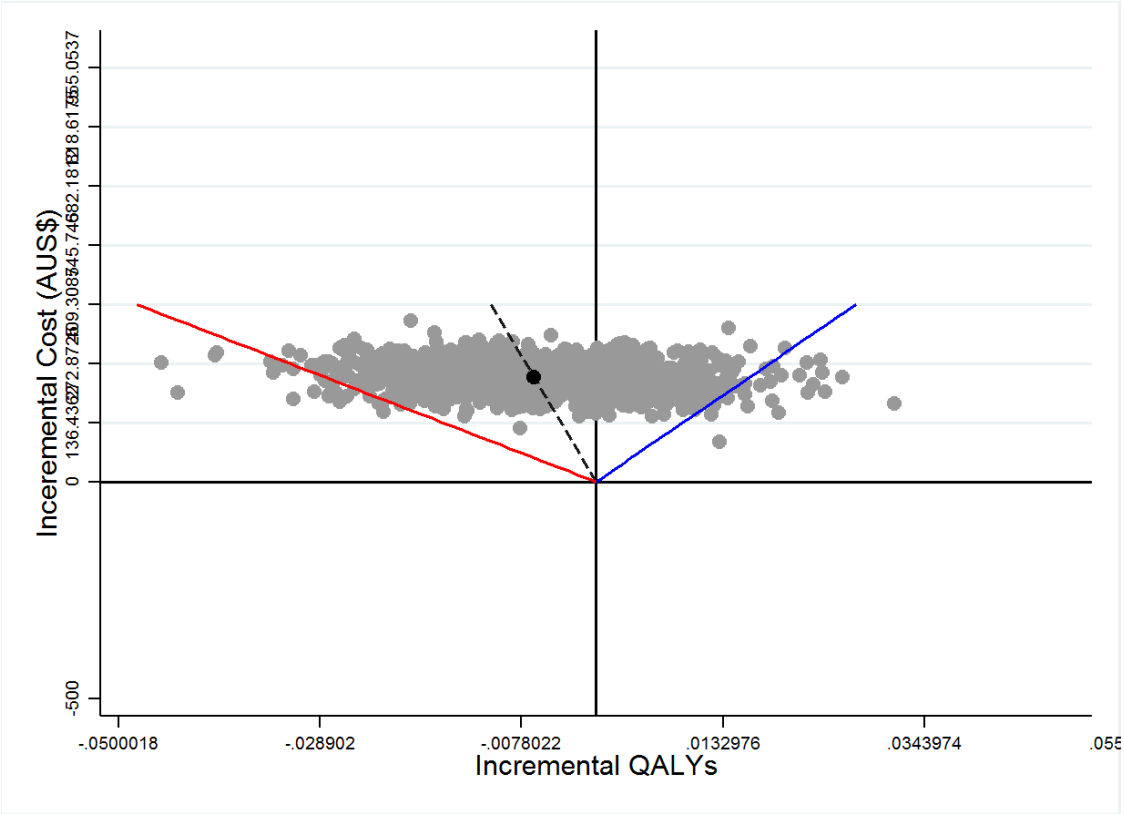


Table E6. Predicted mean costs (AUS$ in 2013) for TB-CBT and control groups at 17 weeks, derived from multiple imputation linear regression models controlled for baseline cost and effect; sensitivity analysis through exclusion of befriending cost

	Mean (SE)			
	TB-CBT	Control	Difference	P value
Total cost	2985.8 (28.8)	2743.4 (27.1)	242.4 (39.5)	<0.001

Table E7. Non-parametric bootstrapping incremental cost and utility analyses, predicted values derived from multiple imputation linear regression models controlled for baseline cost and effect; sensitivity analysis through exclusion of befriending cost

Analysis		SE	95% CI
Cost-analyses			
Incremental cost	241.64	1.175	239.33 to 243.95
Utility analysis			
Incremental QALY	-0.0065	0.0004	-0.007 to 0.006

Incremental: intervention - control; **SE**: Standard Error

Figure E3 Cost-effectiveness acceptability curve (CEAC) for TB-CBT intervention, sensitivity analysis through exclusion of befriending cost.

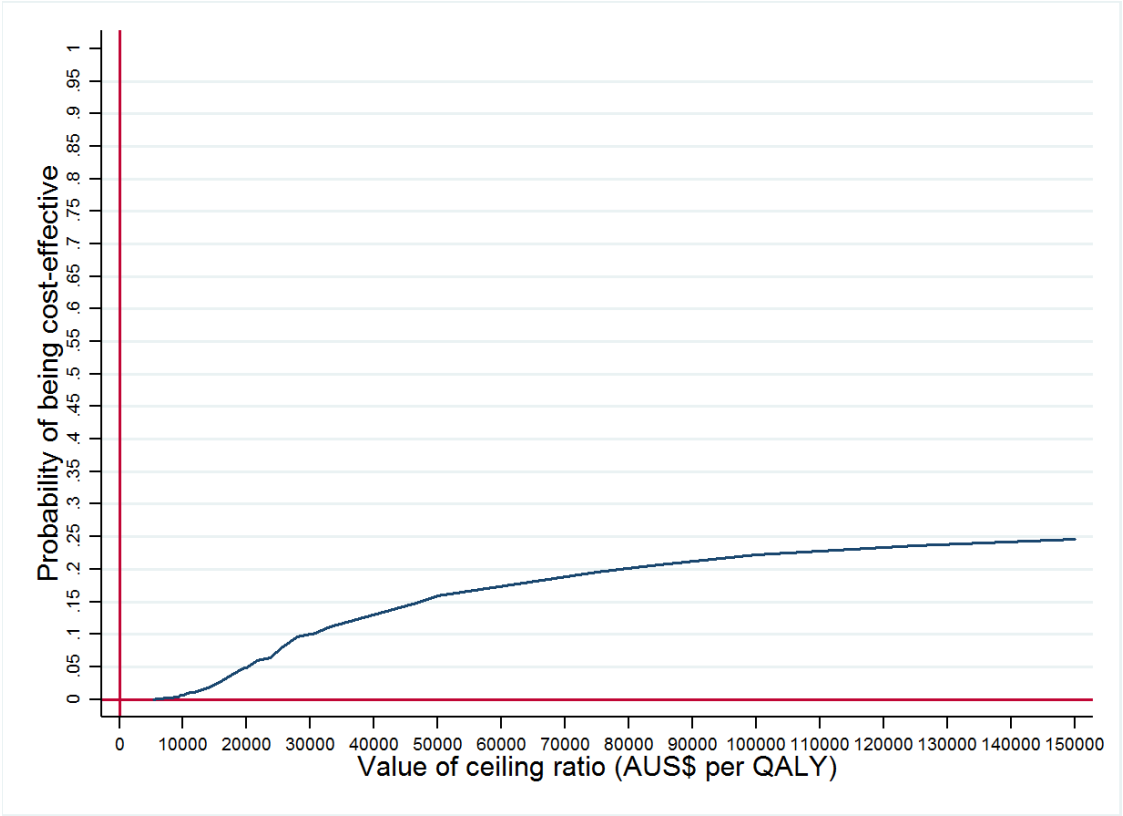


Table 4: Non-parametric bootstrapping incremental cost-utility ratio and probabilities of dominance or inferiority of TB-CBT, sensitivity analysis through exclusion of befriending cost

Analysis	ICUR (95% CI)	More effect Higher cost	inferior	Less effect Lower costs	Dominant
	15045	0.28	0.72	0	0

