Psychosocial predictors of health related quality of life (HRQoL) in Chronic Obstructive Pulmonary Disease (COPD)

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Abbreviations

AIC	Akaike Information Criterion
ADIS	Anxiety Disorders Interview Schedule
CAT	COPD Assessment Test
CBT	Cognitive Behaviour Therapy
CFA	Confirmatory Factor Analysis
CFI	Comparative Fit Index
CHD	Coronary Heart Disease
CHOICE	Choosing Health Care Options in Chronic Care Emergencies
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CRQ	Chronic Respiratory Questionnaire
CRQ-IA	Chronic Respiratory Questionnaire Interviewer Assessment
CRQ-SAS	Chronic Respiratory Questionnaire Self-Administered Standardised
DF	Degrees of Freedom
DSM-5	Diagnostic and Statistical Manual of Mental Disorder, 5th Edition
FEV_1	Forced Expiratory Volume in 1 Second
FVC	Forced Vital Capacity
GAD	Generalised Anxiety Disorder
GP	General Practitioner
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HADS	Hospital Anxiety and Depression Scale
HRQoL	Health Related Quality of Life
HSCL	Hopkins Symptom Checklist
IMD	Index of Multiple Deprivations
IQR	Interquartlie Range

LTC	Long term condition
LTE-Q	List of Threatening Life Events Questionnaire
MCS	Mental Component Score
MeSH	Medical Subject Heading
MAR	Missing at Random
MCAR	Missing Completely at Random
MNAR	Missing Not at Random
MHI	Mental Health Index
mMRC	Modified Medical Research Council Dyspnoea scale
N	Number
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OCD	Obsessive Compulsive Disorder
PCS	Physical Component Score
PDSR	Panic Disorder Self-Report
POMS	Profile of Mood States
PTSD	Post Traumatic Stress Disorder
QOF	Quality and Outcomes Framework
QPD	Quick Diagnostics Panel
RMSEA	Root Mean Square Error of Approximation
SCID	Structured Clinical Interview for DSM
SD	Standard Deviation
SEM	Structural Equation Model
SF-12	Medical Outcomes Study Short Form
SGRQ	St George's Respiratory Questionnaire
SIP	Sickness Impact Profile

SPSS	Statistical Package for the Social Sciences
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
UK	United Kingdom
WHO	World Health Organization
WHOQOL-Bref	World Health Organisation Quality of Life Assessment

Abstract

Poor health related quality of life (HRQoL) is associated with worse health outcomes for COPD patients' and is therefore an important outcome in COPD clinical care and research. The variance in COPD patients HRQoL is not well accounted for by measures of lung function. Psychosocial factors, such as depression and anxiety have been found to be closely associated with poor HRQoL. Panic disorder is also a highly prevalent comorbidity with COPD and is associated with worse patient reported outcomes but there has been little research conducted on the impact of panic on HRQoL in COPD.

The aims of this PhD study were firstly to identify the psychosocial predictors of HRQoL in COPD. Secondly to test whether panic predicts HRQoL in COPD and thirdly to identify whether panic was a better predictor of HRQoL in COPD than depression.

A systematic review was conducted to review the existing evidence for psychosocial predictors of HRQoL in COPD. Eight longitudinal cohort studies were identified and the results were pooled using random effects meta-analysis. There was a large and significant positive correlation between depression and prospective HRQoL at 12 months, and a moderate but significant correlation between anxiety and prospective HRQoL at 12 months. No studies were identified which had looked at the impact of panic disorder on HRQoL in COPD.

A longitudinal cohort study was conducted across 10 general practices in Manchester, UK. 188 participants completed 12 month follow-up (81%). Self-report data were collected on socio-demographics, psychosocial factors, general and respiratory HRQoL and healthcare use. Data on the severity of COPD were collected from general practice notes. In simple linear regression analyses panic significantly predicted physical and emotional respiratory specific HRQoL at 12 months. However, this effect did not remain in multivariable models which included depression. Structural equation models (SEM) were used to explore and quantify the relationships between depression, anxiety, and panic, and respiratory HRQoL at 12 months. The results showed that for both physical and emotional respiratory HRQoL there was a high and statistically significant covariance between depression and anxiety, depression and panic, and anxiety and panic at baseline. However, only depression significantly predicted physical HRQoL at 12 months. Depression was also found to mediate the relationship between anxiety and respiratory HRQoL but not between panic and respiratory HRQoL.

This study has shown that depression is the greatest psychosocial predictor of respiratory HRQoL in COPD. Future work should focus on identifying the effect of panic on short term outcomes in

COPD such as, healthcare use and medication use, using larger samples which would allow the specification of more complex models and using a clinical interview for the identification of panic.

Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

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About The Author

I studied Psychology at the University of Manchester for my undergraduate degree. Following the completion of my degree and after a brief time working as a support worker, I was accepted to train as a Primary Care Mental Health Worker (PCMHW) as part of the Improving Access to Psychological Therapies initiative. During this post I worked in an innovative and forward thinking Primary Care Mental Health team (PCMHT) in Bury delivering low intensity Cognitive Behavioural Therapy (CBT) for patients with common mental health problems. I worked with patients in 1:1 sessions and also developed half day workshops and 6 week long groups for depression, health anxiety and anger management. As a result of running workshops I was invited to deliver them for MacMillan Cancer Support groups and also Breatheasy. Breatheasy is a support group for patients with lung disease which is coordinated nationally by the British Lung Foundation but run locally by people living with lung disease. Working with the members of Breatheasy who had Chronic Obstructive Pulmonary Disease (COPD) highlighted to me the difficulties of living with the condition. It inspired me to run a project as part of my PCMHW training to develop a service for COPD patients within the PCMHT. The service was a great success with both patients and respiratory clinicians. However, it was clear to me that low intensity CBT was not always sufficient to meet the often complex psychological needs of this patient group. As a result I went on to further my training and completed an MSc in Advanced Practice Interventions in Primary Care Mental Health. For my MSc thesis I conducted a substantive review of the effectiveness, acceptability and feasibility of CBT for the treatment of anxiety and depression in patients with COPD.

During my MSc I realised how much I enjoyed research and I sought out a post as a Clinical Studies Officer to gain some practical research training. After 12 months I secured a post as a Senior Research Assistant on the CHOICE NIHR Programme Grant. The CHOICE research programme aimed to understand the psychological factors that predict use of unscheduled care in patients with long term conditions, including COPD. I was delighted to be back working with patients with COPD as well as learning about other long term conditions. During this role I have gained significant practical experience of quantitative research methods. It has also allowed me to re-establish links with the local Breatheasy support groups and to discuss my ideas for COPD research with them. Whilst working on the CHOICE programme the opportunity arose to do a PhD. This was the perfect opportunity for me to embed a PhD project within an established programme of research with an assembled cohort of COPD patients.

1. General Introduction

1.1 Chapter Overview

This introductory chapter provides an overview of the nature, burden, and impact of chronic obstructive pulmonary disease (COPD). COPD has a significant impact on the health-related quality of life (HRQoL) of patients. This chapter also provides a brief conceptual overview of HRQoL and moves on to explain the psychological factors that predict HRQoL with a view to better understanding the relationship between depression, anxiety, and panic, with HRQoL in COPD.

1.2 Chronic Obstructive Pulmonary Disease (COPD)

1.2.1 Symptoms and diagnosis of COPD

COPD is a progressively disabling respiratory disease which is caused by inflammation of the airways and structural changes in the lungs which result in a loss of elasticity in lung tissue (emphysema) and excess mucus in the lungs which blocks airflow.[1;2] COPD is caused by long term exposure to inhaled irritants, such as tobacco smoke and air pollution. In the United Kingdom (UK) tobacco smoking is the most important risk factor for COPD.[3] COPD can also be caused by the air pollution created by the burning of biomass fuels, such as wood, and occupational exposure to air pollution.[4;5]

In the UK a diagnosis of COPD is usually considered in smokers who are over the age of 35 and present with one of the following symptoms: dyspnoea (breathlessness), a chronic cough, regular sputum production, a wheeze, and frequent episodes of bronchitis.[6] COPD is characterised by exacerbations of its symptoms. Exacerbations are particularly common in the winter months and become increasingly more frequent as the disease progresses.[7]

COPD is a disease with a systemic nature and therefore has an impact on other systems within the body as well as the lungs. Common systemic manifestations of COPD have been identified as: cardiovascular problems, skeletal muscle wasting, osteoporosis, anaemia, gastroesophageal reflux disease, depression and anxiety.[8;9] It is thought that the systemic impact of COPD is caused by airflow obstruction and inflammation of the airways, but the exact cause is not yet known.[8;10;11]

The Global Initiative for Lung Disease (GOLD) has developed guidelines for the identification and diagnosis of COPD.[1] The GOLD guidelines recommend that a test of lung function called spirometry is used to confirm a clinical diagnosis of COPD and should then be repeated annually

as part of the ongoing management of COPD. Spirometry is a measure of the volume of air that a patient can exhale (forced vital capacity [FVC]) and the amount of air they can exhale in one second (known as forced expiratory volume in one second [FEV_1]). It is the most reproducible and objective way available of measuring airflow limitation.[1]

Both the GOLD guidelines and the National Institute for Health and Care Excellence (NICE, 2010) recommend that the results of spirometry tests are used to diagnose COPD. The guidelines state that in order to receive a diagnosis the patient must be experiencing symptoms of COPD and have a ratio of $FVC/FEV_1 < 0.7$. The GOLD guidelines then recommend that the patient's FEV_1 score is compared to the score predicted for a patient of the same age, gender and height (known as the FEV % predicted) which is then used to classify COPD in to four stages of severity (Table 1.1). However, the NICE guidelines use only three classifications for the severity of COPD (mild to severe) and instead view patients with $FEV_1 \geq 80\%$ of that predicted for their age, gender and height as normal instead of classifying them as having mild COPD (Table 1.1).[6]

The GOLD and NICE guidelines for COPD acknowledge that spirometry results alone cannot provide a comprehensive picture of health status in people with COPD.[1;6] Due to the nature of COPD as a progressive and multi component illness, the guidelines recommend that patients receive a fully comprehensive assessment in addition to lung function tests.[1;6] The most recent version of the GOLD guidelines, published in 2014 recommend that the severity of COPD should be categorised using a comprehensive approach which includes assessment of symptoms (Modified Medical Research Council Dyspnoea Scale [mMRC]),[12] spirometry results, HRQoL (COPD Assessment Test [CAT])[13] and risk of exacerbations (Table 1.2).[1] This new framework provides a combined approach to COPD assessment which allows a more accurate monitoring of risk, a guide for stepping up treatment, and puts HRQoL at the centre of COPD assessment. However, there is some criticism that the new categories still overlook some important factors in COPD progression, such as, smoking status and comorbidites, and that they lack validation within primary care COPD samples.[14]

Table 1.1: Diagnosis and severity classification of COPD

FEV_1/FVC ratio	FEV_1	GOLD Stage[1]	NICE[6]
< 0.7	$FEV_1 \geq 80\%$ predicted	Stage 1- Mild	
<0.7	$50\% \leq FEV_1 < 80\%$ predicted	Stage 2- Moderate	Mild
< 0.7	$30\% \leq FEV_1 < 50\%$ predicted	Stage 3 – Severe	Moderate
<0.7	$FEV_1 < 30\%$ predicted	Stage 4 – Very Severe	Severe

FVC – Forced vital capacity, FEV_1 – Forced expiratory volume in 1 second, GOLD – Global Initiative for Chronic Obstructive Lung Disease, NICE – National Institute for Health and Care Excellence

Table 1.2: GOLD assessment of COPD using symptoms, breathlessness, spirometry and exacerbations[1]

Patient Group	Description	Indicators
Group A	Low risk, less symptoms	GOLD severity stage 1 or 2 0-1 exacerbations per year No hospital admissions for exacerbation CAT score > 10 or mMRC grade 0-1
Group B	Low risk, more symptoms	GOLD severity stage 1 or 2 0-1 exacerbations per year No hospital admissions for exacerbation CAT score >10 or mMRC grade ≥ 2
Group C	High risk, less symptoms	GOLD severity stage 3 or 4 ≥ 2 exacerbations per year or ≥1 hospital admission for exacerbation CAT score ≥ 10 or mMRC grade 0-1
Group D	High risk, more symptoms	GOLD severity stage 3 or 4 ≥ 2 exacerbations per year or ≥ 1 hospital admission for exacerbation CAT score ≥ 10 or mMRC grade ≥2

GOLD – Global Initiative for Chronic Obstructive Pulmonary Disease, CAT – COPD Assessment Test, mMRC – Modified Medical Research Council Dyspnoea Scale

1.2.2 Prevalence and burden of COPD

Prevalence

COPD is an important cause of morbidity and mortality worldwide. The World Health Organization (WHO) estimates that 65 million people worldwide live with COPD and that the disease is responsible for approximately 5% of all deaths.[15] COPD is also ranked as the eleventh highest cause of disease burden and is predicted to rise to the seventh by 2030.[16]

Despite declining smoking rates, the prevalence of COPD is rising. Between 2009 and 2010 the NHS Information Centre for Health and Social Care reported that 861,341 people were living with COPD in Great Britain, a prevalence of 1.6%. This was an estimated increase of 26,000 people from 2008 to 2009. The estimates for 2012 to 2013 show that there were 1 million people living with COPD and that the disease was responsible for 25,000 deaths in that year.[5] This indicates a rate of increase in COPD prevalence which is higher than that of other long term conditions, such as coronary heart disease.[6]

The prevalence of COPD is greater in older patients and adults over the age of 40 who are almost two times more likely to develop COPD for each 10 year increase in age. This high prevalence rate is maintained even when smoking status, pack years (1 pack year is equivalent to smoking 20 cigarettes per day for 1 year) and education are controlled for.[17]

The true prevalence of COPD is however difficult to determine. Current prevalence estimates are based on diagnosed cases alone but there are thought to be some 3 million people living in the UK with undiagnosed COPD.[18;19] COPD is a progressive disease and people with mild COPD may not immediately recognise noticeable symptoms. For example, people with mild COPD often misattribute symptoms as part of ageing and either consciously or subconsciously adjust (i.e. reduce) their physical activity leading to under detection and diagnosis. Among those who reduce their physical activity the true impact of COPD symptoms can go unnoticed and they may delay seeking medical advice. Avoiding and reducing exercise can also result in a reduction in cardiopulmonary fitness or some atrophy of muscles, for example in the legs.[20] A further explanation for the under diagnosis of COPD can be the high prevalence of other comorbid physical conditions, such as heart disease. Comorbidities can often be viewed as being more severe by health care professionals and sometimes require more immediate treatment than COPD, especially milder forms of COPD. COPD symptoms can also sometimes be misattributed to asthma, especially by patients who have been treated for asthma previously. Symptoms of asthma and COPD are similar and can co-occur, but they are distinct syndromes and require separate management owing to the fact that the airway obstruction caused by asthma is reversible whereas in COPD it is not.[21] Under diagnosis of COPD can result in lengthy delays in the

treatment and management of COPD symptoms, for example giving smoking cessation advice which is key strategy for halting the progression of the disease.[1]

Burden

Living with COPD places a burden on individual patients and often requires them to make significant changes to their lifestyle. COPD can place considerable limitations on patients' ability to perform activities of daily living due to the progressive worsening of symptoms. A qualitative study of 10 patients with severe COPD found that breathlessness was reported as the most distressing symptom which was said to be at its worst at night and during the winter months.[22] The participants in this study described how they experienced bouts of breathlessness and a decline in their ability to engage in social activities which meant that they were unable to plan trips or social events in advance, preferring instead to wait and see how they would feel on any given day. They also highlighted how breathlessness had led to a change in their role within their families and to a loss of intimacy within their personal relationships. Completing activities of daily living, such as housework or shopping, and also self-care activities such as washing were described as very challenging. Taking a bath or a shower was very difficult for many patients who found that the prolonged exposure to the steam increased their breathlessness. This led to an increasing reliance on partners and family members for help which some people with COPD can find difficult to accept. Participants also recognised how the experience of breathlessness led to a feeling of fear and to the onset of symptoms of anxiety and panic.[22]

O'Neill et al. (2002) conducted a qualitative study of 21 women with COPD who were engaged on a pulmonary rehabilitation course. They found that stigma and shame were keenly felt by participants as they viewed their disease as self-inflicted by smoking. They also described feeling shame because they had significantly reduced their physical activity.[23] These findings are supported by more recent qualitative work which included patients with mild to moderate COPD where patients described experiencing self-judgement, guilt and shame, as well as a sense of losing control of their lives.[24]

In addition to the personal and social impact COPD also incurs significant resource and economic burden on healthcare systems. In 2010 COPD was estimated to cost the USA $50 billion, of which $30 billion was attributable to health care costs.[25] In 2011 Fletcher et al. conducted a cross sectional study of 2426 COPD patients of working age across six countries that included 400 patients from the UK. The aim was to determine the cost of COPD in patients of working age (i.e. between 45 and 67 years of age).[26] Seventy per cent of the sample was not working at the time of the study and 26.4% reported that they had left employment because of their COPD. Fletcher et al. (2011) found that the total annual cost for their sample of COPD patients was £3.63 million.

They found that the greatest proportion of healthcare usage was in primary care but that hospital care accounted for 68% of the total cost of healthcare use. The mean monthly cost for healthcare use across the six countries was £125 per patient, but the mean monthly cost in the UK was higher at £277 per patient per month. The cost of the working hours lost was calculated to be £556 per patient, a total of £376,412 across the cohort as a whole.[26]

Healthcare use in COPD is closely linked to psychosocial factors and HRQoL. COPD patients' use of healthcare can be significantly elevated by the presence of psychosocial factors such as depression. A systematic review with meta-analysis has shown that COPD patients who have comorbid depression are almost 50% more likely to use urgent and unscheduled healthcare than those without depression.[27] Furthermore, the use of urgent health care and unscheduled hospital admissions can have a negative impact on the HRQoL of COPD patients. Wang et al. 2005 found that 50% of patients had survived after a hospital admission for acute exacerbation of COPD, although their HRQoL was poor and predicted further visits to the emergency room.[28]

1.2.3 Management of COPD

COPD is a progressive disease for which there is no cure and there is no conclusive research to show that any of the currently available pharmacological therapies are able to modify decline in lung function.[1] The GOLD guidelines for the management and treatment of stable COPD centre around two goals. Firstly to reduce symptoms by improving exercise tolerance and improving health status. Secondly to prevent disease progression, by reducing risk factors (i.e. smoking), preventing and treating exacerbations, and reducing mortality.[1]

In order to reduce symptoms one of the main goals of treatment is to limit exacerbations, and prevent any further decline in patients' functioning.[1;6] Therefore, for patients who smoke treatment initially centres on smoking cessation.[29] Smoking cessation, or reducing exposure to any inhaled irritants that cause COPD, is the only intervention which is able to slow the progress of the disease.

Both the GOLD and NICE guidelines recommend pharmacological therapy in the form of short and long acting bronchodilators, glucocorticoids (steroids) and other medications such as antibiotics and vaccines to reduce the frequency and severity of symptoms in COPD, and to increase patients' ability to tolerate exercise.[1;6;30] Pharmacological treatment is recommended to be stepwise and closely monitored so that patients can be stepped up or down to different pharmacological treatments according to the severity of their disease.[1;6;30]

For patients with the most severe COPD symptoms and severe resting hypoxemia oxygen therapy can be prescribed.[1;6] Oxygen therapy in patients with severe hypoxemia is known to reduce mortality but there is an ongoing debate in the literature as to its effectiveness when it is used by patients over the long term.[31;32] Oxygen needs to be inhaled for at least 15 hours per day to be effective and therefore places significant limitations on patients' lifestyle if prescribed.[1;6]

Treatment guidelines also recommend non-pharmacological therapies for the treatment of COPD, such as pulmonary rehabilitation programmes and self-management interventions. Pulmonary rehabilitation is used to improve exercise capacity, ability to complete activities of daily living and HRQoL.[1;6;33] Pulmonary rehabilitation programmes can vary in content between services but usually include exercise training, smoking cessation, nutrition counselling, and educational components.[1] A Cochrane review and meta-analysis of 31 pulmonary rehabilitation programmes has shown that it can significantly improve patients' HRQoL.[34] There is increasing evidence from Cochrane reviews that self-management interventions are important for the treatment of stable COPD. Self-management interventions refer to any interventions that are structured and aimed at improving patients health behaviours and ability to manage their own disease.[35] Zwernick et al. conducted a Cochrane review of 29 studies which looked at the impact of self-management interventions on COPD outcomes and found that they were successful in improving HRQoL, reducing hospital admissions, and improving self-reported symptoms of breathlessness.[35]

1.3 Health Related Quality of Life (HRQoL) and COPD

1.3.1 Definition of HRQoL

The measurement of quality of life specifically related to health (HRQoL) has become increasingly important in healthcare practice and research. Quality of life is a subjective concept which refers to patients' self-assessment of their satisfaction with the multiple dimensions of their life. Jones et al. (1995) describes quality of life succinctly and in lay terms as the gap between, *'that which is desired and that which is achievable'*.[20(p187s)] HRQoL can therefore be seen as the gap between patients desired health state and their actual health state.[20] Like quality of life more broadly, HRQoL also covers multiple dimensions, such as evaluation of physical and mental health, symptoms, disability, impairment, impact on daily activities, and effectiveness of treatment.[36] An interview study conducted with 21 Dutch COPD patients has identified that the most important components of HRQoL are physical health (fatigue and physical functioning), social health (ability to participate in social activities, companionship and emotional support), and coping with COPD.[37]

Within the HRQoL literature a clear distinction is made between general HRQoL, and HRQoL which is specific to a certain disease or group of diseases, such as COPD or respiratory diseases. The two concepts are acknowledged as related to each other but are distinct and cannot be used to represent each other.[38;39] HRQoL that is specific to one disease or illness can provide specific insights into patients' disease and how they live with that disease as well as offering information about their general health status. Measure of HRQoL which are specific to respiratory diseases or COPD have also been found to be more closely associated with measures of lung function and to better discriminate between different stages of severity in patients with COPD.[40] Measures which are designed to assess general HRQoL have a wider focus which often includes information about abilities, relationships, perceptions, life-satisfaction, and wellbeing and can be better used to compare groups of patients with different conditions.[41]

1.3.2 HRQoL and COPD

The general HRQoL of COPD patients is significantly worse than that seen in the general population[42] and also in populations of patients with other respiratory conditions.[43] In a 5-year longitudinal study which compared HRQoL of COPD and asthma patients, Koskela et al. (2014) found that HRQOL of COPD patients declined over time but remained stable in patients with asthma.[43]

Poor HRQoL has a negative impact on health outcomes in COPD. COPD Patients with poor HRQoL have been found to have increased breathlessness,[44] reduced physical functioning[45;46], increased exacerbations[47], hospital admissions[48-50], and mortality.[51-53] Antonelli-Incalzi et al. (2009) found that poor HRQoL in COPD patients was associated with an increased risk of mortality as well as having a lower BMI, older age and cerebrovascular disease. In this study, higher FEV_1 and a better performance on the 6 minute walk distance test were found to be predictive of less mortality.[52]

Due to the extent of the negative impact of poor HRQoL in COPD it has become an increasingly important outcome in both research and clinical practice.[52] Lung function alone, (as measured by FEV_1), is an unreliable marker of severity of COPD patients' symptoms and the burden that they experience from the disease.[54] The exercise limitation that COPD patients experience cannot be accounted for by measures of lung function alone.[1] Agusti et al. (2010) studied over 2000 clinically stable COPD patients across 12 countries and found that lung function among COPD patients was only weakly associated with the severity of their breathlessness, their HRQoL, number of comorbidites, exercise capacity, and number of exacerbations in the previous 12 months.[55] Patients who report even mild dyspnoea (for example MRC grade 0.5) still have worse HRQoL when compared with healthy older adults.[51;56] Therefore, there is a growing case to better

understand what drives HRQoL in COPD patients given its central role in defining health status and the experience of patients living with COPD.[50]

1.3.3 Conceptual models and predictors of HRQoL in COPD

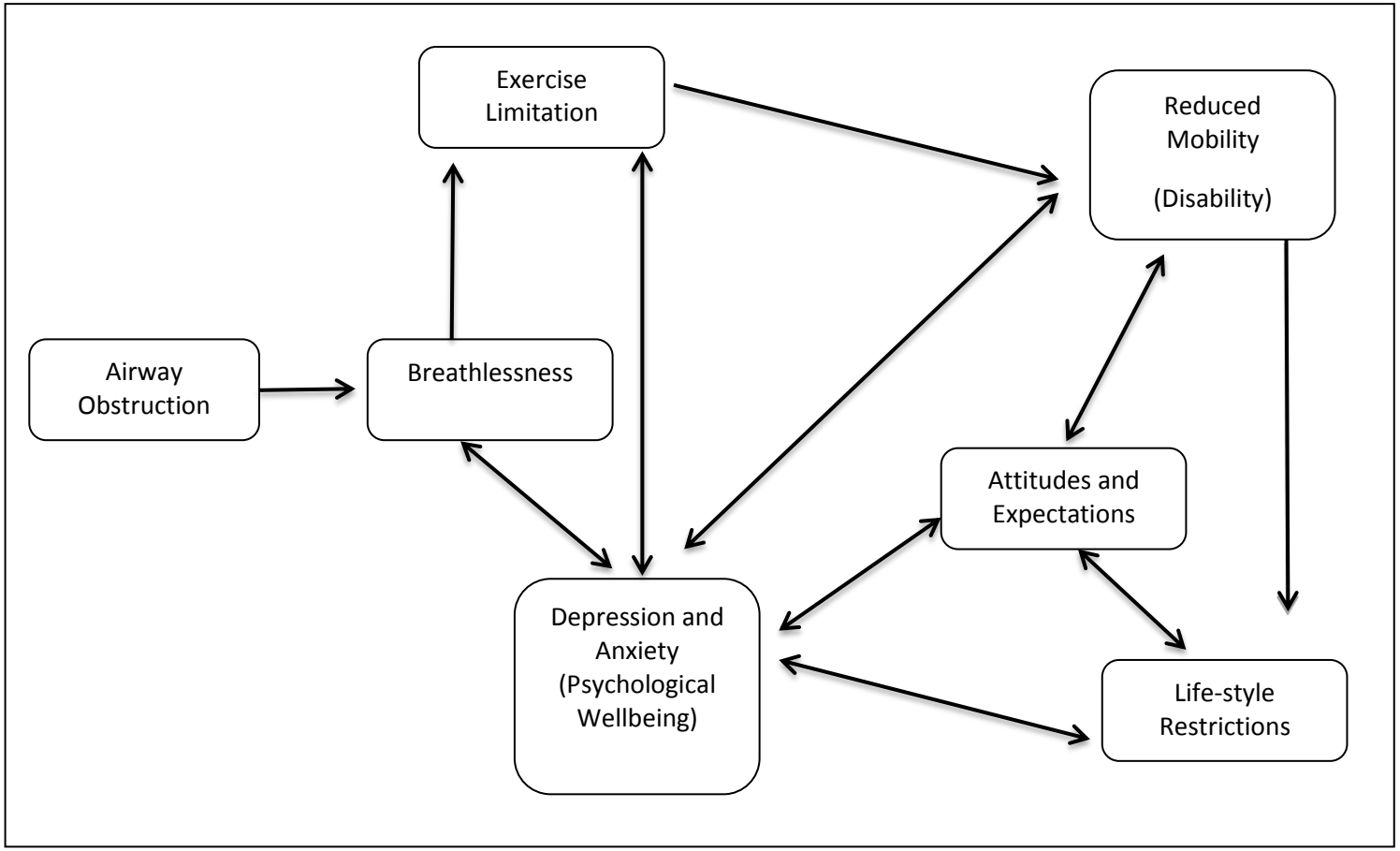
HRQoL is a multidimensional concept which has been described in varying ways across different illnesses and areas of healthcare practice and research. Figure 1.1 shows The Jones model of HRQoL which is a theoretical model of HRQoL specific to COPD. It explains the impact of COPD symptoms, particuarly, dyspnoea, on HRQoL.[20] This model proposes that breathlessness, (one of the main symptoms of COPD), impacts patients' psychological wellbeing (i.e. depression and anxiety), exercise limitation, mobility, attitudes and expectations, and life-style behaviour. The model identifies psychological wellbeing, and specifically depression and anxiety, as central to HRQoL in COPD. It proposes that there is a reciprocal relationship between breathlessness and psychological wellbeing. It then suggests that there are reciprocal relationships between psychological wellbeing and exercise limitation, reduced mobility, attitudes and expectations, and life-style behaviour.[20]

Studies have been designed to determine what physical disease factors predict HRQoL in COPD using both general and COPD specific measures of HRQoL. Garrido et al. (2006) conducted a large multisite study of more than 10,000 COPD patients in primary care in Spain and found that gender, lung function (FEV_1), use of oxygen therapy, and use of health care predicted both generic physical and mental HRQoL.[57] They also found that age, body mass index, and level of education predicted physical, but not mental HRQoL. In a two year prospective cohort study of both COPD and asthma patients which used a respiratory specific measures of HRQoL it was found that lung function was only weakly correlated with change in HRQoL over two years. In multiple linear regression analyses significant predictors of decline in HRQoL were being male, having a lower level of education, experiencing more breathlessness and other respiratory symptoms, as well as lower body mass index.[58] Other studies have also found that functional capacity, specifically the number of steps a patient can take, and breathlessness predict HRQoL.[59;60]

Variation in the HRQoL of COPD patients remains largely unexplained by objective measures of disease severity such as spirometry for lung function and dyspnoea measures.[61] HRQoL has also been found to be closely correlated with psychological factors, such as anxiety and depression, which are also proposed as important in the Jones model of HRQoL in COPD. The results of many studies to date have largely shown support for the Jones et al. (1995) model[20] and have identified a range of both physical and psychological factors that are associated with HRQoL for COPD patients. Tsiligianni et al. (2011) conducted a meta-analysis which showed that dyspnoea,

depression and anxiety were the factors most highly correlated with respiratory specific HRQoL.[62] Depression and anxiety are highly prevalent in COPD patient populations and as the Jones model suggests, these psychological symptoms significantly impact functioning, lifestyle and attitudes of COPD patients. The next section of this chapter will summarise what is known about the nature, prevalence, and impact of depression and anxiety in COPD.

Figure 1.1: Jones's (1995) conceptual model of HRQoL in COPD[20]



1.4 Depression, Anxiety, and COPD

1.4.1 Definition and symptoms of depression and anxiety

Depression is a common mental health problem which can affect how people feel physically, how they think and how they behave. Depression is thought to affect more than 350 million people worldwide and the WHO has classified depression as the leading cause of disability and a major contributor to the global burden of disease.[63-65]

The Diagnostic and Statistical Manual of Mental Disorders is a tool for the diagnosis and classification of mental disorders produced by the American Psychiatric Association.[66] It is currently in its 5th edition (DSM-5) which replaced the DSM-IV in 2013.[67] However, there were few changes to the diagnostic criteria for depression. According to the DSM-5 a diagnosis of major depressive disorder can be given when a person experiences depressed mood and/or a loss of interest or pleasure in daily activities every day for at least two weeks. A total of five of the following symptoms must also be experienced: a significant change in appetite and/or weight, a change in sleep which can be either insomnia or hypersomnia, fatigue and loss of energy, feelings of worthlessness or excessive and inappropriate guilt, diminished ability to concentrate and suicidal thoughts and/or behaviour.[66] The symptoms must cause a significant impairment to social, occupational or educational functioning, and must not be better accounted for by substance abuse, medical illness, other psychiatric illness or bereavement.

Anxiety can be a normal reaction to stress which is experienced by most people at different times in their lives. However, anxiety can become excessive and prolonged and cause significant disruption to the day to day functioning. The DSM-5 identifies a range of anxiety disorders which include: generalised anxiety disorder (GAD), obsessive compulsive disorder (OCD), post-traumatic stress disorder (PTSD), social phobia, specific phobias, and acute stress disorders.[66] A study of anxiety disorders in the general population across Australia, Germany, America and Holland found that prevalence ranged from 5.6 to 18.1%; GAD and panic disorder, with or without agoraphobia, accounted for over half of the prevalence.[68] GAD is characterised by excessive anxiety and worry which occurs on most days for at least 6 months.[66] According to the DSM-5 to receive a diagnosis of GAD the anxiety and worry must be characterised by three or more symptoms which can include: restlessness, fatigue, difficulty concentrating, irritability, muscle tension and sleep disturbance.[66]

1.4.2 Prevalence of depression and anxiety in long term conditions

Depression and anxiety disorders are highly prevalent in people with long term physical health conditions - known in the UK as long term conditions (LTCs).[69] In a large study of patients with asthma, arthritis, angina, diabetes, and depression Moussavi et al. found 23% of patients who had two or more long term conditions also had depression and the prevalence of depression was the highest in patients who had asthma at 18.1%. In a smaller Spanish primary care study of 120 patients with depression or dysthymia diagnosed according to the DSM-IV criteria, 31.7% were found to have a comorbid physical condition.[70]

The prevalence of depression in patients with LTCs may be even higher as research shows that depression often goes unrecognised in patients with physical health problems. Depression prevalence in the context of LTCs may be underestimated for a variety of reasons. The diagnosis of depression can often be overshadowed by the physical health problems which may be perceived as more important or pressing by both clinicians and patients.[71] A qualitative study has looked at the barriers surrounding the recognition of depression in patients with LTCs in primary care.[72] The results showed that depression is often under recognised by health professionals because it is normalised within the context of the patients LTC and/or health professionals feel uncertain about the use of formal screening for depression and experience difficulties in negotiating appropriate labels for depression with patients.[73]

1.4.3 Prevalence of depression and anxiety in COPD

COPD patients are significantly more likely to have depression than the general population However, prevalence estimates for depression in COPD populations have been found to vary between the type of COPD patients studied and the method by which depression is identified. In 2002 Van Manen et al. conducted a systematic review of ten studies which found that the prevalence of depression ranged from 6 to 42%.[74] In 2011 a systematic review with meta-analysis found that the prevalence of depression among COPD patients was 24.6% compared with 11.7% among patients without COPD.[75] Schneider et al. (2010) conducted a large population based study in Switzerland which included over 35,000 COPD patients compared with controls. They found that those people who were diagnosed with COPD were more likely to receive a diagnosis of new onset depression than those who did not have COPD.[76] Schneider found that the highest risk of depression was among patients with the most severe COPD but also showed that COPD patients were more likely to have a history of depression before being diagnosed with COPD than controls.[76] The prevalence of depression is also higher among patients with COPD than in patients with other LTCs. Van den Bernt et al. (2009) conducted a prospective cohort study which found

that patients with COPD were significantly more likely to be diagnosed with depression than those with diabetes or than controls.[77]

Estimates of the prevalence of anxiety in COPD populations have also been found to be higher in both general populations[68] and in clinical populations with other respiratory conditions such as asthma.[78] Willgoss et al. (2013) conducted a systematic review of anxiety disorders in patients with COPD and found that the prevalence among inpatients was 10-55% and 13-46% in outpatients.[79] This systematic review also investigated the prevalence of specific anxiety disorders in COPD patients and found that there was a considerable variation in rates between anxiety conditions. GAD was found in 6-33%, panic disorder in 0-41%, specific phobia in 10-27%, and social phobia in 5-11%.[79]

1.4.4 Impact of depression and anxiety in COPD

Depression and anxiety significantly impact quality of life and level of functioning of COPD patients, affect their use of healthcare services and increase mortality rates.[80] Often this negative impact cannot be accounted for by the severity of COPD or patients level of physical functioning, for example their exercise ability.[75;81]

Patients with COPD and comorbid depression are able to walk for shorter distances than those without depression, and 11 to 18% of the variance in physical functioning seen in COPD patients can be attributed to the presence of depression.[82-86] Furthermore, both depression and anxiety are strong predictors of increased use of health care in both outpatient and primary care services, and also predict hospital admissions.[87;88] A systematic review in 2012 found that patients with one of four LTCs (COPD, asthma, diabetes and coronary heart disease) who also have depression are nearly 50% more likely to use urgent healthcare than those without depression.[27] Meta-regression was used to examine the differences in the impact of depression on urgent care use across the four conditions and it was found that patients with COPD and depression were 40% more likely to use urgent health care than those with asthma, diabetes and CHD. This finding is important as a study of hospital admissions for patients with moderate-to-severe COPD concluded that patient outcomes, including life expectancy and health-related quality of life, were poor following an admission for acute exacerbation of COPD.[28] Furthermore, Atlantis et al. (2014) found that having depression or anxiety comorbid with COPD significantly increased the risk of mortality.[80]

Suicidal ideation and behaviour is a common symptom of depression in the general population.[89] Several studies have reported that risk of suicide is higher among people with comorbid chronic

physical illness and depression.[6;71] A large nested case control study conducted in UK primary care found that there was a significant increased risk of nonfatal self-harm for males diagnosed with COPD[90] and of completed suicide in women with COPD.[91]

Despite finding an increased risk of self-harm and suicidal ideation, and behaviour in COPD it is often unclear how much is due to depression and how much to COPD as both conditions are frequently comorbid and overlap in symptoms.[71] However, Goodwin (2011) found that patients with COPD have significantly increased odds of experiencing suicidal ideation when compared with those participants without COPD, even when demographics, lifetime major depression, panic disorder, and drug and alcohol dependence were controlled for.[92] Furthermore, COPD was significantly associated with increased odds of a suicide attempt, and this relationship also remained when demographics, lifetime risk of major depression, panic disorder, and drug and alcohol dependence and nicotine dependence were controlled for. These findings suggest that there is a link between both suicidal ideation and active suicidal behaviour in COPD which is independent of depression. However, the risk of suicidal thoughts and behaviour may be significantly increased when COPD patients have comorbid depression.

1.4.5 Impact of depression and anxiety on HRQoL in COPD

The impact of depression on HRQoL was studied in a large study across 45 health conditions.[93] Depression was found to have the third most significant effect on HRQoL after Parkinson's disease, rheumatism, and obesity. Moussavi et al. (2007) measured the health status of patients with chronic conditions and comorbid depression across 60 countries. The measure of health status they used covered physical health status, the impact of health problems on everyday life, vision and mobility, interpersonal activities, energy, and affect.[69] Moussavi et al. found that participants who had depression and a LTC had significantly lower mean health scores than those who had LTCs without depression, even when sociodemographic and economic factors and country of origin were controlled for.

Depression and anxiety are known to have a negative impact on the HRQoL of patients with COPD. Cully et al. (2006) conducted a cross sectional study of 179 patients with moderate COPD in the USA and found that both depression and anxiety were predictive of poorer quality of life, but that in some cases anxiety was more predictive of poor HRQoL than depression.[84] Giardino et al. (2010) also found that anxiety was significantly associated with poor HRQoL and reduced physical functioning in a sample of patients with moderate to severe COPD when age, gender, COPD severity and depression were controlled for. Giardino et al. also highlighted that although anxiety had a significant impact on HRQoL for both men and women the effect was stronger in men.[94]

Cleland et al. (2007) conducted a cross sectional questionnaire study of the HRQoL of 110 UK primary care patients with mild to moderate COPD. Cleland et al. found that 21% had a clinically significant score for depression and 33% for anxiety. Out of those participants who indicated that they had the poorest quality of life 42% also had clinically significant levels of depression and 53% anxiety.[95] Correlation and multiple regression analysis confirmed a significant relationship between anxiety and depression scores and the quality of life measure.

There is evidence that depression and anxiety are strongly associated with poor HRQoL and that, in some cases, anxiety may have a greater impact on HRQoL than depression.[84;94] However, the findings from studies to date are mainly derived from cross-sectional studies and as a result the inferences we can draw from them are limited to the fact that there is a strong relationship between depression, anxiety, and HRQoL. No evidence to date shows that that depression and/or anxiety causes poor HRQoL in COPD.

While anxiety is recognised as an important factor in COPD that is closely associated with HRQoL there has been less research about the association between specific anxiety disorders and HRQoL in COPD. Instead anxiety has tended to be treated as a general concept or set of symptoms and the potential impact of specific disorders on HRQoL, such as panic disorder, have been somewhat overlooked. Some studies have shown that panic disorder is a highly prevalent comorbidty in COPD, the symptoms of which COPD patients find particularly distressing.[96;97] The nature, impact and importance of panic disorder in COPD and in particular its potential impact on HRQoL will now be discussed in detail.

1.5 Panic Disorder and COPD

1.5.1 Symptoms and diagnosis of panic disorder

Panic disorder is one of a group of anxiety disorders which also includes: generalised anxiety disorder (GAD), obsessive compulsive disorder (OCD), post-traumatic stress disorder (PTSD), social phobia, specific phobias and acute stress disorders. In the UK panic disorder has a prevalence of 1.7% in the general population and it is estimated that 2.7% of the population experience sub-threshold symptoms of panic.[98] This suggests that some patients experience panic attacks but that these are not frequent enough to meet the criteria for a diagnosis of panic disorder.

Panic disorder is characterised by the recurrence of panic attacks. Panic attacks are intense feeling of apprehension or impending doom which have a very sudden onset and are associated with a wide range of symptoms of which people may experience some or all. Common symptoms

of panic attacks can include: breathlessness, palpitations, chest pain, choking, dizziness, tingling in the hands and feet, hot and cold flushes, sweating, faintness, trembling and feelings of unreality.

According to the most recent version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), to be diagnosed with panic disorder, a person must experience recurrent and unexpected panic attacks. The panic attacks must be accompanied by at least one month or more of persistent worry about having future panic attacks or worry about the perceived consequences of the attack, for example losing control, having a heart attack or going mad.[66] The panic attacks must not be due to the direct effects of a substance such as alcohol, drugs or caffeine and must not be better accounted for by any other medical disorder. Panic disorder can be diagnosed with or without agoraphobia. Agoraphobia is the active avoidance of being in places or situations from which escape might be difficult or embarrassing, or in which help might not be available if panic symptoms are experienced .[66]

1.5.2 Prevalence and diagnosis of panic disorder in COPD

The prevalence of panic disorder in respiratory patients is known to be high. Previous studies have shown that there is a close reciprocal relationship between respiratory disease and panic disorder. The lifetime prevalence of respiratory disease in people with panic disorder was found to be 47%, which was significantly higher than those with other anxiety disorder, such as obsessive compulsive disorder.[99] In 2013 a systematic review found seven studies that had measured the prevalence of panic disorders in COPD.[79] The prevalence of panic was found to range from 0-41% for COPD patients who were in hospital and from 8-21% for COPD patients being treated in the community.[79] In 2014 Ohayon et al. reported the results of a telephone interview study of over 8500 people across UK, Germany, and Spain.[100] The results showed a 2.5% prevalence of COPD in their sample. The total prevalence of any anxiety disorder in the COPD patient sample was 39.5%. Ohayon et al. found that the prevalence of panic disorder for the COPD patients was 7.6%, compared to 1.1% in the non-COPD participants; after adjusting for age, gender and body mass index, COPD patients were seven times more likely to be diagnosed with panic disorder than non COPD patients.[100;101]

As with depression there is evidence that panic is not widely diagnosed in people with LTCs. A diagnosis of panic disorder requires all causes of symptoms by physical health conditions to be ruled out.[66;101] Therefore, panic disorder can be difficult to diagnose in patients with COPD as there is a similarity between some of the symptoms of panic disorder and the symptoms of a COPD exacerbation. This crossover in symptoms between the two conditions can make it difficult to determine whether symptoms, such as breathlessness, are caused by the respiratory features

of COPD or by a panic attack. When breathless, patients with COPD may often experience panic symptoms, such as shortness of breath, palpitations, sweating, faintness, dizziness, numbness and tingling sensations, flushes, trembling and shaking, and light-headedness. As such, COPD patients would not meet the criteria for panic disorder unless they experienced panic attacks that were in the absence of the symptoms of breathlessness caused by COPD.