Appendix F to Chapter 7

Appendix F1, Definition of smoking states

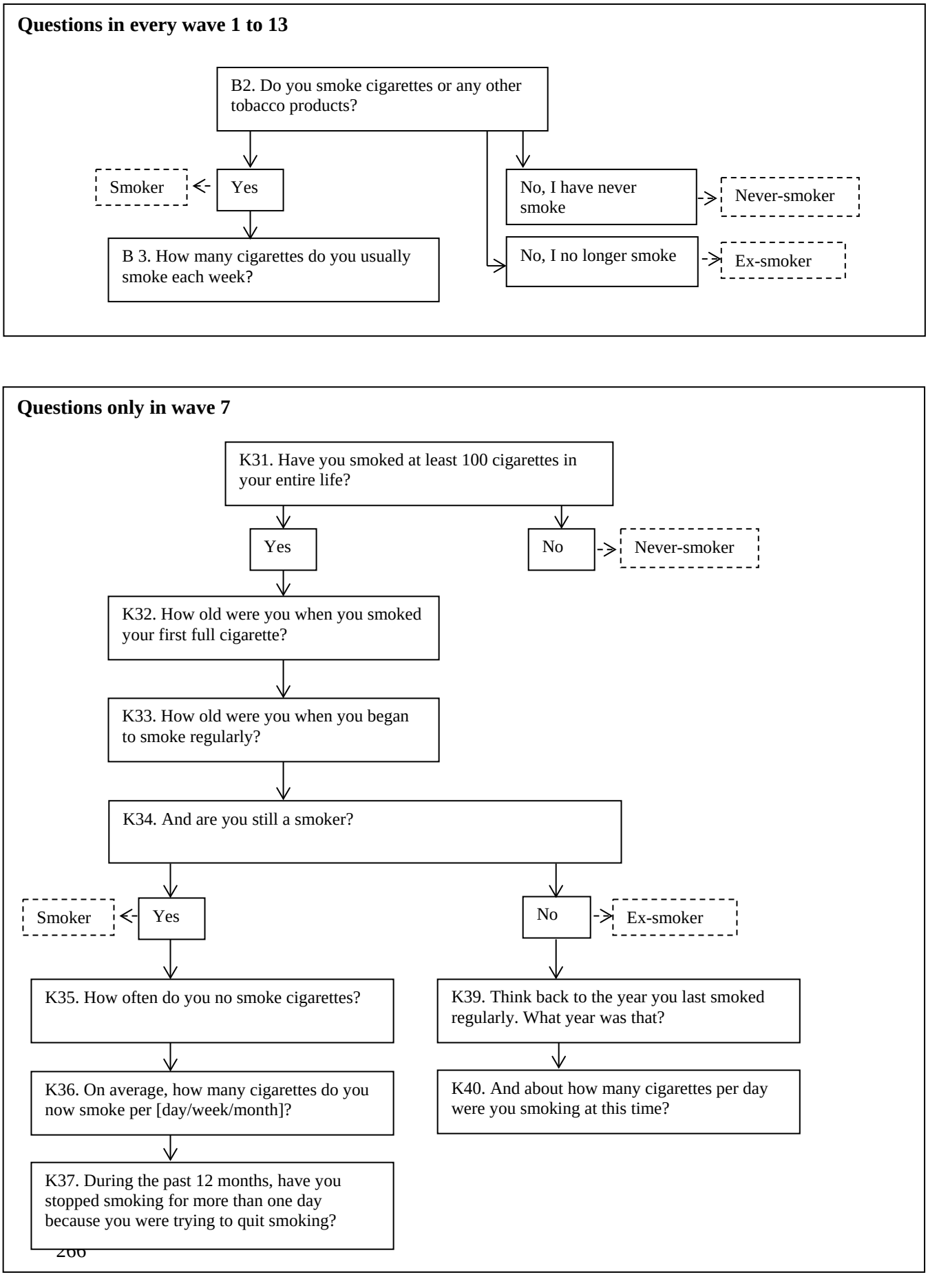
Definition of smoking states

Figure 1 shows the sequence of relevant questions about smoking behavior in HILDA survey. The first two questions B2 and B3 were asked in every wave of the survey. In Wave 1, respondents were asked: “Do you smoke cigarettes or any other tobacco products?” They were provided with three options, “No, I have never smoked”, “No, I have given up smoking”, and “Yes”, identifying never-smokers, ex-smokers, and current smokers, respectively. In Wave 2 and subsequent waves, respondents were asked the same smoking question with the following response options: “No, I have never smoked”, “No, I no longer smoke”, “Yes, I smoke daily”, “Yes, I smoke at least weekly (but not daily)”, and “Yes, I smoke less often than weekly”. The first and second options define never-smokers and ex-smokers, respectively. The last three options define current smokers.

The next nine questions (K31-K40) were only asked in wave seven. And they used to confirm ex-smoker and smoker status of the participants. Respondents, who reported smoking at least 100 cigarettes in their lifetime and who, at the time of survey, smoked either every day or some days were defined as Current Smoker. Respondents who reported smoking at least 100 cigarettes in their lifetime and who, at the time of the survey, did not smoke at all were defined as Former Smoker. Respondents who reported never having smoked 100 cigarettes were defined as Never Smoker. These set of questions used to validate the responses to B2 and B3 questions and a guide for correction of wrong sequence of smoking.

Appendix

Figure F1 Flow diagram of smoking questions



Appendix F2, Table 1, 2, 3 & 4

Table F2-1, Sample definition and codding sequence

ID	Wave	Smoking state	A (cessation subsample)	B (restricted subsample)	C (main coding sequence)	D (sensitivity 1)	Year (before & after)
10001	1	Non-smoker					
10001	2	Smoker					
10001	3	Smoker					
10001	4	Smoker					
10001	5	Smoker	0				
10001	6	Ex-smoker	1				
10001	7	Smoker					
10001	8	Smoker	0				
10001	9	Ex-smoker	1				
10001	10	Ex-smoker					
10001	11	Ex-smoker					
10002	1	Smoker			0		-5
10002	2	Smoker			0	0	-4
10002	3	Smoker			0	0	-3
10002	4	Smoker			0	0	-2
10002	5	Smoker	0	0	0	0	-1
10002	6	Ex-smoker	1	1	1		0
10002	7	Ex-smoker			1	1	1
10002	8	Ex-smoker			1	1	2
10002	9	Ex-smoker			1	1	3
10002	10	Ex-smoker			1	1	4
10002	11	Smoker					
10003	1	Smoker	0				
10003	2	Ex-smoker	1				
10003	3	Ex-smoker					
10003	4	Smoker	0				
10003	5	Ex-smoker	1				
10003	6	Ex-smoker					
10003	7	Smoker					
10003	8	Ex-smoker					
10003	9	Smoker					
10003	10	Smoker					
10003	11	smoker					

Table F2-2. Piecewise two-way fixed effect regression model outputs for outcome variables, in Cessation analysis, sensitivity analysis (SE)

	Intercept $\beta_0^{(1)}$	Slope pre $\beta_1^{(1)}$	Slope post $\beta_1^{(2)}$	Pre-post slopes difference test	Change of intercept pre to post β_2	rho
Physical Functioning	82.305 (0.978)	-0.639 ** (0.192)	-0.347 ** (0.161)	0.292 (0.242)	-1.046 (0.815)	0.693
Role-Physical	76.739 (1.524)	-0.754 ** (0.294)	-0.032 (0.247)	0.722 * (0.384)	-1.99 (1.334)	0.604
Bodily Pain	71.397 (0.906)	-0.677 ** (0.199)	-0.242 (0.146)	0.435 * (0.231)	-2.009 ** (0.842)	0.652
General Health	64.444 (0.759)	-0.777 *** (0.147)	-0.290 ** (0.133)	0.487 ** (0.206)	1.804 ** (0.683)	0.754
Social Functioning	83.004 (0.978)	0.146 (0.192)	0.0247 (0.162)	-1.512 * (0.880)	-1.512 * (0.880)	0.621
Role-Emotional	83.416 (1.416)	-0.014 (0.281)	-0.294 (0.246)	-0.281 (0.371)	0.518 (1.274)	0.561
Mental Health	73.425 (0.700)	0.130 (0.135)	-0.028 (0.122)	-0.158 (0.182)	-0.230 (0.553)	0.663
Vitality	58.586 (0.769)	-0.026 (0.150)	0.182 (0.127)	-0.008 (0.193)	-0.690 (0.638)	0.679
Physical Component Summary (PCS)	48.593 (0.406)	-0.409 *** (0.080)	-0.159 ** (0.067)	0.250 ** (0.104)	-0.688 * (0.375)	0.694
Mental Component Summary (MCS)	48.704 (0.439)	0.198 (0.093)	0.013 (0.076)	-0.186 (0.111)	-0.190 (0.369)	0.646
SF-6D	0.759511 (0.005391)	-0.000578 * (0.000101)	-0.008450 (0.004782)	0.000807 (0.001318)	-0.008450 * (0.004782)	0.66958

*p<0.10, **p < 0.05, *** p < 0.001
SE: Standard Error; **SF-36**: Medical Outcomes Study Short Form; **SF-6D**: Short Form-6 Dimension

Table F2-3. Number of missing values in each panel of some interested variables, main sample population, over 13 waves of Annual Data Collection Waves in the Household Income and Labour Dynamics in Australia (HILDA), 2001-2013

Number of missing values in each panel	Smoking		PF		SF-6D		PCS / MCS		Education	
	No. of panels	%	No. of panels	%	No. of panels	%	No. of panels	%	No. of panels	%
1	5,137	50.42	5,518	51.52	6,072	48.31	5,927	49.62	3,244	74.54
2	2,060	20.22	2,079	19.41	2,682	21.34	2,424	20.29	499	11.47
3	988	9.70	1,008	9.41	1,290	10.26	1,214	10.16	212	4.87
4	624	6.12	645	6.02	785	6.25	738	6.18	115	2.64
5	443	4.35	468	4.37	567	4.51	520	4.35	80	1.84
6	320	3.14	332	3.10	396	3.15	370	3.10	51	1.17
7	206	2.02	214	2.00	253	2.01	243	2.03	45	1.03
8	130	1.28	149	1.39	173	1.38	176	1.47	34	0.78
9	119	1.17	128	1.20	153	1.22	137	1.15	30	0.69
10	83	0.81	86	0.80	94	0.75	93	0.78	17	0.39
11	53	0.52	54	0.50	67	0.53	61	0.51	14	0.32
12	25	0.25	29	0.27	35	0.28	39	0.33	11	0.25
13	-	-	1	0.01	2	0.02	2	0.02	-	-
Overall	10,188	100.00	10,698	100.00	12,569	100.00	11,944	100.00		
Number of observation with missing value	24,119	14.07	25,270	14.74	30,313	17.68	28,627	16.70	7,358	4.29

SF-6D: Short Form-6 dimension; **RP**: Respondent Person; **MCS**: Mental Component Summary; **PCS**: Physical Component Summary

Appendix F3 Transitional probabilities

The aim of this appendix was to estimate the conditional Markov transitional probability matrix of staying in the same smoking status or moving between take-up, cessation and relapse states using 13 survey waves of Household Income and Labour Dynamics of Australia (HILDA). This information can be used as input parameters in simulation or disease progression models which smoking is a habit is a key factor.

The long-term evolution of the smoking habit in general population is unclear because most of previous studies were clinical trial assessing the effectiveness of a smoking intervention in a specified group of participants. Long term projections of smoking behavior and transitional probabilities estimation by using cross sectional data has already been published [461, 462]. Internationally there are a few representative general population-based longitudinal studies of smoking transition. International Tobacco Control (ITC) Four Country survey, including Australia [463, 464] investigated the individual level predictors of smoking cessation. In Australia, we have been unable to identify any previous studies.

The transitional probabilities that were calculated in this study were conditional when general population mortality was not considered. Our purpose was to estimate how a surviving population distributes itself among smoking states [465].

F3-1 Methods

F3-1.1 Sample population and inclusion criteria

The study used complete smoking status data over at least thirteen consecutive waves of HILDA survey for included participants. The flow chart diagram for generating main sample was presented in Figure 7-1.

F3-1.2 Definition of smoking in sample population

In Wave 1, respondents were asked: “Do you smoke cigarettes or any other tobacco products?” They were provided with three options, “No, I have never smoked”, “No, I have given up smoking”, and “Yes”, identifying never-smokers, ex-smokers, and current smokers, respectively. In Wave 2 and subsequent waves, respondents were asked the same smoking question with the following response options: “No, I have never smoked”, “No, I no longer smoke”, “Yes, I smoke daily”, “Yes, I smoke at least weekly (but not daily)”, and “Yes, I smoke less often than weekly”. The first and second options define never-smokers and ex-smokers, respectively. The last three options define current smokers.

If we ignore wave 1 from our analysis, there would be possibility to assign respondents in our sample to one of the following five smoking groups: never-smokers (one who has never smoked), ex- smoker (one who used to smoke sometimes but never smoke a cigarette now), light smoker (one who smokes less often than weekly), moderate smoker (one who smokes weekly), and heavy smokers (one who smokes daily). The advantage of this approach in smoking status is its ability to generate more detailed analysis of smoking status transition.

He detailed description of defining smoking status is presented in Appendix F1, Definition of smoking states.

F3-1.3 Markov state-transition model matrix

A stochastic Markov chain model with five smoking discrete states was defined: never-smoker, ex-smoker, light-smoker, moderate smoker and heavy smoker. We can define a transition matrix, $P = [P_{ij}]$, as a matrix of probabilities showing the likelihood of smoking staying unchanged or moving to any of the other R-1 states over a given time horizon. The expected

population vector for participants at time *t+1*, conditional to the vector of population alive at time *t*, was calculated as:

$$\boldsymbol{E(N_{x+t}|N_x) = N_x P_x \dots P_{x+1}}$$

Stata IC version 13.1 was used in all analyses.

F3-2 Results

Complete data were available for 171,439 person-years from 21,700 individual participants (respondent persons). Men were more likely than women to be current daily smoker (20.52% and 16.04%, across 12 waves of HILDA survey respectively). In both sexes, rate of current smokers has declined over HILDA survey (overall 24.19% in wave one to 18.28% in wave thirteen). Current daily smoker status is less prevalent in not indigenous origin, highly educated, legally married, physically active, never drink alcohol and employed persons. Other descriptive statistics are summarized in Appendix F2, Table F2-2, Descriptive statistics of the 171,439 Person-Years (observations) from 21,700 Respondent Persons over 13 waves of Annual Data Collection Waves in the Household Income and Labour Dynamics in Australia (HILDA), 2001-2013, Main sample.

The transitional probabilities are presented in the following tables:

Table F3-1 Transition matrix of smoking state by age and sex

State at age x	Male					Female				
	NS	ES	HS	MS	LS	NS	ES	HS	MS	LS
X=<20										
NS	0.94	0.00	0.03	0.01	0.02	0.96	0.00	0.02	0.01	0.01
ES	0.01	0.56	0.28	0.09	0.06	0.00	0.57	0.23	0.10	0.10
HS	0.00	0.10	0.81	0.05	0.04	0.00	0.07	0.85	0.05	0.03
MS	0.00	0.23	0.50	0.11	0.16	0.00	0.14	0.44	0.28	0.14
LS	0.00	0.28	0.30	0.20	0.22	0.00	0.29	0.38	0.16	0.16
Total %	78	4	13	2	3	81	3	12	2	2
X=20-29										
NS	0.99	0.00	0.00	0.00	0.01	0.99	0.00	0.01	0.00	0.00
ES	0.00	0.74	0.14	0.06	0.06	0.00	0.81	0.12	0.03	0.04
HS	0.00	0.12	0.83	0.04	0.01	0.00	0.12	0.82	0.04	0.02
MS	0.00	0.25	0.28	0.36	0.11	0.00	0.23	0.29	0.38	0.10
LS	0.01	0.35	0.21	0.16	0.28	0.00	0.35	0.22	0.16	0.27
Total %	54	14	25	4	3	59	15	21	3	2
X=30-39										
NS	1.00	0.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00	0.00
ES	0.00	0.88	0.06	0.03	0.03	0.00	0.90	0.06	0.02	0.02
HS	0.00	0.09	0.86	0.03	0.02	0.00	0.11	0.84	0.04	0.01
MS	0.00	0.24	0.27	0.39	0.11	0.00	0.29	0.31	0.31	0.09
LS	0.00	0.31	0.14	0.18	0.37	0.00	0.42	0.13	0.19	0.25
Total %	46	24	25	3	2	50	26	20	2	2
X=40-49										
NS	1.00	0.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00	0.00
ES	0.00	0.93	0.04	0.02	0.01	0.00	0.93	0.04	0.01	0.02
HS	0.00	0.09	0.87	0.03	0.01	0.00	0.10	0.87	0.02	0.01
MS	0.00	0.23	0.32	0.35	0.09	0.00	0.22	0.34	0.34	0.10
LS	0.00	0.36	0.17	0.12	0.36	0.00	0.38	0.18	0.20	0.24
Total %	39	34	24	2	1	45	32	19	2	1
X=50-59										
NS	1.00	0.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00	0.00
ES	0.00	0.96	0.02	0.01	0.01	0.00	0.95	0.04	0.00	0.01
HS	0.00	0.09	0.88	0.02	0.01	0.00	0.10	0.86	0.03	0.01
MS	0.00	0.27	0.29	0.30	0.14	0.00	0.23	0.35	0.31	0.11
LS	0.00	0.46	0.17	0.07	0.30	0.00	0.32	0.17	0.10	0.41
Total %	38	41	19	1	1	51	32	15	1	1
X=60-69										
NS	1.00	0.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00	0.00
ES	0.00	0.98	0.01	0.01	0.00	0.00	0.97	0.02	0.00	0.01
HS	0.00	0.12	0.82	0.04	0.03	0.00	0.15	0.80	0.04	0.01
MS	0.00	0.28	0.28	0.32	0.12	0.00	0.33	0.32	0.23	0.12
LS	0.00	0.29	0.12	0.24	0.35	0.00	0.36	0.26	0.14	0.24
Total %	63	31	5	1	0	54	36	8	1	1
X=70-79										
NS	1.00	0.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00	0.00
ES	0.00	0.99	0.01	0.00	0.00	0.00	0.98	0.01	0.01	0.00
HS	0.00	0.13	0.84	0.03	0.00	0.00	0.12	0.82	0.04	0.03
MS	0.00	0.24	0.41	0.29	0.06	0.00	0.28	0.28	0.32	0.12
LS	0.00	0.39	0.00	0.17	0.44	0.00	0.29	0.12	0.24	0.35
Total %	32	60	7	1	0	63	31	5	1	0

X=80-89										
NS	1.00	0.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00	0.00
ES	0.00	0.99	0.00	0.00	0.01	0.00	0.99	0.00	0.01	0.00
HS	0.00	0.21	0.79	0.00	0.00	0.00	0.01	0.82	0.09	0.00
MS	0.00	0.00	0.67	0.33	0.00	0.00	0.14	0.43	0.00	0.43
LS	0.00	0.67	0.33	0.00	0.00	0.00	0.40	0.20	0.40	0.00
Total %	35	62	3	0	0	70	27	3	0	0
X=90-99										
NS	1.00	0.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00	0.00
ES	0.00	1.00	0.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00
HS	0.00	0.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
MS	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
LS	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Total %	31	63	6	0	0	71	29	0	0	0

NS: non-smoker, **ES**: ex-smoker, **LS**: light smoker, **MS**: moderate smoker, **HS**: heavy smoker

Table F3-2 Transitional probabilities between smoking states in overall general population and by age

Covariates	NS	ES	HS	MS	LS
Overall					
NS	0.99	0.00	0.01	0.00	0.00
ES	0.00	0.94	0.04	0.01	0.01
HS	0.00	0.11	0.85	0.03	0.01
MS	0.00	0.24	0.32	0.33	0.11
LS	0.00	0.35	0.19	0.16	0.30
Sex					
Men					
NS	0.99	0.00	0.01	0.00	0.00
ES	0.00	0.94	0.04	0.01	0.01
HS	0.00	0.10	0.86	0.03	0.01
MS	0.00	0.24	0.31	0.34	0.11
LS	0.00	0.34	0.18	0.15	0.33
Women					
NS	0.99	0.00	0.01	0.00	0.00
ES	0.00	0.93	0.04	0.01	0.02
HS	0.00	0.11	0.84	0.04	0.01
MS	0.00	0.23	0.33	0.33	0.11
LS	0.00	0.36	0.20	0.17	0.27

Table F3-3 Transitional probabilities between smoking states by age in general Population

Covariates	NS	ES	HS	MS	LS
<19					
NS	0.95	0.00	0.03	0.01	0.02
ES	0.00	0.57	0.26	0.09	0.08
HS	0.00	0.08	0.84	0.05	0.03
MS	0.00	0.18	0.46	0.21	0.15
LS	0.00	0.29	0.34	0.18	0.19
20 to 29					
NS	1.00	0.00	0.00	0.00	0.00
ES	0.00	0.89	0.06	0.02	0.05
HS	0.00	0.10	0.85	0.04	0.02
MS	0.00	0.26	0.29	0.37	0.11
LS	0.00	0.36	0.13	0.16	0.27
30 to 39					
NS	1.00	0.00	0.00	0.00	0.00
ES	0.00	0.89	0.06	0.02	0.03
HS	0.00	0.10	0.85	0.04	0.01
MS	0.00	0.26	0.28	0.35	0.11
LS	0.00	0.36	0.14	0.18	0.32
40 to 49					
NS	1.00	0.00	0.00	0.00	0.00
ES	0.00	0.93	0.04	0.01	0.02
HS	0.00	0.10	0.87	0.02	0.01
MS	0.00	0.23	0.33	0.35	0.10
LS	0.00	0.37	0.17	0.16	0.30
50 to 59					
NS	1.00	0.00	0.00	0.00	0.00
ES	0.00	0.95	0.03	0.01	0.01
HS	0.00	0.10	0.87	0.02	0.01
MS	0.00	0.25	0.32	0.31	0.12
LS	0.00	0.39	0.17	0.08	0.36
60 to 69					
NS	1.00	0.00	0.00	0.00	0.00
ES	0.00	0.98	0.01	0.00	0.01
HS	0.00	0.12	0.84	0.03	0.01
MS	0.00	0.27	0.33	0.32	0.08
LS	0.00	0.38	0.20	0.10	0.32
70 to 79					
NS	1.00	0.00	0.00	0.00	0.00
ES	0.00	0.99	0.00	0.00	0.00
HS	0.00	0.14	0.81	0.05	0.00
MS	0.00	0.10	0.80	0.10	0.30
LS	0.00	0.50	0.25	0.25	0.00
80 to 89					
NS	1.00	0.00	0.00		
ES	0.00	1.00	0.00		
HS	0.00	0.00	1.00		
>100					
NS	1.00				

Appendix G1

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Health State Utility Value in Chronic Obstructive Pulmonary Disease (COPD); The Challenge of Heterogeneity: A Systematic Review and Meta-Analysis

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G1 Reviewers' comments

Major points

1. The main result of the study is the heterogeneity of the results of utilities. It is possible that some of this heterogeneity is due to the inclusion of "heterogeneous" patients. To avoid this effect, the authors should only include studies with well-characterised COPD patients. In other words, patients that fulfil the spirometric criteria for COPD. Otherwise they may include chronic asthma, chronic non-obstructive bronchitis or other chronic respiratory diseases together with COPD and this obviously may be a cause of heterogeneity. In Table 2 there are 10 studies without spirometric data. These studies should be excluded for the main analysis. Alternatively, the authors could perform a sensitivity analysis including studies without spirometry, but not in the main analysis.