Despite the crossover between symptoms of panic attacks and those experienced during COPD exacerbations it is possible to diagnose panic disorder in COPD patients. The DSM-5 criteria for the diagnosis of panic attacks state that the attacks must be recurrent, unexpected and accompanied by worry of at least one month duration about future panic attacks.[66] Therefore, one way to determine if panic comorbid with COPD is occurring in the absence of a respiratory cause is to make an assessment of patients' anticipatory anxiety about future panic attacks. This would include any changes in behaviour that they may make in order to avoid panic attacks and to confirm that at least some of the attacks occur spontaneously.[102] A study of COPD patients by Smoller et al. (1990) was conducted to identify, and then exclude, panic attacks that occurred in situations associated with pulmonary symptoms.[103] The authors found a panic disorder prevalence of 8%, where panic attacks were occurring independent of pulmonary symptoms. Another key criterion for a diagnosis of panic disorder in patients with COPD is evidence of significant behaviour change, such as the development of agoraphobic avoidance, in order to avoid future panic attacks.[66] Smoller et al. (1999) found that avoidance of situations in which it is feared that panic attacks might occur is common and happens in approximately one third of COPD patients.[101] Avoidance of situations which cause panic can lead to a decline in activity and to an increasingly sedentary lifestyle which can further impact patients' future health status, leading to a vicious circle of decline in functioning and health status.

1.5.3 Conceptual models of panic disorder in COPD

Several models have been proposed to explain the development and maintenance of panic disorder in the general population. These include: The cognitive model[104], the biological 'false-alarm' model,[105;106] and the psychodynamic model.[107]

Empirical studies of people in the general population have shown that identification of respiratory symptoms may not be the optimal method to differentiate people who are having a panic attack from those who are not.[102;108-110] Vickers et al. (2005) conducted an interview study of over 8000 people aged between 15 and 54 in the USA and found that cognitive symptoms were more easily identified in people who had panic disorder than those who had just one panic attack. Vickers et al. reported that it was specifically a fear of dying which had the strongest association with panic

disorder. Therefore, it is the difference in cognitive symptoms which differentiates people who have experienced a panic attack from those who go on to develop panic disorder. This thesis will focus on the cognitive model of panic which has received support for use in patients with COPD and will now be discussed in detail.[104]

Clark's cognitive model of panic has been given particular credence in previous research of panic disorder in COPD.[102] Biological models of panic such as the 'false-alarm' model have been somewhat discredited because of the importance they place on the respiratory symptoms of panic, such as breathlessness and feelings of suffocation.[102;105] The focus on respiratory symptoms make diagnosis of panic disorder difficult in patients with COPD as they already experience significant respiratory distress because of their physical condition. Therefore, if using the DSM-5[66] criteria to diagnose panic it would be difficult to separate the cause of the respiratory symptoms and attribute them to either a COPD exacerbation or panic attack without an assessment of the simultaneously occurring cognitive symptoms.[102]

The cognitive model of panic model (Figure 1.2) is based on Beck's cognitive behavioural formulation of emotional states.[111] Beck proposes that a person has core beliefs which they develop in the early years of their life. Core beliefs can be maladaptive and can cause people to make misappraisals of the level of threat they are experiencing in situations which they perceive might be dangerous. It is the misappraisal of the level of perceived threat that can then lead to the development of emotional disorders such as depression, anxiety, and panic.[112] Clark's cognitive model builds upon this theory to explain panic disorder. The cognitive model explains how people, who experience apprehensive thoughts and physical sensations as catastrophic in any given situation, will experience panic attacks. The model describes how apprehensive thoughts are triggered when an individual perceives a situation as threatening. When apprehensive thoughts are experienced they trigger bodily sensations of panic, such as breathlessness, palpitations, chest pain, choking, dizziness, tingling in the hands and feet, hot and cold flushes, sweating, faintness, trembling, and feelings of unreality. It is the experience of these symptoms which is unpleasant and can then lead the person to make a catastrophic misinterpretation about how they will cope in the trigger situation. Some common examples of catastrophic misinterpretations are: 'I will have a heart attack,' 'I will pass out,' 'I will die.' The cognitive model is configured as a cycle which indicates that the catastrophic misinterpretation of the situation will then increase the person's perception of the situation as dangerous or a threat, and in turn the apprehensive thoughts and bodily sensations will intensify. This cycle then becomes self-perpetuating: the perception that the situation is dangerous is reinforced by the experience of physical symptoms of panic and it seems that their catastrophic misinterpretation will be realised because their symptoms are worsening all the time.

Support for the use of the cognitive model of panic in COPD comes from studies which have shown that COPD patients who experience panic attacks have significantly more catastrophic cognitions about physical symptoms than those without panic attacks (Figure 1.3).[113-115] Patients with COPD will regularly experience many of the symptoms of a panic attack because of their physical illness. It is hypothesised that COPD patients are faced with more opportunities in which to pair these physical symptoms with the apprehensive thoughts that can lead to panic attacks. Bailey et al. (2005) conducted a series of interviews with COPD patients to identify whether anxiety precipitates breathlessness and concluded that there was a circular nature to breathlessness which took the form of a dyspnoea-anxiety-dyspnoea cycle.[116] In an interview study of 53 COPD patients Howard et al. (2008) found that 63% (n=37) participants had experienced a panic attack in the previous year. Of the group who had experienced a panic attack 68% described cognitive as well as physical symptoms when describing their panic attack. The most common cognitive symptom was fear of dying, followed by fear of choking, fear of losing control, and feelings of unreality. Howard et al. also studied the illness representations of these patients and found that patients who met the criteria for panic disorder perceived more severe consequences and had more negative emotional representations of their COPD, irrespective of disease severity.[117]

A possible limitation of the cognitive model of panic for COPD patients is the use of the terminology around the catastrophic misinterpretation of bodily sensations. Porzelius et al. (1992) suggests that the use of the term 'catastrophic misinterpretation' could confuse and impede treatment strategies because breathlessness, which is triggered by the apprehensive thoughts proposed in the model, is based in the reality of a physical condition for COPD patients.[113] Therefore, Porzelius recommends that when treating panic disorder in COPD patients the focus should be on identifying and working with the elements of the cognitive model that focus on apprehensive thoughts. He recommends that some treatment techniques such as exposure and hyperventilation should be avoided.[113]

Figure 1.2: Clark's 1986 Cognitive Model of Panic [104]

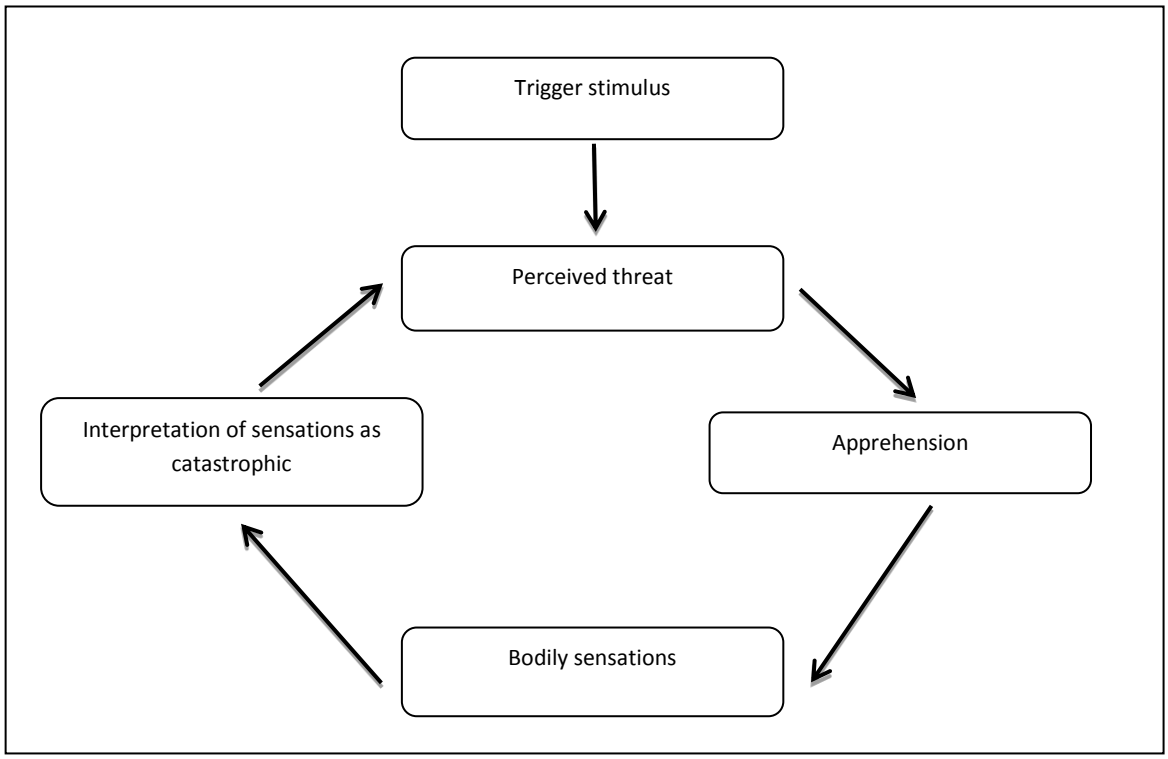
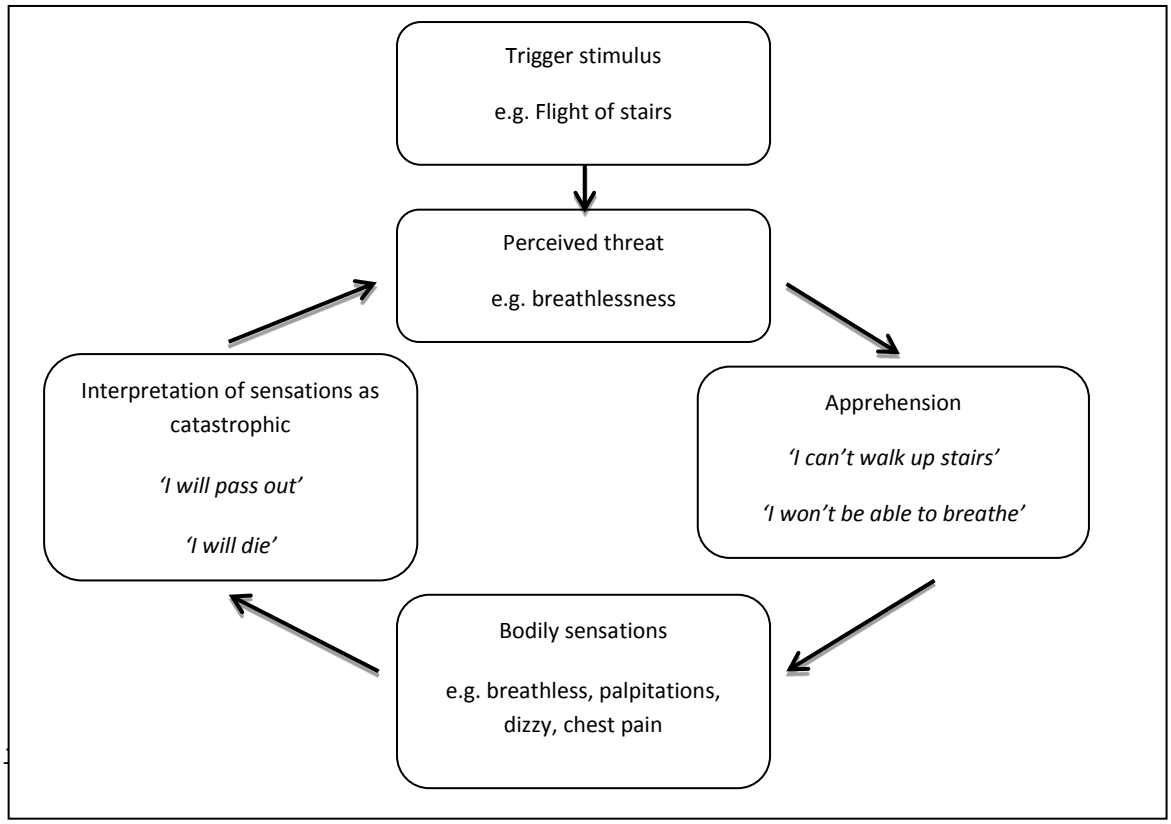


Figure 1.3: A COPD example of Clark's 1986 Model of Panic



1.5.4 The impact of panic disorder in COPD

Patients with panic disorder in the general population experience high unemployment rates, miss more days of work, claim more social welfare benefits, use more healthcare services, and have worse quality of life and more impaired physical functioning than those without panic disorder.[118] The prevalence of depression is also higher among people who have panic disorder than those who do not. In a UK sample of the general population Skapinakis et al. (2011) found that the prevalence of depression was 50% in participants with panic disorder and agoraphobia, 23% in those without agoraphobia, and 10.6% for those with sub-threshold symptoms of panic. When socio demographic and psychological variables, (including depression), were controlled for, patients with panic disorder and agoraphobia had significantly worse functional impairment than those without panic disorder.[98]

Anxiety disorders and panic attacks are associated with worse health outcomes in COPD. Patients with anxiety disorders (that included panic) have been shown to use significantly more healthcare services and have more hospital admissions of a longer duration than patients without anxiety disorders.[119] The negative impact of panic disorder among COPD patients has been found to persist even when there is no difference between participants in terms of their breathlessness. Moore et al. (1998) conducted a study to compare the functional status of 28 respiratory patients (17 with COPD; 11 with asthma) with panic disorder, with those without respiratory conditions. They used a measure of functional status that assessed changes in activities and levels of dyspnoea and fatigue whilst performing ten common activities such as walking, washing hair, and getting dressed. They found that despite there being no difference in symptoms of breathlessness between the two groups, patients with panic disorder reported significantly poorer functional status. Increased severity of depression and anxiety also correlated highly with poorer functional status across both the panic and no panic groups.[120]

Willgoss et al. (2012) interviewed 14 clinically stable COPD patients in Manchester, UK about their experiences of anxiety.[96] Participants reported that they attributed the cause of their anxiety to concerns about the progressive nature of COPD and the disability they feared they would experience in the future. Willgoss et al. describe how participants were particularly able to recall any episodes of panic in detail and that there was a clear distinction between panic attacks that were predicted by episodes of breathlessness, and those attacks that occurred as if 'out of the blue.' Participants described feeling out of control and helpless during panic attacks and as a result they explained that they developed a fear of breathlessness and future attacks. It was this fear of future panic attacks that Willgoss et al. identified as having a disabling impact on participants' everyday lives, social functioning and healthcare use. He hypothesised that it is the

anticipation of future attacks of breathlessness, whether predicted by panic or by COPD, that leads patients to avoid everyday activities and to become isolated from family and friends and, in some cases, resulted in unnecessary hospital admissions.[96]

Panic attacks in COPD may increase patients' perceptions of the severity of their symptoms. Patients with asthma with higher scores on the panic-fear scale have been shown to have a higher threshold for detecting resistive loads (i.e. a test which increases the effort and work of breathing).[121;122] Meek et al. (2000) found that COPD patients' ratings of dyspnoea were higher when they were asked to recall their clearest memory of dyspnoea and focus their attention on it. Meek hypothesised that this was due to the negative emotions that were evoked by recalling episodes of dyspnoea.[123]

Livermore et al. (2008) set out to test the response to resistive load testing in 52 patients with moderate to severe COPD, with and without panic attacks. The results were compared with those from age matched controls who had no medical illness. Livermore found that 38% of the COPD patients had experienced panic attacks and 17% met the criteria for panic disorder.[124] The hypothesis for this study was that COPD patients with panic attacks or panic disorder would have a heightened perception to resistive loads. Livermore et al., found that participants with panic attacks experienced a similar increase in perceived dyspnoea to other participants, but that participants with panic reported a significantly greater level of perceived difficulty in breathing compared with those patients without panic and healthy controls. There were no differences in COPD severity as measured by FEV_1 between participants with and without panic. Therefore, it can be assumed that rather than respiratory functioning, increased anxiety and panic results in heightened rather than blunted sensitivity to inspiratory loads. Giardino et al. (2010) also used resistive load testing with COPD patients with and without panic and compared the findings with matched controls. They found that COPD patients with panic reported greater dyspnoea in response to inspiratory resistive loading compared with matched controls. However, when anxiety sensitivity was controlled for in the analysis there were no longer any significant differences between the groups in the reporting of dyspnoea. Giardino et al., concluded that anxiety sensitivity was a partial mediator of dyspnoea reporting, therefore panic was significantly associated with higher anxiety sensitivity, which was in turn associated with dyspnoea ratings.[125]

Panic attacks may have a negative impact on the outcome of some COPD treatment programmes. There is evidence that patients with COPD and comorbid panic disorder may experience negative consequences from treatment programmes which are designed to improve self-management in COPD. Dowson et al. (2010) studied 76 COPD patients admitted to hospital with a severe exacerbation of COPD in New Zealand to test a COPD education and self-management plan over

24 weeks. They compared results for COPD patients with and without panic disorder who had no significant differences in terms of COPD severity. Dowson et al. (2010) found that the education and self-management plan improved the perceived control the panic disorder group had over the self-management tasks related to COPD. However, among those with panic disorder, the education and self-management plan significantly increased body vigilance and distress associated with having COPD.[126] These findings are consistent with evidence that COPD patients who experience panic attacks have more catastrophic cognitions and are more aware and concerned with their bodily sensations, regardless of symptoms of breathlessness or lung function.[113]

1.5.5 Panic disorder and HRQoL in COPD

In this chapter I have so far outlined that panic disorder is highly prevalent in COPD patients and highlighted work that has shown that panic negatively impacts on patients' perception of their symptoms, affects physical functioning and use of health care and potentially reduces the effectiveness of treatment programmes to manage COPD symptoms. However, despite the significant impact of panic on COPD outcomes there has been little research which has looked at the impact of panic on HRQoL in COPD.

HRQoL is an increasingly important outcome in COPD. We know that lung function alone cannot account for the variation in the severity of COPD symptoms and the burden that patients experience from their symptoms.[51;54;56;58] Poor HRQoL has been found to have a negative impact on patients' symptoms, physical functioning, and frequency of exacerbations, hospital admissions and mortality. Therefore, HRQoL is a central component for the comprehensive assessment of COPD severity and is being increasingly used to inform treatment decisions as recommended by the GOLD guidelines.[1]

Much of the research in to the psychological factors associated with HRQoL in COPD has focussed on depression with fewer studies of the impact of general anxiety. Depression and anxiety have been shown to be closely associated with poor HRQoL in COPD in cross-sectional studies. However, the impact of specific anxiety disorders, such as panic disorder, on HRQoL in COPD is less well understood. Despite being seven times more prevalent among people with COPD compared with the general population panic is not widely diagnosed in COPD patients. It is possible that this is because of difficulties in differential diagnosis as there is some crossover between the symptoms of the two conditions which can make the cause difficult to isolate.[102] However, cognitive models of panic, such as Clark's model,[104] provide a conceptual method to

differentiate symptoms of panic attacks from those of COPD exacerbations. They also show how cognitive symptoms of panic can exacerbate the severity of COPD symptoms in a vicious cycle.

In the general population panic disorder has been found to result in a general HRQoL which is significantly worse than that of patients with physical illnesses and comparable to those patients with depression.[127] Furthermore, in a systematic review Davidoff et al. (2012) found that panic disorder resulted in a substantial impairment of the quality of life of patients with panic disorder which persisted even after remission of panic symptoms was achieved through treatment.[118]

People who experience panic disorder can avoid situations that may trigger panic which, in its worst cases, this avoidance can develop into agoraphobia which results in patients leading very sedentary lifestyles. Many COPD patients already find physical activity challenging and become increasing sedentary and socially isolated as a result of their physical symptoms. This has an impact on the development of depression and reduction in HRQoL in COPD. With the added complexity of comorbid panic disorder, which is known to increase perception of the severity of COPD symptoms, COPD patients are likely to become even more sedentary and isolated. There is therefore a compelling case to better understand panic disorder when comorbid with COPD and to identify the impact of panic disorder on HRQoL in COPD. A better understanding of which psychological factors drive HRQoL in COPD can inform how best to manage HRQoL in COPD, with a view to tailoring interventions to target the most important drivers of HRQoL and benefit patient outcomes.

1.6 Thesis Aims

The aim of this thesis is to identify the psychosocial factors which predict HRQoL in COPD with a particular focus on understanding the relationship between panic and HRQoL in COPD. The key research questions are:

I. What are the psychosocial predictors of HRQoL in COPD?
II. Does panic predict HRQoL in COPD?
III. Is panic a better predictor of HRQoL in COPD than depression?

The next chapter describes a systematic review with meta-analysis which was conducted to address the first research question. The review was designed to identify and examine the existing evidence for psychological predictors of HRQoL in COPD. Subsequent chapters will then describe the design, analysis and results of a longitudinal cohort study designed to investigate research questions two and three.

2. Systematic Review with Meta-analysis

2.1 Chapter Overview

This chapter presents the results of a systematic review and meta-analysis which aimed to identify psychosocial factors which predict HRQoL in COPD. I originally conducted this review in 2012 and an earlier version of this review has been published in the International Journal of Chronic Obstructive pulmonary Disease.[128] A copy of the published version of this review can be found in Review Appendix A. Following publication, the review was updated in April 2014 and it is the updated results which are presented in this chapter.

A brief background of the review will now be presented followed by a detailed description of the methods used. The results of the updated review are then presented followed by a discussion of their implications for future research and practice.

2.2 Background

HRQoL is an important outcome in COPD as it has a significant impact on physical functioning, hospital admissions and mortality.[48-51;57;61;129;130] Depression and anxiety are highly prevalent comorbidities in COPD patient population and may explain variation in respiratory specific HRQoL over and above measures of lung function. Several cross-sectional studies have shown that depression and anxiety are closely associated with HRQoL in COPD.[131-136]

2.2.1 Overview of cross-sectional studies

A meta-analysis by Tsiligianni et al. (2011) found that depression and anxiety were highly correlated with respiratory specific HRQoL. The correlation was second only to the relationship between dyspnoea and HRQoL.[62] Since this review was published in 2011 several studies have investigated the relationship between depression and HRQoL using cross-sectional designs in different patient groups. Lou et al. (2012) conducted a cross-sectional case control study which found that COPD patients were significantly more likely to be depressed than those without COPD and those who were depressed were also more likely to be anxious.[137] Furthermore, they found that those COPD patients who were depressed or anxious were significantly more likely to have poorer respiratory HRQoL in each of the HRQoL domains measured.[137] Iguchi et al. (2013) found that depression was highly correlated with poor respiratory HRQoL in a sample of COPD patients admitted to a pulmonary rehabilitation facility in Japan.[138] Naberan et al. (2012) conducted a study of primary care COPD patients in Spain with the aim of identifying gender differences in

quality of life as measured by a general and respiratory specific HRQoL measure.[139] Despite being younger, more likely to be non-smokers and having better lung function, females were found to have significantly more exacerbations, emergency room visits, symptoms of anxiety and depression and poorer HRQoL than males. Naberan et al. (2012) also found that, for both males and females, depression and anxiety had the highest correlations with both general and respiratory specific HRQoL measures.[139] When data were analysed using multivariate logistic regression probable cases of anxiety (defined as a score of 11 or more on the HADS anxiety scale[139]) remained a significant predictor of respiratory HRQoL.

Some cross sectional studies have examined the association between depression and more generic measures of HRQoL, such as the Medical Outcomes Study Short Form (SF-36).[140] However, even when HRQoL is measured using these more generic measures, depression and anxiety still account for a significant proportion of the variance in people with COPD.[85;86]

Findings to date are thus mainly derived from cross sectional studies and although results suggest that there is a significant association between depression, anxiety, and HRQoL in COPD, they are not able to determine causal associations between these factors. It is therefore unclear whether depression and anxiety predict HRQoL prospectively. It is important to consider the temporal and causal association between depression and/or anxiety and HRQoL in order to inform the development of future interventions aimed at improving HRQoL.

This chapter aims to systematically review all exisiting longitudinal prospective studies that have measured depression, anxiety and HRQoL in COPD to assess the ability of depression and anxiety disorder to predict future HRQoL.

2.2.2 Aims of this review

The aim of this review was to systematically review all longitudinal prospective cohort studies which have investigated the relationship between depression and anxiety disorders and HRQoL in COPD. Where possible the results from individual studies were pooled using meta-analysis techniques to assess the power of depression and anxiety disorders to predict future HRQoL in COPD.

2.3 Review Methods

The methods and results for this review are reported in line with the PRISMA guidelines.[141]

2.3.1 Information sources and search strategy

Studies were identified for inclusion in this review by searching the following electronic databases from inception to 17 April 2014: Medline, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), British Nursing Index and Archive, PsycINFO and Cochrane database. The search strategy was designed using MeSH terms and key words relating to COPD, depression, anxiety, panic, HRQoL and longitudinal cohort studies for each database. Please see Review Appendix B for the full search strategy. Searches of electronic databases were supplemented by hand searches of the reference lists of included papers and relevant reviews.

2.3.2 Eligibility criteria

Studies were eligible for inclusion in this review if they:

1. Used a non-experimental prospective cohort design.
2. Did not include any standardised experimental intervention. This was to ensure that samples included in the review had not been exposed to any intervention which may have modified the association between depression, anxiety and HRQoL over the duration of the study.
3. Included patients with a diagnosis of COPD confirmed by spirometry as FEV_1/FVC ratio <0.70 or FEV_1 <80% of the predicted values according to GOLD (Global Initiative for Chronic Obstructive Lung Disease) criteria.[1] Studies that included a cohort of patients with a range of chronic physical health problems which included COPD were eligible only where data for COPD confirmed by spirometry were reported separately.
4. Used validated self-report measures of either general or respiratory specific HRQoL.
5. Used validated diagnostic clinical interviews or self-report measures of depression and anxiety. Clinical and sub threshold symptoms of depression and anxiety were included. Studies where depression and anxiety were measured using a subscale of a quality of life measure (HRQoL) were excluded.

Studies were not excluded by date of publication, sample size or follow up period. However, those studies that were unpublished, published in abstract form only or were not published in the English language were not included in this review.

2.3.3 Study selection

Titles and abstracts were screened and full papers of potentially relevant abstracts were retrieved. Full text versions of abstracts were independently screened and final decisions about eligibility were made at a consensus meeting which was attended by the author and the supervisors of this PhD thesis.

Further information was requested from authors of 10 papers of whom 7 responded to provide additional information on their papers and 4 were then eligible for inclusion in this review.

2.3.4 Data extraction

An electronic form was developed in Microsoft Excel for the purpose of data extraction. Data were extracted independently by two researchers (AB [author], CA [CHOICE Programme Researcher]) who each looked at all studies. Data were extracted on study design, method and place of recruitment, sample age, sex, and smoking history, method of COPD diagnosis and severity classification (FEV_1). Scores for HRQoL depression and anxiety were extracted at both baseline and follow up. Any disagreements between researchers were resolved through discussion.

The main aim of this review was to assess the strength of the longitudinal association between anxiety disorders, depression, and HRQoL in COPD. Where this data was not available in the published papers authors were contacted by email or letter to request the appropriate data. Where the length of follow up varied, data was extracted and included in the meta-analysis for the time point closest to 12 months after the baseline measures were administered.

2.3.5 Quality assessment

Quality assessment included an evaluation of the design, conduct and analysis of each study and was used to determine the level of bias which will influence the strength of any inferences drawn from this review. Studies were rated for their quality using criteria adapted from guidance on the assessment of observational studies[142] and the Quality Assessment Tool for Quantitative Studies.[143] Any disagreements were resolved through discussion within the supervisory team.

The aim of the quality assessment was to assess both internal and external validity of all included studies. In this review, internal validity relates to how confident we can be that the effect of patient's psychological status on their HRQoL is a true effect. External validity refers to whether the specific results from the sample selected can be generalised to the wider COPD population.

There are five main types of bias that were considered when making assessment of the quality of the included studies:

I. Selection bias - whether or not the study sample was representative of the population it was recruited from. In order to assess selection bias in this review data was extracted on the number of patients selected for potential participation in each study and then the number actually recruited in to the study. The method of sampling was also considered.

II. Response bias – whether or not there are any systematic differences between those who are recruited and take part in the study and those who do not. To assess response bias in this review we looked for evidence of any significant differences on key variables between those who were recruited in to the study and those who were not.

III. Measurement bias – assessment of the validity and reliability of the measures used in the COPD patient population. In order to assess measurement bias the papers were scrutinised for evidence that the measures chosen for each variable of interest were valid and reliable and that information was recorded on how each measure was administered.

IV. Attrition bias - occurs when participants drop out of a study and there are systematic differences between those who drop out and those who complete follow up. To assess attrition bias we looked for evidence that the response rate at study follow up was ≥70% and that there were no statistically significant differences on key variables between those who completed the study and those who did not.

V. Confounding – occurs when an outcome of a study is distorted due to the impact of other variables, or confounders, which have not been controlled for in the analysis. Confounding bias can be controlled for in a study by only selecting patients with one level of confounder or by adjusting for confounders in the statistical analysis. Therefore, we looked for evidence that confounding variables had been identified and controlled for in each study eligible for inclusion in this review.

The full quality assessment conducted for this review included assessment of each of the above mentioned points: selection bias, response bias, the reliability and validity of data collection methods, withdrawals and dropouts and whether confounding variables were adequately controlled for. However, three key criteria were identified for which each study was given a score (0-3) in order to rank the quality of each study. The three key criteria chosen were selection bias, confounding bias and attrition bias.[143] Each study was awarded one point for each of the three criterions that it met.

The three key criteria were: [143]

I. Selection bias - a response rate of 70% or greater at baseline at baseline was required to be awarded 1 point

II. Confounding bias – studies were awarded 1 point if they had controlled for confounding variables in their analyses

III. Attrition bias - a response rate of ≥ 70% was required at study follow up to be awarded 1 point

The scores from the three key criteria were then used as a framework for the narrative synthesis of the results.

2.3.6 Data analysis and synthesis

Data analysis was conducted in Stata (version 12.1, StataCorp LP, Texas, USA) and Comprehensive Meta-analysis (version 2.2.064). Where possible, indices of association between depression or anxiety and total scores for HRQoL measures were included in the meta-analysis. However, where total scores were not available the most appropriate subscale score was used. For the St. George's Respiratory Questionnaire (SGRQ)[144] the impact subscale was used as it provides a measure of social functioning and psychological disturbance associated with respiratory disease.[144]

The aim of this review was to extract regression coefficients where possible. However, since regression coefficients were not available in any of the studies, correlation coefficients were extracted and transformed for meta-analysis using Fisher's Z transformation in order to normalise the distribution of r, making the variance independent of the unknown true value of the correlation.[145] Z scores were then pooled across the studies using a random-effects model to account for variation between studies. The pooled effect size was then converted back to a correlation coefficient.[146] A pooled correlation coefficient of r = 0.10 was considered small, r = 0.25 as moderate and r = 0.40 as large.[147] Where papers did not report either a correlation

coefficient or the data required to compute a correlation coefficient I contacted the corresponding author and requested the missing data. Four authors responded and supplied the relevant data.[148-151] Statistical heterogeneity was investigated using I^2 which measures the percentage of the variation across studies that is due to heterogeneity that cannot be explained by chance.[152] Low heterogeneity is indicated by an I^2 result of ≤25%, moderate around 50% and high heterogeneity is ≥75%.[152]

2.4 Review Results

Electronic and hand searches identified 449 citations excluding duplicates. Of these, 290 citations were excluded on the basis that their abstracts did not meet the eligibility criteria for this review. The full texts of 159 citations were then reviewed. Eight studies were identified that met the criteria for inclusion in the systematic review.[39;148-151;153-156] [39;148-151;153-155] All eight studies looked at the impact of depression on prospective HRQoL and five looked at the impact of anxiety on prospective HRQoL.[39;148-151] Five studies were eligible for inclusion in meta-analysis for depression [148-151;154] and four were eligible for meta-analysis for anxiety.[148-151] The flow of the studies and the reasons for exclusion are presented in the PRISMA flow chart in Figure 2.1.[141]

2.4.1 Characteristics of studies and populations

The characteristics of each study are summarised in Table 2.1. In total there were data for 1837 COPD patients, of which 65.3% (n=1199) were male. Seven of the studies included both male and female COPD patients and one was limited to male patients.[148] The mean age across the studies ranged from 64.6 years [39] to 73.5 years.[153] Length of follow-up ranged from 3 months [149] to 5 years.[148]

The majority of participants (61.8, n=883) were recruited from hospital outpatient settings. [39;148;150;151;155] The remaining 38.3% (n=547) of participants were patients recruited in hospital following an admission for acute exacerbations of COPD who were then followed up prior to their discharge from hospital.[149;153;154] Oga et al. (2007)[148] excluded patients who had experienced an acute exacerbation in the last six weeks, and Engstrom et al. (2001)[39] reported that none of the patients in their sample had been admitted for an acute exacerbation at the time they participated in the study. All included studies recruited patients with a mean predicted FEV_1 <50%, which indicates severe COPD.[1]

Six out of the eight studies[148-151;153;154] measured HRQoL using COPD specific measures including the SGRQ and the Chronic Respiratory Questionnaire (CRQ).[157] One study [155] used the Sickness Impact Profile (SIP),[158] and another used both the SIP and the SGRQ.[39]

Depression was measured using the depression subscale of the Hospital Anxiety and Depression Scale (HADS)[159] in six out of the eight studies.[39;148-151;153] Andenaes et al. (2006)[154] used the Hopkins Symptom Checklist (HSCL),[160] and Graydon et al. (1995)[155] used the Profile of Mood States (POMS).[161]

Anxiety symptoms were measured using the anxiety subscale of the Hospital Anxiety and Depression Scale (HADS) [159] in each of the five studies which included anxiety.[39;148-151] None of the studies specifically measured panic disorder or any other specific anxiety disorders.

Figure 2.1: PRISMA Search flow chart

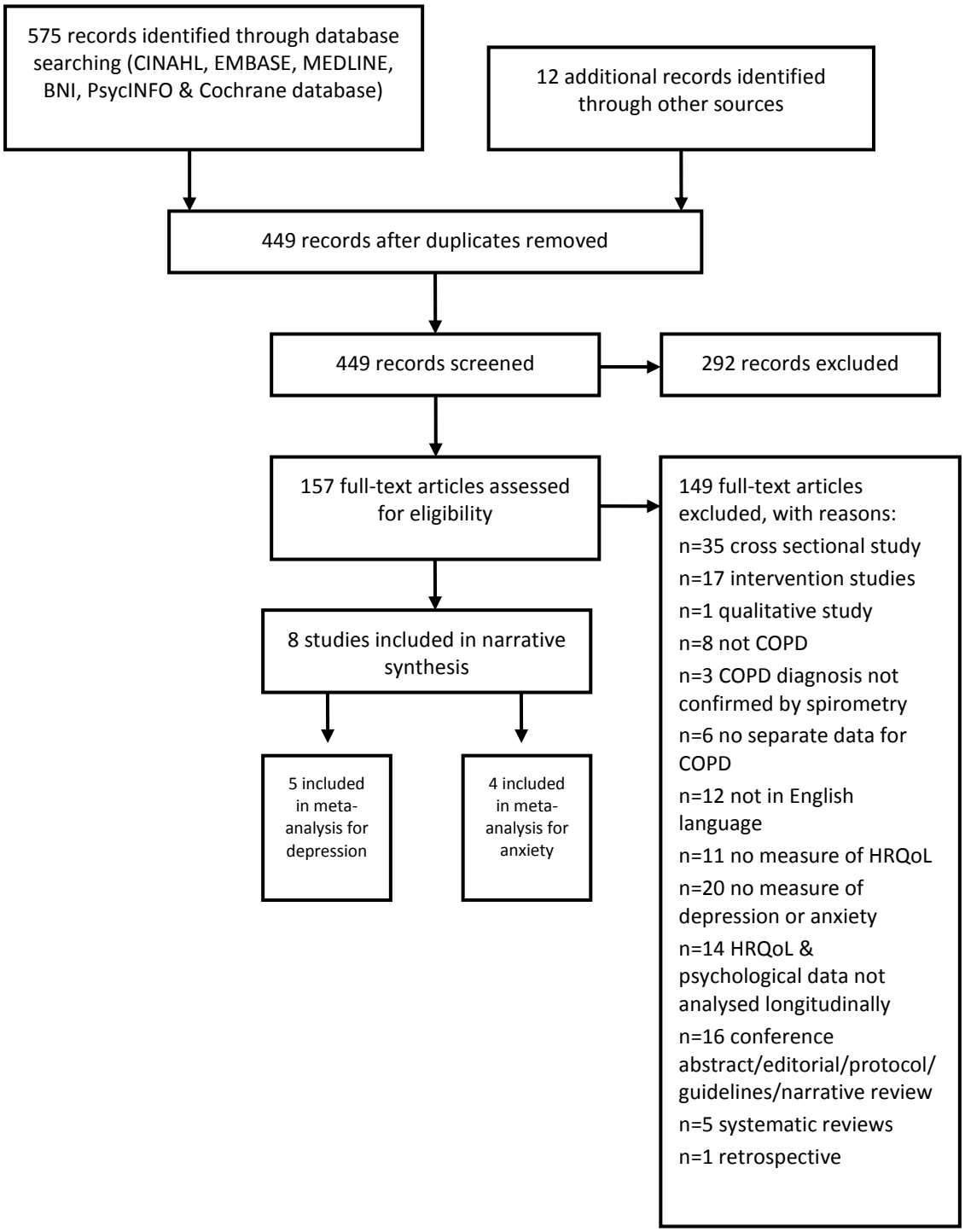


Table 2.1: Characteristics of included studies

1st Author Year Reference	Country	Recruitment & Sample	Mean Age	% Male	Mean FEV_1% predicted & GOLD Severity Stage	HRQoL measures & mean scores	Psychological measures & mean scores	Length of Follow-up
Ng 2007 [153]	Singapore	376 consecutive patients hospitalised for acute exacerbations April 2002 & October 2004. FEV_1 <70% predicted, with or without chronic cough & sputum. Current or ex-smoker with history of ≥20 pack years.	Not depressed (n =209) 71.1 (sd 8.2) Depressed (n=167) = 73.5 (sd 8.5)	Total 85.1 (n=320) Not depressed 85.6 (n=179) Depressed 84.4 (n=141)	Not depressed (n=209) 48.2 (sd 20.2) Depressed (n=167) 47.3 (sd 21.8) Stage III - Severe COPD	SGRQ Not depressed 42.4 (se 3.4) Depressed 52.4 (se 3.1)	HADS 44.4% (n=167) depressed at baseline (score of ≥8 on HAD-D)	6 months & 1 year - mean 313 days (sd 13)
Oga 2007 [148]	Japan	137 consecutive male outpatients between September 1995 and April 1997. Moderate to very severe COPD (Maximal FEV_1/FVC ratio of <0.7 & post bronchodialator FEV_1 <80% of predicted normal). Smoking history of >20 pack years.	69.0 (sd 0.6)	100% (n=137)	45.9 (se 1.3) Stage III - Severe COPD	SGRQ - Japanese version 36.2 (se 1.4) CRQ - Japanese version 5.4 (se 0.08)	HADS - Japanese version HAD-D 3.9 (se 0.3) HAD-A 4.7 (se 0.3)	5 years

1st Author Year Reference	Country	Recruitment & Sample	Mean Age	% Male	Mean FEV_1% predicted & GOLD Severity Stage	HRQoL measures & mean scores	Psychological measures & mean scores	Length of Follow-up
Andenaes 2006 [154]	Norway	92 hospital patients diagnosed with COPD between September 1997 and February 2000	67.6 (sd 9.5)	41.2 (n=21)	39.8 (sd 16.5) Stage III – Severe COPD	SGRQ 65.9 (sd 10.9) WHOQOL - BREF physical 10.6 (sd 2.1) psychological 13.1 (sd 2.5) social 14.8 (sd 1.9) environmental 13.5 (sd 1.9)	HSCL-25 2.1 (sd 0.5)	1 month post discharge, 6 & 9 months
Engstrom 2001 [39]	Sweden	68 hospital outpatients, every 10th outpatient at Department of Pulmonary Medicine FEV_1 <80% predicted 40-75 years stratified into 3 groups: FEV_1 <30% (22.3%, n=21), 30-50% (36.4%, n=25), 50-80% (60.9, n=22)	Overall 64.6 (sd 6.8) <30% 64.1 (sd 6.8) 30-50% 64.8 (sd 7.3) 50-80% 64.1 (sd 6.4)	Overall 63.2 (n= 43) <30% 57.1 (n=12) 30-50% 64.0 (n = 16) 50-80% 68.2 (n = 15)	39.9 (sd 17.0) Stage III – Severe COPD	SGRQ 46.0 (sd 18.3) <30% 54.3 (sd 14.6) 30-50% 47.5 (sd 17.1) 50-80% 36.4 (sd 19.1) SIP - Swedish version 8.5 (sd 8.1) <30% 10.6 (sd 7.0) 30-50% 9.9 (sd 9.3) 50-80% 4.9 (sd 6.8	HADS - Swedish version HAD-D 5.2 (SD 4.5) HAD-A 4.4 (SD 3.8) MACL 3.0 (SD 0.6) <30% 2.9 (SD 0.5) 30-50% 3.1 (SD 0.5) 50-80% 3.1 (SD 0.8)	12 months

1st Author Year Reference	Country	Recruitment & Sample	Mean Age	% Male	Mean FEV_1% predicted & GOLD Severity Stage	HRQoL measures & mean scores	Psychological measures & mean scores	Length of Follow-up
Graydon 1995 [155]	Canada	143 hospital outpatients FEV_1 <50% predicted (Severe COPD) Data analysed for 71 patients who completed follow up	66.4 (sd not reported)	67.6 (n=48)	31.73% (sd 8.62) Stage III – Severe COPD	SIP 16.4 (sd 10.2)	POMS (negative mood scales) 38.0 (sd 28.6)	30 months
Coventry 2011 [149]	United Kingdom	79 patients admitted for acute exacerbation and referred to nurse led early discharge service FEV_1 <80% predicted	65.3 (sd 9.9)	44 (n=56)	42.2% (sd 18.4) Stage III – Severe COPD	SGRQ Total 58.8 (sd 14.6)	HADS HAD-D 7.0 (sd 3.8) HAD-A 8.8 (sd 4.3) HAD Total 15.8 (sd 7.0)	90 days & 365 days
Wilke 2014 [150]	Netherlands	85 COPD patients at outpatient clinic GOLD stage III or IV Recruited between January 2008 and June 2009	65.8 (sd 9.2)	62.4 (n=53)	34.3 (sd 13.6) Stage III Severe COPD	SGRQ Total 54.9 (sd 16.4)	HADS HAD-D 6.1 (sd 4.0) HAD-A 5.5 (sd 4.2)	4, 8 & 12 months

1st Author Year Reference	Country	Recruitment & Sample	Mean Age	% Male	Mean FEV_1% predicted & GOLD Severity Stage	HRQoL measures & mean scores	Psychological measures & mean scores	Length of Follow-up
Liang 2014 [151]	China	450 patients from 10 General hospitals FEV_1/FVC ratio <0.7 & FEV_1 <80% of predicted value Recruited between August 2004 & June 2006	65.2 (sd 10.6)	68.7 (n=309)	48.3 (sd 15.8) Stage III Severe COPD	SGRQ Total* 45.6 (sd 18.6)	HADS Mean HAD scores not reported	12 months

FEV_1 – Forced expiratory volume in 1 second. sd = standard deviation. SGRQ – St George's Respiratory Questionnaire. HADS – Hopsital Anxiety and Depression Scale. FVC – Forced vital capacity. CRQ – Chronic Respiratory Questionnaire. HAD-A – Hospital Depression and Anxiety Scale anxiety subscale. HAD-D – Hospital Depression and Anxiety Scale depression subscale. WHOQOL-BREF – World Health Organisation Quality of Life Instrument. HSCL-25 – Hopkins Symptoms Checklist. MACL – Mood Adjective Checklist. SIP – Sickness Impact Profile. POMS – Profile of Mood States.