Although some papers did not report spirometry results, they clearly mentioned that COPD diagnostic guidelines were followed and spirometry tests were performed, not only through the registration process (COPD patient samples were recruited from registry data bases) but also by investigators as part of inclusion criteria of included studies. We have made this statement clear in the inclusion criteria of current paper and individually for every study within the Table 2.

In order to address this comment fully, interaction tests were performed with subgroup analysis of studies which reported and not reported FEV1% value (following table; correspond to Table 6 in the manuscript). The test didn't show any difference between the two groups. In both group heterogeneity was very significant.

Group		Utility value /effect size (95% CI)	Heterogeneity /Cochran's Q test chi-squared			*I2* Heterogeneity statistics	Tau-squared
			χ2	df	P value		
Study type	RCT	0.68 (0.65-0.71)	429.11	12	<0.001	97.2%	0.0020

	Cross sectional	0.67 (0.64-0.70)	873.45	18	<0.001	97.9%	0.0044
Pack yrs	35-45 Pack yr	0.71 (0.67-0.75)	344.46	5	<0.001	98.5%	0.0024
	46-55 Pack yr	0.65 (0.60-0.70)	306.75	6	<0.001	98.0%	0.0046
	Not reported	0.67 (0.63-0.70)	681.17	18	<0.001	97.4%	0.0043
FEV1 % pred	FEV1 30-49%	0.66 (0.63-0.69)	293.19	11	<0.001	96.2%	0.0022
	FEV1 50-80%	0.66 (0.59-0.73)	350.79	6	<0.001	98.3%	0.0078
	Not reported	0.69 (0.66-0.73)	661.61	12	<0.001	98.2%	0.0031
Stages included in the studies	I, II, III, IV	0.68 (0.64-0.72	435.77	8	<0.001	98.2%	0.0037
	I, II, III	0.66 (0.61-0.72)	37.53	1	<0.001	97.3%	0.0014
	II, III	0.66 (0.59-0.72)	212.10	4	<0.001	98.1%	0.0058
	II, III, IV	0.70 (0.66-0.74)	196.50	5	<0.001	97.5%	0.0023
	III, IV	0.62 (0.52-0.71)	26.07	2	<0.001	92.3%	0.0063
	Not specified	0.67 (0.58-0.76)	242.13	6	<0.001	97.5%	0.0124
Age	< 64	0.69 (0.65-0.73)	381.02	6	<0.001	98.4%	0.0023
	65-69	0.68 (0.68-0.71)	814.64	17	<0.001	97.9%	0.0040
	> 70	0.61 (0.52-0.71)	28.44	2	<0.001	93.0%	0.0067
Charlson Index	< 2.49	0.69 (0.65-0.74)	80.92	2	<0.001	97.5%	0.0018
	> 2.5	0.66 (0.41-0.82)	23.38	1	<0.001	95.7%	0.0211
	Not reported	0.67 (0.65-0.70)	1200.20	26	<0.001	97.8%	0.0032

df: degree of freedom; RCT: Randomized control trial;
Subgroup analyses were done only when at least two studies were in each subgroup

In addition, T-test and analysis of variance (ANOVA) were applied for comparing estimated utility means between subgroups (following table).

Difference between estimated utility value means in subgroups

One-way ANOVA analysis of variance for mean estimated utility by COPD stages	SS	df	MS	F statistics	P value
Between groups	0.2537	3	0.0846	12.40	<0.001
Bartlett's test for equal variances: chi2(3) = 1.1370 Prob>chi2 = 0.768					

Two-sample t test with equal variances	diff	SE	P value Ha: diff <0	P value Ha: diff !=0	P value Ha: diff >0
Stage I / Stage II	0.042	0.0373141	0.862	0.276	0.138
Stage II / Stage III	0.058	0.032487	0.956	0.088	**0.044**
Stage III / Stage IV	0.10	0.0306422	0.998	**0.004**	**0.002**
Study type: RCT / cross-sectional	0.07	0.0451579	0.931	0.138	0.069
Cigarette: 35-45 Pack yr / 46-55 Pack yr	0.06	0.0457979	0.906	0.188	0.094
FEV1 30-49% / FEV1 50-80%	0 006	0.0505905	0.456	0.912	0.544
Age: < 64 / 65-69	0.016	0.0485167	0.704	0.740	0.297
Year-of-publication					
<2008 / 2008-2011	0.130	0.0427302	0.996	**0.0088**	0.0044
2008-2011/ 2012-2014	0.142	0.031917	**0.0002**	**0.0003**	0.9998
2012/2014 / >2014	0.119	0.0439269	0.9916	**0.0168**	**0.0084**

df: degree of freedom; **SS**: Sum of the Squares; **SE:** Standard Error; **MS:** Mean Squire; **FEV1% pred:** predicted amount as a percentage of the forced expiratory lung volume in one second;

2. In relation to this issue. The text reads that no influence of FEV1 on utilities could be found (page 9). More detailed information about this crucial result should be given. How was this relationship calculated? It would be very interesting to see the utilities by FEV1 severity categories and/or a figure with the relationship between both variables. How many of the included studies contributed to this calculation?

   This conclusion was based on general utility value of COPD reported by included studies. In order to show how much heterogeneity can be explained by FEV1%, interaction test has been run (Table 5 in the manuscript, the degrees of freedom give the total number of studies

contributed to each interaction test). Estimated mean FEV1% was cut into two groups 30-49% and 50-80%. No difference has been detected in utility value or heterogeneity index between these two groups. This means that heterogeneity in general utility value cannot be explained by reported FEV1%. In order to make it clearer, we have conducted separate meta-analyses for estimated utility values in each stage of COPD, reported by 17 published papers (Table 3). The current literature review had collected papers which measured utility values of each stage of COPD (up to the current date, 2015). The new results were presented in Table 4 and Figure 3. These analyses showed that utility values were changing in accordance with COPD stages.

3. Page 9. It reads that BODE index did not have significant association with utility score, but again, how many studies reported BODE index? Is this statement really valid?

   The whole section of "subgroup analysis" has been completely revised. In order to consider the size of studies and alleviate constraints around regression models, interaction tests were performed and regression analysis was disregarded. Please refer to the "Subgroup analysis" section of the paper and table 4.

4. Page 8. It is intriguing that hand search captured references 26-28, because two of them included EQ-5D in the title. Are the authors confident about the quality of their automatic search?

   This issue might be related to a mistake in the process of abstract scanning. In order to correct any errors and make a prefect search, the literature review and the generated database in Endnote were reviewed again by another independent reviewer. Applications of inclusion and exclusion criteria for non-duplicated citations were reviewed in a joint meeting between reviewers. A few corrections were made:

   1. A study with extreme utility value was excluded.
   2. A study with reported general utility value was found. (This study was detected as "included Studies only reported utility values for stages of COPD").

3. The analysis analyses were redone with the modified inclusion and exclusion criteria of the articles.

5. Search finished in 2013. In the best-case scenario, this paper could be published at the end of 2015 or more likely beginning of 2016. This means 3 years later. The search should be updated.

   The search was updated up to the current date (25th June 2015). Extra studies (eight studies) were detected and added to this literature review. This update version of literature review has been carried out by two independent reviewer.

Minor points.

1. Abstract. What does “number of cigarette” mean? Is it pack-years, or mean number of cigarettes a day?

   Many thanks. Yes, it was changed into “pack-years of smoking” through the manuscript.

2. Page 4. The paragraph starting on line 26 should be moved to Discussion and Table 1 deleted, because it is not related to the objective of the current manuscript.

   This paragraph and table 1 have been deleted. In this way, consistency was achieved.

3. Page 5. Paragraph starting line 18 should be moved to Discussion.

   This paragraph was deleted.

4. Page 5, line 38. In agreement with the major points, it should be clearly specified the criteria for COPD (that should include spirometric confirmation).

   This statement has been change into the following:

   “studies in which their sample population was specifically categorized as COPD, defined by standard criteria for COPD diagnosis and spirometric confirmation (clearly addressed in methodology of included studies),”

5. Page 6, line 10. Studies with small sample sizes were included; therefore, this is not an EXCLUSION criterion.

   A new inclusion criterion was defined:

“studies with more than 10 participants”

And the section has been changed into the following statement:

“Studies with different epidemiological designs (i.e. case control, randomized control trial (RCT), cohort, etc.) were included.”

Appendix G2

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Systematic Review

Do Model-Based Studies in Chronic Obstructive Pulmonary Disease Measure Correct Values of Utility? A Meta-Analysis

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is a progressive chronic disease that has considerable impact on utility-based health-related quality of life. Utility is a key input of many decision analytic models used for economic evaluations. **Objective:** To systematically review COPD-related utilities and to compare these with alternative values used in decision models. **Methods:** The literature review comprised studies that generated utilities for COPD-related stages based on EuroQol five-dimensional questionnaire surveys of patients and of decision models of COPD progression that have been used for economic evaluations. The utility values used in modeling studies and those from the meta-analysis of actual patient-level studies were compared and differences quantified. **Results:** Twenty decision modeling studies that used utility value as an input parameter were found. Within the same span of publication period, 13 studies involving patient-level utility data were identified and included in the meta-analysis. The estimated mean utility values ranged from 0.806 (95% confidence interval [CI] 0.747–0.866) for stage I to 0.616 (95% CI 0.556–0.676) for stage IV. The utility scores for comparable stages in modeling studies were different (significant difference 0.045 [95% CI 0.041–0.052] for stage III). Modeling studies consistently used higher utility values than the average reported patient-level data. **Conclusions:** COPD decision analytic models are based on a limited range of utility values that are systematically different from average values estimated using a meta-analysis. A more systematic approach in the application of utility measures in economic evaluation is required to appropriately reflect current literature.

Keywords: chronic obstructive pulmonary disease (COPD), EQ-5D, health state utility value, Markov model, meta-analysis, modeling, utility.

Introduction

Economic models of chronic obstructive pulmonary disease (COPD) are intended to simulate disease progression and quantify the impact of interventions on outcomes primarily in terms of quality-adjusted life-years (QALYs). An important aspect of these models is health state utility value (HSUV) (commonly referred to as utility), which, associated with the major stages of COPD, and disutility related to major events such as exacerbations form the basis of QALY outcomes. A systematic search of the health economic literature located a large number of studies reporting progression models [1–24] that included utility values for one or more stages of COPD.

The utility values used to estimate the base case in each model were dependent on information from a single study, which has been standard practice in the health economic literature. Utilities used in COPD models to date have come from summary measures derived from the EuroQol five-dimensional questionnaire (EQ-5D) index, a generic instrument of HSUV, and show variation in utility assumption across models. This variation is likely to have an impact on the generalizability of model outputs and raises the question as to whether the model would have produced outcomes that were sufficiently different to have an impact on cost-effectiveness decisions.

In recent years, meta-analysis has emerged as a strategy to generate overall utility values for common health states. This has included studies of utility values for HIV/AIDS [25], chronic kidney disease [26], diabetes [27], and various types of cancer [28,29]. To date, there has been only one meta-analysis of utility values of COPD stages [30], which is surprising given the large number of evaluations of COPD therapies that have been routinely undertaken. These results have not been used as inputs to COPD modeling studies.

The aim of this study was to conduct a systematic review of utilities assigned to the different stages of COPD used in modeling studies and to compare these with summary measures from meta-analyses of available utility studies within the publication period of modeling studies derived from patients with COPD. We also examined the implications of differences between utility used in past models and estimates of the average utility for health states

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G2 First reviewer's comments

1. Reviewer #1: This paper described the results of a very extensive systematic review on utility values in different COPD stages followed by a meta-analysis. The review on patient-reported utilities does not seem to miss important papers. The review with regard to COPD modelling studies using utilities is complete. In general the paper is well written, but the English language needs to check. It is unfortunate that in the past months two other reviews on this topic were published which makes the current study less informative. I have some major and minor comments that can be found below.

Abstract:

1. Background: utilities are not a key outcome of models, utilities are input and QALYs are output.

   Response to Reviewer No 1, comment No. 1 The sentence was changed into: "Utilities are a key input of many decision analytic models used for economic evaluations."

Introduction:

2. "Utilities…..form the basis of QALY outcomes. In almost all currently available COPD models QALYs are calculated based on the COPD stages, but maybe even more important on the number of exacerbations. In general a certain disutility is applied when an exacerbation occurs.

   Response to Reviewer No 1, comment No. 2: It was changed into: "An important aspect of these models is Health State Utility Value (HSUV) (commonly referred to as utilities) which, associated with major stages of COPD, or disutility related to the major events such as exacerbations form the basis of QALY outcomes."

3. "To date there have been no meta-analyses of utility values of COPD stages". This is not true. Pickard AS et al published a review on this topic in Respiratory Medicine 2008 and

very recently two other reviews/meta-analyses have been published: Srivastava et al PharmacoEconomics 2015 and Einarson TR, J Med Econom 2015. I am aware that the latter two have been published very recently, which may have been later than the submission of the current paper. The study of Einarson et al also described the utilities in COPD making a distinction between original research studies and economic evaluation studies.

Response to Reviewer No 1, comment No. 3: The first literature review [Pickard, 2008] was aimed on utility values in Asthma and COPD. There are some critiques regarding this study. It covers only 8 studies which estimating utility value. Two out of nine included COPD studies should have not been considered in the review because they reported median values of utility and the disease was not confirmed by spirometry test [Hazell & Savoia]. In addition one of the included studies [Punekar] had merged utility values of stage III and IV into a single stage III value. This value should have been discarded from the analysis. Above that, observations of a single study [Punekar] should have been combined to create a single value in adherence with Cochrane manual recommendations.

The second systematic literature review [Einarson] covered only two databases, Medline and Embase, and 44 citations were captured. The utilities were elicited by using different measurement instruments; EQ-5D Index, EQ VAS, SF-6D, TTO, SG, Feeling thermometer (Schunemann et al 2007), SF-6D, HUI (Miller et al 2006) and output of one Markov model. Studies with patients in unstable or end-stage conditions were pooled with other states of the disease. In one included study (Maiwenn J. Al et al 1998), only 42% of control group and 58% of transplant group were COPD patients and other types of obstructive and coronary diseases were included. The utility used by another included study (Hajizadeh et al 2012) was based on proxies from Congestive Heart failure, general population estimates and a review of literature (Tengs et al 2000) which had merged utility value of different kinds of lung diseases into one value. Four included citations have been published after our literature review (Chen et al 2014; Jodar-Sanchez et al 2013; Kim et al 2014 and Lin et al 2014).

Utility estimation mapped from other SGRQ was included (Milne et al 2014). In addition, estimated mean utility values for stages of disease were derived from simple mean calculation without incorporating variances around utility values in each included study; in other word meta-analysis was not the statistical approach. This study did not meet the recommendations of Peasgood et al 2015, for a good practice in health economic meta-analysis.

The most recent literature review [Sirvastava] was a qualitative study covering humanistic and economic burden of COPD. In the humanistic section, the study focused on 32 non-RCT studies which almost thirty percent of them were conference abstracts. Different types of HR-QoL measures were included. No quantitative analyses were carried out by this study. Some suggested associations between study characteristics and patient conditions such as demographic, disease symptoms, comorbidities, resource use and cost were proposed. This study recommended that a comprehensive quantitative study is needed for a reliable conclusion (our current study is comprehensive quantitative approach).

The sentence was changed into: To date there have been only one meta-analyses of utility values of COPD stages, …"

Methods:

4. Inclusion criterion two: …into COPD disease severity stages (you mean: level of airflow obstruction), but I do not understand what the authors mean with "on any medication or therapy". It seems like they only include patients who are on any medication, but in another paragraph of the methods they mention that they only use baseline data from intervention studies to avoid an effect of treatment. This needs to explain.

   Response to Reviewer No 1, comment No. 4: This inclusion criterion was changed into: "•studies in which their sample population was specifically categorized as COPD as defined by standard criteria for COPD diagnosis and spirometric confirmation (should clearly be addressed in methodology of included studies)."

5. Please explain page 4, modelling studies paragraph: what do the authors mean by: Model for describing progress of any phenotype of COPD disease as first outcome…"All COPD patients groups are included?

   Response to Reviewer comment No. 5: Based on old definitions, Emphysema and Chronic Bronchitis were defined as different phenotypes of COPD. We wanted to emphasise that in our literature review different kind of definitions were addressed to have a comprehensive coverage of citations. This sentence was changed into: “Model for describing progress COPD as a first outcome”.

Results

6. Table 1: the study of Einarson seems to include a couple of other studies that are not included in the current study, but this seemed to be studies in very specific subgroups of patients, such as end-stage patients/patients awaiting lung transplantation. The authors should check this study to compare the results.

   Response to Reviewer No 1, comment No. 6: Please refer to the point 2 of this feedback. A complete description of Einarson’s article was provided. The following citations: Chen et al 2014; Jodar-Sanchez et al 2013; Kim et al 2014 and Lin et al 2014 were published after our study. Because we wanted to have time coherence between utility studies and modelling studies, the utility studies were confined to the date of last published model based study (Samyshkin, et al, 2013). So we included only utility studies published before 2014.

7. The study of Starkie et al should not be included as this is a mapping study which is mentioned as exclusion criterion in the methods. This study is about calculating the utilities based on the St George's Respiratory Questionnaire score. Or did the authors include the actual EQ-5D-based values?

   Response to Reviewer No 1, comment No. 7: In the methodology section of this study it was clearly mentioned that "SGRQ and EQ-5D were administered at baseline and every 24 weeks over 3 years". From table 3 of this article (attached) it can be understood that observed utility is measured directly by administration of EQ-5D. This value was incorporated in the meta-analysis.

Table 3 – Mean (SD) observed EQ-5D utility scores compared to mean predicted EQ-5D utility scores by disease severity using the best-fitting OLS, GLM, and two-part models validation sample.

Model	Disease severity		
	Moderate	Severe	Very severe
No. of observations	1681	2380	827
Observed	0.752 (0.22)	0.708 (0.23)	0.672 (0.22)
Predicted OLS	0.752 (0.14)	0.704 (0.15)	0.667 (0.15)
Predicted GLM	0.754 (0.15)	0.705 (0.15)	0.667 (0.14)
Predicted 2 part	0.755 (0.15)	0.706 (0.15)	0.666 (0.14)
QALYs, observed	2.16 (0.68)	1.99 (0.74)	1.75 (0.75)
QALYs, predicted	2.18 (0.52)	2.01 (0.57)	1.80 (0.58)

Mean (SD) QALY scores by COPD disease severity group, using the observed utility scores compared to the predicted utility scores to generate QALY scores in the full data set.
GLM, generalized linear model; OLS, ordinary least squares; QALYs, quality-adjusted life-years.

8. Figure 4 is difficult to read. Please make the X more visible.

   Response to Reviewer No 1, comment No. 8: This figure has been changed to a more simplified figure.

9. Table 5 is difficult to read and less informative.

   Response to Reviewer No 1, comment No. 9: The table was simplified. This table shows how the model based studies has been grouped. Without this grouping, the main conclusion which was summarized in figure 2 cannot be understood.