*Data taken from related paper Lin et al. 2009 [162]

The prevalence of anxiety and depression varied at baseline (Table 2.1). The three studies which recruited patients following an admission to hospital reported that patients in their sample were experiencing symptoms of depression at baseline.[149;153;154] Ng et al. (2007)[153] report that 44.4% of their sample had symptoms of depression at baseline, but did not report mean HADS scores. Three of the studies which recruited hospital outpatients report that their sample had symptoms of depression at baseline but that these were not clinically significant.[39;148;155] However, Oga et al. (2007)[148] reported a significant increase in depressive symptoms in their sample over the 5 year study period. Liang et al (2014)[151] report that 20.7% (n=93) of their sample of outpatients had symptoms of depression at baseline and 7.6% had symptoms of anxiety, they do not report the mean HADS scores.

Five studies measured anxiety using the HADS. The three studies that were of hospital outpatients report that their samples were experiencing symptoms of anxiety at baseline but the symptoms were not clinically significant.[39;148;150] However, Coventry et al. (2011)[149] found that their sample of COPD patients admitted to hospital and discharged to a nurse led early discharge service had a mean HADS anxiety score of 8.8 which indicates clinically significant symptoms of mild anxiety.[159] Liang et al. (2013)[151] do not report the mean scores for anxiety or depression at baseline.

2.4.2 Quality of included studies

The results of the quality review are presented in Table 2.2.

The quality of the studies varied greatly. Ng et al. (2007)[153] was the highest quality study, meeting all three of the predefined quality criteria.[143] Four studies met two of the essential quality criteria [149-151;154]and three studies did not meet any of the criteria[39;148;155]

Seven out of the eight studies reported attrition rates at follow-up, three of which found that those who dropped out were significantly more likely to be older than those who completed the study.[151;154;155] Wilke et al. 2014[150] found no significant difference in age between those who completed the study and those who did. However, Wilke et al. (2014) did find that those who did not complete 12 month follow up were more likely to be living alone ($p=0.001$), to have greater impairment in their physical functioning ($p<0.05$) and to be more dependent on care ($p<0.005$). There was also a trend for those who did not complete 12 month follow up to have more symptoms of anxiety but this was not significant ($p=0.08$). Liang et al. (2014)[151;163] also found that those who dropped out had greater physical impairment, worse lung function, more dyspnoea and worse HRQoL than those who completed follow up. Oga et al. (2007)[148] followed their cohort of COPD patients for five years and they found that at five year follow up over 40% of patients had

died. Those who had died were found to be significantly older, more breathless and to have worse HRQoL than those who completed follow up.

Table 2.2: Quality review for included studies

1st Author Year Reference	Selection bias		Response bias		Measurement bias	Confounding bias	Attritions bias		Total quality Score
	Information on recruitment method?	Response rate	Comparison of those who did & did not respond?	Were HRQoL measures valid & reliable?	Were psychological measures valid and reliable?	Were confounding factors controlled for in analysis?	How many patients completed follow up (FU)?	Comparison of those who did & did not complete FU?	
Ng 2007 [153]	No	376/503 (74.8%)	No	Yes	Yes	Yes	275/376 completed 1 year FU (73.1%)	No	3
Oga 2007 [148]	Consecutive male patients outpatients	No	No	Yes	Yes	No	72/137 completed 5 year FU (52.6%)	No	0
Andenaes 2006 [154]	No	97/107 (90.7%)	No	Yes	No – 2 depression questions omitted	Yes	51/92 completed 9 month FU (55.4%)	Yes	2
Engstrom 2001 [39]	Every 10th patient meeting inclusion criteria invited	No	No	Yes	Yes	No	Not reported	No	0
Graydon 1995 [155]	Invited by letter & telephone FU	No	No	Yes	Yes	No	71/143 completed 30 month FU	Yes	0

1st Author Year Reference	Selection bias		Response bias		Measurement bias	Confounding bias	Attritions bias		Total quality Score
	Information on recruitment method?	Response rate	Comparison of those who did & did not respond?	Were HRQoL measures valid & reliable?	Were psychological measures valid and reliable?	Were confounding factors controlled for in analysis?	How many patients completed follow up (FU)?	Comparison of those who did & did not complete FU?	
	call						(49.7%)		
Coventry 2011 [149]	Patients referred to early discharge services & recruited by respiratory nurse specialists	79/123 (64%)	No	Yes	Yes	Yes	62/79 completed 365 day FU (78%)	No	2
Wilke 2014 [150]	Recruited by chest physicians at the outpatient clinic	No	No	Yes	Yes	Yes	85/105 completed 12 month FU (81%)	No	2
Liang 2014 [151]	No	No	No	Yes	Yes	Yes	450/491 completed 12 month FU (91.6%)	Yes	2

2.4.3 Longitudinal association of depression with HRQoL in COPD

Eight longitudinal cohort studies investigated the association between depression and HRQoL in COPD (Table 2.1).

Ng et al (2007)[153] scored the highest score of 3 in the quality review. Ng et al. found that depressed patients had significantly worse HRQoL at baseline across all subscales of the SGRQ, and this was maintained at 12 month follow up. However the authors did not analyse the predictive effect of depression on HRQoL across the 12 month period.

Four studies scored 2 in the quality review.[149-151;154] Andenaes et al. (2006)[154] studied patients who were admitted to hospital with COPD and followed them up at 1, 6 and 9 months post discharge from hospital. Andenaes et al. found that there was a significant correlation between depression at baseline and HRQoL at follow up at 6 and 9 months. Depression was significantly correlated with the respiratory specific SGRQ Impact subscale ($r=0.28$, $n=51$, $p<0.05$, 95%CI not reported) and also the physical domain ($r= -0.64$, $n=51$, $p<0.01$, 95% CI not reported), psychological domain ($r= -0.62$, $n=51$, $p<0.01$, 95% CI not reported), and environmental domain ($r= -0.41$, $n=51$, $p<0.01$, 95% CI not reported) of the WHOQoL-Bref but not with the social domain ($r= -0.23$) (Table 3). Coventry et al. (2011)[149] also scored 2 in the quality review. Coventry et al. report that depression at baseline was significantly correlated with respiratory specific HRQoL at both 3 month ($r = 0.52$, $p<0.001$) and 1 year follow-up ($r = 0.64$, $p<0.001$) in patients discharged from hospital under the care of early discharge services (Table 3). Liang et al. (2013)[151] recruited a large sample (n=450) of patients from general hospital in China and found that depression was significantly associated with prospective HRQoL at 12 months ($r=0.40$, $p<0.001$). However, in multivariable logistic regression analyses Liang et al. report that depression, as measured at baseline, was not a significant predictor of deterioration of HRQoL over 12 months. The variables that continued to have a significant predictive impact on deterioration of HRQoL in the multivariable model were dyspnoea, physical functioning and the number of exacerbations in the preceding 12 months.[151] Wilke et al. (2014) recruited 85 COPD outpatients with advanced COPD who were clinically stable in the Netherlands. They found that over a 12 month period HRQoL remained stable with there was no significant change in SGRQ scores; 41.2% (n=35) reported an improvement in HRQoL and 43.5% (n=37) reported a decline in HRQoL. In univariate analysis patients whose HRQoL improved did report a significant decrease in symptoms of depression over the 12 months period (Mean change = -1.5, SD 3.2, $p<0.05$). For those patients whose HRQoL deteriorated there was no change reported in symptoms of depression. However, in those where HRQoL remained stable there was a non-significant trend of an increase in symptoms of depression (mean change = 1.5, SD 5.6). In multiple regression analyses Wilke et al. (2014) found

that physical functioning, dyspnoea and fatigue, symptoms of depression at baseline explained 48.4% (p<0.001) of the variance in change in HRQoL over 12 months.

There were three studies that did not meet any of the key quality criteria and therefore scored zero[39;148;155] but report similar results to the higher quality studies. Firstly Oga et al. 2007[148] reported that depression measured at baseline was significantly correlated with respiratory specific HRQoL at 1 year follow up (r=0.47, p <0.001); this association remained after 5 years (r=0.47, p<0.001) in the sample of outpatients with severe COPD.[148] Secondly, Engstrom et al. (2001) found that depression as measured by the HAD-D (*b* = 0.39, p<0.001), 6 minute walk distance (*b* = 0.05, p<0.05) and vital capacity (*b* = 0.15, p<0.001) were the best predictors of HRQoL, explaining 59% of the variance in multiple regression analyses when SGRQ scores were exluded.[39] Finally, Graydon et al. (1995) found that negative mood, as measured by the POMS at baseline, was significantly correlated with HRQoL after 12 months (r = 0.49, p<0.0001, 95% CI not reported).[155] However, they do not include depression as a predicator variable in their multiple regression analyses.

2.4.4 Meta-analysis of longitudinal association between depression and HRQoL in COPD

Five studies were eligible for inclusion in the meta-analysis for depression (Table 2.3).[148-151;154]

We aimed to extract regression coefficients for meta-analysis where possible. However, since regression coefficients were not available in the majority of the studies, correlation coefficients were extracted and transformed for meta-analysis.

The random-effects meta-analysis (Figure 2.2) of the five studies found that there was a large positive correlation between depression at baseline and HRQoL measured at follow-up (r=0.44, 95% confidence interval 0.34 to 0.53, p <0.001). A moderate to high degree of heterogeneity was found across the studies (Q=8.10 df=4 p=0.088, I^2 50.64%).[152]

When the random-effects meta-analysis for depression was repeated excluding the study which scored zero on the key quality[148] reviewthe result remained similar (r=0.43, 95% confidence interval 0.29 to 0.55, p<0.001). However, there was a higher degree of heterogeneity (Q=7.6 df=3 p=0.055, I^2 60.54%).

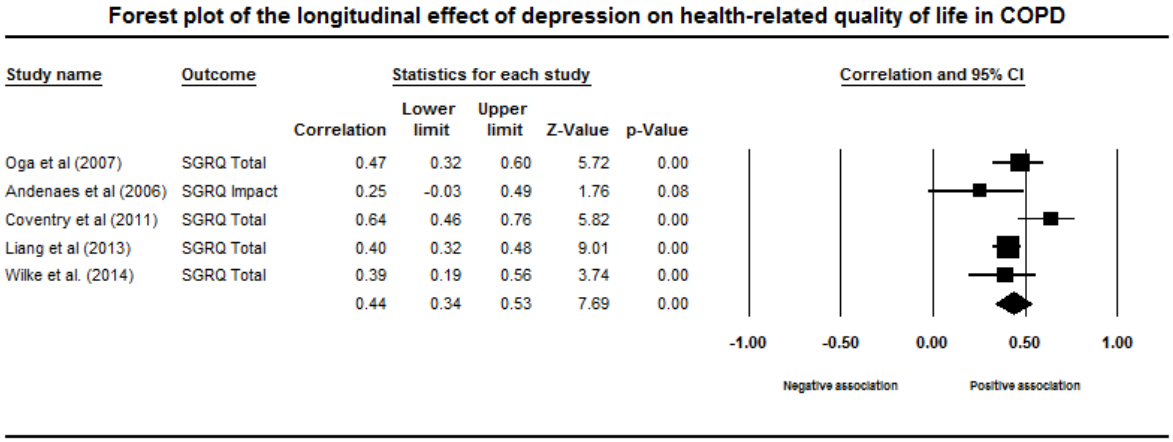
Table 2.3: Longitudinal correlations between depression and HRQoL in COPD

1st Author Year Reference	Depression Measure	HRQoL Measure	Length of follow up	Sample size	Correlation (r)	p
Andenaes 2006 [154]	HSCL-25	SGRQ Symptoms	9 months	51	-0.079	NS
	HSCL-25	SGRQ Impact	9 months	51	0.279	<0.05
	HSCL-25	SGRQ Activities	9 months	51	-0.138	NS
	HSCL-25	WHOQOL Physical	9 months	51	-0.638	<0.001
	HSCL-25	WHOQOL Psychiatric	9 months	51	-0.622	<0.001
	HSCL-25	WHOQOL Social	9 months	51	-0.225	NS
	HSCL-25	WHOQOL Environment	9 months		-0.405	<0.01
Oga 2007 [148]	HAD-D	SGRQ Total	1 year	128	0.471	<0.001
	HAD-D	CRQ Total	1 year	128	-0.581	<0.001
	HAD-D	SGRQ Total	5 years	72	0.473	<0.001
	HAD-D	CRQ Total	5 years	72	-0.549	<0.001
Coventry 2011 [149]	HAD-D	SGRQ Total	3 months	79	0.517	<0.001
	HAD-D	SGRQ Total	1 year	62	0.636	<0.001

1st Author Year Reference	Depression Measure	HRQoL Measure	Length of follow up	Sample size	Correlation (r)	p
Wilke 2014 [150]	HAD-D	SGRQ Total	1 year	85	0.391	<0.001
Liang 2013 [151]	HAD-D	SGRQ Total	12 months	450	0.402	<0.001

HSCL-25 – Hopkins Symptoms Checklist. SGRQ – St George's Respiratory Questionnaire. CRQ – Chronic Respiratory Questionnaire. HAD-D – Hospital Anxiety and Depression Scale depression subscale. NS - not significant

Figure 2.2: Forest plot for depression



2.4.5 Longitudinal association of anxiety with HRQoL in COPD

Four cohort studies investigated the longitudinal association between anxiety and HRQoL in COPD (Table 2.1).[148-151]

Three of the studies met 2 of the key quality criteria for this review.[149-151] Coventry et al. (2011) found that anxiety at baseline was significantly correlated with respiratory specific HRQoL at 3 months (r=0.40, p=0.002) in patients admitted to hospital with an acute exacerbation. However, this result did not remain significant at 1 year follow-up (r= 0.26, p=0.052).[149] Wilke et al. (2014) found that there was a significant correlation between anxiety and HRQoL at 12 month follow up in their outpatient sample (r=0.318, p<0.005).[150] Liang et al. (2013) also found that anxiety was significantly correlated with HRQoL at 12 month follow up (r=0.370, p=<0.001) in patients recruited from general hospital.[151] Oga et al. (2001) did not meet any of the key quality criteria for this review, they also found that anxiety was correlated with respiratory specific HRQoL at 1 year (r=0.41, p<0.001) and that the effect remained significant at 5 year follow up (r=0.51, p<0.001).[148]

2.4.6 Meta-analysis of longitudinal association between anxiety and HRQoL in COPD

Four studies were eligible for inclusion in the meta-analysis (Table 2.4).[148-151]

As with depression we had aimed to extract regression coefficients for meta-analysis where possible. However, since regression coefficients were not available in any of the studies, correlation coefficients were extracted and transformed for meta-analysis.

The random-effects meta-analysis of the four studies (Figure 2.3) shows that anxiety at baseline was associated with a moderate and significant positive correlation with HRQoL at follow-up (r= 0.36, 95% confidence interval 0.30 to 0.42, p<0.001). A low degree of heterogeneity was found across the studies (Q=1.47 df=3 p=0.690, I^2 0%).

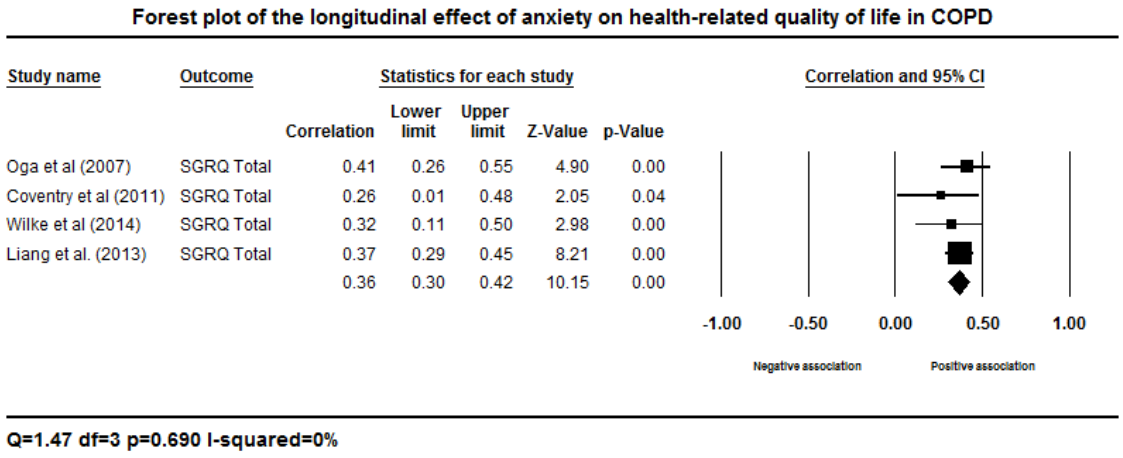
When the random-effects meta-analysis was repeated excluding the study which scored zero on the key quality review the result remained very similar (r=0.35, 95% confidence interval 0.28 to 0.42, p<0.001) but with a low degree of heterogeneity (Q=0.95 df=2 p=0.621, I^2 0%).

Table 2.4: Longitudinal correlations between anxiety and HRQoL in COPD

1st Author Year Reference	Anxiety Measure	HRQoL Measure	Length of follow up	Sample size	Correlation (r)	p
Oga 2007 [148]	HAD-A	SGRQ Total	1 year	128	0.412	<0.001
	HAD-A	CRQ Total	1 year	128	-0.534	<0.001
	HAD-A	SGRQ Total	5 years	72	0.505	<0.001
	HAD-A	CRQ Total	5 years	72	-0.641	<0.001
Coventry 2011 [149]	HAD-A	SGRQ Total	3 months	79	0.369	0.002
	HAD-A	SGRQ Total	1 year	62	0.258	0.05
Wilke 2014 [150]	HAD-A	SGRQ Total	1 year	85	0.318	0.003
Liang 2013[151]	HAD-A	SGRQ Total	1 Year	450	0.370	

HAD-A – Hospital Anxiety and Depression Scale anxiety subscale. SGRQ – St George's Respiratory Questionnaire. CRQ – Chronic Respiratory Questionnaire.

Figure 2.3: Forest plot for anxiety



2.5 Review Discussion

The aim of this systematic review and meta-analysis of longitudinal cohort studies was to assess the temporal association between psychological factors of depression and HRQoL, and anxiety disorders and HRQoL in COPD. Eight studies were identified in total, of which five met the criteria for inclusion in the meta-analysis for depression and four for anxiety. Results indicated that both depression and anxiety predict future HRQoL. The association was stronger for depression than anxiety.

2.5.1 Strengths and limitations

This review has several strengths and some limitations which will now be discussed.

Strengths

Firstly, the search was designed to take a broad approach to the identification of papers which included depression and anxiety. Terms to identify both clinically significant and sub threshold depression and anxiety symptoms were included. Measures of depression and anxiety were also required to be validated. One prospective cohort study conducted in 21 Spanish primary care centres was excluded from this study because it had not used a validated measure of depression.[164] The authors of this study were contacted and confirmed they had not used any specific validated scales to measure depression or anxiety. In this study Monteagudio et al (2011) found that there was no significant change in the number of patients with depression and/or anxiety for patients with a clinically relevant (SGRQ score change of >4 points) over 12 months. The second strength was that the search strategy for this review was designed to identify cohort studies which had investigated the strength of the longitudinal association between depression, anxiety or panic disorder and HRQoL in COPD. This has not been done before. The decision to exclude studies where samples had been exposed to any intervention was made to ensure that any prospective change in HRQoL would not be confounded by treatment effects. Furthermore, cohort studies are often easier to recruit to than randomised controlled trials and therefore the samples may be less open to threats to their external validity.[165]

The search resulted in the identification of 449 studies, a relatively small number for a systematic review. Therefore, it is possible that the inclusion of methodological terms to locate only prospective studies may have reduced the sensitivity of the search. However, at least two studies were identified which were not included in a recent meta-analysis of studies which measured factors that influence HRQoL in COPD. [62 149;155] Therefore, I am confident that all potentially eligible and relevant longitudinal studies were identified. Finally, the detection of between-study

variance can be interpreted as a positive finding since the very likely present heterogeneity has been identified and appropriately accounted for using a random-effects model.[166]

Limitations

This review has some weaknesses. Firstly, a quality scoring system was used that presents an overall quality score which rates methodological weaknesses equally. There is a lack of empirical support for the assumption that all methodological weaknesses have equal weight. Therefore, details are presented of the performance of each study on each methodological criteria and also three criterion which are deemed to be most important for longitudinal studies are highlighted.[143] The quality review highlighted several methodological issues with the studies eligible for inclusion in this review. One of the studies which was rated as the highest quality[153] was not eligible for inclusion in the meta-analysis as data on the longitudinal association between baseline depression or anxiety and HRQoL at follow up were not available. The three studies which did report this data were of varying quality. Only one study [149] provided information on sampling and recruitment procedures and recruitment response rates. Therefore, it was not possible to evaluate whether the sampling method was open to selection bias in the included studies of lower quality. Furthermore, none of the studies provide any comparison between those who were and those who were not recruited, making evaluation of possible response bias impossible. The inconsistent reporting of response and attrition bias throughout the studies has implications for the inferences that can be drawn from this review. It may be that the results cannot be generalised to older COPD patients as older patients were less likely to complete follow-up in two studies[39;153] although these studies were not eligible for inclusion in the meta-analysis.

All of the included studies used validated measures of HRQoL and psychological factors. However, one study[154] which used the Hopkins Symptom Checklist (HSCL-25) to measure depression modified the measure. Two of the items which are common symptoms of depression and relate to suicidal ideation and loss of libido were removed by the authors. This reduces the validity of the measure and may have resulted in an underestimate of the prevalence of depressive symptoms in this sample.

Where total scores for HRQoL measures were not available for meta-analysis the most appropriate subscale was chosen. In the case of one paper[154] the SGRQ impact subscale was chosen as it provides a measure of social functioning and psychological disturbance and may have maximised any observed association between depression and HRQoL.

Unpublished studies were not included in this review which may have introduced publication bias as studies that report higher effect sizes are more likely to be published.[167] I did not formally test for publication bias is this review because of the small number of studies eligible for inclusion.[168] Finally, one of the assumptions made in random-effects meta-analysis is that study effects should be normally distributed. This is not always easy to confirm when the number of studies included in the model is small. However, random effects methods have been found to be relatively robust even under extreme distributional scenarios.[169]

2.5.2 Implications for research and practice

The results of the meta-analysis show that depression and anxiety predict future HRQoL. These findings are consistent with the results of a recently published systematic review and meta-analysis that assessed the association between psychological and symptom based factors and HRQOL in COPD patients.[62] Tsiligianni et al (2011) found that depression, anxiety, exercise and dyspnoea were more highly correlated with HRQoL in COPD than $FEV_{1,}$ [62] but this finding was based only on cross-sectional studies and therefore did not include several studies which were eligible to be included for meta-analysis in our review.[148;149;154] The review presented in this thesis, which is the first to only include longitudinal studies, has further advanced our knowledge of the association between depression and anxiety and HRQoL in COPD by showing that depression and anxiety are correlated with prospective HRQoL. Unfortunately we were not able to compare the association between depression and anxiety and HRQoL with that of FEV_1 as the necessary data was not reported in the published papers. Two authors were contacted [148;149] and invited to provide the correlations between FEV_1 and HRQoL. However, only one author responded and therefore, the analysis could not be completed. This should be a priority for future longitudinal research in this area.

Future studies in this area would be improved by including specific anxiety disorder which are prevalent in COPD. Panic disorder has a prevalence in COPD estimated to be at least seven times that of the prevalence in the general population.[100] Panic disorder is also known to have a significant negative impact on quality of life in the general population[118;127] and in patients with long term conditions such as heart failure[170] and diabetes.[171] However, no studies were identified in this review which had considered the impact of panic attacks or panic disorder in COPD. Panic attacks and panic disorder comorbid with COPD have been found to predict greater levels of distress relating to physical health,[126] and to predict worse health outcomes including increased hospital admissions[119] and poorer functional status.[120] Therefore, it is important to investigate if

panic disorder is a significant driver of HRQoL in COPD as it may be a more important predictor than depression or generalised anxiety.

The findings from this review highlight the importance of regularly assessing patient centred outcomes such as HRQoL in people with COPD, regardless of their disease severity as measured by lung function. HRQoL is an important marker of functioning and is potentially mediated by extra-pulmonary features of COPD such as anxiety and depression. Whereas self-management and education have had limited impact on the psychological health of COPD patients,[172-174] case management that draws on integrated and collaborative approaches has been shown to reduce depression and improve physical health in people with diabetes and coronary heart disease,[175] although their effectiveness and safety in COPD is unknown.[176] As well as scope for testing the acceptability and effectiveness of collaborative care models in COPD there is also a need to test mediational models which propose that psychological processes and improvements in psychological health predict improvements in HRQoL and possibly improve physical health outcomes and responses to rehabilitation.[177]

2.5.3 Conclusions

The findings of this review confirm that there is an association between depression and HRQoL, anxiety and HRQoL which endures over time. However, this longitudinal analysis does not show cause and effect between depression and anxiety and future HRQoL. Future studies should identify psychological predictors of poor HRQoL in well-designed prospective cohorts with a view to isolating the mediating role played by anxiety disorders and depression. Future longitudinal cohort studies should also seek to identify the prospective impact of panic on HRQoL in COPD.

2.6 Chapter Summary

This chapter has addressed the first research question for this thesis by systematically reviewing the existing evidence for psychosocial predictors of HRQoL in COPD. The results show that depression and anxiety are significantly associated with prospective HRQoL and therefore should be targeted for treatment in COPD patients with a view to improving HRQoL. However, this review also identified that there are no existing studies which have investigated the impact of panic disorder on HRQoL in COPD.

The next chapter will describe the design of a longitudinal cohort study which aimed to identify whether panic predicts HRQoL in COPD and whether panic is a better predictor of HRQoL than depression in COPD.

3. Methods

3.1 Study Design

This PhD study was nested within a larger longitudinal cohort study, the CHOICE Health Survey. The CHOICE Health Survey was one strand of the CHOICE (Choosing Health Care Options in Chronic Care Emergencies) Research Programme Grant which was funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research Programme (Grant Reference Number RP-PG-0707-10162).

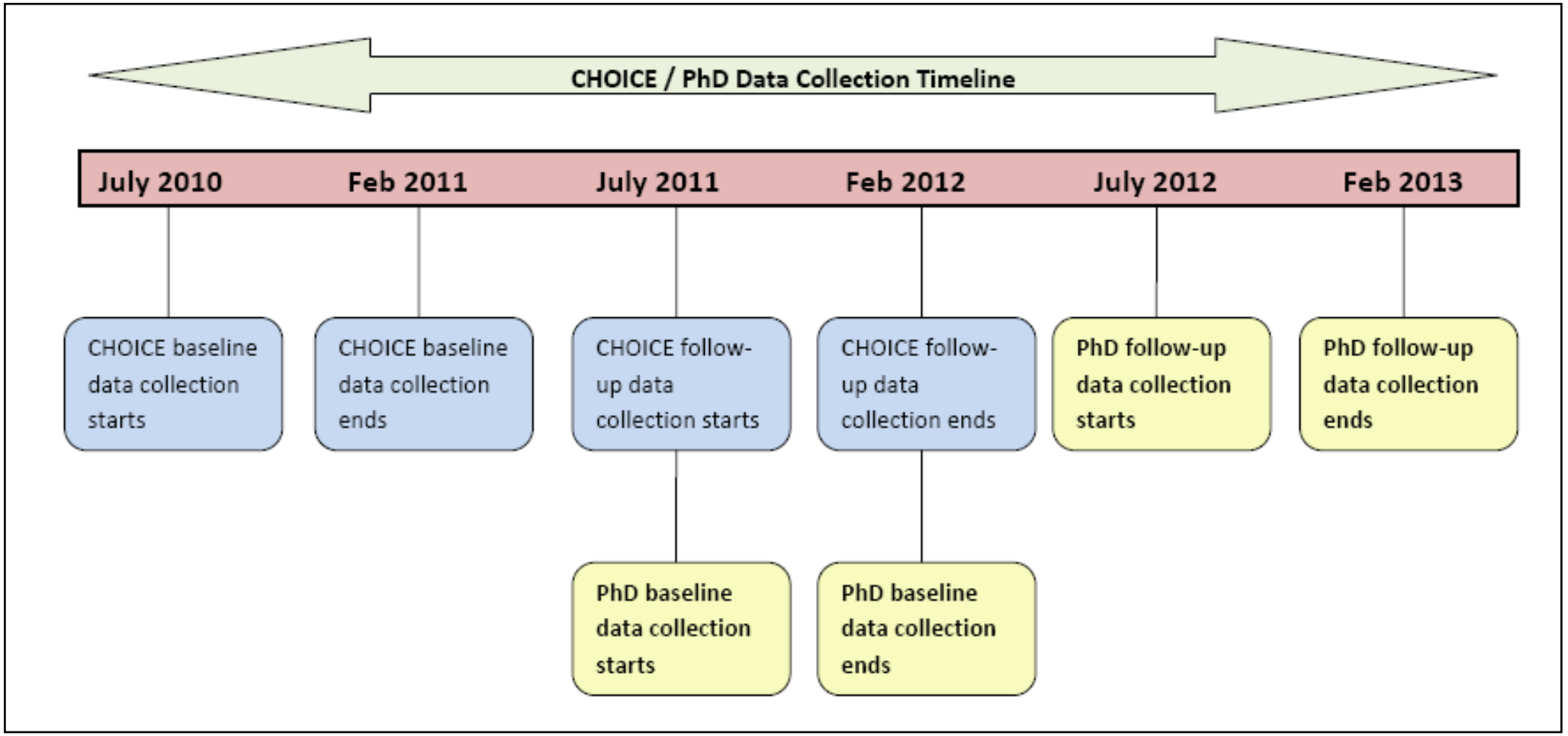
The CHOICE Health Survey was a self-reported questionnaire study that was underway in 10 general practices in central Manchester at the time that this PhD study began. The aim of the CHOICE Health Survey was to identify the psychosocial predictors of the use of unscheduled care in patients with long term conditions (LTCs). The Survey focused on four exemplar LTCs which were: asthma, diabetes, COPD and coronary heart disease (CHD). These four conditions were chosen because they are associated with high numbers of emergency hospital admissions and are among the most common discharge diagnoses from emergency departments.[178;179]

The sample of COPD for this PhD study was recruited from the COPD patients who formed part of the CHOICE Health Survey cohort. As the CHIOCE Health Survey had already begun collecting self-report data on psychosocial variables, including depression and anxiety, it presented an excellent opportunity to nest this PhD study within it. Nesting this PhD study within the CHOICE Health Survey offered the opportunity to include a longitudinal assessment of the relationship between psychological factors and HRQoL in COPD. This enabled questions to be answered about the predictive power of psychological factors and in particular panic disorder on respiratory specific HRQoL that had not been addressed in previous cross-sectional studies (Chapter 2).[128] Recruitment for this PhD study was therefore completed as part of the CHOICE Health Survey (Figure 1). A substantial amendment was sought to invite participants to take part in this PhD project as part of the larger CHOICE Health Survey. The additional study was referred to as the Quality of Life Study and a copy of the substantial amendment be seen in Methodological Appendix A.

Recruitment to the baseline phase of the CHOICE Health Survey was complete at the time that the baseline phase of this PhD study began (Figure 1). This meant that there was a ready assembled cohort of COPD patients recruited to the CHOICE longitudinal Health Survey and were thus available to be invited to take part in this PhD study. Using a recruited cohort of COPD patients ensured that sample size targets for this PhD study could be met efficiently and afforded more time to develop the necessary skills to answer the research questions with advanced methods, such as structural equation modelling (SEM).

The eligibility criteria for the CHOICE Health Survey and this PhD study will now be described followed by an explanation of how general practices and patients were recruited to take part in this study in the context of the CHOICE Health Survey.

Figure 3.1: Data collection timelines for the CHOICE Health Survey and this PhD study



3.1.1 Participants

3.1.1.1 Eligibility criteria for the CHOICE Health Survey

Patients were eligible to take part in the CHOICE Health Survey if they met the following inclusion criteria. A list of all patients who met this criteria was generated at each practice from the Quality and Outcomes Framework (QOF) register for asthma, CHD, COPD and Diabetes and then reviewed against the exclusion criteria by the General Practitioner.

I. Aged over 18 years or over

II. Had one of the following diagnoses:

    a. Asthma

    b. Chronic Obstructive Pulmonary Disease (COPD)

    c. Coronary Heart Disease (CHD)

    d. Diabetes

Patients were excluded from the study if they:

I. Were terminally ill, defined as patients who are on the palliative care register at the general practice.
II. Had a cognitive impairment (i.e. dementia).
III. Had received a recent diagnosis of cancer.
IV. Were acutely psychotic, where the general practitioner deemed that receiving the questionnaire would be distressing.

3.1.1.2 Eligibility criteria for PhD Study

All participants who returned the CHOICE Health Survey at baseline and met the following criteria were eligible for inclusion in this PhD study:

I. Had a diagnosis of COPD as defined by registration on the QOF register for COPD at each practice.[180] In order to be placed on the QOF register patients must have a diagnosis of COPD confirmed by spirometry. Spirometry is a test of lung function which provides a measure of the degree of airflow obstruction experienced by a patient. It provides two results which can be used to diagnose COPD: FVC (forced vital capacity) and the FEV_1 (forced expiratory volume in one second) measurements.[1] The FVC is the total volume of air that a patient can exhale in one breath. The FEV_1 is the volume of air that a patient can exhale in the first second of the spirometry test. The result for FEV_1 is compared with the

values that are predicted for a patient of the same gender, age and height of the patient being tested which gives the FEV_1 percent predicted.[1]

Diagnosis of COPD is confirmed where the FEV_1/FVC ratio <0.70 or FEV_1 <80% of the predicted values for the patients age, height and gender.[1]

3.1.1.2 Recruitment of general practices

The CHOICE Health Survey aimed to recruit patients with asthma, diabetes, COPD and CHD across the NHS Manchester area. In order to recruit General Practices to the project members of the research team arranged to meet with GPs and practice manager and presented the details of the study to them. GPs were given copies of all of the study materials and information on how they would be reimbursed for their participation.

Once a General Practice had given consent to participate they were asked to produce lists of all patients who appeared on their QOF registers for asthma, diabetes, COPD and CHD. Staff from the mental health and primary care research networks then visited the practices to identify eligible patients and to send out the baseline CHOICE Health Survey. Research network staff were given a recruitment procedure manual and they were trained in the recruitment procedure and supported through the process by the author of this thesis.

3.1.1.3 Recruitment of patients

All patients registered as having asthma, diabetes, COPD, and CHD on the General Practice database who met the inclusion criteria were invited to complete the CHOICE Health Survey baseline questionnaire between October 2010 and February 2011 (Figure 1). Non-responders were mailed a reminder questionnaire after 2 weeks. In October 2011 there was a 12 month follow-up of all participants who completed the CHOICE Health Survey at baseline. At this stage all COPD patients who had taken part in the CHOICE Health Survey at baseline were also invited to take part in this PhD study (Figure 1). All eligible participants were sent a new Participant Information Sheet (Methodological Appendix B) which explained that their CHOICE Health Survey follow-up questionnaire included questions for an additional study (i.e. the quality of life study) which aimed to identify psychological factors that impact on HRQoL in people with COPD.

Patients were initially invited to take part by a letter from their General Practice which was signed by their GP (Methodological Appendix C). The letter was sent out with a copy of the CHOICE Health Survey follow-up questionnaire (Methodological Appendix D) and a copy of a new

participant information sheet (Methodological Appendix B). The letter requested that if patients did not want to take part they could return their questionnaire blank inside the prepaid envelope. If a patient returned a blank questionnaire they were excluded from receiving any other mailing or reminder questionnaires. If participants did not return their questionnaire within two weeks, either blank or completed, a reminder letter was mailed to them with another copy of the questionnaire. A copy of the reminder letter can be seen in Methodological Appendix E.

Twelve months after completing the PhD baseline questionnaire all responders were reassessed for their continued eligibility in the study and all those who remained eligible were sent a follow-up questionnaire. The follow-up questionnaire pack included the same self-report measures as the baseline pack (Methodological Appendix D). If patients did not respond to the initial follow-up questionnaire a reminder letter was again mailed to them two weeks later with a new copy of the questionnaire. If there was still no response a reminder phone call was made to ask participants if they would like another copy of the questionnaire. In order to allow reminder phone calls to be made a substantive amendment to the CHOICE Health Survey was sought from the NHS ethics committee (Methodological Appendix F). The letter which accompanied the reminder questionnaire was also amended at this stage to inform patients that if they did not return the questionnaire they may receive a phone call from the author (Methodological Appendix G). Before any reminder calls were made the author checked with the relevant general practice for each patient to ensure that they had not passed away or were in hospital, or if there was any other reason why they could not be called.

3.2 Baseline Questionnaire Measures

The next section of this chapter describes the content and where relevant, details about validity and reliability of predictor and outcomes measures used in the cohort study.

3.2.1 Predictor variables

3.2.1.1 Demographic and clinical characteristics

Data were collected on participants' age and gender as part of the questionnaire in order to describe the sample. Participants were also asked to state if they lived alone (yes/no), and if they did, for how long (years, months).

In order to assess how many additional physical health problems participants had they were asked to self-report (yes/no) the following:

I. Heart disease
II. Asthma
III. Diabetes
IV. Chronic Obstructive Pulmonary Disease
V. Cancer
VI. Stomach or bowel problems
VII. High blood pressure
VIII. Arthritis or other joint problems

Participants were provided with a free text box to enter any other medical conditions that they had which were not included in the above list.

3.2.1.2 Severity of COPD

COPD is a multidimensional illness and its severity cannot be determined by measures of lung function alone.[1] However, for this study it was important to include an objective measure of the severity of COPD symptoms in order to isolate the independent effects of psychological factors on HRQoL.

Therefore, for those COPD patients who took part in this study and consented to have their general practice notes reviewed as part of the CHOICE Health Survey data on FEV1 % predicted (forced expiratory volume in 1 second) was extracted from general practice notes as part of the CHOICE study. The FEV_1 % predicted is a measure of the amount of air a patient can exhale in 1 second compared with compared to the score that is predicted for a patient of the same age, gender and height. It is the measure used to classify COPD severity by both the GOLD and NICE Guidelines for COPD.[1;6;181]

3.2.1.3 Panic disorder

Description

Data were collected on the prevalence of panic attacks and panic disorder using the Panic Disorder Self-Report (PDSR). The PDSR is a 24 item self-report measure of panic disorder based on the Anxiety Disorder Interview Schedule IV (ADIS-IV) [182;183]. The ADIS-IV is a lengthy structured interview which is modelled on the 4th edition of the Diagnostic and Statistical Manual of Mental Disorder IV criteria for anxiety disorders.[67]

The PDSR begins with the following description of panic attacks in order to ensure that all those completing the measure are clear about their definition:

> *"Panic attacks are discrete episodes of intense fear, apprehension, or terror that are accompanied by a number of physical symptoms. Panic attacks can either occur for no apparent reason (spontaneously) or upon entering into or being in situations which have become associated with them (for example, long lines, travels, etc.) Do not consider fear to be a panic attack if it lasts most of the day."*[183]

This statement is followed by three dichotomous questions which are considered essential for diagnosis of panic disorder according to the DSM-IV.[67] These three questions are:

I. *During the last six months, have you had a panic attack or sudden rush of intense fear or anxiety?*
II. *Was at least one panic attack unexpected, as if it came out of the blue?*
III. *Did it happen more than once?*

If the participant answers 'no' to any of the three questions above they are not required to complete the remainder of the questionnaire. However, if patients answer 'yes' to the first three questions they are asked to complete the remainder of the questions which relate to anticipatory anxiety, change in behaviour associated with panic disorder (Q4 - Q6), symptoms (Q7), interference with daily functioning (Q8 - Q9), duration (Q10), and triggers (Q11 - Q12).

Reliability and validity

Newman et al. (2006)[183] compared the diagnosis of panic disorder using the PDSR with diagnosis using the ADIS-IV in a sample of students (n=139) in the United States and found that the optimal diagnostic cut off score for the PDSR was 8.75 or above. Newman et al. (2006) report that the cut off score of 8.75 results in a sensitivity (which is the ability to determine the absence of panic disorder) of 89% and a specificity (ability to determine the presence of panic disorder) of 100% for the PDSR. Therefore, Newman et al. (2006) concluded that they were confident that a cut off score of 8.75 can differentiate those with diagnosable panic disorder from those who had experienced panic attacks but did not meet the criteria for panic disorder because the rate of the PDSR falsely detecting panic disorder is 0%.