Discussion:

10. The authors emphasize that there is a need for a much more systematic approach for incorporating utility values into COPD models. The current review is indeed a step forward. However, the newer COPD models are all patient-level models or linked regression models which include more patient characteristics. This is because the older Markov models with states based on airflow obstruction only include a limit amount of patient heterogeneity, which becomes more and more important as treatment for COPD is increasingly personalized. So newer models will probably not use the GOLD classification and therefore not the utilities calculated in this meta-analysis.

    Response to Reviewer No 1, comment No. 10: Patient-level simulation models still need evidence based data that one of the most reliable one can be generated by well-designed meta-analysis study. So we think this study can still be an example for good practice in modelling studies.

11. The authors conclude that modelling studies in general use higher utility values than obtained in the meta-analysis. What does this mean for the evaluations performed with these models? Are the estimated QALYs too high or too low? The authors should say something about the impact.

    Response to Reviewer No 1, comment No. 11: Thank you for this suggestion. In order to investigate the impact of the estimated utility values derived from meta-analysis on output of the COPD model, two approaches have been adopted. We tried to contact modellers of captured studies to use our estimates as a sensitivity analysis scenario. On the other hand, results of sensitivity analyses form included modelling studies were also summarized and investigated. Please refer to the WebTable 4, 5 &6 and Figure 3.

    Only two studies reported the detailed result of sensitivity analyses of utility values [Oba & Earnshaw]. Oba ran SAs for three-and five-years' time horizons for two clinical trials. Range of utility values used in the SAs, reported Incremental Cost Effectiveness Ratio (ICER) and percentages of change were summarized in WebTable 5 & 6. A linear

regression model was defined (figure 3). It showed that there was a significant evidence of a positive association between utility and ICER (p value <0.001); one percentage change in utility value was associated with 0.37% (95% CI 0.30 – 0.45) change in ICER. Figure 3 shows the observed and predicted values of the linear regression model. Predicted % changes in ICER based on the calculated % differences in stage I utility value (Table 4) are demonstrated. It can be interpreted that if the meta-analysis mean utility values are incorporated in the modelling studies the mean % of change in ICER will be between -2.2% to -3.5% at different stages of COPD. It should be considered that some modelling studies used much higher values than the mean estimated, especially in stage II and III.

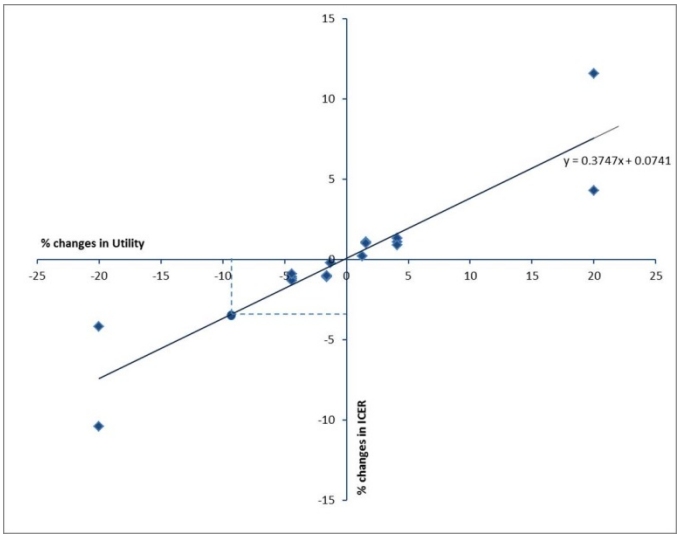

Figure 3 Percentage of changes in model output (%Δ ICER) according to percentage of changes in utility values (%Δ Utility) as an input parameter, linear regression model with prediction line. Prediction of %Δ ICER (-3.5%) after -9.3% change in utility is demonstrated as the cross point of dotted lines.

1. Reviewer #2: This manuscript contains a lot of information, not all of which may be necessary in communicating the results of their research. Their study objective is an excellent one, but the current style of the manuscript is somewhat confusing (possibly due to copy-editing issues) and is somewhat one-dimensional in its conclusion without addressing exceptions or nuances found in the economic models. It may be better to focus on the meta-analysis and refrain from commenting on issues of the modelling studies, unless a more thorough and systematic critique of the modelling studies can be conducted.

Response to Reviewer No 2 comment No. 1: The main aim of this study is to emphasize the importance of good practice guideline in model-based researches; one of these aspects is how to find a better estimation for input parameters. Meta-analysis is one of these approaches. From this point of view, other aspects of the models were out of scope of this study. In accordance with the reviewer point of view, we agree that another study is needed to address appropriateness of the developed model in COPD. Given the current state of knowledge, a recent published article:

“Hoogendoorn, M., et al. (2014).”Cost-Effectiveness Models for Chronic Obstructive Pulmonary Disease: Cross-Model Comparison of Hypothetical Treatment Scenarios." Value in Health 17(5): 525-536.”

was aimed to compare different COPD models with respect to structure and cost inputs. Unfortunately this article did not take utility into consideration. Our current study was aimed to utility input with consideration of good practice guideline in modelling studies and provided complementary evidences to the above mentioned article.

2. I also think some of the content could be simplified - for example, Table 1. "Characteristics of the patients based studies included in the meta-analysis". Since these characteristics are not actually utilised in the analysis, I would personally rather see a simpler list, with a title such as 'QoL studies included in the meta-analysis" and getting rid of columns that have more than 50% missing values.

   Response to Reviewer No 2 comment No. 2: Thank you, Table 1 was merged into Table 2 and moved to the “Web supplementary material”.

Methods:

3. PRO studies - if the only thing included in the meta-analysis were utility values, why were 'papers using utility values mapped from other reported quality-of-life studies' excluded?

Response to Reviewer No 2 comment No. 3: There is a controversy against using utility values mapped from quality of life measures in health economic appraisal. The following statement is quoted from “Applied methods of cost-effectiveness analysis in health care. Oxford. 2011, page107-108:

“They (mapping studies) all seem to predict increasingly poorly as health states become more serious. Reimbursement agencies such as NICE have indicated that they are prepared to consider evidence from mapping studies in the absence of more direct evidence. … it is worth stating that all forms of mapping are “second best”, and the existence of a range of techniques should not be taken as an argument for relying on mapping instead of obtaining direct preference-based measurements in prospectively designed studies.”

Because of high controversy around this matter, we decided to exclude mapping studies.

4. Modelling studies - why is the inclusion criterion 'health utility studies', shouldn't the main inclusion criteria be 'economic evaluations using modelling methods'?

   Response to Reviewer No 2 comment No. 4: This criterion was changed into “Modelling studies in COPD”. We did not want to confine our search strategy to economic evaluation.

Discussion:

5. The vast majority of economic evaluations in COPD test the parameters included in their model, including utility values, in one-way sensitivity analyses; some modelling studies such as Price et al, actually test both a set of literature-based and patient-data based utilities. Thus their contention that their study is 'superior to other literatures that used a single value for utility in COPD stages' is misleading; moreover, it is unclear whether they are comparing themselves to other patient-level QoL studies or to the economic evaluation studies. In either case, the studies are not comparable as inferior or superior, and the most they should do is discuss the merits of a meta-analysis compared to a single-source study. In doing so, they should also address the merits of using regression-based outputs such as the

one found in Rutten van Mollken 2006 (CHEST) which examine the covariates with the most significant impact on EQ-5D. Were attempts made to adjust for such covariates, or to ensure there was minimum heterogeneity to conduct the meta-analysis?

Response to Reviewer No 2 comment No. 5: Thank you for this comment, it contains curtail points that can be addressed as follows:

1. The related statement regarding superiority of the current study was deleted. In fact we did not want to suggest this study was superior to other modelling or economic evaluation researches. Our suggestion is that modelling studies need to be base inputs on systematically collected information process such as meta-analysis rather than a single value from published literature.
2. Regression-based outputs give valuable information regarding covariates that should be addressed and measured during research process. Rutten van Mollken 2006 study was a good example that shows specifically what kind of factors can affect EQ-5D derived utility scores in COPD patients. We have made the following statements in the manuscript to address the reviewers points: “Regression-based studies such as Rutten et al 2006 [62], tried to explain that which kind of factors can be associated with and impact on EQ-5D derived utility values in COPD patient. Especial attention in measuring, reporting and incorporating covariates such as gender, number of hospital and emergency department visits in the year before baseline measurement, measurement of comorbidity, country of origin of COPD patients and considering different utility value set and tariffs and is recommended”.
3. In order to take into account the possible covariates effect on heterogeneity in the meta-analysis, we applied restricted selection criteria: EQ-5D only utility values, UK tariff of utility and level of FEV1 % pred. Other factors such as gender, previous ED visits, and comorbidity were not specified clearly by the included studies; so controlling of these potential covariates were not possible.

6. Rutten et al also discuss the validity of using EQ-5D values in economic evaluations and their discussion should be addressed against the paper's conclusion that 'more accurate [than EQ-5D] measurements of utility values in different contexts...as input parameters of modelling studies.'

   Response to Reviewer No 2 comment No. 6: This is true. We did not want to conclude in contradictory with Rutten et al results. Our suggestion for the future studies is to be more specific in inclusion of patients and reporting HSUV in order to cover all health states of COPD in more comparable way between studies. This section was changed into ". Future research should focus on more specific measurements of utility values at different health states of COPD as input parameters of modelling studies, with consideration of potential confounding factors that are associated with utility value in COPD [62]".

7. Limitations: The authors do not go into very much detail around limitations of their study. There is not much discussion around the comparability of the studies included in the meta-analysis, only citing that 'random effects' was used; was Fixed Effects not tested at all? Were there specific study parameters that needed to be controlled for? The authors also acknowledge that no quality appraisal of the included studies was conducted, which is a requisite component of a systematic literature review. Can they comment on how that might have improved the meta-analysis, for example, by including study quality in the weighting?