Rationale for using the PDSR in this PhD

At the time of the design of this study the gold standard method for the diagnosis of panic disorder is a clinical interview based on the DSM-IV-TR criteria for panic disorder conducted by an appropriately qualified clinician.[67] However, since then a new edition of the DSM has been

released (DSM-5) and this is now the gold standard for diagnosis of panic disorder.[66] There is currently no recommended self-report instrument to screen and diagnose panic disorder in the general population owing to a lack of evidence about their validity and reliability.[184]

Diagnostic clinical interviews such as the ADIS are time consuming and costly and within the confines of this nested questionnaire study it was not possible to assess panic disorder using a clinical interview. Therefore, it was necessary to select the best available self-report measure. Several panic measures were considered before the PDSR measure was chosen. Firstly the use of the panic item on the Hospital Anxiety and Depression Scale (HADS) was considered.[159] The HADS anxiety subscale includes a single item that can be used to assess panic. This item asks participants if they '*get sudden feelings of panic*' (Item 7). Lowe et al. (2003) studied the properties of the HADS panic item against the Patient Health Questionnaire (PHQ), and against a physician's diagnosis of panic in a sample of medical and psychosomatic outpatients.[185] Lowe found that when the score for the panic item on the HADS was combined with a score of ≥10 on the anxiety subscale of the HADS it had a sensitivity of 91% and a specificity of 75% to detect panic.[185] They therefore recommended the scale for screening of panic disorder. However, the use of the single panic item on the HADS anxiety subscale to identify panic disorder has only been validated in German and Dutch and is yet to be validated in English.[185;186]

The Quick PsychoDiagnostics Panel (QPD) was also considered for use in this study.[187] The QPD has a high positive likelihood ratio (LR+ =23.7), which indicates that those who reach the cut-off score for panic on the QPD are highly likely to have panic. The sensitivity (71%) and specificity (97%) of the QPD are also high, although it does not match the PDSR, which was 89% and 100% respectively.[183;188] Furthermore, the QPD requires the purchase of expensive software for which there was no resource in this study.[187;188] Finally, the Mental Health Index-5 (MHI-5) was considered.[189] The MHI-5 has been recommended as a screening instrument for panic disorder and has a sensitivity of 100% but a specificity of only 65%.

When compared with other measures the PDSR was considered to offer the best fit between capturing the data necessary to indicate the presence of panic disorder in patients with COPD and ease of completion for participants. As discussed above the PDSR provides a clear description of a panic attack in order to aid participants' understanding, and only requires them to answer a minimum of three questions if they do not have panic. A meta-analysis of strategies to improve response rates in randomised controlled trials which use questionnaires has found that the use of shorter questionnaires with greater clarity may help to improve response rates.[190]

In order to identify panic disorder in patients with a medical condition such as COPD it is important to distinguish between panic that occurs due to breathlessness on exertion for

example, and panic attacks that occur spontaneously and are not triggered by COPD symptoms, but are perhaps triggered by anxious cognitions.[191] As discussed in chapter one Livermore et al. (2010) describes that in order for panic disorder to be diagnosed in patients with COPD (and therefore distinguishable from other diagnoses, such as anxiety due to a general medical condition), the following criteria must be met:

I. There must be anticipatory anxiety about future panic attacks
II. At least some of the panic attacks must be unexpected and unpredictable in nature and they must not only occur in response to situations which cause shortness of breath in COPD.

The PDSR addresses these criteria with three questions (Q4, Q5 and Q6) which seek to draw out panic symptoms that are driven by anxious cognitions or have resulted in a change in behaviour.

I. 'Have you ever worried a lot (for at least one month) about having another panic attack?'
II. 'Have you ever worried a lot (for at least one month) that having the attacks meant you were losing control, going crazy, having a heart attack, seriously ill, etc?'
III. 'Did you ever change your behaviour or do something different (for at least one month) because of the panic attacks?'

3.2.1.4 Depression and anxiety

Description

Depression and anxiety are common mental health problems which are highly prevalent in COPD patient populations and have been shown to be closely associated with HRQoL in cross-sectional studies (Chapter 2).[128] Depression is diagnosed when a person experiences depressed mood and/or a loss of interest and pleasure in daily activities for a period of at least 2 weeks. Depression is also characterised by a range of other symptoms which include: significant change in appetite and/or weight, change in sleep which can be either insomnia or hypersomnia, fatigue and loss of energy, feelings of worthlessness or excessive and inappropriate guilt, diminished ability to concentrate, and suicidal thoughts and/or behaviour.[66] Anxiety is characterised by worry and rumination and physical symptoms such as restlessness, fatigue, difficulty concentrating, irritability, muscle tension, and sleep disturbance.[66]

In this PhD study depression and anxiety were measured using the Hospital Anxiety and Depression Scale (HADS).[159] The HADS is a 14 item scale designed to measure symptoms of depression and anxiety in general hospital patients.[159] It is split in to two subscales: seven items

relate to depression (HADS-D) and seven items to anxiety (HADS-A). Each item is scored on a 4 point scale from 0-3, giving a total score out of 21 for each sub-scale.

Reliability and validity

The gold standard for identification and diagnosis of depression and anxiety is diagnostic clinical interview conducted by a physician.[181] Therefore the HADS score does not allow a definitive diagnosis of either depression or anxiety to be made but it can screen for symptoms of depression and anxiety. A cut-off score of 8 on either subscale is widely used to indicate 'caseness' for depression or anxiety.[159;192] Lowe et al. (2004) compared the HADS with several other self-report measures, physician diagnosis, and the Structured Clinical Interview for DSM-IV (SCID)[193;194]. Lowe et al. found that the HADS had good internal consistency and was able to identify 88% of cases of major depression as identified by the SCID interview. Physician diagnosis was low with only 40% of major depression cases being successfully identified.[194]

The HADS has been well validated in populations of patients with physical illness.[192] In a systematic review of studies that had used the HADS Bjelland et al. (2002) found that Cronbach's alpha had a mean of .83 and ranged from .68 to .93 for HADS-D and between .67 to .90 for HADS-A with a mean of .82. Cronbach's alpha is used to assess the internal consistency or reliability of measures. For a measure to have internal consistency all items need to measure the same underlying construct and therefore should be highly correlated with each other.[195;196] Cronbach's alpha closer to 1 represent greater internal consistency for a measure;[196] for research purposes a Cronbach's alpha of 0.7 or 0.8 is considered as satisfactory.[195] Therefore the HADS can be said to have good internal consistency. Furthermore, Hermann et al. (1997) found that the retest reliability is high ($r>0.80$) for both the HADS-D and HADS-A, which implies that it can withstand fluctuations in mood which may occur in physically ill populations attending for treatment.[197]

3.2.1.5 Threatening life events

Description

The experience of threatening life events is known to cause stress which is understood to have a negative impact on both physical and mental health.[198] The number of threatening life events that participants had experienced in the year before completing the baseline questionnaire and the year between the baseline and follow-up questionnaire were measured using the List of

Threatening Experiences Questionnaire (LTE-Q).[199] The LTE-Q measures whether or not a respondent has experienced any of 12 threatening personal situation or events. These include: serious injury to yourself and family or close friends, bereavement, marital or relationship difficulties, employment difficulties, financial difficulties, problems with the police, and having something valuable lost or stolen.[199] The total score of positive responses gives a measure of the participants exposure to recent threatening life experiences which may cause them stress.[199]

Reliability and validity

In samples of the general population the LTE-Q has shown to have high test-retest reliability and high specificity and sensitivity when compared with a semi-structured interview.[200;201] The LTE-Q has not been formally validated for use with COPD patients, although it has been used previously to measure life event stress in COPD studies. Lu et al. (2012)[202] used the LTE-Q to measure the experience of life event stress and its association with depression and general HRQoL in COPD patients and in controls without COPD. They found that there was no difference in the number of stressful life events experienced by COPD and non COPD patients. However, the association between stressful life events and depression and general HRQoL was significantly greater for COPD patients than non COPD controls.[202]

3.2.1.6 Healthcare use

Self-report data were collected about participants' use of both scheduled and unscheduled healthcare in the follow-up questionnaire. Scheduled and unscheduled healthcare use is an important outcome in COPD and is hypothesised to be an important predictor of other health outcomes, such as HRQoL.

Data were collected on healthcare use for the purpose of this PhD study in the 12 month follow-up questionnaire. Participants were asked to record the number of times that they had used the following services in the previous 12 months (e.g. the period between the baseline and follow-up questionnaire): visited GP for a non-emergency appointment, asked for an emergency appointment from GP or out-of-hours service, attended a hospital outpatient appointment, called an ambulance, attended casualty/emergency department, admitted to hospital due to an emergency health problem.

3.2.1.7 Health-related Quality of Life (HRQoL)

Measuring HRQoL in COPD

HRQoL is a multidimensional concept which is often discussed in relation to chronic illness and refers to patients' perspective of the quality of aspects of their lives which are affected by their illness.[203] There are four core components which are often considered to be integral factors of HRQoL: physical status, functional status, psychological status, and social and occupational status.[204]

Measures of HRQoL can be either general measures which can be used across all patient populations, or disease specific measures. The use of a general measure as the primary measure of HRQoL for COPD patients is not recommended. General measures have been shown to be insensitive to the HRQoL of patients with mild COPD,[40;144] to underestimate the true impact of symptoms on patients' HRQoL and to be insensitive to treatment effects in randomised controlled trials.[20]

Engstrom et al. (2001) conducted a study which compared measure of the general and disease specific impact of COPD on HRQoL.[39] Engstrom et al. found that different domains of HRQoL in COPD (i.e. physiological, functional, and psychological) were only poorly to moderately associated with each other, suggesting that thorough assessment of the consequences of COPD requires a battery of measures which can measure both the disease specific effects and the overall burden of COPD on functioning and wellbeing.[39] The use of respiratory or COPD specific measures is now considered best practice for evaluating the impact of COPD on HRQoL. Therefore, a respiratory specific measure of HRQoL was chosen as the outcome measure for this PhD study and general HRQoL was measured as a predictor variable.

Jones (1995) has proposed that there are two types of questions that can be used to measure HRQoL in COPD.[20] The first are global questions which aim to identify the general impact of COPD on patients, for example, *'How much impact does your chest disease have on your daily activity?'* The second type of questions is a decomposed question. Decomposed questions ask about the different types of impact that COPD can have on specific activities or areas of a patient's life, for example, *'how does your breathlessness impact on your ability to walk up the stairs?'* Research into early measures of HRQoL of life in COPD has shown that the use of only global questions may result in underestimates of the impact of COPD on patients HRQoL.[20] Therefore, respiratory or COPD specific complex measures which include specific, and decomposed questions are recommended for use in research and clinical practice.

For the purpose of this PhD study both general and respiratory specific measures of HRQoL were used. Two general measures of HRQoL were included in the baseline questionnaire as predictor variables. The outcome variable for this study was a respiratory specific measure of HRQoL which includes both global and decomposed questions.

3.2.1.7.1 General measures of HRQoL

Two measures were used to collect data on participant's general HRQoL at baseline. These were the Short Form-12 (SF-12) and the EQ-5D.

SF-12

Description

The SF-12 is a 12 item version of the widely used Medical Outcomes Study (SF-36) questionnaire. It measures 8 domains of HRQoL, including: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems and mental health. The SF-12 provides two summary scores of general HRQoL, a physical component score (PCS), and a mental component score (MCS). Higher scores on both the PCS and MCS indicate better health status. Zero is the lowest score and indicates worst HRQoL and 100 is the highest scores and indicates the best general HRQoL.

Reliability and validity

The SF-12 been found to replicate the results of the SF-36 and is recommended for use whether shorter questionnaires are required.[205] The SF-12 has also shown excellent measurement properties in studies of COPD patient populations.[206;207]

EQ-5D

Description

The EQ-5D was developed by the EuroQol group as a simple generic measure of health for clinical and academic appraisal.[208] The EQ-5D is designed for self-completion and is suited for use in postal surveys and in face- to-face interviews. It consists of two sections: the EQ-5D descriptive system and the EQ-5D Visual Analogue Scale (EQ-5D VAS). The descriptive system is comprised of the following five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Within each dimension there are 3 ratings for a patient to choose from: *'no problems,'* '*some problems,' and* '*severe problems'*. To score the EQ-5D a single summary score is

generated by applying societal preference weights to the answers given by the participants. A score of zero represents *'dead'* and a score of 1 represents *'best possible health'*.[209] It is also possible to score less than zero, which is said to represent a health state worse than death.[209]

The EQ-5D VAS is a 20 centimetre thermometer which asks patients to rate their health status as somewhere between 0 and 100 where 0 represents, *'worst imaginable health'* and 100 represents, *'best imaginable health.'*[208]

Reliability and validity

The reliability and validity of the EQ-5D has been tested in patients with COPD.[40;209] Pickard et al. (2008) conducted a systematic review of the EQ-5D in asthma and COPD patients and found that it had good construct validity and test-retest reliability.[209]

3.2.2 Outcome variable

3.2.2.1 Respiratory specific measure of HRQoL

Description

The outcome measure for this study was a respiratory specific measure of HRQoL. Both general and disease specific measures are recommended for use in COPD[39] and as discussed above both were included in the questionnaire for this study. However, a respiratory specific measure of HRQoL was chosen for the main outcome measure in this PhD study as there is evidence that they are able detect smaller changes in COPD symptoms and the effect of symptoms on HRQoL than general measures of quality of life.

There are several commonly used COPD specific measures of HRQoL which include the St George's Respiratory Questionnaire (SGRQ) and the Chronic Respiratory Questionnaire (CRQ).[144;157] For the purpose of this study the Chronic Respiratory Questionnaire – Self Administered Standardised version (CRQ-SAS)[210] was used. The CRQ-SAS is a 20 item self-report measure of the health related quality of life of COPD patients. It was developed from the original interviewer administered version of the CRQ (CRQ-IA).[157]

The CRQ-SAS consists of questions which measure four dimensions: dyspnoea, fatigue, emotional function, and mastery. Mastery refers to the amount of control COPD patients feel they have over day to day tasks. The CRQ-SAS is identical to the CRQ-IA on all dimensions except for the dyspnoea dimension. The CRQ-IA dyspnoea dimension asks patients to state any five daily activities which are important to them and to rate how breathless these activities make them on a scale ranging from, *'extremely short of breath'* to *'not at all short of breath.'* Including

personalised activities was found to improve the validity of the questionnaire and its ability to detect small changes in dyspnoea.[211] However, the individualised section was also found to be time consuming and often confusing for patients when it was presented to them in a self-report format. Therefore a self-administered, standardised questionnaire was developed – the CRQ-SAS. This scale includes five activities selected by patients in previous trials on the basis that they were most likely to predict dyspnoea. The five activities chosen were:[211]

I. Feeling emotional, such as angry or upset
II. Taking care of basic needs (bathing, showering, eating or dressing)
III. Walking
IV. Performing chores (housework or shopping for groceries)
V. Participating in social activities

Reliability and validity

Schunemann et al. (2005)[212] conducted a randomised controlled trial (n=177) to test the performance of the self-administered CRQ (CRQ-SAS) versus the interviewer led (CRQ-IA) in patients before and after they attended pulmonary rehabilitation. They aimed to determine how the self-administration of the questionnaire and standardisation of the dyspnoea items influenced the measurement properties of the questionnaire. They also compared the CRQ-SAS with other HRQoL measures such as the St George's Respiratory Questionnaire (SGRQ).[144] Schunemann et al., found that scores on the CRQ-SAS were consistently lower than the CRQ-IA, which indicated worse HRQoL. However, the scores were only significantly lower on the mastery dimension at baseline measurement (p=0.03). Schunemann et al. (2003) have suggested that the CRQ-SAS produces lower scores because patients might be more willing to acknowledge the impact of their breathlessness on daily activities in the absence of an interviewer. In both cross-sectional and longitudinal analysis the CRQ-SAS and CRQ-IL showed similar correlations to the other HRQoL questionnaires.

3.3 Sample Size

3.3.1 Sample size for multiple regression analyses

The aims of the regression analyses were:

I. to determine if panic predicts HRQoL in COPD
II. to determine if panic is a better predictor of HRQoL than depression

Therefore, the primary outcome variable for the regression analysis was physical HRQoL and the secondary outcome variable was emotional HRQoL. The two outcome variables were measured using the CRQ. There were a total of fourteen predictor variables included in the linear regression analysis and were potentially available for inclusion in the multiple regression analyses if found to be significant predictors of HRQoL in simple regression analyses. The outcome and predictor variables are summarised in Table 3.1.

The statistical power analysis program G*Power was used to calculate the required sample size for the regression analyses.[213] The power analysis was based on the results of previous studies of the relationship between psychosocial factors and HRQoL in COPD which were discussed in Chapter 2.[128] There have been no previous studies of panic as a predictor of HRQoL in COPD. Therefore, the power calculation was based on the existing studies that have studied the relationship between depression and HRQoL, and anxiety and HRQoL in COPD.

It was calculated that a sample size of 149 would be sufficient to detect an effect of 0.20 between depression or anxiety and HRQoL at the 5% level. However, larger effect sizes of closer to 0.50 (correlation coefficient) have been found between depression and HRQoL and are in presented in Chapter 2 of this thesis.[128] To detect an effect of 0.50 at the 5% level would require a sample size of 68. Therefore, conservatively taking the larger sample size of 149 and accounting for a 20% attrition rate at 12 month follow-up the required minimum sample size for this study is 179.

Table 3.1: Summary of predictor and outcome variables for regression analysis

		Measure
Outcome Variables		
	Physical respiratory HRQoL	CRQ Physical Subscale
	Emotional respiratory HRQoL	CRQ Emotions Subscale
Predictor Variables		
	Age	Self-report questionnaire
	Gender	Self-report questionnaire
	Living alone	Self-report questionnaire
	Threatening life events	List of Threatening Events Questionnaire (LTE-Q)
	COPD Severity	FEV_1 % predicted (general practice notes)
	Panic	Panic Disorder Self Report (PDSR)
	Depression	Depression subscale of the HAD-D
	Anxiety	Anxiety subscale of the HAD-A
	General physical HRQoL	SF-12 Physical subscale
	General mental HRQoL	SF-12 mental subscale
	General health status	EQ-5D
	Scheduled healthcare use	Self-report questionnaire
	Unscheduled healthcare use	Self-report questionnaire

3.3.2 Sample size for structural equation modelling (SEM)

Analysis of data using structural equation modelling (SEM) is often thought to require large sample sizes.[214] However, the sample size required depends on the complexity of the specified model which will be tested. Complex models which require the testing of many parameters (a parameter is an hypothesised effect which requires statistical analysis in the model) will require more participants.[214] Jackson (2003) developed a rule of thumb for sample size in SEM which is based on the ratio of cases to the number of parameters you wish to estimate.[215] The ideal ratio suggested for use in SEM where the maximum likelihood estimation method is used is 20:1.[215] For example, a model that hypothesised that 10 parameters will have an effect will require a minimum sample size of 200.

This PhD study aimed to test the effect of 3 parameters (depression, anxiety and panic) on the outcome of respiratory specific HRQoL using SEM. Therefore, it was concluded that a sample size of 60 would be needed to undertake SEM analyses.

3.4 Statistical Analysis

Statistical analyses were carried out using either IBM SPSS (IBM SPSS Statistics, version 20) or Stata version 12 and later Stata version 13.[216;217] Data were initially entered in to SPSS to be cleaned for accuracy of data entry. Descriptive statistics were run using SPSS but missing data analysis was conducted in Stata. Regression and SEM analyses where also conducted using Stata.

3.4.1 Data preparation and cleaning

The data were initially entered by the author into SPSS where it was cleaned. Descriptive statistics were then performed to check that all values were within the expected ranges for each item on a scale and outliers were checked. An accuracy check of data entry was conducted for 30% of the questionnaires entered.

3.4.2 Missing data

The amount of missing data points were initially identified when the data was entered in to SPSS and the descriptive statistics were run. The data were then transferred in to Stata where analysis of missing values was performed using the command ‘mvpatterns’ in order to identify the amount and pattern of missing data.

The impact of missing data on statistical analyses is dependent on the amount of data that is missing, the pattern of the missing data, and the reasons why it is missing. However, the pattern of missing data is usually considered to be more important than the amount of data missing. [218;219] Data that is missing at random does not pose as much of a serious threat to results as data which is missing according to an identifiable pattern, known as missing not at random. This type of data can bias the results and affect the internal validity of the results. Missing data can be characterised in 3 ways: [218]

I. MCAR - Missing Completely at Random
   Data that is missing completely at random is not related to any of the observed or unobserved variables in the population which has been studied and there will be no observable pattern to the missing data.

II. MAR – Missing at Random
   Data which is missing at random is related to a variable that has been measured but is not related to the value of that variable, so there is no observable pattern to the missing data. MAR is usually seen when, for example, a participant accidently misses a question on a questionnaire.

III. MNAR – Missing Not at Random
   If data is deemed to be missing not at random there will be an observable pattern to the missing data. This may occur, for example, when a question on a questionnaire is deliberately missed by many participants.

There are several approaches that can be used to handle missing data. A complete case analysis is a commonly used approach which involves excluding all cases with missing data from the analysis. However, deleting cases with missing data can significantly bias results and seriously affect the internal validity of a study. Another method for handling missing data is imputation, for example, by imputing mean scores for an item where that item is missing. The missing data in this PhD study were found to be missing at random and therefore it was necessary to use the multiple imputation method to impute the missing values.[220]

Multiple imputation involves creating models to predict missing values based on existing values from other variables that are correlated with the missing variables.[221] However, instead of creating just one prediction of the missing value, multiple imputation allows the computation of many estimates for each missing value in order to create several imputed data sets. For this study 100 imputed datasets were generated using Stata. Further analyses were then conducted on each

imputed dataset and the results of each analysis were pooled to produce one overall analysis for full data set. When the estimates are pooled Rubin's rules are used which account for the (within) variation of each dataset and the (between) variation from the imputation.[220] Results are therefore weighted according to how much variation there is between imputations versus how much variation there is according to the linear model.

3.4.3 Testing the assumptions of normality

To test the assumptions of normality, histograms were inspected for each of the self-report questionnaires and demographic and clinical data where appropriate. The results are presented in Statistical Appendix A.

Inspection of the histograms showed that the data were not normally distributed. Therefore, medians and interquartile ranges are presented in addition to means and standard deviations for the description of the sample and non-parametric tests were chosen to analyse the descriptive data.

3.4.4 Simple linear regression

In order to identify the predictors of HRQoL in the sample of COPD patients recruited to this PhD study a series of simple linear regression analyses were conducted to analyse the predictive value of the variables measured at baseline on respiratory specific HRQoL at 12 months. Simple linear regression analyses was conducted for all predictor variables and physical, respiratory specific HRQoL and then for emotional, respiratory specific HRQoL.

The purpose of regression analyses is to estimate how well one variable predicts another by using a linear model to fit the data and therefore estimating the best straight line to summarise the association between variables. The method of least squares is used to find the line that best describes the data or 'line of best fit,' which results in the least difference between the observed data points and the line, or the lowest sum of squared differences.

In simple linear regression one outcome variable is predicted from one predictor variable.

The basic equation for simple linear regression is:

$$Y = a + bX + e$$

Where Y is the outcome variable and X represents the predictor variable; a is the intercept, b is the slope of the line, and e is the error, which is a random variable representing the variability of Y, which is not explained by its relationship with X.[222]

3.4.5 Multiple regression

Multiple regression is used to test a number of different predictor variables which are hypothesised to predict one outcome variable. For this PhD study all baseline variables that were found to be significant predictors of respiratory specific HRQoL at follow-up in simple linear regression analyses at a significance level of 0.05 were entered in to multiple regression models. A set of models were initially tested for physical, respiratory specific HRQoL (Figure 3.2) and then reanalysed with emotional, respiratory specific HRQoL as the outcome variable (Figure 3.3).

Figure 3.2: Multiple regression model - psychosocial predictors of physical, respiratory specific HRQoL

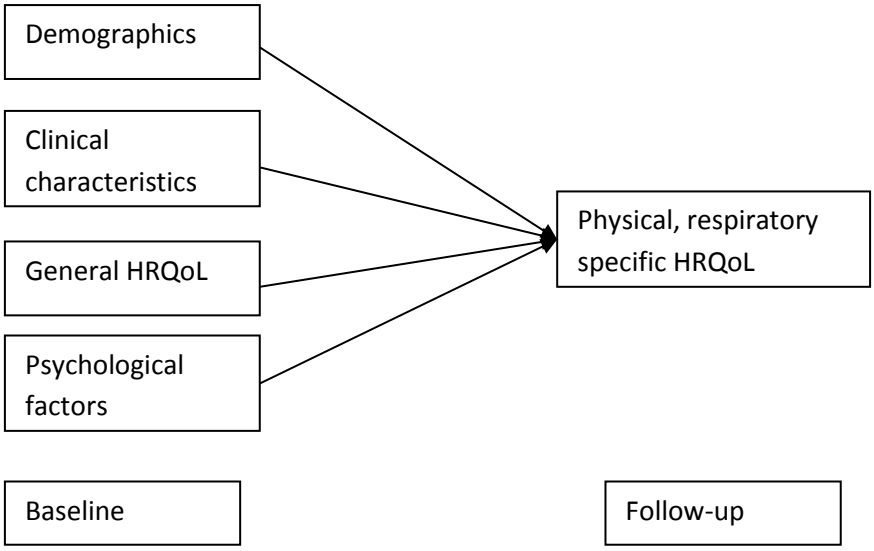
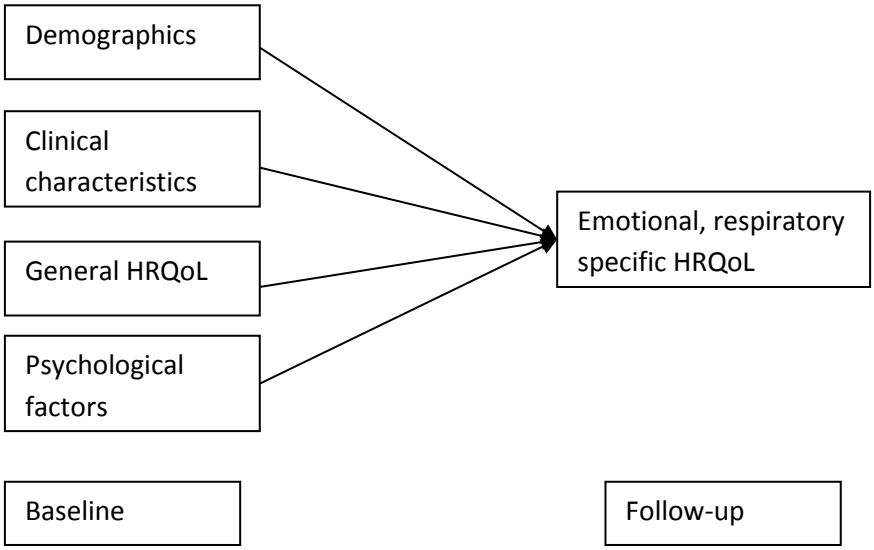


Figure 3.3: Multiple regression model – psychosocial predictors of emotional, respiratory specific HRQoL



In multiple regression analyses the relationship between each predictor and the dependent variable is computed whilst holding constant the effect of the other predictors. The multiple regression method also provides a measure of the overall fit of the suggested model by way of an R^2 value which shows the amount of variance in the outcome variable that the suggested model can account for.[218]

For the purpose of this PhD study all predictor variables were entered simultaneously into the multiple regression models. This technique does not involve making any decisions about the order in which the variables were entered in to the model. The variables included in the model were based purely on previous research and then their significance level from the simple linear regression analysis. There are other methods which can be used to enter variables in to multiple regression analyses, such as hierarchical (blockwise) entry and stepwise methods. In hierarchical entry methods the predictor variables are selected based on previous research and entered in to the model in the order in which they are seen as important based on the literature. In forward stepwise entry methods the predictor variables are entered in to the model in an order which is based on the predictors which have the highest correlation with the outcome variable.[223] The predictor is then only retained in the model if it significantly predicts the outcome. The second predictor variable is then chosen based on which variable can explain the greatest amount of the remaining unexplained variance.[223] In backwards stepwise entry methods all predictor variables are place in the model and the significance value of the t-test for each predictor is analysed. The significance value of the t-test is compared against a removal criterion and removed from the model if it does not make a significant contribution to the power of the model to explain the outcome.[223] The method of simultaneous entry was chosen for this PhD study as it is recommended for testing theories over and above other methods, such as hierarchical (blockwise) entry and stepwise methods. Hierarchical and stepwise entry methods tend to be influenced by random variations in the data and often do not produce results that are replicable.[223]

Both standardised and unstandardised regression coefficients were computed for each multiple regression model in this PhD study. The unstandardised regression coefficient shows the change in the outcome variable for a one unit increase in the predictor variable. For standardised regression coefficients both the outcome and predictor variables are converted in to z scores which show scores in units of standard deviation. Therefore standardised regression coefficients show the change in the outcome variable attributed to a change of one standard deviation in the predictor variable. It is not possible to compare unstandardised regression coefficients across predictor variables as they are a function of the mean and standard deviation of the variable.

Therefore, the use of standardised regression coefficients is useful because it allows us to compare what a 1 unit increase means across predictor variables.

Testing the assumptions of multiple regression

In order to test the goodness of fit of regression models the assumptions of multiple regression should be met.[222] The assumptions are that there should be a linear relationship between the predictor and outcome variables and that the assumption of homoscedasticity should be met. In order to test these assumptions a plot of the standardised residuals (an observable estimate of the unobservable statistical error) was computed to view the linear relationship between each predictor variable and the outcome variable.[222] The assumption of homoscedasticity is met when the variance of the errors is the same across all of the predictor variables.[222] This was tested by examining plots of the residuals for each predictor variable. Homoscedasticity was said to be met where the residuals were scattered about zero, which is the horizontal line, in a relatively even distribution.[222]

3.4.6 Structural equation modelling (SEM)

Following the multiple regression analysis psychological variables were entered in to a structural equation model (SEM). SEM is a technique which allows a theoretical model that is proposed a priori to be tested in three ways.[224] Firstly; SEM provides estimates of the fit of the model to the data which relate to the whole model. Secondly, SEM provides estimates which relate to each hypothesised parameter within the model. Thirdly, SEM is able to simultaneously analyse the inter-relationships (covariance) between each of the variables entered in to the model as well as the model as a whole.[214]

The purpose of using SEM for this PhD study was to gain a detailed understanding of the inter-relationships between depression, anxiety, and panic in predicting HRQoL. SEM offers a more sophisticated and advanced method which is not normally possible in regression analyses. Therefore, it allowed a model to be built which analysed the covariance between each of the psychological predictor variables at baseline and their prospective relationship with HRQoL. SEM also facilitated the specification and testing of one model to investigate if the relationship between anxiety and HRQoL, and/or panic and HRQoL is mediated by depression.

SEM has several advantages over multiple regression analyses. Firstly, SEM is characterised by the inclusion of both observed and latent variables. Latent variables are created where the aim is to represent a theoretical construct within a structural model which is unobservable but can be created out of several of the measured variables included in the data set. Secondly SEM allows

the evaluation of an entire hypothesised theoretical model. Although some SEM can be seen as an extension of multiple regression analyses,[225] the use of SEM facilitates a more sophisticated analyses not normally permissible in regression analyses, such as examining a mediation chain, or examining models where there is a non-recursive relation.[225] In order to examine a mediation chain two sequential regression models would need to be fitted where as SEM allows the simultaneous fitting of both causal pathways.[225] SEM is also able to account for measurement error within the models which regression analyses cannot.[226]

The conduct of SEM has several stages which will now be described in detail.

3.4.7 Stages of structural equation modeling (SEM)

Stage 1: Specifying and testing measurement models

SEM is characterised by two types of models: measurement models and structural models, which are tested in two phases.[224] Firstly, measurement models are specified and estimated. Measurement models are used to relate the variables which were actually observed, (often known as indicators), to theoretical constructs that were not observed and are often known as *latent variables*. Using a measurement model allows the measurement error for each indicator to be identified separately from the latent variable. This method increases the predictive power of the model because measurement error has no predictive or explanatory power.[227] This is an advantage over traditional regression models which assume no error in predictors.

An example of a measurement model is given in Figure 3.4. In this example a measurement model was hypothesised and specified for the construct of depression. Depression was estimated using the seven items of the HADS depression subscale which are proposed to measure depression; these are often described as indicators. In measurement models the extent to which an underlying theoretical construct (e.g. depression) influences the responses given to the indicators is measured using confirmatory factor analysis (CFA).[214;228] In CFA a factor loading is calculated for the relationship between the theoretical construct and each indicator, except for one which is held constant. Factor loadings can be interpreted as regression coefficients, where a high factor loading indicates construct validity. Factor loadings above .40 are considered to be strong and meaningful indicators of the underlying theoretical construct.[227;229;230]

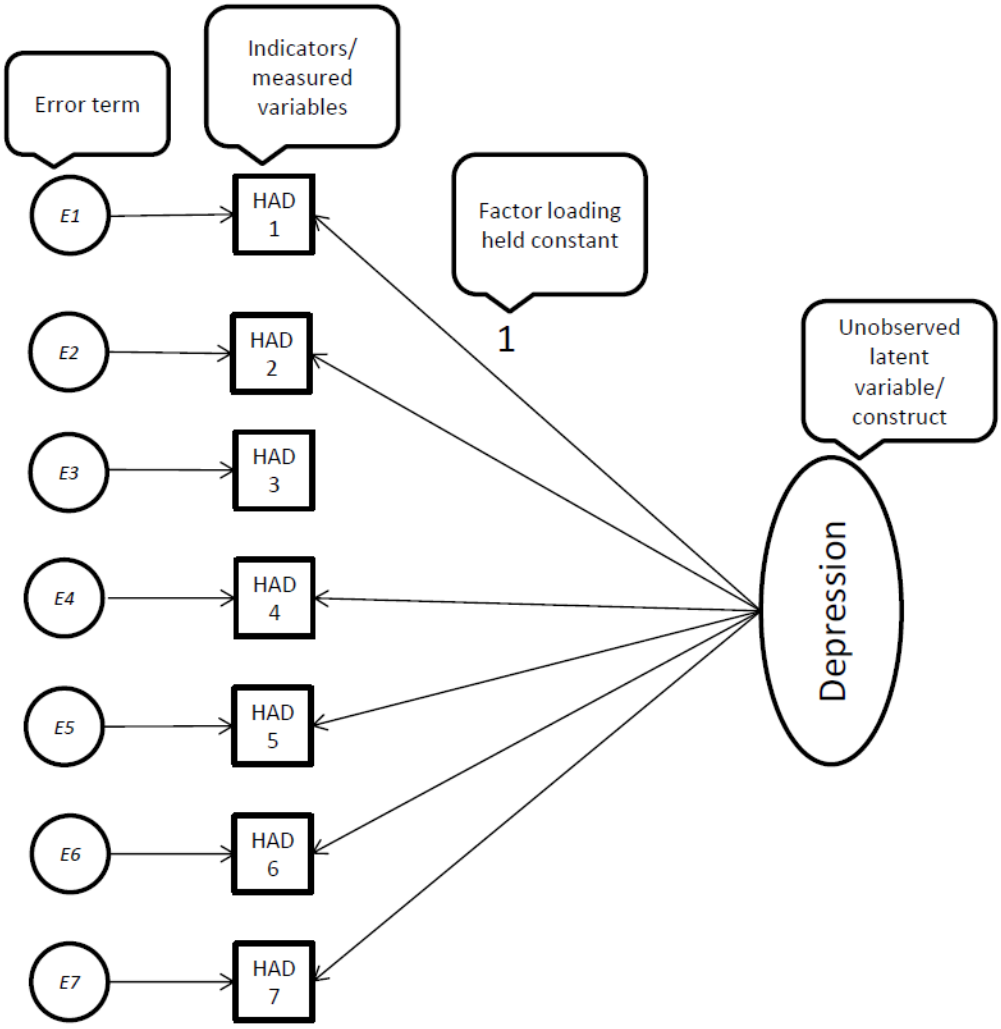
The measurement model shown in Figure 2 represents the hypothesis that HAD1 to HAD7 measure the latent variable depression. The error term represents variance in the indicator that is not accounted for by the latent variable.[214] Error terms are represented by a circle with an arrow

which points to the indicator. This represents that the source of error has an impact on the scores for each indicator.[214]

Once measurement models have been specified they are tested using SEM software. If the relationships between each latent variable fit well they can then be tested in a structural model, which is stage 2 of the SEM process.[224;225]

In this study measurement models were estimated for each of the psychological predictor variables in this study and also for the HRQoL outcome measure.

Figure 3.4: Example of a measurement model for depression



Stage 2: Specifying and testing structural models

Once measurement models had been estimated for each of the psychological predictor variables and the outcome variables, the method of path analysis was used to generate a structural model which could show the causal links between latent variables whilst analysing the inter-relationships between the psychological predictor variables.[227]

For the purpose of this study the following four SEM models were specified a priori:

Structural Equation Model 1: was designed to investigate the inter-relationship between depression, anxiety, panic, and their impact on prospective physical HRQoL (Figure 3.5).

Structural Equation Model 2: was designed to investigate the inter-relationship between depression, anxiety, panic and their prospective impact on emotional HRQoL (Figure 3.6).

Structural Equation Model 3: was designed to test if depression mediated the relationship between anxiety and physical HRQoL and/or panic and physical HRQoL (Figure 3.7).

Structural Equation Model 4: was designed to test if depression mediated the relationship between anxiety and emotional HRQoL and/or panic and emotional HRQoL (Figure 3.8)

Figure 3.5: Structural Equation Model 1

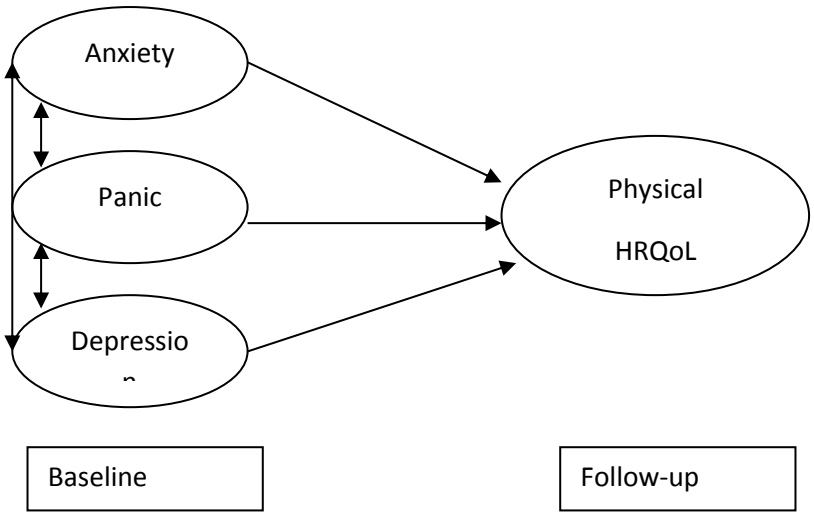


Figure 3.6: Structural Equation Model 2

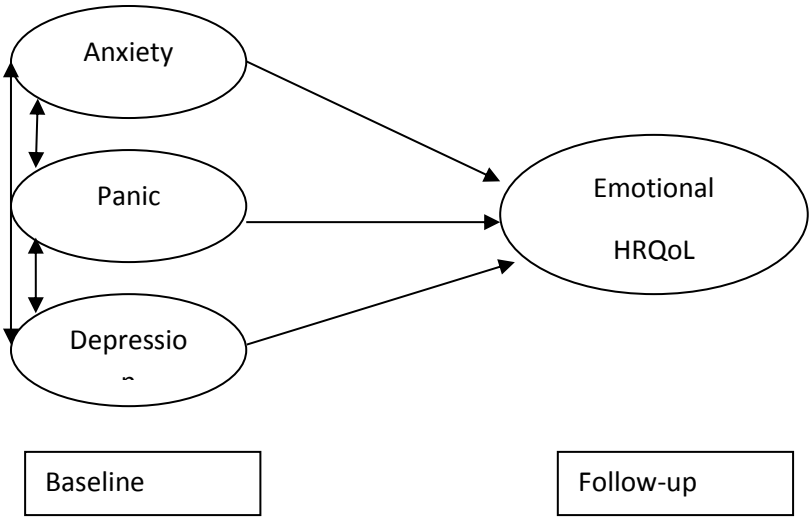


Figure 3.7: Structural Equation Model 3

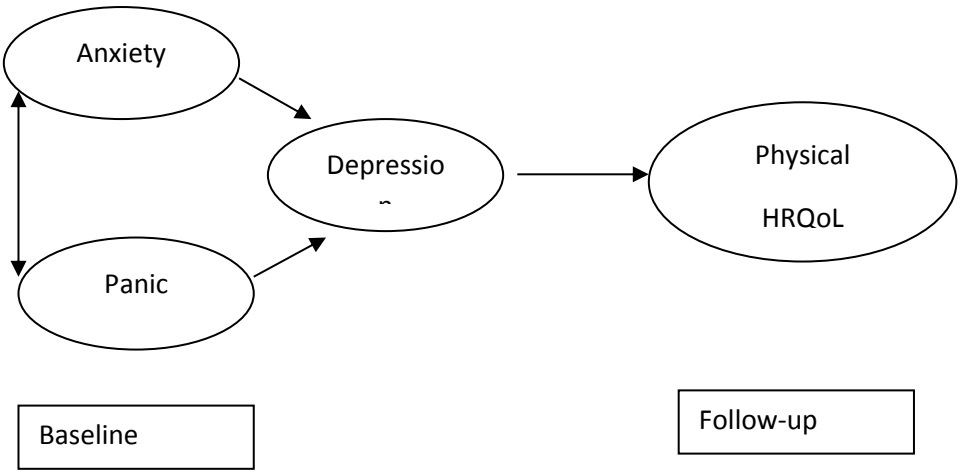
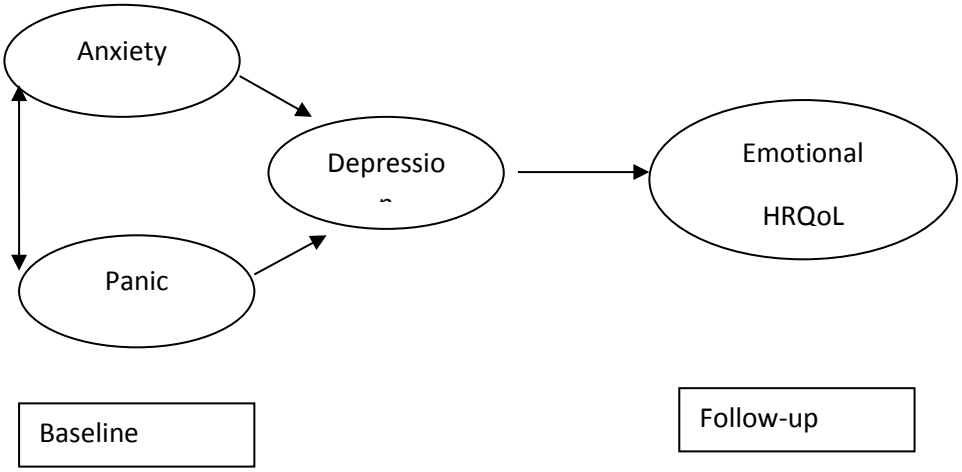


Figure 3.8: Structural Equation Model 4



Stage 3: Testing goodness of fit

Once a hypothesised model has been specified the next stage of SEM is to test the model fit. There are a range of goodness of fit statistics that can be used to assess how well a hypothesised model fits the data when it is tested using SEM. For example, the chi-square test, the comparative fit index (CFI), the root mean square error of approximation (RMSEA), and the Alkaike's Information Criterion (AIC).[231] There is some agreement in the literature on which fit statistics should be reported.[232] A summary of each of the recommended goodness of fit indices can be seen in Table 3.2.

The Chi-square (χ^2) is the only inferential statistic which is used to test how well a SEM model fits the data. All of the other measures are descriptive and therefore exist only as rules of thumb to assess goodness of fit.[232] However; the chi-square test is not necessarily the most useful test of model fit. The chi-square has a disadvantage that it is very sensitive to sample size in that it increases as sample size increases.[224] Therefore, even with modest sample sizes a chi-square will almost always be significant which would indicate that the model tested was a poor fit to the data.[232;233]

Stage 4: Post hoc modifications of models

The fourth and final stage of SEM is to make modifications to the models based on a set of modification indices. Modifications are made to SEM models at this stage with the aim of improving the fit of the model to the data (goodness of fit). However, in this study no post hoc modifications were made to the models according to their fit. The reason for this was because post-hoc modifications that are data-driven have several disadvantages and are not recommended in the absence of strong theories to support them.[234] Making a post-hoc modification can change the purpose of SEM from a confirmatory test of a proposed theory to an exploratory exercise. Models which are over modified can produce results that cannot be generalised in to real life situations and therefore have poor external validity. If a study has poor external validity it means that its results cannot be generalised to the wider population of interest. In applied health services research this is a significant disadvantage as reliable results which can be generalised are required to ensure that research findings can be feasibly implemented in routine settings.

Table 3.2: Summary of the goodness of fit statistics used for structural equation models

Goodness of Fit Indices	Description	Interpretation
Chi-square (χ^2)	The Chi-squared compares the hypothesised model to a saturated model that has no degrees of freedom.[227]	If the null hypothesis can be rejected the model can be said to have a good fit. Therefore, if the χ^2 is small and is not significant good fit is assumed ($p>0.05$).[214;232]
Comparative Fit Index (CFI)	Compares the fit of the hypothesised to a null model that assumes that there is no relationship between the indicator variables.[227;232]	The CFI ranges from 0.0 to 1.0. The larger the CFI the better fit the model is said to be to the data. A CFI of 0.95 indicates a good fit[232;233] and could be interpreted as the hypothesised model fitting the data 95% better than a null model which assumes no relationship between the indicators.[227]
Root Mean Square Error of Approximation (RMSEA)	Examines the amount of error per degree of freedom.[227]	A RMSEA of ≤0.05 indicates good fit; between .05 and .08 indicates reasonable fit, and ≥10 indicates poor fit.[235]
Alkaike's Information Criterion (AIC)	The AIC is used to compare models that have the same set of variables. [214;227] The models compared must be non-hierarchical, or not nested within each other.[214;227]	The AIC can be viewed as a trade-off between the goodness of fit of a model and the complexity of the model. It is useful for choosing between non-hierarchal models which are estimated with the same data.[214] The model with the smallest AIC should be chosen as the preferred model.[214;227]

3.5 Chapter Summary

This chapter has described the methodological design of the longitudinal cohort study conducted for this PhD study.

In summary a longitudinal questionnaire study was conducted nested within the CHOICE Health Survey. COPD patients were recruited from 10 general practices in central Manchester and sent a questionnaire which measured socio demographic characteristics, psychosocial factors, healthcare use and HRQoL. A follow-up questionnaire was sent out 12 months later. Data on the severity of COPD (FEV_1 % predicted) was extracted from medical records held at the general practice. Missing data were analysed and imputed using the multiple imputation method.

The predictors of HRQoL were tested using simple linear regression analyses and multiple regression analyses. Measurement models were constructed for depression, anxiety, panic, and HRQoL. Two SEM models were then specified to investigate the relationships between the psychological variables of depression, anxiety and panic, and whether they predicted physical and emotional HRQoL. Two further SEM models were then constructed to test whether depression mediated the relationship between anxiety, panic, and physical and emotional HRQoL. The results of the regression analyses will be presented in the next chapter. The results of the SEM analyses are presented in Chapters 5 and 6.

4. Descriptive Statistics and Regression Analyses

4.1 Chapter Overview

This chapter presents the recruitment figures and the results of descriptive statistics at baseline, and mean change for variables over the 12 month follow-up period. The results of simple and multiple regression analyses with multiple imputation for missing data are then presented to identify the psychosocial predictors of HRQoL.

Results are reported in accordance with the Strengthening Reporting of Observational Studies in Epidemiology recommendations (STROBE Guidelines).[219]

4.2 Participants

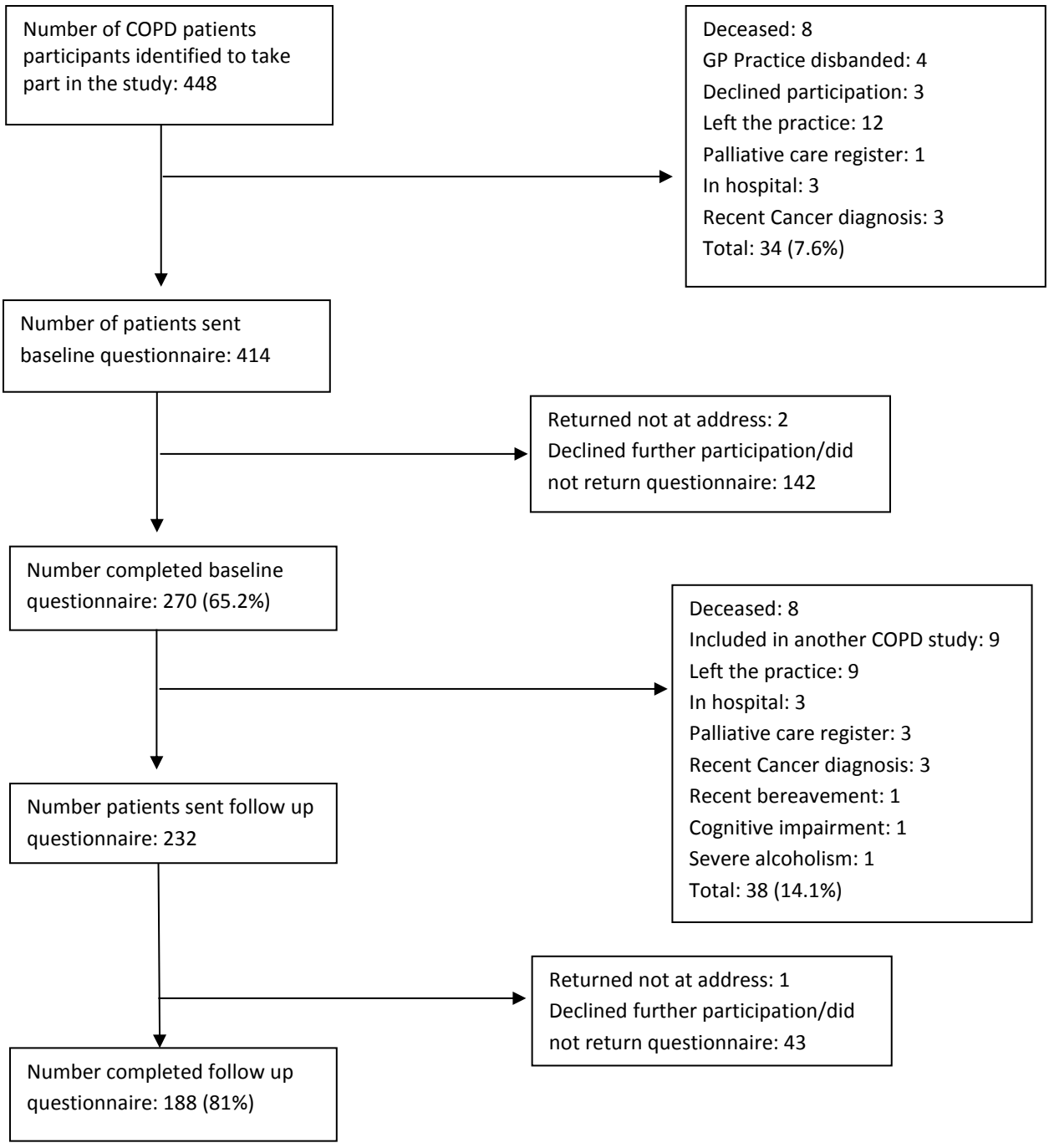
4.2.1 Number of participants at each stage of the study

Figure 4.1 shows the flow of participants through the study.

448 COPD patients completed the CHOICE Health Survey baseline questionnaire and were thus potentially eligible for inclusion in this PhD study. Thirty-four patients were excluded before the initial mailing for this PhD study; 414 participants of CHOICE were sent the baseline questionnaire for this PhD study. 270 participants returned a completed questionnaire at baseline (65% response rate).

Thirty-eight patients were excluded before 12 month follow-up. The mean length of follow-up was 369 days. 188 out of 232 returned a complete follow-up questionnaire (81%).

Figure 4.1: Participant flow chart



4.2 Descriptive Statistics

4.2.1 Baseline demographic and clinical descriptive statistics

Table 4.1 shows the descriptive statistics for demographic and clinical characteristics of participants who returned the questionnaire at baseline.

At baseline, data were available for COPD severity for 165 participants; of these the mean FEV_1 % predicted was 58.2% (SD 18) which indicates moderate COPD. According to the GOLD criteria 8.1% (n=22) had stage 1 mild COPD, 33.3% (n=90) had stage 2 moderate COPD, 16.7% (n=45) had stage III severe COPD, and 2.6% (n=7) had stage IV very severe COPD.

Participants' reported a mean of 2.5 (SD 1.7) comorbid physical health problems, of which arthritis was the most common, occurring in 138 (51%) of participants at baseline (Table 4.2).

Participants mean HADS depression score was 7.0 (SD 4.6) which indicates sub threshold symptoms of depression. 43% (n=116) of participants scored greater than 8 on the HAD depression scale. 24% (n=64) of participants scored greater than 11 which indicates that this sub-group of participants met the criteria for a probable diagnosis of depression in patients with physical health problems.[197] Participants mean HADS anxiety score was 7.6 (SD 4.8) which indicates sub threshold symptoms of anxiety. 46% (n=125) scored greater than 8 on the HAD anxiety scale. 26% (n=69) scored greater than 11 which indicates that they met the criteria for a diagnosis of anxiety. The mean panic score was 4.1 (SD 6.9) with 31.1% of participants reporting that they had experienced symptoms of panic. 14% (n = 39) met the criteria for a diagnosis of panic disorder.

Participants general HRQoL was poor with low mean scores on the SF-12 physical and mental components. Respiratory HRQoL scores were also poor with mean scores of 3.5 (SD 1.5) and 4.4 (1.5) on the Chronic Respiratory Questionnaire physical and emotional subscales respectively.

Over the 12 months before they completed the baseline questionnaire, participants had a mean of 7.4 (SD 7.3) scheduled healthcare contacts and 1.6 (SD 2.9) unscheduled healthcare contacts.

The general practice's that took part in the CHOICE programme were all recruited from deprived areas of Central Manchester. Eight out of the ten practices were in the top 10% of most deprived areas in England according to the Index of Multiple Deprivation (IMD), with 5 in the top 5% and 2 in the top 1%.[236]

Table 4.1: Self-reported demographic and clinical characteristics at baseline

Variable	Statistic		SD/IQR
Age (n=270)	Mean	68.9	10.7
	Median	69.0	62.0-76.0
Comorbid Health Problems (n=270)	Mean	2.5	1.7
	Median	2.0	1.0-3.0
COPD Severity	Mean	58.2	18
FEV_1% Predicted (n=165)	Median	58.2	45.5-69.0
Depression (n=270)	Mean	7.0	4.6
	Median	7.0	3.0-10.0
Anxiety (n=270)	Mean	7.6	4.8
	Median	7.0	4.0-11.0
Panic (n=270)	Mean	4.5	7.0
	Median	0.0	0.0-10.0
Threatening life events (n=270)	Mean	1.2	1.6
	Median	1.0	0.0-2.0
General Physical HRQoL (n=269)	Mean	32.7	11.0
(SF-12 PCS)	Median	30.3	24.3-39.7
General Mental HRQoL (n=269)	Mean	43.2	12.4
(SF-12 MCS)	Median	43.2	33.6-53.6
Respiratory Physical HRQoL (n=270)	Mean	3.6	1.5
CRQ Physical	Median	3.4	2.4-4.8
Respiratory Emotional HRQoL (n=270)	Mean	4.4	1.5
CRQ Emotion	Median	4.4	3.3-5.5
Scheduled healthcare contacts (n=270)	Mean	7.4	7.3
	Median	6.0	3.0-10.0
Unscheduled healthcare contacts (n=270)	Mean	1.6	2.9
	Median	0.0	0.0-2.0

SD - Standard Deviation, IQR - Interquartile Range for the 25^{th} and 75^{th} percentile.

Table 4.2: Frequency of self-reported comorbid health problems

Comorbid condition	n	%
Heart disease	62	22.96
Asthma	125	46.30
Diabetes	46	17.04
Cancer	16	5.93
Stomach	47	17.41
High Blood Pressure	106	39.26
Arthritis	138	51.11
Other condition	155	57.41

4.2.2 Comparison of those who did and did not complete PhD baseline questionnaire

There were 178 COPD patients who completed the initial CHOICE Health Survey but who did not return the baseline questionnaire for this PhD study (referred to as PhD non responders). These patients were compared across demographic characteristics, psychological, and general HRQoL measures.

Independent samples t-tests were used to investigate the difference between PhD responders and non-responders in terms of gender and age. There was no significant difference in gender between CHOICE Health Survey participants who did (50.9% male) and those who did not (48.4% male) complete this PhD study. However, those who responded to the PhD study questionnaire were more likely to be older (mean=68 years, SD 10.6) than those who did not (mean=66, SD 12.9) and this difference was significant ($t(447) = -2.02$, $p<0.05$).

Continuous data for psychological and HRQoL variables were not normally distributed and Mann –Whitney U tests were used to investigate if there were differences between PhD responders and non responders. Data were available from the CHOICE Health Survey to compare PhD responders and non responders across measures of depression, anxiety and general HRQoL as measured by the SF-12 physical and mental component scores (SF-12 PCS and SF-12 MCS). It was not possible to compare PhD responders and non responders on measures of panic or respiratory HRQoL as these factors were not measured in the original CHOICE Health Survey.

Responders to the PhD study had significantly fewer symptoms of depression (median = 4.0) than those who did not (median = 11.0) respond to the PhD study ($U=1695.50$, $Z=-16.57$, $p=<0.001$). PhD responders also had fewer symptoms of anxiety (median = 7.0) than those who

did not (median = 9.0) and this difference was significant (U=20449.50, Z=-2.162, p=0.03). On the general HRQoL measure (SF-12) PhD non responders had lower scores for the mental component score (median = 36.61) than those who did respond (median =42.64) and this difference was significant (U=20513, Z=-2.136, p=0.03). There was no significant difference between those who did (median = 30.46) and those who did not (median = 27.55) respond to the PhD study on the physical component of general HRQoL.

The results of the comparison of PhD responders and non responders show that those CHOICE Health Survey participants who responded to the PhD study had fewer symptoms of depression and anxiety than those who did not. PhD responders also had better emotional HRQoL. There was no significant difference between the two groups in terms of physical HRQoL but there was a trend towards those who responded to the PhD study having better physical HRQoL as well.

4.2.3 Comparison of those who did and did not complete 12 month follow up for PhD study

There were 82 patients who completed the baseline PhD questionnaire but who did not complete 12 month follow up. Those patients who did not complete 12 month follow up were compared with those who did across demographic characteristics, psychological, general HRQoL, and respiratory HRQoL measures.

Independent samples t-tests were used to compare those who did and did not complete 12 month follow up across age and gender. There was no significant difference in the age or gender of those patients who did and did not complete 12 month follow up. Continuous data for psychological and HRQoL variables were not normally distributed so Mann-Whitney U tests were used to compare the two groups.

There was no significant difference in HADS depression scores between those who did (median = 7) and did not (median = 7) complete 12 month follow up (U=7086.5, Z=-1.10, p=.291). Those participant who did not respond at 12 month follow up had a higher median scores for HADS anxiety (median = 8) than those who did not respond (median = 7) but this difference was not significant (U=7229, Z=-.814, p=.416). The median score on the PDSR measure of panic was 0 with a interquartile range of 0-6.6 for responders and 0-11.5 for non responders. This indicates that there may have been a higher rate of panic symptoms in the group who did not respond to 12 month follow up but this difference was not significant (U=7141, Z=-1.162, p=-.245).

Both responders and non responders to 12 month follow up had a median score of 30.3 for the physical component of general HRQoL. Those participants who responded to the 12 month

follow up questionnaire had a higher median score for the mental component score of the SF-12 (median = 43.1) than those who did not (median = 42.1) but this difference was not significant (U=7567.5, Z=-.078, p=-.938). For physical respiratory HRQoL, responders at 12 months had a median score of 3.4 and non responders 3.3; this difference was not significant (U=7886, Z=-.078, p=.938). There was no significant difference between responders at 12 months (median = 4.5) and non responders (median = 4.4) for emotional respiratory HRQoL (U=7416, Z=-.494, p=-.621).

4.2.4 Correlation between baseline predictors and prospective respiratory HRQoL

Spearman's correlations were used to investigate the relationships between the variables measured at baseline: age, comorbidities, FEV_1 % Predicted, all psychological variables (depression, anxiety, panic), general HRQoL, healthcare use, and respiratory HRQoL measured at 12 months (see Table 4.3).

A greater number of comorbidities, threatening life events, symptoms of depression, anxiety, panic, and scheduled and unscheduled healthcare use at baseline were significantly correlated with a decrease in physical and emotional HRQoL at 12 months. Increased FEV_1 % predicted, which indicates better lung function and milder COPD, was significantly correlated with better physical HRQoL at 12 months but was not significantly associated with emotional HRQoL. The results of the Spearman's correlations can be seen in Statistical Appendix B.

4.2.5 Analysis of the change in psychological and HRQoL variables over 12 months

Table 4.3 shows the descriptive statistics and results of Wilcoxon Sign Rank Test for the difference between self-report measures of depression, anxiety, panic, general HRQoL, respiratory specific HRQoL and healthcare use at baseline and follow up. This was for all participants who completed both baseline and follow-up questionnaires (n=188).

The scores on psychological variables remained stable over the 12 months follow-up period with no significant change in depression, anxiety, or panic scores. Median scores on the SF-12 PCS decreased slightly over the 12 months period which indicates a reduction in physical HRQoL but this change was not significant. However, there was an increase of 0.56 in CRQ Physical scores which indicates a small improvement in respiratory specific physical HRQoL; although it was not statistically significant it did meet the criteria for the minimal important difference (0.5) for this scale. [211] There was also a trend towards an improvement in both

general and respiratory specific emotional HRQoL over the 12 months, although neither change was statistically significant.

Over the 12 month follow-up period there was a decrease in both scheduled healthcare (Z=-1.505, p=.132) and unscheduled healthcare use (Z=-.684, p=.494) but this change was not significant.

Table 4.3: Wilcoxon sign rank test for change between baseline and follow-up psychological and HRQoL variables and in healthcare use

		Median	IQR	Z	p
Depression	Baseline	7	3-10		
	12 Months	7	3-10	-.391	.696
Anxiety	Baseline	7	4-10		
	12 Months	7	4-10	-.646	.518
Panic	Baseline	0	0-6.6		
	12 Months	0	0-5.0	-.254	.799
SF-12 PCS	Baseline	30.33	24.21-40.41		
	12 Months	29.34	24.10-38.49	-.200	.841
SF-12 MCS	Baseline	43.31	33.92-53.50		
	12 Months	47.65	33.13-55.21	-1.051	.293
CRQ Physical	Baseline	3.44	2.33-4.89		
	12 Months	4.00	2.00-5.00	-.449	.654
CRQ Emotion	Baseline	4.50	3.31-5.61		
	12 Months	5.00	3.00-6.00	-.937	.349
Scheduled Healthcare Use	Baseline	6.00	3.00-10.00		
	12 Months	5.00	2.00-9.00	-1.505	.132
Unscheduled Healthcare Use	Baseline	0.00	0.00-2.00		
	12 Months	0.00	0.00-2.00	-.684	.494

SD - Standard Deviation, IQR - Interquartile Range for the 25^{th} and 75^{th} percentile.

SF-12 PCS – Physical component Score. SF-12 MCS – Mental Component Score. CRQ – Chronic Respiratory Questionnaire.

4.3 Longitudinal Predictors of Physical Respiratory HRQoL

4.3.1 Simple linear regression analysis of longitudinal predictors of physical respiratory HRQoL

A series of simple linear regression analyses were conducted to examine the relationship between all variables measured at baseline and physical respiratory HRQoL at 12 month follow-up. The results are shown in Table 4.4.

An increase in comorbidities, threatening life events, panic, depression, anxiety, scheduled healthcare use, and unscheduled healthcare use significantly predicted worse physical respiratory HRQoL at 12 month follow up.p<.0.01). Physical respiratory HRQoL was also predicted by COPD severity. An increase in FEV_1 percent predicted, (which indicates better lung function and milder COPD), predicted better physical respiratory HRQoL. Similarly, higher scores on both physical and mental subscales of the SF-12, which indicate better general HRQoL, predicted a significant increase in scores for physical respiratory HRQoL. Age, gender and living alone did not significantly predict physical respiratory HRQoL.

The baseline variables which were found to be significant predictors of physical HRQoL at follow-up in simple linear regression analyses at a level of $p<0.05$ were then entered into a multiple regression model.

Table 4.4: Simple linear regression analyses for baseline predictors of Physical HRQoL at 12 months

Independent variable	Unstandardised *b* (SE)	95% Confidence intervals		Standardised** Beta (β)	t	p
		Lower	Upper			
Age	0.00 (0.01)	-0.02	0.02	0.00	-0.01	0.993
Gender	-0.05 (0.22)	-0.48	0.38	-0.02	-0.24	0.814
Comorbidities	-0.16 (0.04)	-0.29	-0.04	-0.19	-2.58	0.011
Living alone	-0.01 (0.01)	-0.03	0.01	-0.05	-0.74	0.461
Threatening life events	-0.21 (0.07)	-0.35	-0.07	-0.22	-3.02	0.003
FEV_1 % predicted*	0.01 (0.01)	0.00	0.03	0.17	2.09	0.039
Panic	-0.08 (0.02)	-0.11	-0.05	-0.36	-5.20	0.000
Depression	-0.20 (0.02)	-0.24	-0.17	-0.61	-10.50	0.000
Anxiety	-0.14 (0.02)	-0.18	-0.94	-0.41	-6.21	0.000
SF-12 PCS	0.07 (0.01)	0.06	0.09	0.57	9.43	0.000
SF-12 MCS	0.07 (0.01)	0.06	0.09	0.57	9.37	0.000
EQ-5D Total	5.42 (0.61)	4.22	6.63	0.55	8.89	0.000
Scheduled care use	-0.05 (0.01)	-0.08	-0.02	-0.23	-3.21	0.002
Unscheduled care use	-0.12 (0.03)	-0.19	-0.05	-0.24	-3.36	0.001

*Missing data imputed using multiple imputation methods

** Standardised Beta (β) shows the change in physical respiratory HRQoL at 12 months for every 1 standard deviation increase in the predictor variable at baseline.

4.3.2 Multivariable regression models of longitudinal predictors of physical respiratory HRQoL

Table 4.5 shows the results of the multiple regression model for longitudinal predictors of physical respiratory HRQoL. In the multivariable model an increase in symptoms of depression and use of unscheduled healthcare predicted a decline in physical respiratory HRQoL at 12 months. Lower scores for anxiety and both the physical and mental subscales of the general HRQoL measure (SF-12), which indicate less anxiety symptoms and better general HRQoL, were significant predictors of better physical respiratory HRQoL at 12month follow up. The number of physical comorbidities, threatening life events, COPD severity and scheduled healthcare use were no longer significant predictors of physical respiratory HRQoL in the multivariable model. This model explained 49% (adjusted R^2) of the variance in physical respiratory HRQoL.

To assess whether there was high collinearity between the variables entered in to the multivariable regression model multicollinearity between all variables was tested. No tolerance value was found to be >.10 and all variance inflation factors (VIF) were ≤4, therefore it can be assumed that although variables were highly correlated there was no significant problem with collinearity in this model. However, depression had a VIF score that was approaching 4 so a sensitivity analysis was conducted where depression was removed from the multiple regression model.

When depression was removed from the model anxiety was no longer a significant predictor of physical respiratory HRQoL. However, higher scores on both the physical and mental subscales of general HRQoL measure (SF-12) continued to predict better physical respiratory HRQoL. Increased use of unscheduled healthcare use also remained a significant predictor of worse physical respiratory HRQoL. This model accounted for 47% of the variance in physical respiratory HRQoL. The results are shown in Table 4.6.

Table 4.5: Multiple linear regression model for baseline predictors of physical respiratory HRQoL at 12 months

Independent variable	Unstandardised b (SE)	95% Confidence Intervals		Standardised ** Beta (β)	t	p
		Lower	Upper			
Comorbidities	-0.01 (0.05)	-0.11	0.10	-0.01	-0.14	0.891
Threatening life events	-0.09 (0.06)	-0.20	0.02	-0.09	-1.56	0.121
FEV_1 % predicted*	0.01 (0.09)	-0.03	0.02	0.09	1.45	0.150
Panic	-0.02 (0.02)	-0.05	0.01	-0.07	-1.08	0.281
Depression	-0.09 (0.03)	-0.15	-0.02	-0.26	-2.50	0.014
Anxiety	0.07 (0.03)	0.01	0.13	0.21	2.29	0.023
SF-12 PCS	0.04 (0.01)	0.02	0.06	0.29	3.35	0.001
SF-12 MCS	0.03 (0.01)	0.01	0.06	0.27	2.93	0.004
EQ-5D Total	0.47 (0.88)	-1.27	2.22	0.05	0.53	0.594
Scheduled care use	-0.01 (0.01)	-0.04	0.01	-0.06	-1.10	0.272
Unscheduled care use	-0.06 (0.03)	-0.11	-0.01	-0.13	-2.31	0.022

R^2 0.522

Adjusted R^2 0.492

*Missing data imputed using multiple imputation methods

** Standardised Beta (β) shows the change in physical respiratory HRQoL at 12 months for every 1 standard deviation increase in the predictor variable at baseline

Table 4.6: Multiple linear regression model for baseline predictors of physical respiratory HRQoL at 12 months, excluding depression

Independent variable	Unstandardised b (SE)	95% Confidence Intervals		Standardised** Beta (β)	t	p
		Lower	Upper			
Comorbidities	-0.01 (0.05)	-0.12	0.09	-0.01	-0.25	0.806
Threatening life events	-0.07 (0.06)	-0.18	0.05	-0.07	-1.18	0.240
FEV_1 % predicted*	0.01 (0.01)	0.00	0.02	0.10	1.47	0.143
Panic	-0.02 (0.02)	-0.05	0.02	-0.07	-1.03	0.303
Anxiety	0.45 (0.03)	-0.05	0.02	0.14	1.54	0.125
SF-12 PCS	0.05 (0.01)	0.03	0.07	0.37	4.72	0.000
SF-12 MCS	0.05 (0.01)	0.03	0.07	0.37	4.43	0.000
EQ-5D Total	0.55 (0.90)	-1.22	2.32	0.06	0.61	0.541
Scheduled care use	-0.01 (0.01)	-0.04	0.01	-0.07	-1.25	0.214
Unscheduled care use	-0.06 (0.03)	-0.11	0.00	-0.11	-2.05	0.042

R^2 0.505

Adjusted R^2 0.477

*Missing data imputed using multiple imputation methods

** Standardised Beta (β) shows the change in physical respiratory HRQoL at 12 months for every 1 standard deviation increase in the predictor variable at baseline

4.4 Longitudinal Predictors of Emotional Respiratory HRQoL

4.4.1 Simple linear regression analysis of longitudinal predictors of emotional respiratory HRQoL

To assess the baseline predictors of emotional respiratory HRQoL at 12 month follow-up a series of simple linear regression analyses were conducted similar to those for physical respiratory HRQoL presented above. The results are shown in Table 4.7.

Table 8 shows that being older significantly predicted better emotional respiratory HRQoL at 12 month follow up. Whereas having more comorbid health problems, more threatening life events, and using more scheduled and unscheduled health care predicted a decline in emotional respiratory HRQoL at 12 months. Also, having more symptoms of depression, anxietyand panic at baseline significantly predicted worse emotional respiratory HRQoL at 12 months. Better general HRQoL at baseline, as measured by the physical and mental component score of the SF-12 and the EQ-5D, seemed to have a protective effect resulting in better respiratory emotional respiratory HRQoL at 12 months. Gender and COPD severity had no significant effect on emotional respiratory HRQoL at 12 months.

Table 4.7: Simple linear regression analyses for baseline predictors of emotional HRQoL at 12 months

Independent variable	Unstandardised b (SE)	95% Confidence Intervals		Standardised** Beta (β)	t	p
		Lower	Upper			
Age	0.03 (0.01)	0.01	0.05	0.22	3.01	0.003
Gender	0.00 (0.22)	-0.43	0.44	0.00	0.02	0.987
Comorbidities	-0.18 (0.06)	-0.31	0.05	-0.20	-2.81	0.005
Living alone	-0.02 (0.01)	-0.04	0.00	-0.14	-1.92	0.057
Threatening life events	-0.27 (0.07)	-0.41	-0.13	-0.27	-3.80	0.000
FEV_1 % predicted*	0.01 (0.01)	-0.01	0.02	0.11	1.25	0.212
Panic	-0.10 (0.02)	-0.13	-0.07	-0.45	-6.94	0.000
Depression	-0.25 (0.02)	-0.28	0.21	-0.73	-14.65	0.000
Anxiety	-0.23 (0.02)	-0.27	-0.20	-0.70	-13.18	0.000
SF-12 PCS	0.07 (0.01)	0.05	0.08	0.50	7.75	0.000
SF-12 MCS	0.09 (0.01)	0.08	0.10	0.73	14.54	0.000
EQ-5D Total	5.93 (0.60)	4.75	7.10	0.59	9.95	0.000
Scheduled care use	-0.03 (0.01)	-0.06	0.00	-0.16	-2.27	0.025
Unscheduled care use	-0.08 (0.04)	-0.15	0.01	-0.16	-2.27	0.024

*Missing data imputed using multiple imputation methods

** Standardised Beta (β) shows the change in emotional respiratory HRQoL at 12 months for every 1 standard deviation increase in the predictor variable at baseline

4.4.2 Multivariable regression models of longitudinal predictors of emotional respiratory HRQoL

The baseline variables that were found to be significant predictors of emotional respiratory HRQoL at follow-up in the simple linear regression analyses at a level of $p<0.05$ were then entered into a multivariable regression model. The results of which are shown in Table 4.8.

In the multivariable regression analyses having more symptoms of depression and anxiety significantly predicted worse emotional respiratory HRQoL. Higher scores on the mental component of the general HRQoL measure (SF-12) predicted better emotional respiratory HRQoL. Age, comorbidities, threatening life events, panic, general physical HRQoL (SF-12 PCS and EQ-5D) and both scheduled and unscheduled care use were no longer significant predictors of emotional respiratory HRQoL in the multivariable models. This model explained 63% (adjusted R^2) of the variance.

A sensitivity analysis was performed to exclude depression from the multiple regression model because its VIF score approached 4. When depression is removed from the model anxiety and general mental HRQoL (SF-12 MCS) remained significant predictors of emotional respiratory HRQoL. General physical HRQoL (SF-12 PCS) became a significant predictor of emotional respiratory HRQoL. This model explained 61% (adjusted R^2) of the variance. The results of the sensitivity analysis are shown in Table 4.9.

Table 4.8: Multiple linear regression model for baseline predictors of emotional respiratory HRQoL at 12 months

Independent variable	Unstandardised b (SE)	95% Confidence Intervals		Standardised* Beta (β)	t	p
		Lower	Upper			
Age	0.01 (0.01)	-0.01	0.02	0.05	1.00	0.320
Comorbidities	-0.02 (0.04)	-0.10	0.07	-0.02	-0.35	0.728
Threatening life events	-0.04 (0.05)	-0.13	0.06	-0.04	-0.72	0.471
Panic	0.00 (0.01)	-0.02	0.03	0.01	0.24	0.813
Depression	-0.09 (0.03)	-0.15	-0.03	-0.27	-3.04	0.003
Anxiety	-0.07 (0.03)	-0.12	-0.02	-0.21	-2.71	0.007
SF-12 PCS	0.01 (0.01)	-0.01	0.03	0.07	0.95	0.342
SF-12 MCS	0.04 (0.01)	0.02	0.06	0.28	3.54	0.001
EQ-5D Total	0.74 (0.76)	-0.77	2.24	0.07	0.97	0.335
Scheduled care use	0.01 (0.01)	-0.01	0.03	0.03	0.54	0.592
Unscheduled care use	-0.03 (0.02)	0.98	4.68	0.03	-1.24	0.217

R^2 0.649

Adjusted R^2 0.627

*Standardised Beta (β) shows the change in emotional respiratory HRQoL at 12 months for every 1 standard deviation increase in the predictor variable at baseline

Table 4.9: Multiple linear regression model for baseline predictors of emotional respiratory HRQoL at 12 months, excluding depression

Independent variable	Unstandardised b (SE)	95% Confidence Intervals		Standardised* Beta (β)	t	p
		Lower	Upper			
Age	0.01 (0.01)	-0.01	0.02	0.05	1.08	0.282
Comorbidities	-0.02 (0.05)	-0.11	0.07	-0.02	-0.48	0.631
Threatening life events	-0.01 (0.05)	-0.11	0.09	-0.01	-0.23	0.817
Panic	0.00 (0.01)	-0.02	0.03	0.02	0.27	0.787
Anxiety	-0.10 (0.03)	-0.15	-0.05	-0.29	-3.81	0.000
SF-12 PCS	0.02 (0.01)	0.00	0.04	0.16	2.38	0.018
SF-12 MCS	0.05 (0.01)	0.03	0.07	0.39	5.34	0.000
EQ-5D Total	0.81 (0.78)	-0.73	2.35	0.08	1.04	0.301
Scheduled care use	0.00 (0.01)	-0.02	0.02	0.02	0.37	0.715
Unscheduled care use	-0.02 (0.02)	-0.07	0.02	-0.05	-0.94	0.348

R^2 0.630

Adjusted R^2 0.609

*Standardised Beta (β) shows the change in emotional respiratory HRQoL at 12 months for every 1 standard deviation increase in the predictor variable at baseline

4.5 Chapter Summary

This chapter has described the characteristics of the sample of COPD patients recruited in to this longitudinal cohort study. It included a presentation of the results of simple and multiple regression tests designed to identify which psychosocial factors predicted both physical and emotional, respiratory HRQoL.

In summary the response rate at baseline was 65.2%. The majority of patients had moderate COPD[1]. 43% had symptoms of depression and 46% had symptoms of anxiety. Almost one third of the sample (31.1%) reported experiencing symptoms of panic and 14% met the criteria for a diagnosis of panic disorder according to the PDSR.

In simple linear regression analyses panic was a significant predictor of both physical and emotional respiratory specific HRQoL. However, panic did not remain a significant predictor when entered in to multiple regression models. The significant predictors of both physical and emotional, respiratory specific HRQoL in multivariable models were: depression, anxiety, general physical HRQoL, general mental HRQoL, and unscheduled care use.

In the next chapter the specification of measurement models for use in SEM analyses will be described.

5. Measurement Models

5.1 Chapter Overview

The regression models presented in the previous chapter demonstrated that whilst panic predicts respiratory HRQoL in simple linear regression analyses its predictive effect was not maintained when entered into a multivariable model with other psychosocial predictors. It is possible that panic was not a significant predictor of respiratory HRQoL when analysed in multivariable models with depression because depression is the greatest predictor of respiratory HRQoL or that the impact of panic is accounted for by general anxiety. However, this is only speculation and therefore it was important to specify and test the model using SEM to further explore the inter-relationships between the psychological predictors, depression, anxiety and panic, and prospective physical and emotional HRQoL.

As discussed in Chapter 3 (Methods) SEM is a sophisticated statistical technique that estimates the fit of a set of data to a model. The structural equation model is prespecified based on previous literature and research. In the context of this PhD, SEM has several advantages over linear regression analyses as it allows the simultaneous modelling of the inter-relationships between the psychological predictor variables and the estimation of their ability to predict prospective HRQoL. Furthermore, SEM also allows the construction of latent variables through measurement models. Latent variables represent unmeasured constructs that arise out of a collection of measured variables, such as depression, anxiety and panic. It is the construction and analysis of the measurement models for this PhD study which will be outlined in this chapter.

Measurement models demonstrate the relationship between indicators that have been measured and the latent variables, or factors, which the indicators are proposed to contribute to.[214] For example, where depression has been measured using the Hospital Anxiety and Depression Scale (HADS) each of the 7 questions relating to depression which are completed by participant are known as indicators. The response to each indicator is driven by the unobserved latent concept which in this example would be depression. The construction and analysis of a measurement model allows us to see how well each of the indicators (e.g. depression questions on the HADS) contributes to the latent variable (depression). The second stage of SEM is to input the measurement models into the prespecified structural path model. The structural path models for this thesis will be presented in the next chapter (Chapter 6).

5.2 Statistical Analysis of Measurement Models

Measurement models were generated for each of the psychological predictor variables based and also for the outcome variables (physical and emotional respiratory HRQoL) at 12 month follow-up. Each measurement model was specified using the symbols shown in Figure 5.1.

The measurement models were tested using confirmatory factor analysis (CFA) to show whether, in this sample of primary care COPD patients, the proposed relationship between each indicator and the latent concept was supported. Using CFA allows each indicator to have its own error term which allows for variance in answers to each individual question.[227] Each indicator variable was considered to be a strong and meaningful indicator of its respective latent variable if the factor loadings were ≥.40.[227;229;230] The statistical significance of each factor loading was evaluated at an alpha level of 0.05.

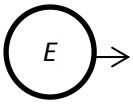
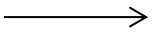
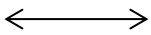
The strength of each model was assessed using goodness of fit indices. Goodness of fit refers to how well the hypothesised model fits the data that was actually observed in the sample. To assess how well the measurement models fit the observed data several fit indices were used. A full description of the fit indices is given in the Methods section (Chapter 3) and the indices which have been used for assessment of the fit of measurement models are summarised here:

I. Chi-square (χ^2) – if a hypothesised model fits the data well the χ^2 is small and would not be significant ($p>0.05$).[214;232]

II. Comparative fit indices (CFI) – The larger the CFI the better fit the model is. A CFI of 0.95 would indicate that the hypothesised model is a 95% better fit than the null model.[227;232;233]

III. Root mean square error of approximation (RMSEA) – A smaller RMSEA indicates better fit. Therefore, a result of ≤0.05 indicates that the data is a good fit for the model; ≤08 indicates it is a moderate fit, and ≥10 indicates it is a poor fit.[227;235]

Figure 5.1: Specification of measurement and SEM models

Symbol	Description	Definition
	Measured variable or indicator	The variables that were directly measured in the questionnaire.
	Latent variable	A variable which has not been directly measured but can be inferred from a selection of variables which were directly measured.
	Error term	The lines which go from the error term to the indicators represent other sources of influence on the indicator over and above the influence of the factor that the indicator is presumed to measure.
	Direction of effect	This single-headed arrow represents the presumed direction of effect between a latent variable (factor) and a measured variable (indicator). The statistical estimates are called factor loadings and can be interpreted as unstandardised regression coefficients.
	Covariance	A double- headed arrow represents covariance between two latent variables.

5.3 Measurement Models for Psychological Variables at Baseline

5.3.1 Measurement model for HADS depression scale

The measurement model for depression was constructed using the 7 questions from the HADS measure which are proposed to indicate symptoms of depression.[159] The 7 questions are represented below as HAD2, 4, 6, 8, 10, 12 and 14.

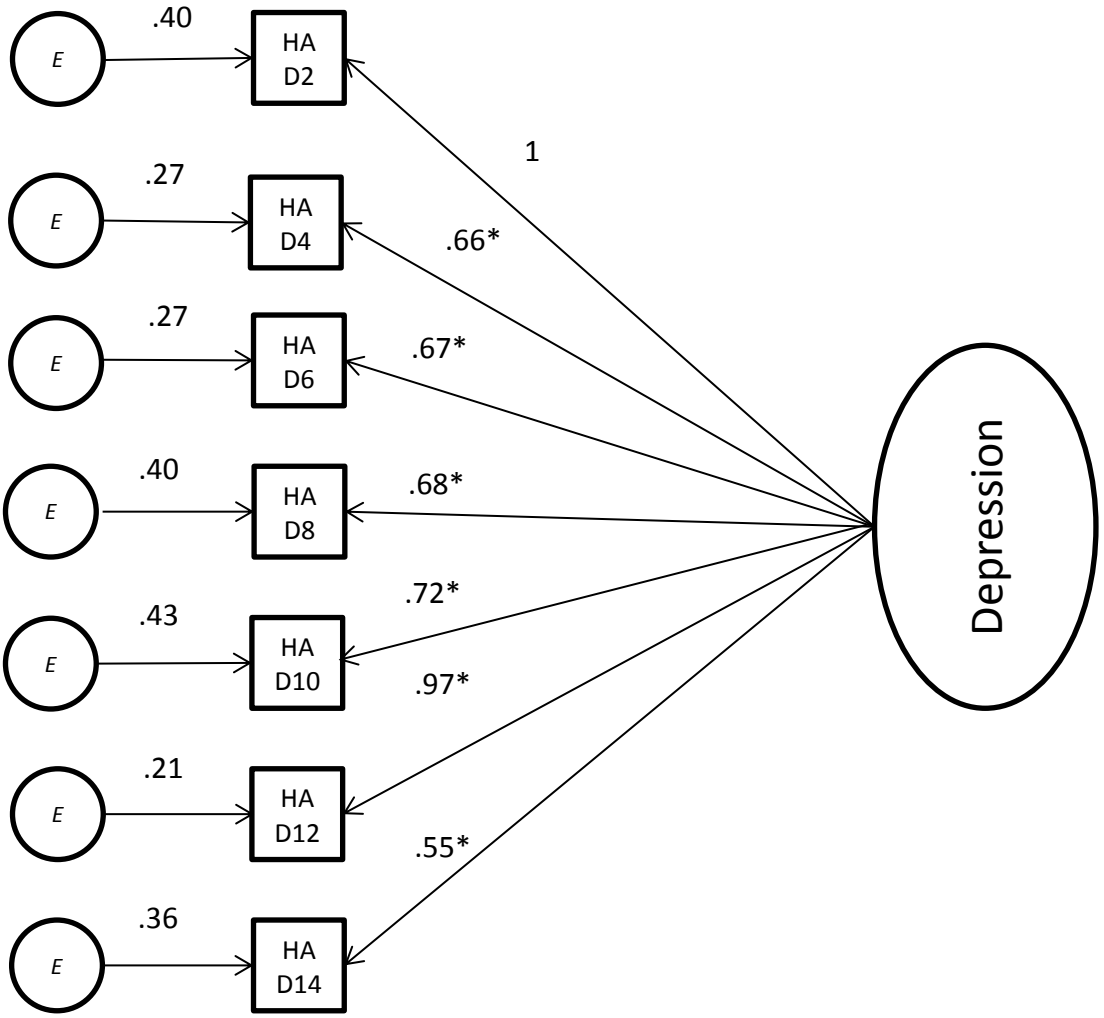
The depression measurement model demonstrated poor fit across two model fit indices (X^2=47.48, df=14, p≤0.01; RMSEA=0.11) and good fit on the CFI (CFI=0.94). The results for model fit indices are shown in Table 5.1.