   Response to Reviewer No 2 comment No. 7: This important comment has two main components that are addressed in the following paragraphs:

   A) Regarding random vs fixed effect model, we followed the general guidelines. We used random effect because of anticipated study heterogeneity and to make a generalizable estimate. We did not find any specific factor contributed to the high level of heterogeneity. We followed the following citations that recommend random-effect model in these situations:

Introduction to Meta-Analysis. Michael Borenstein, L. V. Hedges, J. P. T. Higgins and H. R. Rothstein, 2009 John Wiley & Sons, Ltd. ISBN: 978-0-470-05724-7.

This quotation is from the book:

> "It makes sense to use the fixed-effect model if two conditions are met. First, we believe that all the studies included in the analysis are functionally identical. Second, our goal is to compute the common effect size for the identified population, and not to generalize to other populations.
>
> By contrast, when the researcher is accumulating data from a series of studies that had been performed by researchers operating independently, it would be unlikely that all the studies were functionally equivalent. Typically, the subjects or interventions in these studies would have differed in ways that would have impacted on the results, and therefore we should not assume a common effect size. Therefore, in these cases the random-effects model is more easily justified than the fixed-effect model. Additionally, the goal of this analysis is usually to generalize to a range of scenarios. Therefore, if one did make the argument that all the studies used an identical, narrowly defined population, then it would not be possible to extrapolate from this population to others, and the utility of the analysis would be severely limited".

And also the following citation:

Borenstein M, Hedges LV, Higgins JPT, et al. A basic introduction to fixed-effect and random-effects models for meta-analysis. Research Synthesis Methods. 2010;1(2):97-111.

> "The selection of a model should be based solely on the question of which model fits the distribution of effect sizes and thus takes account of the relevant source(s) of error. When studies are gathered from the published literature, the random-effects model is generally a more plausible match. The strategy of starting with a fixed-effect model and

then moving to a random-effects model if the test for heterogeneity is significant relies on a flawed logic and should be strongly discouraged".

We tried to find the specific factors that can explain systematically the origin of between study variations. Unfortunately, the included studies did not provide detailed information regarding characteristics of patients in each stage of disease such as comorbidity, gender, age and so on. We would like to inform you that we conducted the same meta-analysis on general utility values in COPD to discover the cause of heterogeneity specifically in COPD. Thirty two studies were included in this research. An article based on these analyses is going to publish in COPD: Journal of Chronic Obstructive Pulmonary Disease soon. The following statements and tables were quoted from this article:

Interaction tests were performed with subgroup analysis of studies which reported and not reported FEV1% value (following table; correspond to Table 6 in the manuscript). The test didn't show any difference between the two groups. In both group heterogeneity was very significant.

Table 6: Results of interaction tests for subgroup analyses

Group		Utility value/effect size (95% CI)	Heterogeneity chi-squared /Cochran's Q test			I^2 Heterogeneity statistics	Tau-squared
			χ^2	df	P value		
Study type	RCT	0.681 (0.654-0.707)	429.11	12	<0.001	97.2%	0.0020
	Cross sectional	0.669 (0.638-0.700)	873.45	18	<0.001	97.9%	0.0044
Pack yrs	35-45 Pack yr	0.711 (0.672-0.751)	344.46	5	<0.001	98.5%	0.0024
	46-55 Pack yr	0.651 (0.698-0.703)	306.75	6	<0.001	98.0%	0.0046
	Not reported	0.665 (0.634-0.696)	681.17	18	<0.001	97.4%	0.0043
FEV1 % pred	FEV1 30-49%	0.658 (0.629-0.687)	293.19	11	<0.001	96.2%	0.0022
	FEV1 50-80%	0.658 (0.592-0.725)	350.79	6	<0.001	98.3%	0.0078
	Not reported	0.693 (0.661-0.725)	661.61	12	<0.001	98.2%	0.0031
Stages included in the studies	I, II, III, IV	0.682 (0.641-0.723)	435.77	8	<0.001	98.2%	0.0037
	I, II, III	0.663 (0.610-0.716)	37.53	1	<0.001	97.3%	0.0014
	II, III	0.655 (0.585-0.724)	212.10	4	<0.001	98.1%	0.0058
	II, III, IV	0.698 (0.657-0.738)	196.50	5	<0.001	97.5%	0.0023
	III, IV	0.618 (0.524-0.712)	26.07	2	<0.001	92.3%	0.0063
	Not specified	0.670 (0.584-0.757)	242.13	6	<0.001	97.5%	0.0124
Age	< 64	0.692 (0.654-0.731)	381.02	6	<0.001	98.4%	0.0023
	65-69	0.678 (0.647-0.708)	814.64	17	<0.001	97.9%	0.0040
	> 70	0.613 (0.516-0.709)	28.44	2	<0.001	93.0%	0.0067
Charlson Index	< 2.49	0.693 (0.645-0.741)	80.92	2	<0.001	97.5%	0.0018
	> 2.5	0.615 (0.410-0.821)	23.38	1	<0.001	95.7%	0.0211
	Not reported	0.673 (0.650-0.696)	1200.20	26	<0.001	97.8%	0.0032

df: degree of freedom; **RCT**: Randomized control trial; **FEV1% pred**: predicted amount as a percentage of the forced expiratory lung volume in one second
Subgroup analyses were done only when at least two studies were in each subgroup

In addition, T-test and analysis of variance (ANOVA) were applied for comparing estimated utility means between subgroups (following table).

Table 5 Difference between estimated utility value means in subgroups

One-way ANOVA analysis of variance for mean estimated utility by COPD stages	SS	df	MS	F statistics	P value
Between groups	0.2537	3	0.0846	12.40	<0.001

Bartlett's test for equal variances: chi2(3) = 1.1370 Prob>chi2 = 0.768

Two-sample t test with equal variances	diff	SE	P value Ha: diff<0	P value Ha: diff !=0	P value Ha: diff>0
Stage I / Stage II	0.042	0.0373141	0.862	0.276	0.138
Stage II / Stage III	0.058	0.032487	0.956	0.088	**0.044**
Stage III / Stage IV	0.10	0.0306422	0.998	**0.004**	**0.002**
Study type: RCT / cross-sectional	0.07	0.0451579	0.931	0.138	0.069
Cigarette: 35-45 Pack yr / 46-55 Pack yr	0.06	0.0457979	0.906	0.188	0.094
FEV1 30-49% / FEV1 50-80%	0 006	0.0505905	0.456	0.912	0.544
Age: < 64 / 65-69	0.016	0.0485167	0.704	0.740	0.297
Year-of-publication					
<2008 / 2008-2011	0.130	0.0427302	0.996	**0.0088**	0.0044
2008-2011/2012-2014	0.142	0.031917	**0.0002**	**0.0003**	0.9998
2012/2014 / >2014	0.119	0.0439269	0.9916	**0.0168**	**0.0084**

df: degree of freedom; **SS**: Sum of the Squares; **SE**: Standard Error; **MS**: Mean Squire; **FEV1% pred**: predicted amount as a percentage of the forced expiratory lung volume in one second;

B) The review of literatures were followed the MOOSE guidelines which observed the good practice for meta-analysis in observational studies. The detailed description of the literature review was published elsewhere. In addition, recommendations of Peasgood et al (2015) for meta-analysis of utility values studies were addressed.

> *Peasgood, T., & Brazier, J. (2015). Is Meta-Analysis for Utility Values Appropriate Given the Potential Impact Different Elicitation Methods Have on Values? Pharmacoeconomics. doi: 10.1007/s40273-015-0310-y*

In order to minimize biases and selection of relevant studies all of the following measures were applied:

- Very restricted inclusion and exclusion criteria (excluding values that were not the appropriate utilities) were applied to capture unbiased study population.
- Especial attempted were made to generate a pool of utility values elicited from similar health state of COPD patients population.
- Adopting EQ-5D as the only elicitation method ensured consistency in methodological estimation of utility.
- All available study characteristics were reported transparently and justification for choosing data from studies were clearly explained.
- A comprehensive approach to heterogeneity was made
- Extensive subgroup and sensitivity analyses were conducted.

The following quote from The MOOSE guideline shows approved recommendation for quality assessment in meta-analysis of observational studies and gives justifications for our approach using subgroup analyses instead of quality scoring and weight:

> "We recognize that the use of quality scoring in meta-analyses of observational studies is controversial, as it is for RCTs, because scores constructed in an ad hoc fashion may lack demonstrated validity, and results may not be associated with quality. ….". "We recommend the reporting of quality scoring if it has been done and also recommend

subgroup or sensitivity analysis rather than using quality scores as weights in the analysis."

But we think that as an evidence of best practice, quality assessment of included studies can accompany this kind of meta-analysis. Because of this, we made a recommendation for future studies to perform these measures.

8. References: There is a possibility that the references are not ordered correctly to match between the body of the text and the Reference List. The first reference "[1-20]" in the first paragraph implies these are all the modelling studies found in the systematic literature review; however, #15 is the Health Survey for England, and other modelling studies are mentioned [#46-47] further down the Reference List and is included in Table 3. On another page, reference 36 is noted as being excluded, though it is included in both Tables 1 and 2.

Response to Reviewer No 2 comment No. 8: The reference was checked and reorganized.

9. Copy-Editing: This manuscript could use general copy-editing efforts for several poor uses of grammar and sentence structure. There are several missing prepositions, indefinite/definite articles, misplaced adverbs, and incorrect use of present tense. Generic names of pharmaceutical products are also capitalised for no reason. The formatting in the manuscript was also hard to follow; in particular, the legend in Figure 4 is not properly aligned, making the figure difficult to read (this could have been from a Word to PDF conversion issue).

Response to Reviewer No 2 comment No. 9: The manuscript reviewed by an academic editor and necessary proofreading were applied.

Appendix

G2 Second reviewer's comments

Reviewer #1:

Most comments have been addressed properly and were extensively described in the reply to reviewer comments. However, some comments have not been used to improve the manuscript. In my opinion some of the comments need to be addressed in the discussion.

Comments:

1. The other three reviews on COPD utilities (pickard 2008; Einarson 2015; Srivastava 2015) should be mentioned in the discussion including the differences with the current study.

   Response to Reviewer No 1, comment No. These articles have been cited in the third paragraph of the discussion.

   "This study revealed a high level of heterogeneity in utility values derived from patient-level data for all stages of COPD, with the I2 statistic ranging from 92.7% to 97.9%. This range of diversity has been reported in previous systematic review of literatures in COPD [30, 60 & 61]."