Figure 5.2 presents unstandardised factor loadings for each HAD-D questionnaire indicator on to the latent construct of depression. The factor loading for the indicator HAD-2 was held constant (fixed to 1) to allow the other relationships in the model to be estimated. Figure 5.2 shows that all factor loadings were ≥0.40, which indicates that they are meaningful indicators of the underlying construct of depression.[229;230] All factor loadings were statistically significant at p≤0.05. The standardised factor loadings can be seen in Statistical Appendix C.

Table 5.1: Model fit indices for HADS depression measurement model

X^2	DF	p	RMSEA	CFI
47.48	14	0.000	0.11	0.94

Figure 5.2: Measurement model for HADS depression scale



5.3.2 Measurement model for HADS anxiety scale

The measurement model for anxiety was constructed using the 7 questions from the HADS measure which are proposed to indicate symptoms of anxiety.[159] The 7 questions are represented in the measurement model as HAD1, 3, 5, 7, 9, 11, 13 (Figure 5.3).

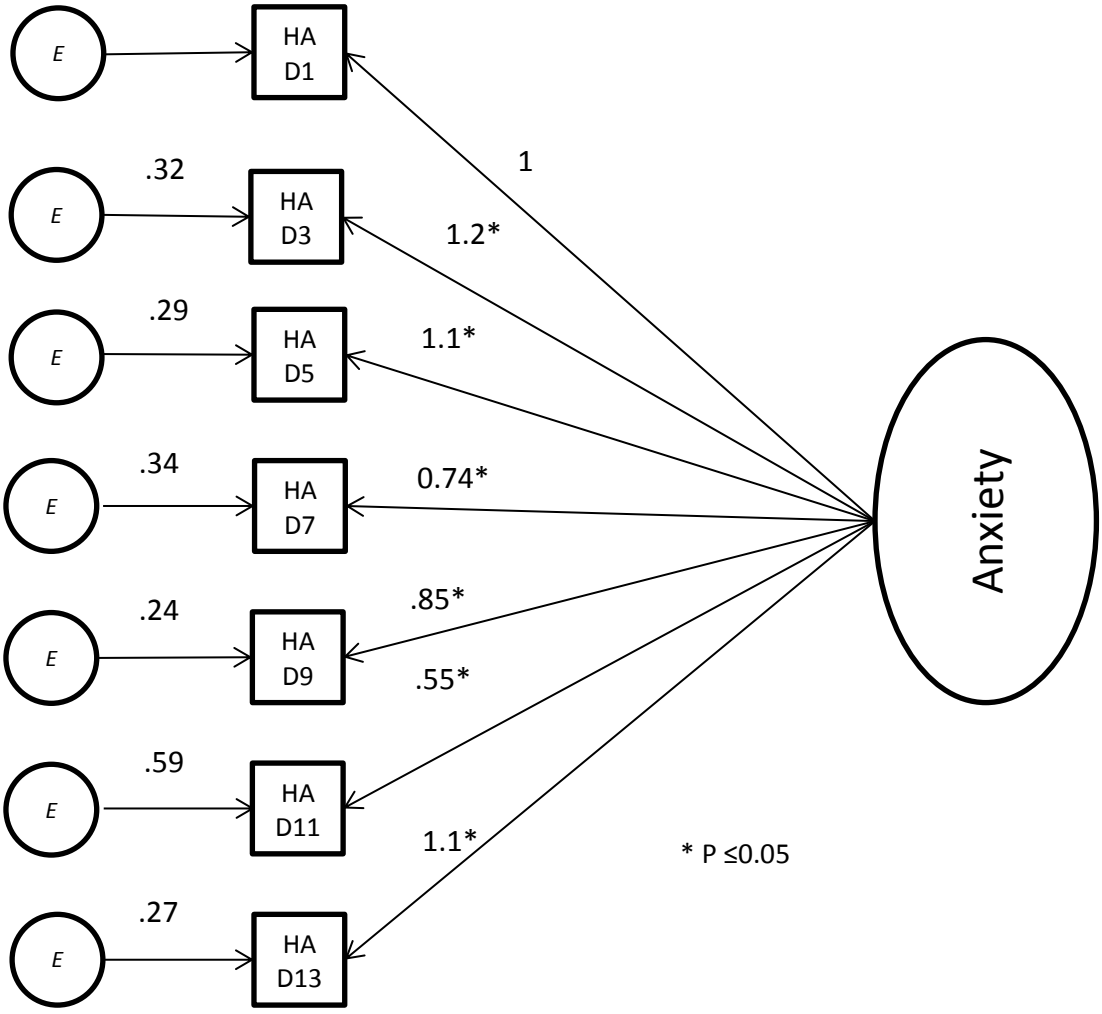
The anxiety measurement model demonstrated poor fit on the chi-squared statistic (X^2=33.46, df=14, p≤0.01), moderate to poor fit on the RMSEA (RMSEA=0.09), but good fit on the CFI (CFI=0.97). The results for model fit indices are shown in Table 5.2.

Figure 5.3 presents unstandardised factor loadings for each HAD-A questionnaire indicator on to the latent construct of depression. The factor loading for the indicator had1 was held constant (fixed to 1) to allow the other relationships in the model to be estimated. Figure 5.3 shows that all factor loadings were ≥0.40, which indicates that they are meaningful indicators of the underlying construct of anxiety and all factor loadings were statistically significant at p≤0.05. The results for standardised factor loadings can be seen in the Statistical Appendix C.

Table 5.2: Model fit indices for HADS anxiety measurement model

X^2	DF	p	RMSEA	CFI
33.46	14	0.000	0.09	0.97

Figure 5.3: Measurement model for HADS anxiety scale



5.3.3 Measurement model for panic

The panic measurement model was constructed using 9 questions from the panic disorder self-report measurement (PDSR) which directly relate to the DSM criteria for diagnosis of panic disorder.[183]

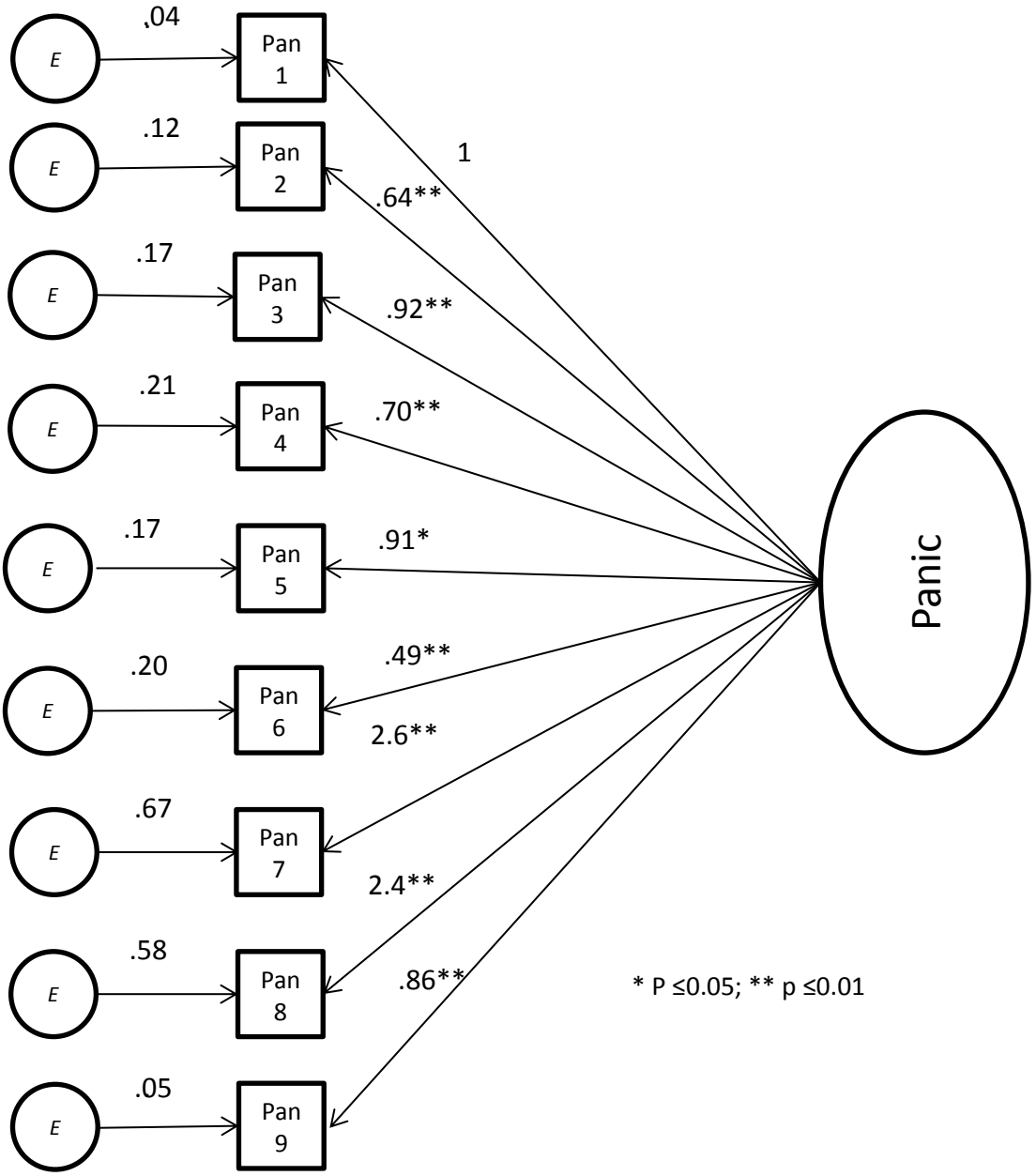
The panic measurement model demonstrated poor fit on the chi-squared statistic (X^2=66.06, df=27, p≤0.01), moderate to poor fit on the RMSEA (RMSEA=0.09) and good fit on the CFI (CFI=0.85). The results for model fit indices are shown in Table 5.3

Figure 5.4 presented unstandardised factor loadings for each PDSR indicator on to the latent construct of panic. The factor loading for the indicator pan1 was held constant (fixed to 1) to allow the other relationships in the model to be estimated. Figure 5.4 shows that all factor loadings were ≥0.40, which indicates that they are meaningful indicators of the underlying construct of panic.[229;230] All factor loadings were statistically significant at p≤0.01 except for pan6 which was significant at the level p≤0.05. The standardised factor loadings can be seen in Statistical Appendix C.

Table 5.3: Model fit indices for panic

X^2	DF	p	RMSEA	CFI
66.06	27	0.000	0.09	0.85

Figure 5.4: Measurement model for panic



5.4 Measurement Models for Respiratory HRQoL Outcome Variables

5.4.1 Measurement model for physical respiratory HRQoL

The measurement model for physical respiratory HRQoL was constructed using the 9 indicators from the Chronic Respiratory Questionnaire which measure the underlying latent construct of physical HRQoL.[210]

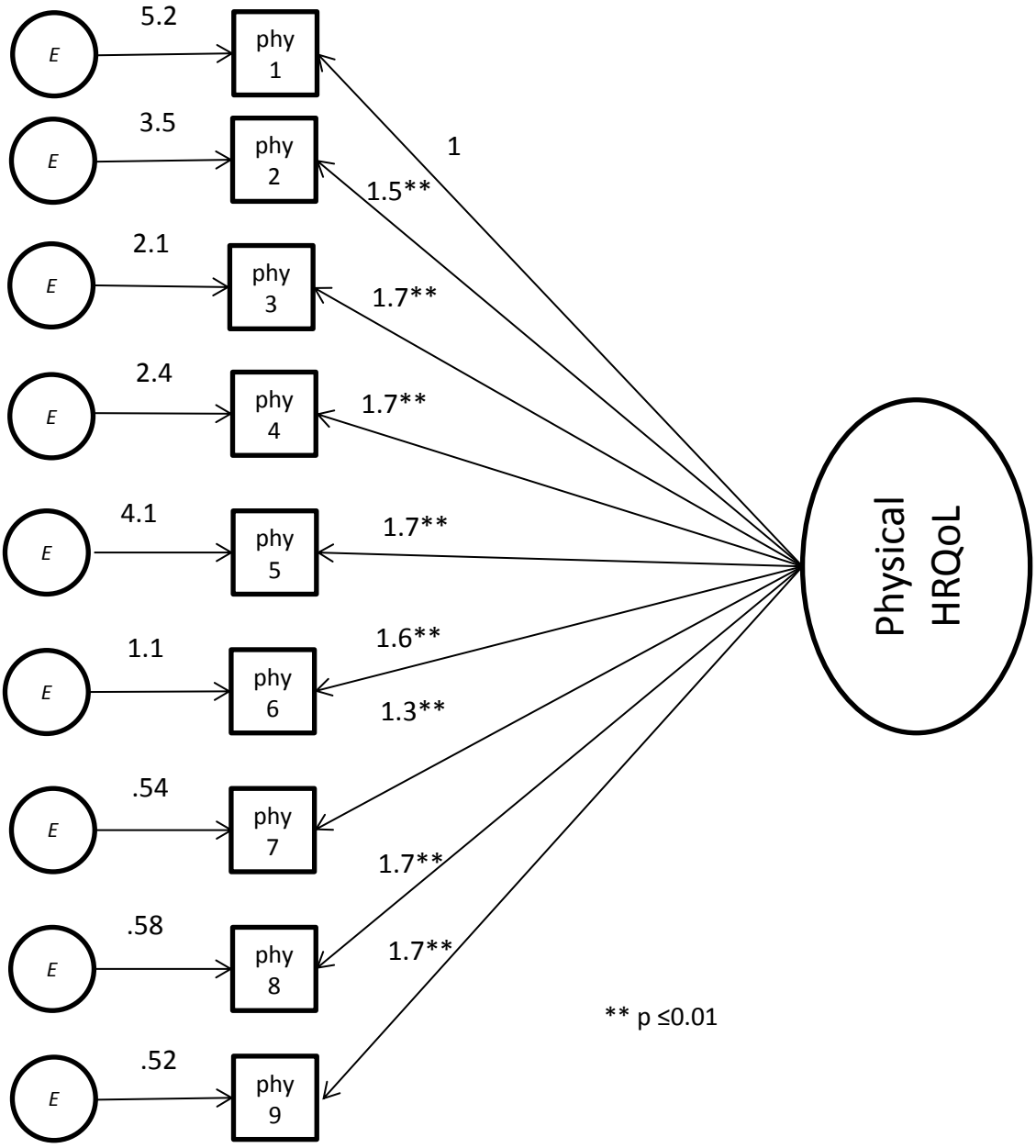
The measurement model for physical respiratory HRQoL demonstrated poor fit on the chi-squared statistic and RMSEA (X^2=331.85, df=27, p≤0.01; RMSEA=0.25), but moderate fit on the CFI (CFI=0.76). The results for model fit indices are shown in Table 5.4.

Figure 5.5 presents the unstandardised factor loadings for each CRQ indicator on to the latent construct if physical respiratory HRQOL. The factor loading for the indicator phy1 was held constant (fixed to 1) to allow the other relationships in the model to be estimated. Figure 5.5 shows that all factor loadings were ≥0.40, which indicates that they are meaningful indicators of the underlying construct of physical respiratory HRQoL.[229;230] All factor loadings were statistically significant at p≤0.01. The standardised factor loadings can be seen in the Statistical Appendix C.

Table 5.4: Model fit indices for physical respiratory HRQoL

X^2	DF	p	RMSEA	CFI
331.85	27	0.000	0.25	0.76

Figure 5.5: Measurement model for physical respiratory HRQoL



5.4.2 Measurement model for emotional respiratory HRQoL

The measurement model for emotional respiratory HRQoL was constructed using the 11 items of the Chronic Respiratory Questionnaire which measure the underlying latent construct of emotional respiratory HRQoL.[210]

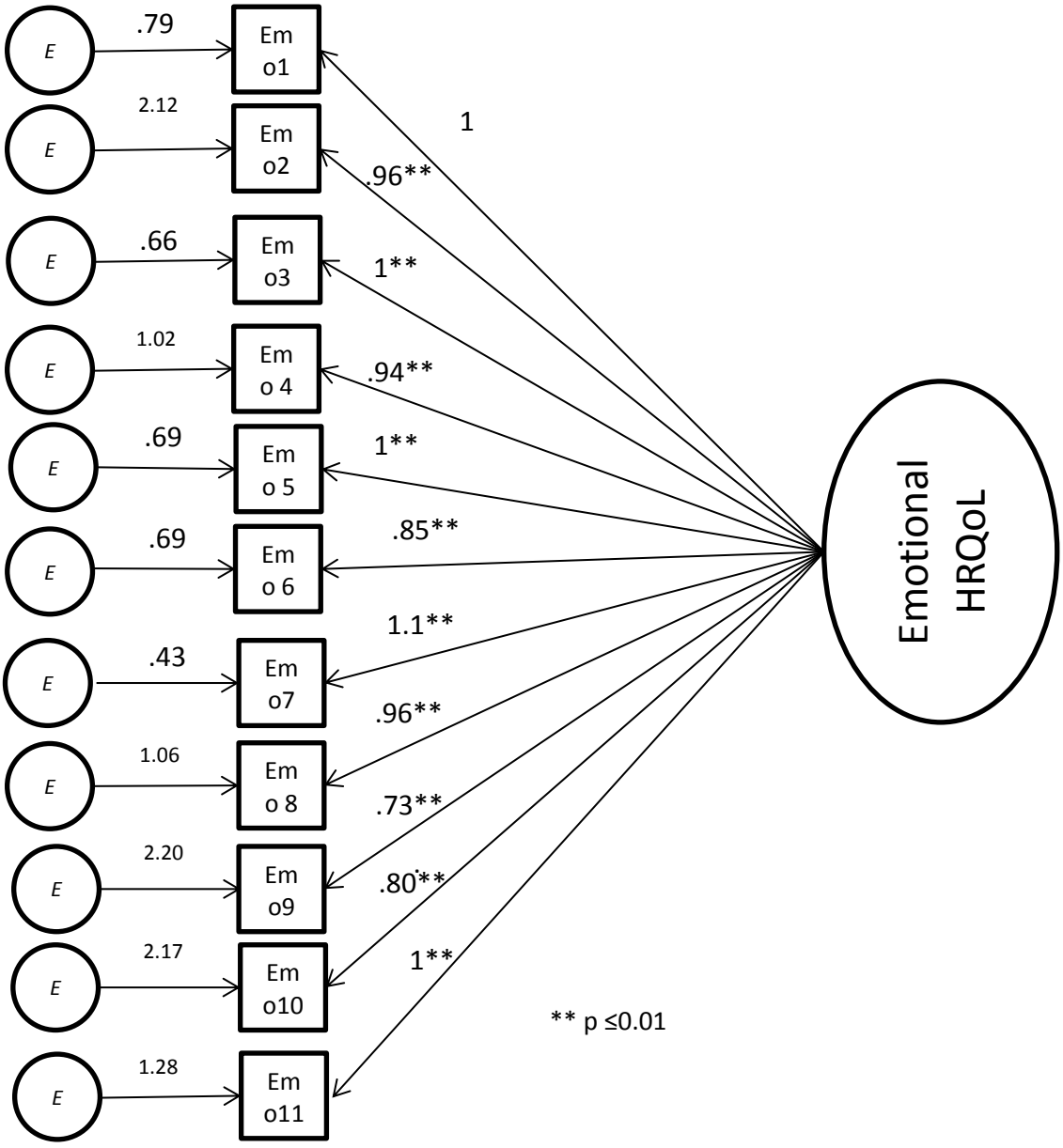
The measurement model for emotional respiratory HRQoL demonstrated poor fit on the chi-squared and RMSEA (X^2=181.73, df=44, p p≤0.01; RMSEA=0.13), but good fit on the CFI (CFI=0.92). The results for model fit indices are shown in Table 5.5.

Figure.5 6 presents the unstandardised factor loadings for each CRQ indicator on to the latent construct if emotional respiratory HRQOL. The factor loading for the indicator emo1 was held constant (fixed to 1) to allow the other relationships in the model to be estimated. Figure 5.6 shows that all factor loadings were ≥0.40, which indicates that they are meaningful indicators of the underlying construct of emotional respiratory HRQoL. All factor loadings were statistically significant at p≤0.01. The standardised factor loadings can be seen in Statistical Appendix C.

Table 5.5: Model fit indices for emotional respiratory HRQoL

X^2	DF	p	RMSEA	CFI
181.73	44	0.000	0.13	0.92

Figure 5.6: Measurement model for emotional respiratory HRQoL



5.5 Chapter Summary

This chapter has described the specification and analysis of measurement models for each of the psychological predictor variables (depression, anxiety, and panic) and the two outcome variables of respiratory specific physical, and emotional, respiratory HRQoL.

The next chapter shows how these measurement models were analysed in structural path models and tested to address the following questions:

I. What are the inter-relationships between depression, anxiety and panic in predicting respiratory HRQoL?
II. Does depression mediate the relationship between anxiety and respiratory HRQoL, and/or panic and respiratory HRQoL

6. Structural Equation Models

6.1 Chapter Overview

In Chapter 5 measurement models were specified and tested for each of the psychological predictor variables and the outcome variables. This chapter will now present the results from the second stage of SEM (described in Chapter 3). The second stage of SEM involved specifying and testing structural path models using the measurement models that have already been tested for goodness of fit. The model fit indices for each of the measurement models were poor to moderate in all cases. However, across all measurement models the factor loadings were high and statistically significant at $p \leq 0.05$, which shows that the indicators measured the latent variables that they were hypothesised to, or that they had good construct validity. These measurement models have now be used to construct structural equation models.

6.2 Statistical Analysis of Structural Models

As with the measurement models described in Chapter 5 the strength of each structural model was assessed using goodness of fit indices. Goodness of fit refers to how well the hypothesised model fits the data that we have actually observed. To assess how well the measurement models fit the observed data several fit indices were used. In addition to the Chi-squared, Comparative Fit Indices (CFI) and RMSEA the Akaike's Information Criterion (AIC) were calculated for the structural models. The AIC is a measure of model fit which can be used to compare the fit of models that use the same set of variables.[227] A full description of the fit indices is given in the Chapter 3.1 and are summarised here for ease of reference:

I. Chi-square (χ^2) – if a hypothesised model fits the data well the χ^2 is small and would not be significant ($p>0.05$).[214;232]

II. Comparative fit indices (CFI) – The larger the CFI the better fit the model is. A CFI of 0.95 would indicate that the hypothesised model is 95% better than the null model.[227;232;233]

III. Root mean square error of approximation (RMSEA) – A smaller RMSEA indicates better fit, a result of ≤0.05 is good, ≤08 indicated moderate fit and ≥10 indicates poor fit.[227;235]

IV. Alkaike's Information Criterion (AIC) – The AIC used to compare the fit of models which use the same set of variables to assess which fits the observed data the best.[227]

Models 1 and 2 were specified to explore if depression, anxiety, and panic, (which were measured at baseline), predicted physical and emotional HRQoL at 12 month follow-up whilst simultaneously modelling the inter-relationships between the psychological variables (Figure 6.1). Models 3 and 4 were then specified to explore whether depression mediated the relationship between anxiety and HRQoL, and/or panic and physical and emotional HRQoL respectively (Figure 6.2)

Figure 6.1: Structural Equation Models 1 and 2

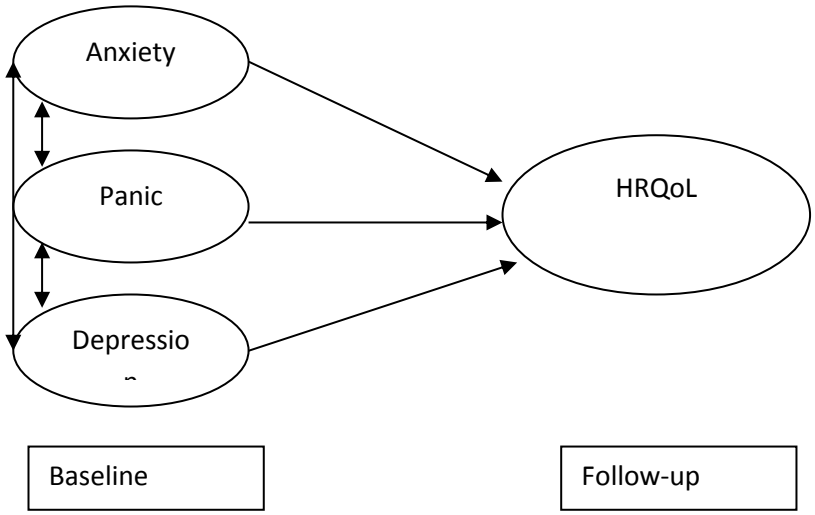
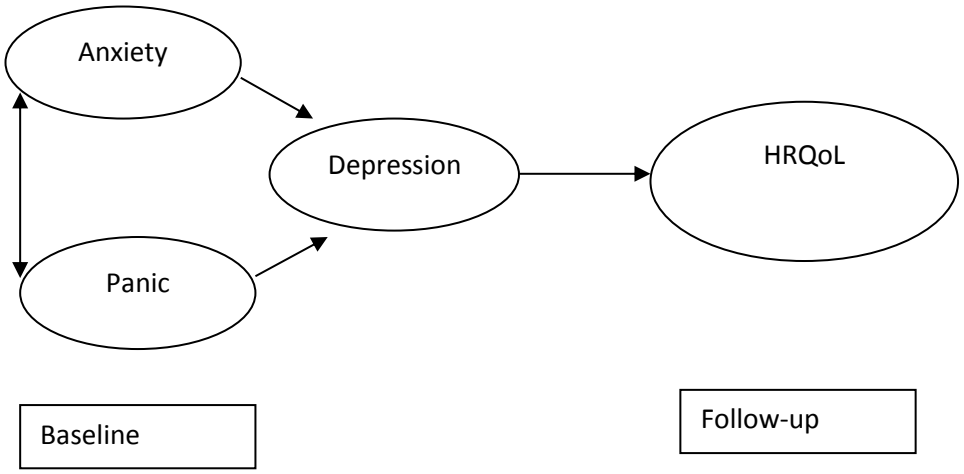


Figure 6.2: Structural Equation Models 3 and 4



6.3 The Relationship between Depression, Anxiety, and Panic in Predicting Respiratory HRQoL

6.3.1 Model 1: depression, anxiety, panic, and physical respiratory HRQoL

The first SEM model tested whether depression, anxiety and panic, measured at baseline, predicted physical respiratory HRQoL at 12 month follow-up when covariance between predictor variables is accounted for (Figure 6.3).

The model showed that there was a high and significantly positive covariance between all three predictor variables (depression, anxiety and panic) at baseline. However, only depression was a significant predictor of physical respiratory HRQoL at 12 month follow-up. This demonstrated that greater severity of depression symptoms at baseline predicted worse physical respiratory HRQoL at follow-up. The model also showed that greater severity of panic symptoms at baseline indicated worse physical respiratory HRQoL 12 months later, although this finding was not significant. The results are presented in Table 6.1.

Table 6.2 shows that the model fit was poor on chi-square (X^2=47.48, df=14, p≤0.01) moderate to poor on the RMSEA (RMSEA = 0.09) and moderate on the CFI (CFI = 0.80).

6.3.2 Model 2: Depression, anxiety, panic, and emotional respiratory HRQoL

The second SEM model tested whether depression, anxiety and panic, predicted emotional respiratory HRQoL at 12 month follow up when covariance between the predictor variables was accounted for (Figure 6.4). The model showed that there was a high and significant level of covariance between all three predictor variables at baseline (depression, anxiety and panic). In the structural model both depression and anxiety were significant predictors of emotional respiratory HRQoL at 12 month follow-up, indicating that greater severity of depression and anxiety symptoms at baseline predicted worse HRQoL at 12 month follow-up. The results are presented in Table 6.3.

The model fit was poor across the model chi-square statistic, RMSEA and CFI (Table 6.4)

Figure 6.3: Structural model of psychological variables at baseline and physical respiratory HRQoL at 12 month follow-up

Standardised model (n = 188)

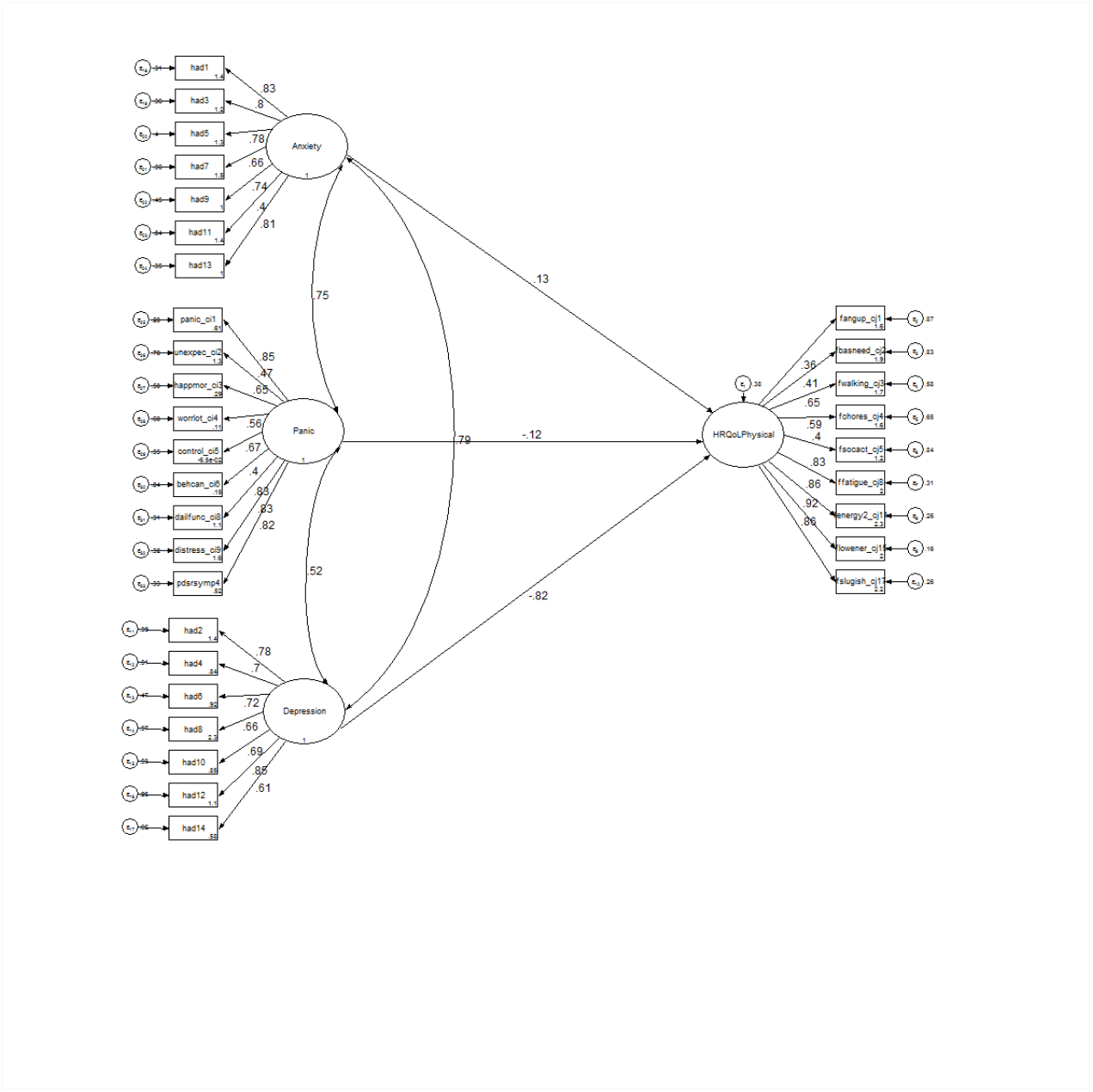


Table 6.1: Structural model of psychological variables at baseline and physical respiratory HRQoL at 12 month follow-up

	Unstandardised coefficient (SE)	95% Confidence interval		p	Standardised coefficient (SE)	95% Confidence interval		p
		Lower	Upper			Lower	Upper	
Covariance								
Depression and Anxiety	0.41 (0.06)	0.29	0.53	0.000	0.79 (0.04)	0.72	0.86	0.000
Depression and Panic	0.16 (0.03)	0.10	0.21	0.000	0.52 (0.07)	0.39	0.65	0.000
Anxiety and Panic	0.19 (0.03)	0.13	0.24	0.000	0.75 (0.05)	0.66	0.84	0.000
Structural Model								
Depression -> Physical HRQoL	-0.88 (0.22)	-1.31	-0.45	0.000	-0.82 (0.11)	-1.03	-0.62	0.000
Anxiety -> Physical HRQoL	0.18 (0.21)	-0.24	0.59	0.410	0.13 (0.16)	-0.18	0.45	0.402
Panic -> Physical HRQoL	-0.28 (0.25)	-0.77	0.21	0.268	-0.12 (0.11)	-0.33	0.09	0.252

Table 6.2: Model fit indices for structural model of psychological variables at baseline and physical respiratory HRQoL at 12 month follow-up

X^2	DF	p	RMSEA	CFI	AIC
1081.38	458	0.000	0.09	0.80	12048.28

Figure 6.4: Structural model of psychological variables at baseline and emotional respiratory HRQoL at 12 month follow-up

Standardised model (n = 188)

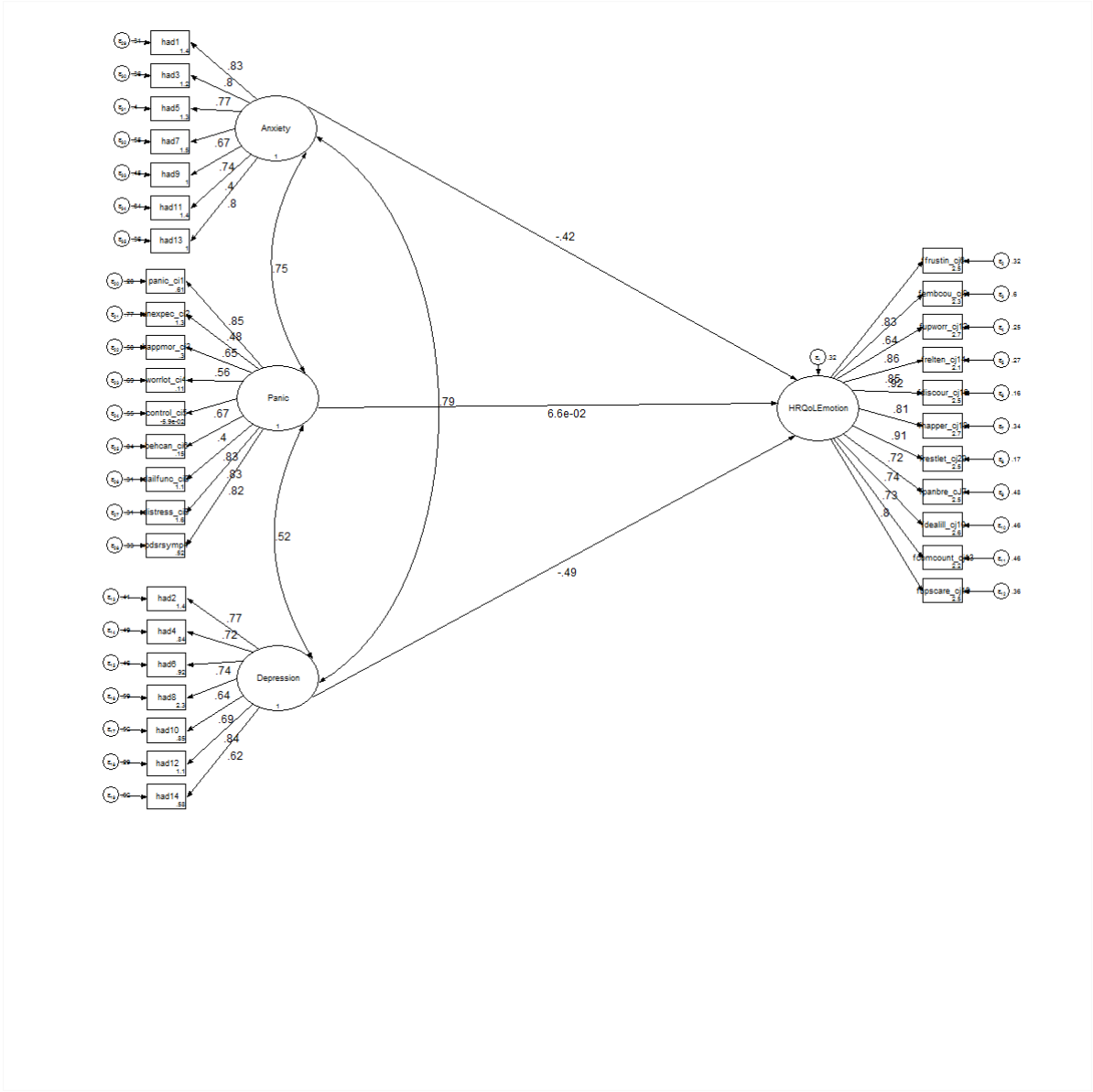


Table 6.3: Structural model of psychological variables at baseline and emotional respiratory HRQoL at 12 month follow-up

	Unstandardised coefficient (SE)	95% Confidence interval		p	Standardised coefficient (SE)	95% Confidence interval		p
		Lower	Upper			Lower	Upper	
Covariance								
Depression and Anxiety	0.41 (0.06)	0.29	0.52	0.000	0.79 (0.04)	0.72	0.87	0.000
Depression and Panic	0.15 (0.03)	0.10	0.21	0.000	0.52 (0.07)	0.39	0.65	0.000
Anxiety and Panic	0.18 (0.03)	0.13	0.24	0.000	0.75 (0.05)	0.66	0.84	0.000
Structural Model								
Depression -> Emotion HRQoL	-0.89 (0.19)	-1.27	-0.51	0.000	-0.49 (0.10)	-0.68	-0.30	0.000
Anxiety -> Emotion HRQoL	-0.92 (0.31)	-1.52	-0.32	0.003	-0.42 (0.14)	-0.69	-0.16	0.002
Panic -> Emotion HRQoL	0.25 (0.34)	-0.42	0.92	0.467	0.07 (0.09)	-0.11	0.25	0.466

Table 6.4: Model fit indices for structural model of psychological variables at baseline and emotional respiratory HRQoL at 12 month follow-up

X^2	DF	p	RMSEA	CFI	AIC
1130.61	521	0.000	0.08	0.85	12295.68

6.4 Mediation Models

6.4.1 Model 3: Anxiety and panic to depression to physical respiratory HRQoL

The two previous models tested have shown that depression at baseline predicted physical and emotional respiratory HRQoL at 12 month follow-up. Furthermore, anxiety predicted emotional respiratory HRQoL at 12 month follow-up. The third SEM model tested was to investigate whether depression mediated the relationship between anxiety and physical respiratory HRQoL at 12 months and/or panic and physical respiratory HRQoL at 12 month follow-up.

The model (Figure 6.5) shows significant positive covariance between anxiety and panic which demonstrates that as anxiety severity increased at baseline panic severity also increased. In the structural, model only anxiety significantly predicted depression at baseline which then significantly predicted physical HRQoL at 12 month follow-up. The result for panic suggests that as panic increased depression symptoms decreased but this result was not significant. The results are shown in Table 6.5

The model fit was poor across the model chi-square statistic, RMSEA and CFI (Table 6.6).

6.4.2 Model 4: Anxiety and panic to depression to emotional respiratory HRQoL

The fourth SEM model tested was to investigate the hypothesis that anxiety and panic predict depression at baseline which then predicts emotional respiratory HRQoL at 12 month follow-up..

The model (Figure 6.6) shows that there was a significant level of covariance between anxiety and panic which suggests that as the severity of anxiety increases so does the severity of panic. The model also showed that as anxiety increased depression significantly increased but as panic increased depression decreased, although this finding was not significant. The results are shown in Table 6.6.

The model fit was poor across the model chi-square statistic, RMSEA and CFI (Table 6.6).