2. The argument of time coherence between utility studies and modelling studies is strange. Because most modelling studies used published studies as input there is always a delay between utility studies and modelling studies using these utilities. To get time coherence the authors should have included utility studies up to for example 2013 and modelling studies up to for example a year later 2014.

   Response to Reviewer No 1, comment No. 2: To address the reviewers comment we have summarised the timing of studies reporting utility values for based on patient surveys using EQ-5D and the modelling studies that use these utility values (following table). While we accept the reviewers point that modelling studies, must use utilities that are published in the

literature prior to their year of publication. The most recent modelling study (Samyshkin 2013) is based on utility values that were calculated form individual level data available to the modelling investigators and is reported as Samyshkin et al, 2013. We have therefore included this study and all prior studies in our meta-analysis to provide an estimate of the mean and variation in utility for key health states at the time of the final modelling study included in our analysis based published modelling and COPD utility studies.

Appendix

Patient-based utility and modelling studies, chronologically tabulated

	Patient-based studies	Patient-based studies included in the meta-analysis	Modelling studies included in the current study.
1	Wu et al, 2015		
2	Kim SH et al, 2014		
3	Kim ES et al, 2014		
4	Jodar-Sanchez et al, 2014		
5	Samyshkin et al, 2013	Samyshkin et al, 2013	Samyshkin Y et al, 2013
6	Solem et al, 2012	Solem et al, 2012	Hertel NRW et al, 2012
7	Asukai et al, 2012	Asukai et al, 2012	Najafzadeh M et al, 2012
8	Fletcher et al, 2011	Fletcher et al, 2011	Menn P et al, 2012
9	Pickard et al, 2011	Pickard et al, 2011	Chandra K et al, 2012
10	Starkie et al, 2011	Starkie et al, 2011	Sun SX et al, 2011
11	Menn et al, 2010	Menn et al, 2010	Price D et al, 2011
12	Punekar et al, 2007	Punekar et al, 2007	Lock K et al, 2011
13	Rutten-van Molken et al, 2007 (The European journal of health economics)	Rutten-van Molken et al, 2007 (The European journal of health economics)	Hoogendoorn M et al, 2011
14	Rutten-van Molken et al, 2006 (Chest Journal)	Rutten-van Molken et al, 2006 (Chest Journal)	Atsou K et al, 2011
15	Stahl et al, 2003	Stahl et al, 2003	Gani et al, 2010
16	Spencer et al, 2005	Spencer et al, 2005	Oba 2009
17	Borg et al, 2004	Borg et al, 2004	Earnshaw et al, 2009
18			Chuck A et al, 2008
19			Rutten-van Molken et al, 2007
20			Maniadakis et al, 2006
21			Oostenbrink JB et al, 2005
22			Spencer M et al, 2005
23			Borg et al, 2004
24			Sin et al, 2004
25			

3. I still think that the relevance of the current review for future COPD models is limited because the last two developed COPD models (Asukai, Pharmacoeconomics 2013 and the newest GSK model which will be published in Medical Decision Making soon) include utility values for stable disease that are dependent on other factors than GOLD stage only, such as age, sex, BMI, co-morbidities. So in contrary to the older Markov models that use FEV1% predicted as measure of disease severity the newer models tried to include more patient characteristics to define severity. The authors should at least mention this development in the discussion as a limitation of their study. They should refer to the new GOLD guidelines which moved from a severity classification based on FEV1 only to a classification based on symptoms, exacerbations and FEV1.

   Response to Reviewer No 1, comment No. 3 This paragraph has been added:

   "New approach in disease progression microsimulation modelling using characteristics at individual level of patients [24] can provide more flexible tool for predicting more accurate measures of outcomes. This can be achieved by incorporating the updated COPD assessment tool introduced in the 2014 GOLD report [61]. This combined assessment approach takes three elements into consideration: spirometric test, exacerbations risk and one of the following disease-specific HR-QoL measures: COPD Assessment Test (CAT) or COPD Control Questionnaire (CCQ). Future meta-analyses will need to take account of these developments and provide appropriate comparisons with the patient-level utilities to determine the applicability of utility values used in more recent COPD models."

4. The authors tried to estimate the impact of using higher utilities values in modelling studies on the final estimate of the cost-effectiveness ratio. The authors concluded that the ICER was significantly sensitive to the utility value. However, using a utility value for mild COPD of 0,806 in the model instead of using 0.889 would have decreased the ICER with

only 3.5% (for example 19.300 per QALY instead of 20.000 per QALY) as I understood it correctly. I do not think this a significant change.

Response to Reviewer No 1, comment No. 4: To address this issue we have added an additional paragraph to the discussion. While we concede that based on available evidence the impact looks “modest”, we have had to rely on just two of the 20 modelling studies that reported the effect of utility values in their sensitivity analysis. We have therefore highlighted the need for routine inclusion of variations in utility in future sensitivity analysis of COPD model based evaluations. Below is the wording of the paragraph that is now included in the discussion:

“What impact does the difference between utility values used in COPD models and patient-based utility values have on economic evaluations of COPD therapies? To examine this issue we estimated the relationship between the change in utility and the impact on the ICER, based on a limited number of studies (see Figure 3). According to a regression analysis of all available studies, the higher utility values reported in the modelling studies are likely to have relatively modest effect on the ICER of around 3.5%. However, it should be noted that our analysis of sensitivity is based on only two of the nine modelling studies that reported the effect of utility value as a factor in their sensitivity analyses (WebTable 4). Given the wide variation in patient-based utility values it would be appropriate for all COPD models to include a variation in utility for key health states in their sensitivity analysis in future.”

5. Although the manuscript had been reviewed by an editor according to the authors, it still contains errors.

Response to Reviewer No 1, comment No. 5 Thank you for your attention to details. Another professional proofreading has been made to correct typos and grammatical errors.

Reviewer #2:

The authors have done a thorough job in responding to reviewer comments. I have a few minor comments below that would benefit from being addressed before publication.

1. In both the introduction and discussion, the authors still state that 'all modelling studies' only use a single reference study; since many modelling studies do conduct sensitivity analyses around utilities, I think it would be better to qualify these statements with something that indicates it is for the base case or point-estimate of the cost-effectiveness, such as "The utility values employed to estimate the base case in all models were based on….". The wording in the Discussion: "Health economic decision models currently do not account for this degree of variation, as all rely on a single value taken from one patient-level data study" could also be softened as at least two of the studies in WebTable1 are based on the pooling of 3 [Asukai et al] or 6 RCTs [Rutten van Molken].

   Response to Reviewer No 2, comment No. 1 The above mentioned statement were changed into:

   - The utility values employed to estimate the base case in each model were depended on information from a single study
   - Health economic decision models currently do not account for this degree of variation, as all most rely on a single value taken from one patient-level data study. We found that one study [41] used aggregated data form three RCTs and another [16] from six RCTs.

2. The addition of the analysis to examine the impact of utilities on the ICER results is an excellent addition, but somewhat misleading as it is only based on two studies, which

reported results and had results in a certain direction. This limitation should be acknowledged, or the section should be moved to the discussion section as being exploratory in nature. The conclusion that ICER results are highly sensitive to utilities is not supported by the results in WebTable 5, which list several economic evaluations where utility only had a modest impact on the results.

Response to Reviewer No 2, comment No. 2 We appreciate for this comment. To address this issue we have added an additional paragraph to the discussion. While we concede that based on available evidence the impact looks “modest”, we have had to rely on just two of the 20 modelling studies that reported the effect of utility values in their sensitivity analysis. We have therefore highlighted the need for routine inclusion of variations in utility in future sensitivity analysis of COPD model based evaluations. Below is the wording of the paragraph that is now included in the discussion:

“What impact does the difference between utility values used in COPD models and patient-based utility values have on economic evaluations of COPD therapies? To examine this issue we estimated the relationship between the change in utility and the impact on the ICER, based on a limited number of studies (see Figure 3). According to a regression analysis of all available studies, the higher utility values reported in the modelling studies are likely to have relatively modest effect on the ICER of around 3.5%. However, it should be noted that our analysis of sensitivity is based on only two of the nine modelling studies that reported the effect of utility value as a factor in their sensitivity analyses (WebTable 4). Given the wide variation in patient-based utility values it would be appropriate for all COPD models to include a variation in utility for key health states in their sensitivity analysis in future.”

3. Under Modelling Studies: "Four modelling studies were excluded because utility was not one of their input parameters [21-24]…" should explain that references 23 and 24 do consider utility, but was excluded [I assume] because they utilise mapping from SGRQ.

   Response to Reviewer No 2, comment No. 3 The statement has been changed into:

   Four modelling studies were excluded because utility was not one of their input parameters [21& 22] or it was generated through mapping procedure [23 & 24].

4. Conclusion: the point about identification of other predictors of utility (other than disease stage) is extremely important and could even be highlighted further as an area of future research, given the increasing move away from disease severity classification that relies solely on lung function (as in the GOLD 2008 guidelines) and more into identification of different COPD phenotypes.

   Response to Reviewer No 2, comment No. 4 The following paragraph has been added in the discussion:

   “New approach in disease progression microsimulation modelling using characteristics at individual level of patients [24] can provide more flexible tool for predicting more accurate measures of outcomes. This can be achieved by incorporating the updated COPD assessment tool introduced in the 2014 GOLD report [61]. This combined assessment approach takes three elements into consideration: spirometric test, exacerbations risk and one of the following disease-specific HR-QoL measures: COPD Assessment Test (CAT) or COPD Control Questionnaire (CCQ). Future meta-analyses will need to take account of these developments and provide appropriate comparisons with the patient-level utilities to determine the applicability of utility values used in more recent COPD models.”

5. Copy-editing: The article has undergone a vast improvement in use of language; however, there are still a few typos (e.g. Table 2 'clinincal') and mixed tense usage (e.g. under the section 'Modelling Studies'), so a final proof read would be beneficial.

   Response to Reviewer No 2, comment No. 5 Thank you for your attention to details. Thank you for your attention to details. Another professional proofreading has been made to correct typos and grammatical errors.