Figure 6.5: Structural model of depression as mediator for anxiety and physical respiratory HRQoL, and/or panic and physical respiratory HRQoL

Standardised model (n = 188)

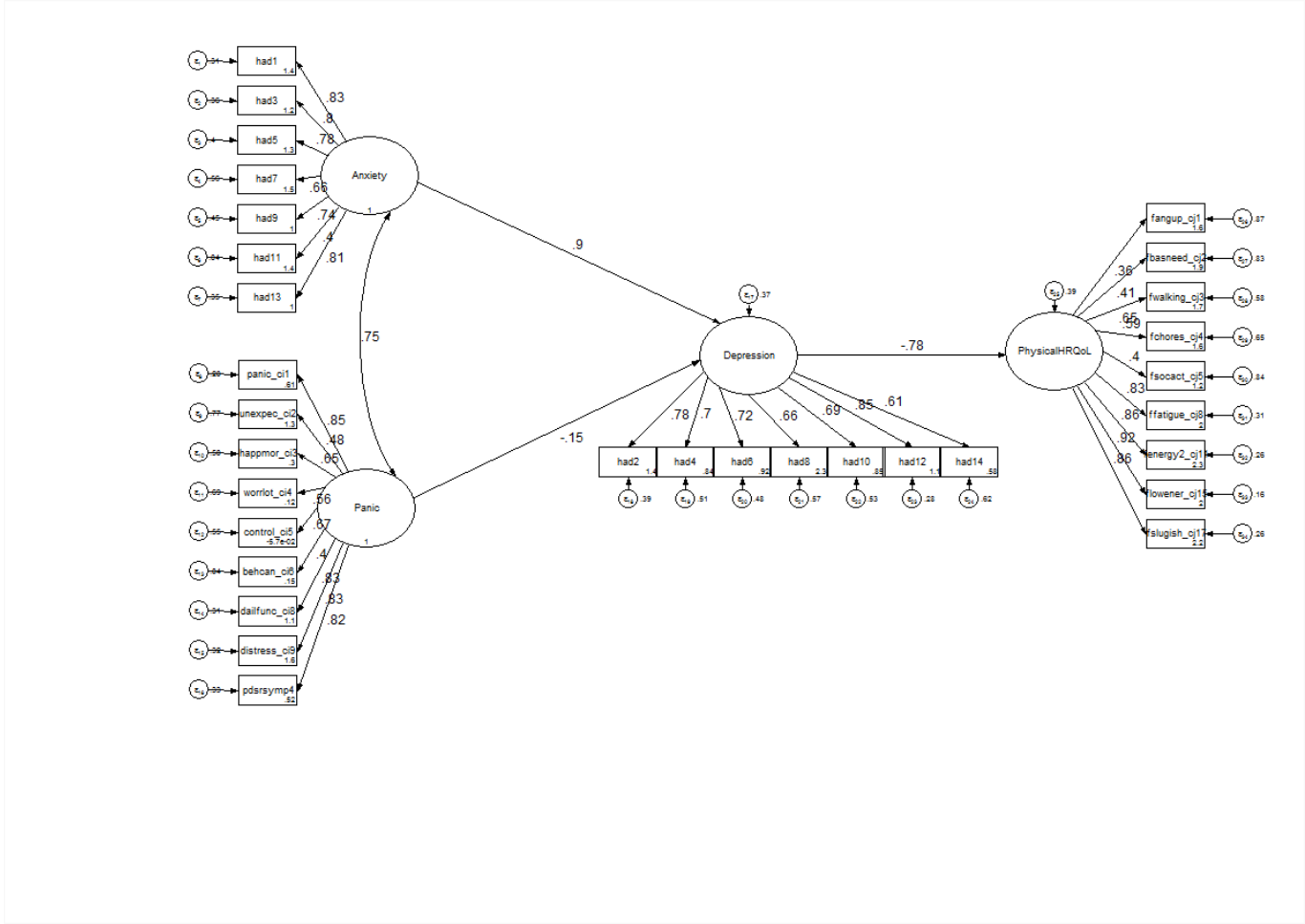


Table 6.5: SEM results for structural model of depression as a mediator for anxiety and physical respiratory HRQoL, and/or panic and physical respiratory HRQoL

	Unstandardised coefficient (SE)	95% Confidence interval		p	Standardised coefficient (SE)	95% Confidence interval		p
		Lower	Upper			Lower	Upper	
Covariance								
Anxiety and Panic	0.19 (0.03)	0.13	0.24	0.000	0.75 (0.05)	0.66	0.84	0.000
Structural Model								
Anxiety -> Depression	1.10 (0.15)	0.81	1.39	0.000	0.90 (0.09)	0.72	1.07	0.000
Panic -> Depression	-0.31 (0.22)	-0.75	0.13	0.162	-0.15 (0.10)	-0.35	-0.58	0.159
Depression -> Physical HRQoL	-0.83 (0.18)	-1.18	-0.48	0.000	-0.78 (0.04)	-0.85	-0.71	0.000

Table 6.6: Model fit indices for structural model of depression as mediator for anxiety and physical respiratory HRQoL, and/or panic and physical respiratory HRQoL

X^2	DF	p	RMSEA	CFI	AIC
1082.73	460	0.000	0.09	0.81	12045.63

Figure 6.6: Structural model of depression as mediator for anxiety and emotional respiratory HRQoL, and/or panic and emotional respiratory HRQoL

Standardised model (n = 188)

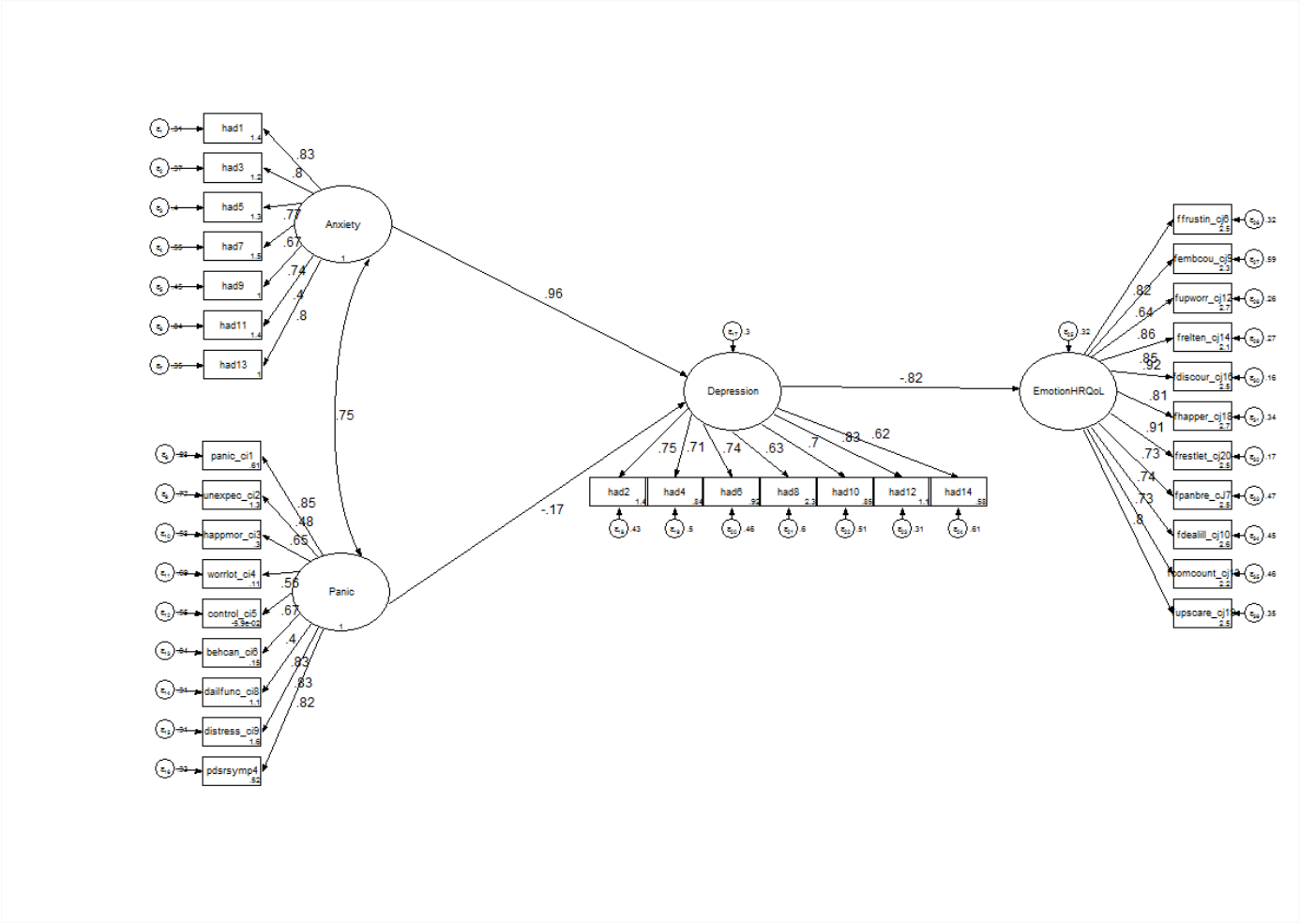


Table 6.7: Structural model of depression as mediator for anxiety and emotional respiratory HRQoL, and/or panic and emotional respiratory HRQoL

	Unstandardised coefficient (SE)	95% Confidence interval		p	Standardised coefficient (SE)	95% Confidence interval		p
		Lower	Upper			Lower	Upper	
Covariance								
Anxiety and Panic	0.19 (0.03)	0.13	0.24	0.000	0.75 (0.05)	0.66	0.84	0.000
Structural Model								
Anxiety -> Depression	1.13 (0.14)	0.85	1.41	0.000	0.96 (0.08)	0.79	1.12	0.000
Panic -> Depression	-0.36 (0.21)	-0.76	0.05	0.083	-0.17 (0.10)	-0.37	0.02	0.079
Depression -> Emotion HRQoL	-1.51 (0.15)	-1.81	-1.21	0.000	-0.82 (0.03)	-0.88	-0.77	0.000

Table 6.8: Model fit indices for structural model of depression as mediator for anxiety and emotional respiratory HRQoL, and/or panic and emotional respiratory HRQoL

X^2	DF	p	RMSEA	CFI	AIC
1143.66	523	0.000	0.08	0.85	12304.73

6.5 Chapter Summary

The results presented in this chapter described the inter-relationships between three psychological variables (depression, anxiety and panic) and their predictive impact on prospective HRQoL.

The results of Model 1 show that there is a significant relationship between depression, anxiety and panic, but that depression was the only significant predictor of physical HRQoL. However, both depression and anxiety significantly predicted emotional HRQoL (Model 2). Panic was not a significant predictor of either physical or emotional HRQoL.

Models 3 and 4 were specified to test whether depression mediated the relationship between anxiety and HRQoL and/or between panic and HRQoL. The results showed that anxiety significantly predicted depression but panic did not. However, in both models 3 and 4 there was a significant covariance between anxiety and panic which may account for the lack of significant relationship between panic and depression.

Across all 4 models the fit of the model to the data was poor to moderate on the chi-square, RMSEA, and CFI goodness of fit indices. The AIC is a predictive fit index which can be used to compare models which use the same variables in the same sample of data but are not hierarchically related.[214] When such models are compared the model with the smallest AIC is said to have the best fit to the data. For this PhD study the model with the smallest AIC was model 3. Therefore, it can be said that model 3 is the most likely to be replicated.[214] Model 3 showed that anxiety significantly predicted depression but panic did not. However, there was a strong and significant covariance between anxiety and panic which may account for the lack of impact of panic on depression.

7. Discussion

7.1 Chapter Overview

This chapter gives an overview and interpretation of the main findings from this study, discusses the strengths and limitations of the study and considers the impact on clinical practice and future research.

7.2 Summary of Main Findings

The aim of this thesis was to answer the following research questions:

I. What are the psychosocial predictors of HRQoL in COPD?
II. Does panic predict HRQoL in COPD?
III. Is panic a better predictor of HRQoL in COPD than depression?

These research questions were answered using a range of methods. Firstly, the existing evidence about the longitudinal relationships between psychological factors and HRQOL was systematically reviewed. Secondly, a longitudinal cohort study was designed and conducted to empirically test if panic predicted respiratory specific HRQOL in COPD patients recruited from primary care in the English NHS. The main results of this thesis will now be summarised.

7.2.1 Summary of systematic review with meta-analysis

The first objective of this thesis was to systematically review all published longitudinal prospective cohort studies which have investigated the predictive relationship between psychosocial factors (depression and anxiety disorders), and respiratory HRQoL in COPD (Chapter 2). An eligibility and search criteria was developed, systematic searches of electronic databases were conducted, and identified papers were checked against the eligibility criteria. A total of eight studies met the eligibility criteria. However, only five were eligible for inclusion in the meta-analysis for depression and four for anxiety. None of the included studies measured the effect of panic on HRQOL. The intention was for results to be pooled using meta-analysis to assess the direction and magnitude of predictive relationships between depression and anxiety and future HRQoL in COPD.

The eight eligible studies did not report results from regression analyses so it was not possible to show whether depression and/or anxiety predicted HRQoL at follow up. The studies were limited to correlational analysis which only allowed investigation about the longitudinal association between depression, anxiety and HRQoL.

Meta-analysis showed that there was a large and significant positive correlation between depression and HRQoL at 12 months, and a moderate but significant correlation between anxiety and prospective HRQoL at 12 months. The results remained the same when studies which were scored as low quality according to the predefined quality criteria were removed from the analyses.

7.2.2 Rationale and hypothesis for longitudinal cohort study

The second objective of this thesis was to conduct primary research to identify whether panic predicts HRQoL in COPD. This element of the thesis tested the hypothesis that panic would be more predictive of the HRQoL of COPD patients than depression. This hypothesis was developed on the basis that in the general population panic disorder has a negative impact on HRQoL which is comparable to the impact of depression.[127] However, in COPD patient populations panic has been found to have a prevalence 7 to 10 times that found in the general population,[100;101] and to have a significantly negative impact on COPD patient's perceptions of symptoms[124;125], physical functioning[120], use of healthcare[119] and treatment outcomes.[126] Furthermore, the proposed model of panic disorder in COPD is Clark's Cognitive Model[104] which explains how, when COPD patients experience distressing symptoms of COPD (e.g. breathlessness on exertion), they can experience catastrophic thoughts and therefore subsequent symptoms of panic. The symptoms of panic that people experience are similar to the respiratory related symptoms that they already experience with COPD. It is proposed that this may result in a misattribution of the severity of the symptoms as solely due to COPD rather than as being exacerbated by panic. This can result in a cycle of panic attacks. It is hypothesised that such catastrophic thinking and misinterpretation of symptoms may result in patients avoiding activities which can trigger symptoms of either panic or COPD. This can mean that patients live increasing sedentary lifestyles. In time this sedentary lifestyle may lead to low mood and reduced HRQoL. The main findings of this thesis, previously presented in chapters' five to seven, are now summarised.

7.2.3 Summary of longitudinal cohort study

A prospective cohort study was conducted with a sample of 270 COPD patients recruited from ten general practices in the UK. Participants were sent a baseline questionnaire that included self-reported assessments of socio demographics, symptoms of depression, anxiety and panic disorder, general and respiratory specific HRQoL, and primary and secondary healthcare use. The same measures (excluding socio-demographics) were repeated 12 months later. Data about the severity of participants COPD (measured using FEV_1 % predicted) were collected

from general practice notes. One hundred and eighty eight (81%) eligible COPD patients completed the questionnaire at both baseline and follow-up and were therefore included in the main analyses for this thesis.

Data were initially analysed using simple linear regression to identify the baseline predictors of physical and emotional respiratory specific HRQoL at 12 months. Physical and emotional respiratory HRQoL relate to a patient's perception about how their COPD affects their physical and emotional health. Physical, respiratory HRQoL was the main outcome measure in this thesis because of some perceived similarity between the measures of depression and anxiety and the emotional respiratory HRQoL measure. Respiratory specific measures of HRQoL have been found to be more sensitive to the specific issues relating to HRQoL which affect COPD patients than general measures and are recommended as best practice for the measurement of the impact of COPD on the HRQoL of patients.[39]

In simple regression analyses having a greater number of comorbidities, more threatening life events, more symptoms of depression, anxiety and panic, and using more health care were all significant predictors (at the 5% level) of worse physical HRQoL at 12 months. Better physical HRQoL was predicted by having milder COPD and better general physical and mental HRQoL at baseline. These predictor variables were then examined in multiple regression analyses where only depression, anxiety, use of unscheduled healthcare, and general physical and mental HRQoL remained significant predictors of respiratory HRQoL.

The simple and multiple regression analyses outlined above were repeated to identify the predictors of emotional HRQoL. Factors that predicted physical HRQoL largely predicted emotional HRQoL. However, in simple linear regression analyses COPD severity was not a significant predictor of emotional HRQoL, and age was a significant predictor. When modelled using multivariable analyses the only significant predictors of emotional respiratory HRQoL were symptoms of depression, anxiety, and general mental HRQoL.

This is the first longitudinal cohort study to investigate the predictive value of panic on HRQoL in patients with COPD. In this UK primary care sample of 270 COPD patients, 14% met the criteria of this study for a possible diagnosis of panic disorder. Panic predicted physical and emotional respiratory HRQoL when tested in a univariable regression model. However, in multivariable regression models panic did not predict HRQoL; depression, anxiety, and unscheduled care use were the only significant predictors other than general HRQoL. Structural equation models (SEM) were then used to investigate the relationship between panic, depression, anxiety and HRQoL further. SEM is a sophisticated statistical technique which has advantages over linear regression models. SEM is able to take account of the inter-

relationships between the predictor variables of depression, anxiety and panic whilst simultaneously modelling their relationship with prospective HRQoL. SEM also allows the specification of a model to investigate potential mediator variables which would take the construction of several regression models.

For this PhD study SEM models were firstly specified to explore and quantify the relationships between depression, anxiety, and panic, and respiratory HRQoL at 12 months. These models were then used to investigate whether depression mediated the relationship between panic and HRQoL at 12 months. The hypothesis that depression might be a mediator between panic, anxiety and HRQoL was driven by studies conducted in the general population which have shown that anxiety often precedes depression.[237-240] Wittchen et al. (2000) investigated the mechanisms that could explain the increased risk of depression in patients with anxiety. They found that, having two or more anxiety disorders, having severe anxiety at baseline, engaging in persistent avoidance and having panic attacks were significantly associated with an increased risk of secondary depression.[238] Starr et al. (2012) also found that anxiety could lead to depression through the promotion of maladaptive responses to anxiety, such as avoidance, rumination or worry and feelings of hopelessness.[241]

The results of the SEM analyses showed that for both physical and emotional HRQoL there was a high and statistically significant covariance between depression and anxiety, depression and panic, and anxiety and panic at baseline. However, only depression significantly predicted physical HRQoL at 12 months. Both depression and anxiety predicted emotional HRQoL at 12 months, but this is thought to be due to the high correlation between symptoms of depression and anxiety and the indicators of the measure of emotional HRQoL. Two SEM models were then constructed to test whether depression mediated the relationship between anxiety and panic, and physical or emotional HRQoL. The results showed that anxiety predicted depression which in turn predicted physical and emotional HRQoL at 12 months, but panic neither predicted depression or HRQOL.

7.3 Methodological Strengths and Limitations

The strengths and limitations of the systematic review that was conducted to meet the first objective of this thesis have previously been discussed in Chapter 3. The strengths and limitations of the longitudinal cohort study will now be discussed.

7.3.1 Prospective cohort study design

The main strengths of this thesis was the prospective cohort study design which allowed the modelling of psychological predictors of HRQoL in a representative sample of primary care patients with COPD. Previous longitudinal cohort studies have measured the impact of depression and anxiety on HRQoL in COPD,[39;148;149;153-155] but most have been limited to correlational analyses.[128] Correlational analysis is restricted in its outcomes to inferences about the strength of the relationship or association between variables but does not allow any inferences to be made about prediction. By identifying the predictors of HRQoL we can anticipate future decline in HRQoL and better identify which patients might benefit from additional support to improve outcomes. Furthermore, the systematic review and meta-analysis conducted as part of this thesis found that previous longitudinal studies were typically of poor methodological quality. In particular problems were identified with selection bias, confounding bias and attrition bias which negatively impacted on the internal and external validity of their findings.[128] In order to minimise these methodological weaknesses in this thesis the longitudinal cohort study aimed to:

I. Minimise selection bias by inviting all COPD patients who were registered on the general practice COPD register and had completed the CHOICE Health Survey within which this thesis was nested to take part. This was done independently from the clinical team who were responsible for the patient's care.

II. Minimise response bias by using self-reported measures to ensure that responses were not influenced by the researcher.

III. Minimise attrition bias at 12 month follow-up by seeking approval to contact non-responders. This resulted in a response rate of 81% at follow-up which is higher than several earlier studies for which the follow-up response rates were around 50%.[148;154;155]

IV. Extend the approach to analyses used by previous studies in this area to look at predictors of HRQoL in COPD using multivariable regression models and to further explore the relationship between the depression, anxiety and panic and prospective HRQoL using structural equation modelling (SEM).

These methodological strengths will now be expanded on and relate to: case definition and recruitment processes, response and attrition bias, measurement and the statistical approach used.

7.3.2 Case definition and study setting

Only patients with a confirmed diagnosis of COPD were included in this study. For each patient, diagnosis was confirmed by their inclusion on the General Practice Quality and Outcomes Framework (QOF) register for COPD.[242] A full research diagnosis using spirometry prior to inclusion would be the gold standard but this was not possible as we did not have the resource or ethical approval to conduct spirometry for each patient within the CHOICE Health Survey. Therefore, the General Practice QOF registers were used to identify eligible patients. Inclusion on this register requires patients to undergo a spirometry test every twelve months. Despite this however, over 30% of patients were missing an up to date spirometry test. Therefore, multiple imputation methods were used to impute missing data on COPD severity.

This PhD study was conducted in 10 General Practices in central Manchester. In the UK most COPD patients are managed in primary care but there is only a modest amount of research that has characterised the clinical features of primary care COPD patients.[243] By setting this PhD study in primary care the results have the potential to be generalised to the large number of COPD patients who are managed in primary care which improves the external validity of the findings.[244]

7.3.3 Minimising response and attrition bias

Previous studies have shown that response rates can be increased by telephone calls either before or after sending out questionnaires.[245;246] However, because this PhD study was nested within a larger programme of research restrictions placed on that programme by the NHS ethics committee meant that I was not able to contact non-responders by telephone at baseline. Only one postal reminder was permitted for those patients who did not send back their baseline questionnaire within two weeks. It is possible that this could have resulted in an

increase in attrition bias and possible systematic differences between those who did and did not respond which would decrease the external validity of the finding. CHOICE Health Survey participants who did and did not respond to this PhD study at baseline were compared across clinical and demographic characteristics. We found that those who did not respond were significantly more likely to be older, have more symptoms of depression and anxiety and worse emotional HRQoL than those who did respond, although there was no difference in their physical HRQoL. I was not able to compare panic and respiratory specific HRQoL scores at baseline between responders and non-responders as these outcomes were not measured in the original CHOICE Health Survey within which this PhD study was nested. The differences between those who did and did not respond to the PhD study may mean that the results of this study cannot be generalised to COPD patients who are older, more depressed or anxious and who have poorer emotional HRQoL.

The representativeness of the sample for this PhD study could have been increased if I had been able to telephone patients who did not initially return their baseline questionnaire. This may have resulted in greater power to detect a difference between depression, anxiety, panic, and prospective respiratory HRQoL.

At twelve month follow up reminder telephone calls were permitted through the addition of a substantial amendment for this PhD study. Therefore, all non-responders who did not return their follow-up questionnaire were reminded by telephone to maximise follow-up rates.

Comparison of those who did and did not respond to twelve month follow up showed that there were no significant differences between the two groups across demographic, psychological (depression, anxiety, and panic), general HRQoL, and respiratory HRQoL variables.

7.3.4 Measurement

This PhD study is strengthened by measuring psychological, clinical and HRQoL variables using validated and reliable self-reported tools where they were available. It was not possible to use measures which would have confirmed a clinical diagnosis of depression, anxiety or panic as this would have required the diagnostic interviews to be administered to patients for which there was not the resource or ethical approval. Instead self-report measures which have been validated for use in COPD patient populations were used to measure depression, anxiety and HRQoL. The systematic review and meta-analysis conducted for this thesis highlighted that some previous studies have not all used validated and reliable measures of depression and HRQoL. For example, Andenaes et al. 2006 omitted two key questions which are important for the diagnosis of depression from their depression measure.[154]

There was no COPD validated measure available for panic disorder. As for depression and anxiety the gold standard for measuring panic is a clinical diagnostic interview.[184] However, for pragmatic reasons a self-report measure was chosen (PDSR) that that has been well validated in the general population and outperformed the other measures of panic that were available.[183] The PDSR is based on the Diagnostic and Statistical Manual-IV (DSM-IV-TR) diagnostic criteria for panic disorder[67] and relates closely to Clark's Cognitive Model of panic. However, despite this measure being well validated in the general population it has not been previously used with COPD patients. Therefore, it was possible that due to the similarity of some symptoms of COPD exacerbations with panic attacks the self-report measure may have lacked the sensitivity to detect all cases of panic in this population.[124;247] This could have resulted in an under identification of panic attacks and panic disorder in this study. Conversely it could be that the measure resulted in an over identification of panic. An over or under identification of panic in this sample could have happened if, when completing the self-report measure for panic, patients had failed to recognise panic symptoms, instead misattributing them to symptoms of a COPD exacerbation or vice versa. A failure to detect all cases of panic or an over identification of panic cases could have either decreased or increased the magnitude of the effect of panic disorder on prospective HRQoL in this study. However, it should be noted that the prevalence of panic disorder (14%) and panic attacks (31%) identified in this study is consistent with the findings of a systematic review of studies which used diagnostic clinical interviews to identify panic.[97] Willgoss et al. (2013) report that the prevalence of panic in COPD primary care outpatient samples ranged from eight to twenty-one percent, whereas in hospital samples the prevalence can be up to 41%.[97]

To assess and control for the severity of COPD in the analysis data were collected on patients lung function COPD ($FEV_{1\,\%}$ predicted) by reviewing their general practice notes. FEV_1 % predicted is determined using a spirometry test of lung function. Spirometry is part of the QOF indicators for COPD in English primary care and should take place as part of an annual COPD review. The NICE quality standards for COPD state that, whilst diagnosis of COPD can initially be determined by history taking and physical examination it must be confirmed by spirometry within 3 to 12 months of the patient being placed on the COPD register.[6] Therefore, it was expected that the majority of patients whom we identified from the practice COPD registers would have had a breathing test using spirometry. However, this was not the case and we found there was some missing lung function data as up-to-date spirometry had not been conducted by the practice for all patients. The main reason for this was that the doctors assessed the patients to be too ill to complete the spirometry test. The amount of missing spirometry data in this study is consistent with results of other studies of COPD patients.

Mowls et al. (2014) found that in a nationally representative USA sample of 16,615 COPD patients. 22.3% self-reported that they had not taken a spirometry test; therefore 77.7% had received one. This is considerably higher than rates found in other studies which report only around 33% of patients have had a spirometry test.[248] I found that data from a spirometry test (FEV_1% predicted) was not available for a total of 105 (61.1%) patients at baseline for this PhD study. As it was likely that patients who had not taken an up to date spirometry test were too ill to do so it could be that those patients with severe COPD were underrepresented in this sample. However, where spirometry data were missing multiple imputation methods were used to impute the FEV_1%predicted. Multiple imputation is a technique which ensures that sample size can be maximised and the power of this study was retained. Multiple imputation is also less open to bias than other imputation techniques such as replacing missing values with the sample mean.[220;249]

7.3.5 Statistical analysis

For this thesis the data were analysed using both multivariable regression models and SEM. The use of these techniques provides more sophisticated analyses of the data than had been seen in previous studies in this area. SEM is a statistical technique which can estimate the predictive value of each variable within a prespecified model as well as estimating the overall value of the model whilst accounting for variance between each variable in the model[214]. Therefore, by using SEM I was able to simultaneously model the relationships between depression, anxiety, and panic and to test their predictive impact on prospective HRQoL. Using SEM also allowed me to investigate whether depression mediated the relationship between anxiety, panic and HRQoL

The primary purpose of this thesis was to investigate whether panic was a better predictor of HRQoL in COPD patients than depression, and therefore more important for future treatment initiatives. The results of multivariable regression models which looked at the predictive power of depression, anxiety and panic on HRQoL in COPD accounted for 49% of the variance in physical HRQoL which is similar to other studies in this area.[39;150] The model accounted for more of the variance in emotional HRQoL, at 63%, which can perhaps be explained by the similarity between the psychological predictor variables and measure of emotional HRQoL on the CRQ.

Using SEM allowed the primary question of this thesis to be answered using a detailed model of the relationships between psychological variables and HRQoL which were identified as the most important predictors of HRQoL in the multivariable regression analysis. However,

because of the relatively small sample size recruited to this study it was not possible to build a more explanatory model which included other possible physical covariates that were measured, such as COPD severity. Building more detailed SEM models which include psychological variables as well as physical covariates should be a focus of future research projects.

The fit of models is SEM is an indication of how well the specified model is able to reproduce the data used.[214] Therefore, the models specified in this PhD study do not replicate the data well. However, having a model that is a good fit does not necessarily mean that it is a valid model. To identify how useful a model is, it is also important to examine the parameter estimates.[214] In the case of this PhD study all parameter estimates were significant and within the recommended range. Model fit could have been improved by using the modification indices.

Model fit could have been improved by adapting the model according to the modification indices. However, I decided not to use modification indices to amend the model because this would have meant making amendments to the model based solely on the statistics rather than the known theory about the variables of interest. The purpose of using SEM for this PhD thesis was to closely examine the relationships between the psychological variables and HRQoL. Therefore, there were several variables which were not included in the SEM analyses. Model fit mayalso have been improved had a more a SEM model been specified which included more parameters which were identified as important predictors of HRQoL in the regression analyses, such as general HRQoL and healthcare use. However, specification of a larger SEM model would have required a larger sample size and this was not possible within the confines of this PhD study.

7.4 Interpretation of Findings

The results of this PhD study show that the greatest psychosocial predictor of respiratory specific HRQoL at 12 months in COPD was depression. This is consistent with research in the general population,[250] in patients with other long term conditions, [251] and those with multiple long-term conditions.[93] Previous cross-sectional studies have shown that depression is highly correlated with HRQoL in COPD[62;138;252] and predicts HRQoL in multivariable models.[253] However, previous studies that used a cross-sectional design have been unable to draw any conclusions about causation.[128] In a longitudinal prospective cohort study Engstrom et al., found that depression, physical functioning, and vital capacity (the maximum amount of air that can be exhaled after a maximum inhalation) explained 59% of the variance in HRQoL.[39]

However, this study lacked external validity due to problems with selection bias, response bias and attrition bias.[128] Anxiety was also found to be a significant predictor of HRQoL in this PhD study. This is consistent with previous research which has shown an association between anxiety and HRQoL in both cross-sectional[84;94;95] and prospective studies.[128]

The predictive effect of panic disorder on HRQoL in COPD was investigated in this PhD study. Panic disorder is an anxiety disorder which is more prevalent in COPD patient populations than in the general population.[68;78;100] Panic has also been found to predict quality of life in asthma,[254-256] which is a respiratory condition which is distinct from COPD but shares some similarity in symptom profiles. In this thesis panic was not shown to be a predictor of HRQoL in multivariable models. This was contrary to the hypothesis that panic would predict HRQoL more than depression. Earlier studies have found that panic is associated with poor outcomes in COPD such as reduced physical functioning status,[120] increased awareness of bodily symptoms,[113] and greater perceived difficulty in breathing where there are is difference in dyspnoea symptoms.[124] Furthermore, in a qualitative interview study with 14 UK COPD patients with stable COPD it was found that patients developed a fear of breathlessness following episodes of panic which negatively impacted on their daily lives.[96]

The analysis plan for this thesis extended the work of previous studies in order to provide a more detailed and sophisticated investigation of the inter-relationships between the psychological variables of panic, depression and anxiety and their impact on prospective HRQoL. This included an investigation using SEM as to whether depression mediated the relationship between anxiety and HRQoL, and/or panic and HRQoL as depression has been found to precede anxiety in studies of the general population.[238-240] The results showed that panic did not predict depression but that anxiety did predict depression. Therefore, this is the first study of COPD patients to show that anxiety predicts depression. This thesis did not find that panic predicted depression in COPD. This finding is contrary to studies of the general population which have shown that having panic attacks is associated with an increased risk of depression.[238;241;257]

It is possible that panic was not found to predict HRQoL or in fact depression for several reasons which will now be discussed. Firstly despite the measure of panic used in this thesis identifying prevalence rates similar to that found in other studies[79] it could be that, with no specific measure of panic for COPD, patients were still being misclassified. Secondly, this PhD study did not look at the impact of those patients who reported severe panic compared to those who reported mild symptoms. It could be that panic has a greater impact for those patients with the most severe symptoms. Thirdly, panic attacks can be short lived. They

develop abruptly and reach a peak within ten minutes, and they do not necessarily happen every day and may only occur in response to certain stimuli. It is possible therefore that such brief panic attacks might not have a sustained impact on patients HRQoL over the long term but they may impact on short term outcomes in COPD, such as medication use and unscheduled healthcare use and hospital admissions. In contrast to panic attacks, depression which has been found to be to be the greatest predictor of HRQoL in COPD, is a chronic condition which can take a relapse and remitting course throughout a person's life.[258] It is perhaps the enduring nature of depression that affects many aspects of COPD patients' lives every day, for example sleep, appetite, concentration, mood and relationships, which makes it the strongest predictor of HRQoL. In studies of depression in the general population it has been shown that patients who meet the criteria for a diagnosis of major depression are likely to spend a quarter of the decade following their commencement of treatment in either sub threshold or threshold depression.[259] Finally, the covariance between panic and anxiety was found to be high in the SEM models and therefore it could be that the impact of panic is reduced in the presence of the longer term impact of general anxiety. When analysed in isolation using simple linear regression analyses panic did have a highly significant negative impact on prospective respiratory HRQoL.

The general practices' that took part in this PhD project were all recruited from inner city Manchester and had poor socioeconomic status. Eight out of the 10 practices were in the top 10% of the most deprived areas in England according to the IMD score for each practice's postcode area.[236] IMD scores take account of 7 dimensions which include: employment, health and disability, education, crime, housing and services and living environment. Therefore, the findings of this study may only be generalised to inner city deprived areas and may not reflect what would be found if the study was repeated in an area of higher socioeconomic status.

7.5 Recommendations for Future Research and Practice

7.5.1 Recommendations for research

The implications for future research are summarised in Table 7.1.

This thesis did not find that panic predicted HRQoL in multivariable regression and SEM models. The results of this study provide the most detailed investigation of the relationship between panic, depression, anxiety and HRQoL to date. However, the result is prone to the possibility of methodological weakness owing to the fact that it used self-reported measures for measuring panic. Panic was found to significantly predict HRQoL in simple linear regression

analyses and previous qualitative interview studies have found that COPD patients report that panic has a distressing impact on their lives.[96] Therefore, further research in this area is needed to confirm the results of this study.

This PhD study is the first to include panic as a potential predictor of HRQoL in COPD. Future longitudinal studies should continue to include panic as a psychological variable. However, they would be improved by including a full diagnostic clinical interview for the identification of panic disorder. This would decrease measurement error and help to ensure that cases of panic disorder are more accurately identified as distinct from COPD exacerbations. However, it is acknowledged that due to the financial and time resource limitations often placed on research and clinical practice it may not be possible to conduct lengthy clinical interviews for large numbers of patients. Therefore, it would be beneficial to develop and validate a COPD specific self-report measure which had high specificity and sensitivity to detect panic attacks and disorder when comorbid with COPD.

Future studies should aim to recruit a larger sample of COPD patents to allow more detailed SEM models to be specified which include both psychological predictors of HRQoL and physical covariates. Furthermore, the recruitment of a larger sample would also allow for analyses to include an examination of effect modification by key variables such as, gender and socioeconomic status. This would improve the external validity of the findings.

This PhD study has focussed on the long term impact of panic on HRQoL. However, as discussed previously panic attacks have a quick onset and a short duration and not all of the patients who experience panic attacks will meet the criteria for panic disorder. Therefore, future research should be conducted to investigate the short term impact of panic on important outcomes for COPD patients', such as medication use and use of unscheduled healthcare. It would also be beneficial to the evidence base in this area to conduct a mixed methods study which would include in-depth interviews with a sub sample of COPD patients who experience panic. Interviews should focus on identifying how panic manifests itself when comorbid with COPD and how it impacts their daily lives. This could help to identify if there are any factors about the relationship between panic and COPD which are unique and could be modifiable in the development of future interventions for use in clinical practice.

Table 7.1: Summary of the implications for future research

Implications for future research
1. Further large scale research us required to investigate the impact of panic in COPD
2. Future studies should include: 2.1 A full diagnostic clinical interview for the identification of panic attacks and disorder
2.2 Stratification within the analyses for factors such as gender and socioeconomic status
2.3 Investigation of the impact of panic attacks and disorder on short term outcomes in COPD, such as medication use and unscheduled care use
2.4 A mixed methods approach which includes in-depth qualitative interviews with COPD patients who experience panic attacks and panic disorder

7.5.2 Implications for healthcare practice

The implications for healthcare practice are summarised in Table 7.2.

The findings of this thesis indicate that, where the focus of clinical practice in COPD is on improving HRQoL, it is important to identify and treat both depression and anxiety. The international GOLD guidelines for the diagnosis and management of COPD acknowledge that depression and anxiety are common in COPD but they do not provide any specific advice for treatment within the context of COPD.[1] The GOLD guidelines recommend that depression and anxiety should be treated as per the clinical guidelines for treatment of depression and anxiety, such as those produced by NICE.[1] In the UK NICE have developed guidelines for the treatment of depression in adults with chronic physical health problems.[181] NICE recommends that depression is treated using a stepped care approach which is flexible to the needs of patients with varying levels of severity of depression and anxiety; individual patients can be stepped up or stepped down to different treatment with different levels of intensity based on their presenting symptoms and treatment progression. At step 1 the model recommends monitoring, psycho education and active assessment; at step 2 low intensity psychological interventions and possibly medication; and at steps 3 and 4 high intensity interventions, collaborative care and multidisciplinary inpatient care if required.[181]

A systematic review of the use of complex interventions for the treatment of depression and anxiety in COPD has found that interventions which include exercise components as well as psychological therapies are the most effective.[174] In the UK the current focus of treatment for depression and anxiety in the general population is on CBT delivered in primary care in the context of the Improving Access to Psychological Therapies (IAPT) initiative.[20] The systematic review in COPD found that although CBT interventions showed small improvements in both depression and anxiety but these were not significant.[174] Therefore, further research is needed to understand how best to harness the proven benefit of CBT for COPD patients and to explore the relative effectiveness of other psychological interventions which may be more effective and acceptable to this patient group such as, brief psychodynamic therapy.

The current focus of guidelines is very much on the management of depression in the context of chronic physical health problems. However, the results of this study showed that anxiety predicted depression and that in isolation panic had a significantly negative impact on the HRQoL of COPD patients. Therefore, there is a possible role for identifying and treating both general anxiety and panic early in clinical practice. It is important to screen for anxiety and panic disorder in COPD patients and to provide treatment as part of existing cognitive behavioural approaches. This is consistent with the NICE guidelines for the treatment of depression in adults with physical health problems which recommend that when depression is accompanied by symptoms of anxiety that anxiety should usually be treated first as the effective treatment of anxiety can improve outcomes for depression.[181]

Table 7.2: Summary of implications for healthcare practice

Implications for healthcare practice
1. Continue to identify and treat depression in order to improve the HRQoL of patients with COPD.
2. Consider screening for general anxiety and panic disorder
3. If comorbid anxiety and depression are present, consider treating anxiety first in line with NICE guidelines.[180]
4. Treat anxiety and panic disorder as per existing cognitive behavioural approaches.

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9. Appendices

9.1 Review Appendix A – Published Review (Blakemore et al. 2014)

Copy of published systematic review

International Journal of Chronic Obstructive Pulmonary Disease

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REVIEW

Depression and anxiety predict health-related quality of life in chronic obstructive pulmonary disease: systematic review and meta-analysis

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Background: The causal association between depression, anxiety, and health-related quality of life (HRQoL) in chronic obstructive pulmonary disease (COPD) is unclear. We therefore conducted a systematic review of prospective cohort studies that measured depression, anxiety, and HRQoL in COPD.

Methods: Electronic databases (Medline, Embase, Cumulative Index to Nursing and Allied Health Literature [CINAHL], British Nursing Index and Archive, PsycINFO and Cochrane database) were searched from inception to June 18, 2013. Studies were eligible for inclusion if they: used a nonexperimental prospective cohort design; included patients with a diagnosis of COPD confirmed by spirometry; and used validated measures of depression, anxiety, and HRQoL. Data were extracted and pooled using random effects models.

Results: Six studies were included in the systematic review; of these, three were included in the meta-analysis for depression and two were included for the meta-analysis for anxiety. Depression was significantly correlated with HRQoL at 1-year follow-up (pooled r=0.48, 95% confidence interval 0.37–0.57, P<0.001). Anxiety was also significantly correlated with HRQoL at 1-year follow-up (pooled r=0.36, 95% confidence interval 0.23–0.48, P<0.001).

Conclusion: Anxiety and depression predict HRQoL in COPD. However, this longitudinal analysis does not show cause and effect relationships between depression and anxiety and future HRQoL. Future studies should identify psychological predictors of poor HRQoL in well designed prospective cohorts with a view to isolating the mediating role played by anxiety disorder and depression.

Keywords: long-term conditions, COPD, quality of life, panic

Background

Chronic obstructive pulmonary disease (COPD) is responsible for approximately 5% of deaths worldwide and is predicted to become the third leading cause of death by 2030.[1] It is a chronic respiratory disease that typically results in a wide range of extrapulmonary comorbidities, such as cardiovascular disease, skeletal muscle dysfunction, osteoporosis, diabetes, anemia, and depression.[2,3] COPD severity has traditionally been assessed using measures of airflow obstruction, such as forced expiratory volume in one second (FEV_1). However, the therapeutic focus in COPD has started to shift away from an emphasis on lung function and mortality to management of comorbidities and more patient-centered outcomes related to functioning and health status. This trend is reflected in the increased use and reliance on patient-centered outcomes such as health-related quality of life (HRQoL) to assess the impact of therapeutic strategies in COPD.[4]

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HRQoL is a multidimensional concept that refers to quality of life that is directly related to health or illness. It often includes domains related to the physical, social, and psychological impact of illness.[5] HRQoL is concerned with a patient's experience of illness and can be defined as the subjective perception of the impact of health status on satisfaction with daily life.[5–7] COPD severity is associated with impaired HRQoL,[8–10] but poor HRQoL can also exacerbate symptoms of COPD (such as breathlessness) and can have a significant impact on physical functioning, the probability of hospital admission, and mortality.[11–18]

There are a range of psychological factors that might explain variation in respiratory-specific HRQoL over and above markers of disease severity, such as FEV_1. Depression and anxiety have both been found to be important predictors of HRQoL in cross-sectional studies,[19–24] with anxiety explaining over 40% of the variance in HRQoL in some cases.[20] Tsiligianni et al conducted a meta-analysis of cross-sectional studies and reported that depression and anxiety were highly correlated with respiratory-specific HRQoL; a higher correlation was only found between dyspnea and HRQoL.[25] Further studies conducted since this review have confirmed this finding,[26] with one population-based study in Singapore showing that the impact of depression on HRQoL in COPD was significantly greater than in people without COPD.[27] Some cross-sectional studies have also examined the association between psychological health and more generic measures of HRQoL, such as the Medical Outcomes Study Short Form.[28] However, even when HRQoL is measured using these generic measures, depression and anxiety still account for a significant proportion of the variance in people with COPD.[29,30]

Findings to date are thus mainly derived from cross-sectional studies, and although results suggest that there is a significant association between depression, anxiety, and HRQoL in COPD, they are not able to determine causal associations between these factors. It is important to consider the temporal and causal association between depression and/or anxiety and HRQoL in order to inform the development of future interventions aimed at improving HRQoL. We have therefore conducted a systematic review with meta-analysis of longitudinal prospective studies to assess the ability of depression and anxiety to predict future HRQoL in patients with COPD.

Methods

The methods and results for this review are reported in line with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[31]

Information sources and search strategy

Studies were identified for inclusion in this review by searching the following electronic databases from inception to June 18, 2013: Medline, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), British Nursing Index and Archive, PsycINFO, and Cochrane database. The search strategy was designed using Medical Subject Headings (MeSH) terms and key words relating to COPD, depression, anxiety, panic, HRQoL, and longitudinal cohort studies for each database. Electronic searches were supplemented by hand searches of reference lists of included papers and relevant reviews.

Eligibility criteria

Studies were eligible for inclusion in this review if they:

- used a nonexperimental prospective cohort design
- did not include any standardized experimental intervention; this was to ensure that samples included in the review had not been exposed to any intervention which may have modified the association between depression, anxiety, and HRQoL over the duration of the study
- included patients with a diagnosis of COPD confirmed by spirometry as an FEV_1/forced vital capacity ratio <0.70 or FEV_1 $<80\%$ of the predicted values according to GOLD (Global initiative for chronic Obstructive Lung Disease) criteria;[32] studies that included a cohort of patients with a range of chronic physical health problems including COPD were eligible only where data for COPD confirmed by spirometry were reported separately
- used validated self-report measures of either general or respiratory-specific HRQoL
- used validated diagnostic clinical interviews or self-report measures of depression and anxiety; clinical and subthreshold symptoms of depression and anxiety were included.

Studies where depression and anxiety were measured using a subscale of a quality of life measure were excluded. Studies were not excluded by date of publication, sample size, or follow-up period. However, studies that were unpublished, published in abstract form only, or were not published in the English language were not included in this review.

Study selection

Titles and abstracts were screened (by AB) and full papers of potentially relevant abstracts were retrieved. Full text versions of abstracts were independently screened and final decisions about eligibility were made at a consensus meeting with all review authors. Further information was requested from authors of seven papers, of whom five responded to provide additional information on their papers.

Data extraction

An electronic form was developed in Microsoft Excel for the purpose of data extraction. Data were extracted independently by two researchers (AB, CA) who each looked at all studies. Data were extracted on study design, method and place of recruitment, sample age, sex, smoking history, method of COPD diagnosis, and severity classification (FEV_1). Scores for HRQoL depression and anxiety were extracted at both baseline and follow-up. Any disagreements between researchers were resolved by discussion.

The main aim of this review was to assess the strength of the longitudinal association between anxiety, depression, and HRQoL in COPD. Where these data were not available in the published papers, authors were contacted by email or letter to request the appropriate data. Where the length of follow-up varied, data were extracted and included in the meta-analysis for the time point closest to 12 months after the baseline measures were taken.

Quality assessment

Studies were rated for their quality by two researchers (AB, CA) using criteria adapted from guidance on the assessment of observational studies[33] and the Quality Assessment Tool for Quantitative Studies.[34] Any disagreements were resolved by discussion.

The quality review included assessment of selection bias, response bias, the reliability and validity of data collection methods, withdrawals and dropouts, and whether confounding variables were adequately controlled for. Three key criteria were deemed as essential to the quality review and each study was awarded one point for each criterion met; this was then used as a framework for narrative synthesis of the results. These key criteria were: response rate of 70% or greater at baseline; control for confounding factors in analysis; and response rate greater than 70% at follow-up.[34]

Data analysis and synthesis

Data analysis was conducted in Stata (version 12.1; StataCorp LP, College Station, TX, USA) and Comprehensive Meta-analysis (version 2.2.064; BioStat International, Inc., Tampa, FL, USA). Where possible, indices of association between depression or anxiety and total scores for HRQoL measures were included in the meta-analysis. However, where total scores were not available, the most appropriate subscale score was used. For the St George's Respiratory Questionnaire (SGRQ)[35] the Impact subscale was used because it provides a measure of social functioning and psychological disturbance associated with respiratory disease.[35] We aimed to extract regression coefficients where possible. However, since regression coefficients were not available in any of the studies, correlation coefficients were extracted and transformed for meta-analysis using Fisher's Z transformation in order to normalize the distribution of r, making the variance independent of the unknown true value of the correlation.[36] The Z scores were then pooled across the studies using a random effects model to account for variation between studies. The pooled effect size was then converted back to a correlation coefficient.[37] A pooled correlation coefficient of r=0.10 was considered small, r=0.25 as moderate, and r=0.40 as large.[38] Where papers did not report either a correlation coefficient or the data required to compute a correlation coefficient, we contacted the corresponding author and requested the missing data. Two authors responded and supplied the relevant data.[39,40] Statistical heterogeneity was investigated using I^2 which measures the percentage of the variation across studies that is due to heterogeneity and cannot be explained by chance.[41] Low heterogeneity is indicated by an I^2 result of ≤25%, moderate heterogeneity by around 50%, and high heterogeneity is ≥75%.[41]

Results

Electronic and hand searches identified 380 citations excluding duplicates. Of these, 236 citations were excluded on the basis that their abstracts did not meet the eligibility criteria for this review. The full texts for 144 citations were reviewed. Six studies were identified that met the criteria for inclusion in the systematic review,[39,40,42–45] of which three were eligible for inclusion in meta-analysis for depression[39,40,43] and two for anxiety.[39,40] The flow of the studies and reasons for exclusion are presented in the PRISMA flow chart in Figure 1.[31]

Characteristics of studies and populations

The characteristics of each study are summarized in Table 1. In total, there were data for 895 COPD patients, of whom 69.8% (n=625) were male. Five of the studies included both male and female COPD patients and one was limited to male patients.[39] The mean age across the studies ranged from 64.6 years[44] to 73.5 years.[42] Length of follow-up ranged from 3 months[40] to 5 years.[39]

The majority of participants (61.1%, n=547) were recruited in hospital following admission for acute exacerbations of COPD.[42,43] The remaining 38.9% (n=348) were recruited from hospital outpatient settings. One study excluded patients who had experienced an acute exacerbation in the previous 6 weeks,[39] and another reported that none of the patients in their sample had been admitted for an acute

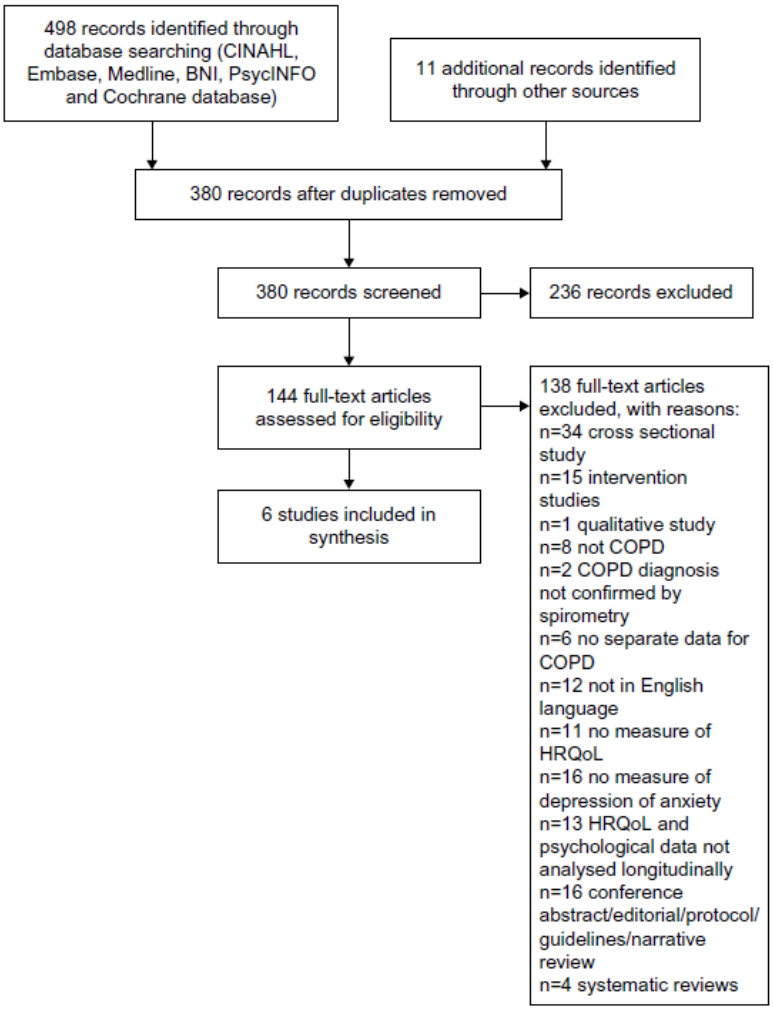

Figure 1 Search flowchart.
Abbreviations: BNI, British Nursing Index and Archive; CINAHL, Cumulative Index to Nursing and Allied Health Literature; COPD, chronic obstructive pulmonary disease; HRQoL, health-related quality of life.

exacerbation at the time they participated in the study.[44] All included studies recruited patients with a mean predicted FEV_1 <50%, which indicates severe COPD.[32]

Four of the six studies[39,40,42,43] measured HRQoL using COPD-specific measures, including the SGRQ and the Chronic Respiratory Questionnaire.[46] One study[45] used the Sickness Impact Profile,[47] and another used both the Sickness Impact Profile and the SGRQ.[44] Four of the six studies[39,40,42,44] measured symptoms of depression using the Hospital Anxiety and Depression Scale (HADS).[48] One study[43] used the Hopkins Symptom Checklist,[49] and one study used the Profile of Mood States.[50] Three studies measured anxiety symptoms using the HADS.[39,40,44] No study measured panic disorder or any other specific anxiety disorders.

The prevalence of anxiety and depression varied at baseline (Table 1). The three studies that recruited patients following an admission to hospital reported that patients in their sample were experiencing symptoms of depression at baseline.[40,42,43] One study reported that 44.4% of their sample had symptoms of depression at baseline, but did not report mean HADS scores.[42] Three of the studies that recruited hospital outpatients reported that their sample had symptoms of depression that were not clinically significant at baseline.[39,44,45] However, one study of outpatients reported

Table 1 Characteristics of included studies

Reference	Country	Recruitment and sample	Mean age, years (± SD)	% Male	Mean FEV_1% predicted and GOLD severity stage	HRQoL measures and mean scores	Psychological measures and mean scores	Length of follow-up
Ng et al[42]	Singapore	376 consecutive patients hospitalized for acute exacerbations between April 2002 and October 2004. FEV_1 <70% predicted, with or without chronic cough and sputum. Current or ex-smoker with history of ≥20 pack years	Not depressed (n=209) 71.1±8.2 Depressed (n=167) 73.5±8.5	Total 85.1 (n=320) Not depressed 85.6 (n=179) Depressed 84.4 (n=141)	Not depressed (n=209) 48.2±20.2 Depressed (n=167) 47.3±21.8 Stage III, severe COPD	SGRQ Not depressed 42.4 (SE 3.4) Depressed 52.4 (SE 3.1)	HADS 44.4% (n=167) depressed at baseline (score of ≥8 on HAD-D)	6 months and 1 year mean 313±13 days
Oga et al[39]	Japan	137 consecutive male outpatients between September 1995 and April 1997. Moderate to very severe COPD (maximal FEV_1/FVC ratio of <0.7 and post-bronchodilator FEV_1 <80% of predicted normal). Smoking history of >20 pack years	69.0±0.6	100% (n=137)	45.9 (SE 1.3) Stage III, severe COPD	SGRQ, Japanese version 36.2 (SE 1.4) CRQ, Japanese version 5.4 (SE 0.08)	HADS-Japanese version HAD-D 3.9 (SE 0.3) HAD-A 4.7 (SE 0.3)	5 years
Andenaes et al[43]	Norway	92 hospital patients diagnosed with COPD between September 1997 and February 2000	67.6±9.5	41.2 (n=21)	39.8±16.5 Stage III, severe COPD	SGRQ 65.9±10.9 WHOQOL-BREF physical 10.6±2.1 psychological 13.1±2.5 social 14.8±1.9 environmental 13.5±1.9	HSCL-25 2.1±0.5	1 month post-discharge, 6 and 9 months
Engstrom et al[44]	Sweden	68 hospital outpatients, every tenth outpatient at Department of Pulmonary Medicine.FEV_1 <80% predicted. 40–75 years.stratified into 3 groups: FEV_1 <30% (22.3%, n=21); 30%–50% (36.4%, 50%–80% 64.1±6.4 n=25); 50%–80% (60.9, n=22)	Overall 64.6±6.8 <30% 64.1±6.8 30%–50% 64.8±7.3 50%–80% 64.1±6.4	Overall 63.2 (n= 43) <30% 57.1 (n=12) 30%–50% 64.0 (n=16) 50%–80% 68.2 (n=15)	39.9±17.0 Stage III (severe COPD)	SGRQ 46.0±18.3 <30% 54.3±14.6 30%–50% 47.5±17.1 50%–80% 36.4±19.1 SIP-Swedish version 8.5±8.1 <30% 10.6±7.0 30%–50% 9.9±9.3 50%–80% 4.9±6.8	HADS-Swedish version HAD-D 5.2±4.5 HAD-A 4.4±3.8 MACL 3.0±0.6 <30% 2.9±0.5 30%–50% 3.1±0.5 50%–80% 3.1±0.8	12 months
Graydon et al[45]	Canada	143 hospital outpatients, FEV_1 <50% predicted (severe COPD) Data analysed for 71 patients who completed follow up	66.4 (SD not reported)	67.6 (n=48)	31.73±8.62 Stage III (severe COPD)	SIP 16.4±10.2	POMS (negative mood scales) 38.0±28.6	30 months
Coventry et al[40]	UK	79 patients admitted for acute exacerbation and referred to nurse-led early discharge service FEV_1 <80% predicted	65.3±9.9	44 (n=56)	42.2±18.4 Stage III (severe COPD)	SGRQ 58.8±14.6	HADS HAD-D 7.0±3.8 HAD-A 8.8±4.3 HAD total 15.8±7.0	90 days and 365 days

Abbreviations: FEV_1, forced expiratory volume in 1 second; GOLD, Global initiative for chronic Obstructive Lung Disease; HRQoL, health-related quality of life; SGRQ, St George's Respiratory Questionnaire; HADS, Hospital Anxiety and Depression Scale; FVC, forced vital capacity; CRQ, Chronic Respiratory Questionnaire; HAD-A, Hospital Depression and Anxiety Scale anxiety subscale; HAD-D, Hospital Depression and Anxiety Scale depression subscale; WHOQOL-BREF, World Health Organization Quality of Life Instrument; HSCL-25, Hopkins Symptoms Checklist; MACL, Mood Adjective Checklist; SIP, Sickness Impact Profile; POMS, Profile of Mood States; SD, standard deviation; SE, standard error.

a significant increase in depressive symptoms in their sample over a 5-year study period.[39]

Three studies measured anxiety using the HADS; two were studies of hospital outpatients and neither reported clinical levels of anxiety at baseline;[39,44] one was a study of patients admitted to hospital and discharged to a nurse-led early discharge service and reported a mean HADS anxiety score of 8.8, indicating mild anxiety symptoms.[40,48]

Quality of included studies

The results of the quality review are presented in Table 2. The quality of the studies varied greatly. One study met the requirements for all three of the quality criteria,[42] two studies met two of the criteria,[40,43] and three studies did not meet any.[39,44,45] Five out of the six studies studies[39,40,42,43,45] reported attrition rates at follow-up, two of which found that those who completed the study were more likely to be younger than those who did not.[43,45] Furthermore, in one study,[39] over 40% of patients who did not complete follow-up at 5 years had died. In this study, patients who had died were found to be significantly older, more breathless, and had worse HRQoL than those who did complete follow-up.

Longitudinal association of depression with HRQoL in COPD

Six longitudinal cohort studies investigated the association between depression and HRQoL in COPD (Table 1), but only three studies could be included in the meta-analysis for depression.[39,40,43]

Ng et al[42] scored the highest score of 3 in the quality review and reported that depressed patients had significantly worse HRQoL at baseline across all subscales of the SGRQ, and this was maintained at 12-month follow-up. However, the authors did not analyze the predictive effect of depression on HRQoL across the 12-month period. Two of the studies scored 2 in the quality review.[40,43] Andenaes et al[43] studied patients who were admitted to hospital with COPD and reported a significant correlation between depression at baseline and HRQoL on follow-up at 6 and 9 months. In this study, depression was significantly correlated with the respiratory-specific SGRQ Impact subscale (r=0.28, n=51, P<0.05, 95% confidence interval [CI] not reported) and also the physical domain (r=–0.64, n=51, P<0.01, 95% CI not reported), psychological domain (r=–0.62, n=51, P<0.01, 95% CI not reported), and environmental domain (r=–0.41, n=51, P<0.01, 95% CI not reported), but not with the social domain (r=–0.23) of the WHOQoL-BREF (World Health Organization Quality of Life Instrument). Coventry et al[40] found that depression at baseline

Table 2 Quality of the included studies

Reference	Information on recruitment method?	Response rate	Comparison of those who did and did not respond?	Were HRQoL measures valid and reliable?	Were psychological measures valid and reliable?	Were confounding factors controlled for in analysis?	How many patients completed FU?	Comparison of those who did and did not complete FU?	Total quality score*
Ng et al[42]	No	376/503 (74.8%)	No	Yes	Yes	Yes	275/376 completed 1-year FU (73.1%)	No	3
Oga et al[39]	Consecutive male patients outpatients	No	No	Yes	Yes	No	72/137 completed 5-year FU (52.6%)	No	0
Andenaes et al[43]	No	97/107 (90.7%)	No	Yes	No – two depression questions omitted	Yes	51/92 completed 9-month FU (55.4%)	Yes	2
Engstrom et al[44]	Every tenth patient meeting inclusion criteria invited	No	No	Yes	Yes	No	Not reported	No	0
Graydon et al[45]	Invited by letter and telephone FU call	No	No	Yes	Yes	No	71/143 completed 30-month FU (49.7%)	Yes	0
Coventry et al[40]	Patients referred to early discharge services and recruited by respiratory nurse specialists	79/123 (64%)	No	Yes	Yes	Yes	62/79 completed 365-day FU (78%)	No	2

Note: *The total quality score is calculated by awarding 1 point for each of the following criteria: 1) response rate >70% at baseline, 2) confounding factors controlled for in the analysis, and 3) response rate of >70% at FU.
Abbreviations: FU, follow-up; HRQoL, health-related quality of life.

was significantly correlated with respiratory-specific HRQoL at 3 months (r=0.52, P<0.001) and 1-year follow-up (r=0.64, P<0.001) in patients discharged from hospital under the care of early discharge services (Table 3). Three studies did not meet any of the key quality criteria.[39,44,45] Firstly, Oga et al[39] reported that depression measured at baseline was significantly correlated with respiratory-specific HRQoL at 1-year follow-up (r=0.47, P<0.001); this association remained after 5 years (r=0.47, P<0.001) in the sample of outpatients with severe COPD.[39] Secondly, Engstrom et al found that depression as measured by the Hospital Depression and Anxiety Scale depression subscale (b=0.39, P<0.001), 6-minute walk distance (b=0.05, P<0.05), and vital capacity (b=0.15, P<0.001) were the best predictors of HRQoL, explaining 59% of the variance in multiple regression analyses when SGRQ scores were excluded.[44] Finally, Graydon et al found that negative mood, as measured by the Profile of Mood States at baseline, was significantly correlated with HRQoL after 12 months (r=0.49, P<0.0001, 95% CI not reported).[45] However, they did not include depression as a predictor variable in their multiple regression analyses.

Meta-analysis of longitudinal association between depression and HRQoL in COPD

Three studies were eligible for inclusion in meta-analysis for depression.[39,40,43] Random effects meta-analysis of the three studies (Figure 2) found a large positive correlation between depression at baseline and HRQoL measured at follow-up (r=0.48, 95% CI 0.37–0.57, P<0.001). A moderate to high degree of heterogeneity was found across the studies (Q=6.60 df=2, P=0.037, I^2=69.7%).[41]

Longitudinal association of anxiety with HRQoL in COPD

Two cohort studies report the longitudinal association between anxiety and HRQoL in COPD (Table 4).[39,40] The study by Coventry et al met two of the key quality criteria for this review and found that anxiety at baseline was significantly correlated with respiratory-specific HRQoL at 3 months (r=0.40, P=0.002) but this did not remain significant at 1-year follow-up (r=0.26, P=0.052).[40] The second study did not meet any of the key quality criteria but reported that anxiety was correlated with respiratory-specific HRQoL at 1-year (r=0.41, P<0.001) and 5-year follow-up (r=0.51, P<0.001).[39]

Meta-analysis of longitudinal association between anxiety and HRQoL in COPD

Two studies were eligible for inclusion in the meta-analysis.[39,40] The random effects meta-analysis of the two studies (Figure 3) found that anxiety at baseline was associated with a moderate and significant positive correlation with HRQoL at follow-up (r=0.36, 95% CI 0.23–0.48, P<0.001). A low degree of heterogeneity was found across the studies (Q=1.22, df=1, P=0.269, I^2=18.3%).

Discussion

We conducted a systematic review and meta-analysis of longitudinal cohort studies to assess the temporal association between depression and anxiety and HRQoL in COPD. We identified six studies in total, of which three met the criteria for inclusion in the meta-analysis. Results indicated that both depression and anxiety predict future HRQoL. The association was stronger for depression than for anxiety.

Table 3 Longitudinal correlations between depression and HRQoL in chronic obstructive pulmonary disease

Reference	Depression measure	HRQoL measure	Length of follow-up	Sample size	Correlation (r)	P-value
Andenaes et al[43]	HSCL-25	SGRQ symptoms	9 months	51	−0.079	NS
	HSCL-25	SGRQ impact	9 months	51	0.279	<0.05
	HSCL-25	SGRQ activities	9 months	51	−0.138	NS
	HSCL-25	WHOQOL physical	9 months	51	−0.638	<0.001
	HSCL-25	WHOQOL psychiatric	9 months	51	−0.622	<0.001
	HSCL-25	WHOQOL social	9 months	51	−0.225	NS
	HSCL-25	WHOQOL environment	9 months	51	−0.405	<0.01
Oga et al[39]	HAD-D	SGRQ total	1 year	128	0.471	<0.001
	HAD-D	CRQ total	1 year	128	−0.581	<0.001
	HAD-D	SGRQ total	5 years	72	0.473	<0.001
	HAD-D	CRQ total	5 years	72	−0.549	<0.001
Coventry et al[40]	HAD-D	SGRQ total	3 months	79	0.517	<0.001
	HAD-D	SGRQ total	1 year	62	0.636	<0.001

Abbreviations: HSCL-25, Hopkins Symptoms Checklist; SGRQ, St George's Respiratory Questionnaire; CRQ, Chronic Respiratory Questionnaire; HAD-D, Hospital Anxiety and Depression Scale depression subscale; HRQoL, health-related quality of life; NS, not significant; WHOQOL-BREF, World Health Organization Quality of Life Instrument.

Table 4 Longitudinal correlations between anxiety and HRQoL in chronic obstructive pulmonary disease

Reference	Anxiety measure	HRQoL measure	Length of follow-up	Sample size	Correlation (*r*)	*P*-value
Oga et al[39]	HAD-A	SGRQ total	1 year	128	0.412	<0.001
	HAD-A	CRQ total	1 year	128	−0.534	<0.001
	HAD-A	SGRQ total	5 years	72	0.505	<0.001
	HAD-A	CRQ total	5 years	72	−0.641	<0.001
Coventry et al[40]	HAD-A	SGRQ total	3 months	79	0.369	0.002
	HAD-A	SGRQ total	1 year	62	0.258	0.052

Abbreviations: HAD-A, Hospital Anxiety and Depression Scale anxiety subscale; HRQoL, health-related quality of life; SGRQ, St George's Respiratory Questionnaire; CRQ, Chronic Respiratory Questionnaire.

Strengths and limitations

This review has several strengths. Firstly, the search was designed to take a broad approach to the identification of papers that included depression and anxiety. Terms to identify both clinically significant and subclinical depression and anxiety symptoms were included. Secondly, the search strategy for this review was designed to find cohort studies that had investigated the strength of the longitudinal association between depression, anxiety or panic disorder, and HRQoL in COPD which has not been done before. The decision to exclude studies where samples had been exposed to any intervention was made to ensure that any prospective change in HRQoL would be unconfounded with treatment effects. Furthermore, cohort studies are often easier to recruit into than randomized controlled trials, and therefore the samples may be less open to threats to their external validity.[51] The search resulted in identification of 380 studies, a relatively small number for a systematic review. Therefore, it is possible that inclusion of methodological terms to locate only prospective studies may have reduced the sensitivity of the search. However, we are confident that our search identified all potentially eligible relevant studies and we believe we have identified at least two studies[40,45] not included in a recent meta-analysis of studies that measured factors influencing HRQoL in COPD.[25] Finally, the detection of between-study variance can be interpreted as a positive finding since the very likely present heterogeneity has been identified and appropriately accounted for using a random effects model.[52]

This review has some weaknesses. Firstly, we used a quality scoring system that presents an overall quality score which rates methodological weaknesses equally. There is a lack of empirical support for the assumption that all methodological weaknesses have equal weight. Therefore, we present details of the performance of each study on each methodological criterion and also highlight the three criteria deemed to be most important for longitudinal studies.[34] The quality review highlighted several methodological issues with the studies eligible for inclusion in this review. One of the studies that was rated as the highest quality[42] was not eligible for inclusion in the meta-analysis because data on the longitudinal association between baseline depression or anxiety and HRQoL at follow-up were not available. The three studies that did report this data were of varying quality, with two meeting two of the specified quality requirements,[40,43] and one failing to meet any.[39] Only one study[40] provided information on sampling and recruitment procedures and recruitment response rates.

Therefore, it was not possible to evaluate whether the sampling method was open to selection bias in the included studies of lower quality. Furthermore, none of the studies provide any comparison between those who were and those who were not recruited, making evaluation of possible response bias impossible. The inconsistent reporting of response and attrition bias throughout the studies has implications for the

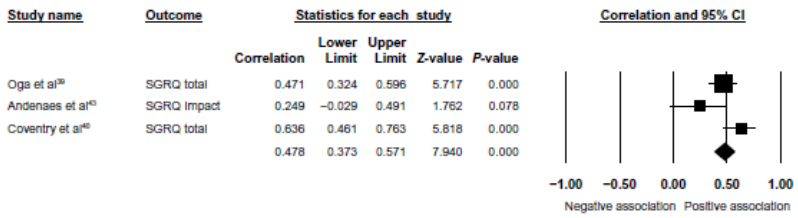

Figure 2 Forest plot of the longitudinal effect of depression on health-related quality of life in COPD.
Notes: Heterogeneity χ^2=6.60 (*df*=2); *P*=0.037; I^2=69.7%.
Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; SGRQ, St George's Respiratory Questionnaire.

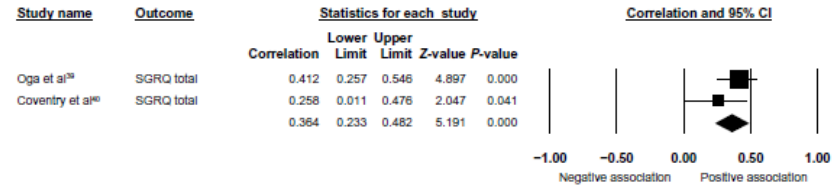

Figure 3 Forest plot of the longitudinal effect of anxiety on health-related quality of life in COPD.
Notes: Heterogeneity χ^2=1.22 (*df*=1); *P*=0.269; I^2=18.3%.
Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; SGRQ, St George's Respiratory Questionnaire; HAD-A, Hospital Anxiety and Depression Scale anxiety subscale.

inferences that can be drawn from this review. It may be that the results cannot be generalized to older COPD patients because they were less likely to complete follow-up in two studies,[42,44] although these studies were not eligible for inclusion in the meta-analysis. All of the included studies used validated measures of quality of life and psychological factors. However, one study[43] that used the Hopkins Symptom Checklist (HSCL-25) modified the measure, removing two of the items relating to suicidal ideation and loss of libido, which are symptoms commonly associated with depression. This reduces the validity of the measure and may have resulted in an underestimate of the prevalence of depressive symptoms in this sample. Unpublished studies were not included in this review, which may have introduced publication bias into this review because studies that report higher effect sizes are more likely to be published.[53] Where total scores for HRQoL measures were not available for meta-analysis, the most appropriate subscale was chosen. In the case of one paper,[43] the SGRQ impact subscale was chosen because it provides a measure of social functioning and psychological disturbance that would maximize any observed association between depression and HRQoL. We did not formally test for publication bias in this review due to the small number of studies eligible for inclusion.[54] Finally, one of the assumptions made in random effects meta-analysis is that study effects should be normally distributed. This is not always easy to confirm when the number of studies included in the model is small. However, methods have been found to be relatively robust even under extreme distributional scenarios.[55]

Implications for research and practice

The results of the meta-analysis show that depression and anxiety predict future HRQoL. These findings are consistent with the results of a recently published systematic review and meta-analysis that assessed the association between psychological and symptom-based factors and HRQoL in COPD patients.[25] Tsiligianni et al found that depression, anxiety, exercise, and dyspnea were more highly correlated with HRQoL in COPD than FEV_1,[25] but this finding was based only on cross-sectional studies and therefore did not include several studies which were eligible to be included for meta-analysis in our review.[39,40,43] Our review, which is the first to only include longitudinal studies, has further advanced our knowledge of the association between depression and anxiety and HRQoL in COPD by showing that depression and anxiety are correlated with prospective HRQoL. Unfortunately, we were not able to compare the association between depression and anxiety and HRQoL with that of FEV_1 because the necessary data were not reported in the published papers. Two authors were contacted[39,40] and invited to provide the correlations between FEV_1 and HRQoL. However, only one author responded, so the analysis could not be completed. This should be a priority for future longitudinal research in this area.

Future studies would be improved by including other common mental health problems that are prevalent in COPD. Panic disorder has a prevalence in COPD estimated to be ten times that of the prevalence in the general population.[56,57] Panic disorder is known to have a significant negative impact on quality of life in the general population[58,59] and in patients with long-term conditions such as heart failure[60] and diabetes.[61] However, no studies were identified in this review that had considered the impact of panic attacks or panic disorder in COPD. Panic attacks and panic disorder comorbid with COPD have been found to cause greater levels of distress relating to physical health,[62] and to predict worse health outcomes, including increased hospital admissions[63] and poorer functional status.[64] Therefore, it is important to investigate if panic disorder is a significant driver of HRQoL in COPD because it may be a more important predictor than depression or generalized anxiety.

The findings of this review highlight the importance of regularly assessing patient-centered outcomes such as HRQoL in people with COPD, regardless of their disease severity as measured by lung function. HRQoL is an important marker of functioning, and is potentially mediated by extrapulmonary

features of COPD such as anxiety and depression. Whereas self-management and education have had limited impact on the psychological health of COPD patients,[65–67] case management that draws on integrated and collaborative approaches has been shown to reduce depression and improve physical health in people with diabetes and coronary heart disease,[68] although their effectiveness and safety in COPD is unknown.[69] As well as scope for testing the acceptability and effectiveness of collaborative care models in COPD, there is also a need to test mediational models proposing that psychological processes and improvements in psychological health predict improvements in HRQoL and possibly improve physical health outcomes and responses to rehabilitation.[70]

Conclusion

The findings of this review confirm that there is an association between depression, anxiety, and HRQoL that endures over time. However, this longitudinal analysis does not show cause and effect between depression and anxiety and future HRQoL. Future studies should identify psychological predictors of poor HRQoL in well designed prospective cohorts with a view to isolating the mediating role played by anxiety disorders and depression.

Acknowledgments

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Author contributions

AB: planned and designed this systematic review and meta-analysis, the inclusion and exclusion criteria, and search strategies; conducted the search, identified eligible papers, extracted the data, and performed the meta-analysis; interpreted findings and wrote the drafts of the paper for submission; coordinated with coauthors to collate comments; and wrote the final draft of the paper. CD: supervised the planning and design of this review and meta-analysis; assisted in the development of inclusion and exclusion criteria, development of search strategies, meta-analysis, interpretation of findings, and drafting of the paper; and approved the final version of the paper. EG: supervised the planning and design of this review and meta-analysis; assisted in the development of inclusion and exclusion criteria, development of search strategies, meta-analysis, interpretation of findings, and drafting of the paper; and approved the final version of the paper. PB: supervised the planning and design of this review and meta-analysis; assisted in the development of inclusion and exclusion criteria, development of search strategies, meta-analysis, interpretation of findings, and drafting of the paper; and approved the final version of the paper. EK: supervised the planning and design of this review and meta-analysis; assisted in the development of inclusion and exclusion criteria, development of search strategies, meta-analysis, interpretation of findings, and drafting of the paper; and approved the final version of the paper. CA: Made a substantial contribution to the acquisition and interpretation of data by assisting in data extraction, reviewing the quality of included papers, drafting of the paper, making critical revisions to the final draft and approved the final version of the paper. PAC: supervised the planning and design of this review and meta-analysis, assisted in the development of inclusion and exclusion criteria, development of search strategies, meta-analysis, interpretation of findings, drafting of the paper; and approved the final version of the paper.

Disclosure

None of the authors had competing interests to declare.

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9.2 Review Appendix B – Search Strategy

Systematic review search strategy

	Search Term
Concept 1: COPD	
	1. COPD.mp.
	2. pulmonary disease, chronic obstructive/
	3. COAD.mp.
	4. chronic obstructive airways disease.mp.
	5. obstructive lung disease.mp.
	6. chronic airway obstruction.mp.
	7. airflow limitation.mp.
	8 Bronchitis, chronic/
	9. chronic bronchitis.mp.
	10. emphysema/
Concept 2: Psychological factors	
	11. depression/
	12. depressive disorder/
	13. depressive disorder.mp.
	14. depressive disorder$.mp.
	15. depressive symptom$
	16. reactive depression.mp.
	17. adjustment disorder$.mp.
	18. depressive disorder, major/
	19. major depression.mp.
	20. masked depression.mp.
	21. moderate depression.mp.
	22. recurrent depression.mp.
	23. minor depression.mp.
	24. mild depression.mp.
	25. chronic depression.mp.
	26. dysthymic disorder/
	27. dysthymia.mp.
	28. atypical depression.mp.
	29. geriatric depression.mp.
	30. low mood.mp.
	31. affect/
	32. affective disorder$.mp.
	33. affective symptoms/
	34. cognition disorder/
	35. psychophysiological disorders/
	36. psychosomatic disorder$.mp.
	37. psychiatric symptom$.mp.
	38. anxiety/
	39. anxiety.mp.
	40. anxiety disorder$.mp.
	41. health anxiety.mp.
	42. anxiety neurosis.mp.
	43. (mixed anxiety and depression).mp.
	44. (comorbid anxiety and depression).mp.
	45. neurosis.mp.

		Search Term
	46.	neurotic disorder$.mp.
	47.	mental health/
	48.	mental health.mp.
	49.	mentally ill persons/
	50.	mentally ill person$.mp.
	51.	mental illness.mp.
	52.	mental disease$.mp.
	53.	mental distress.mp.
	54.	mental stress.mp.
	55.	distress.mp.
	56.	stress, psychological/
	57.	stress.mp.
	58.	adjustment disorders/
	59.	adjustment disorder$.mp.
	60.	adaptation psychological/
	61.	psychological adjustment.mp.
	62.	panic disorder/
	63.	panic disorder$.mp.
	64.	panic attack$.mp.
	65.	panic/
	66.	fear/
Concept 3: Longitudinal study design		
	67.	cohort studies/
	68.	cohort studies.mp.
	69.	cohort study.mp.
	70.	longitudinal studies/
	71.	longitudinal stud$.mp.
	72.	prospective studies/
	73.	prospective stud$.mp.
	74.	follow-up studies/
	75.	follow-up stud$.mp.
	76.	epidemiological studies/
	77.	epidemiological stud$.mp.
	78.	retrospective studies/
	79.	retrospective stud$.mp.
Concept 4: Health Related Quality of Life		
	80.	quality of life/
	81.	health related quality of life.mp.
	82.	physical functionijng.mp.
	83.	health status.mp.
	84.	health outcome$.mp.
	85.	health measure$.mp.

9.3 Methodological Appendix A – NHS Ethics Amendment 1

Substantial Amendment to Ethics

NHS
National Patient Safety Agency

National Research Ethics Service

NOTICE OF SUBSTANTIAL AMENDMENT

For use in the case of all research other than clinical trials of investigational medicinal products (CTIMPs). For substantial amendments to CTIMPs, please use the EU-approved notice of amendment form (Annex 2 to ENTR/CT1) at http://eudract.emea.eu.int/document.html#guidance.

To be completed in typescript by the Chief Investigator in language comprehensible to a lay person and submitted to the Research Ethics Committee that gave a favourable opinion of the research ("the main REC"). In the case of multi-site studies, there is no need to send copies to other RECs unless specifically required by the main REC.

Further guidance is available at http://www.nres.npsa.nhs.uk/applicants/review/after/amendments.htm.

Details of Chief Investigator:	
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Full title of study:	CHOICE (Choosing Health Options in Chronic Care Emergencies) quantitative study - Developing effective strategies to reduce unscheduled care in chronic disease.
Name of main REC:	North West 8 Research Ethics Committee – Greater Manchester East Street
REC reference number:	09/H1013/80
Date study commenced:	GP recruitment commenced May 2010
Protocol reference *(if applicable)*, current version and date:	0904
Amendment number and date:	Substantial amendment 6, 6 May 2011

Type of amendment (indicate all that apply in bold)

(a) Amendment to information previously given on the NRES Application Form

Yes (*No*)

If yes, please refer to relevant sections of the REC application in the "summary of changes" below.

(b) Amendment to the protocol

Yes (*No*)

If yes, please submit either the revised protocol with a new version number and date, highlighting changes in bold, or a document listing the changes and giving both the previous and revised text.

(c) Amendment to the information sheet(s) and consent form(s) for participants, or to any other supporting documentation for the study

(*Yes*) *No*

If yes, please submit all revised documents with new version numbers and dates, highlighting new text in bold.

Is this a modified version of an amendment previously notified to the REC and given an unfavourable opinion?

Yes (***No***)

Summary of changes

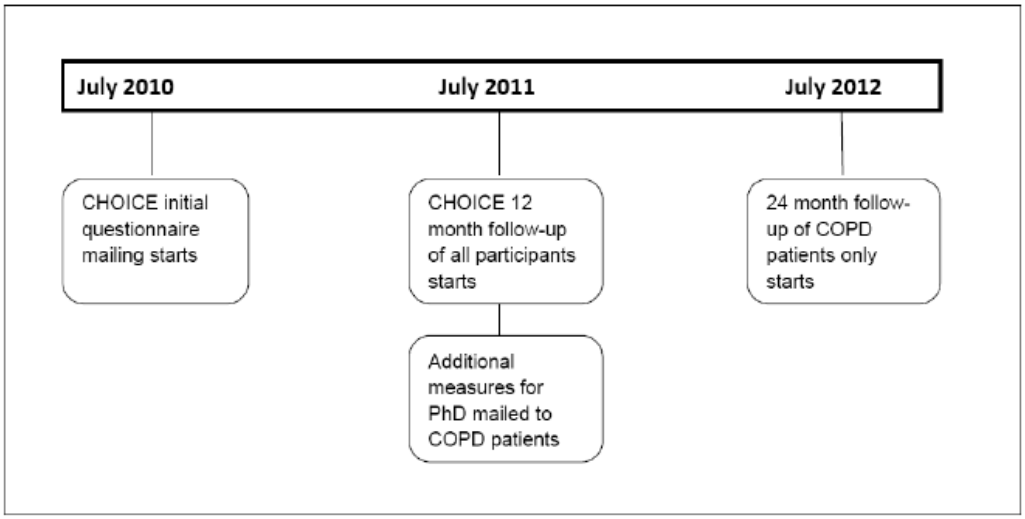
Briefly summarise the main changes proposed in this amendment using language comprehensible to a lay person. Explain the purpose of the changes and their significance for the study. In the case of a modified amendment, highlight the modifications that have been made.

If the amendment significantly alters the research design or methodology, or could otherwise affect the scientific value of the study, supporting scientific information should be given (or enclosed separately). Indicate whether or not additional scientific critique has been obtained.

The purpose of this amendment is to request the addition of 2 measures to the CHOICE quantitative project 2a follow-up questionnaire (09/H1013/80). This amendment is in addition to Notice of Substantial Amendment 5, which is also being submitted to the committee at the same time. And relates to a new PhD project, which was previously presented informally (11 March 2011) to the chair for consideration.

The 2 measures which we propose to include will be for completion only by participants who responded to the initial CHOICE questionnaire and have Chronic Obstructive Pulmonary Disease (COPD). It is expected that this will be approximately 350 COPD patients. In addition we would like to add a further follow up questionnaire for patients with COPD at 24 months, extending the follow-up period, for the COPD cohort of patients only. This is summarised in a timeline below.

Summary of the data collection timeline



This addition to the project is for the purpose of a **PhD project** which is being undertaken as part of, and funded by, the CHOICE NIHR Programme Grant. The PhD is being undertaken by Amy Blakemore, one of the Senior Research Assistants who has been employed on the grant since February 2010. The title of the PhD project is 'Psychosocial predictors of health related quality of life in patients with Chronic Obstructive Pulmonary Disease.' The PhD is being supervised by Dr Christopher Dickens and Dr Peter Coventry, and falls within the School of Medicine at the University of Manchester. Dr Christopher Dickens is a co-investigator/collaborator on the grant.

As explained in substantial amendment 5, the CHOICE 12 month follow-up questionnaire mailings will begin in July 2011 for all participants who responded to the initial questionnaire (July 2010) and gave their consent. For the purpose of this PhD project, **we would like to add 2 additional measures to the CHOICE 12 month follow-up questionnaire which**

would be mailed to those individuals who have COPD. These measures would be included as part of the existing CHOICE mail pack and would be presented in the same format as the existing questionnaire but will only be mailed to the COPD patients. The pre-validated measures we would like to include are:

1) **Panic Disorder Self Report (PDSR)**
   Newman et al. (2006).
   The PDSR is a 24 item self report measure of panic disorder which is based on the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 1994). See page 14-17 of the attached questionnaire 'COPD PhD Questionnaire FU_Version 1_06.05.2011.'

2) **The Chronic Respiratory Questionnaire self report version (CRQ – SR).**
   Williams et al. (2001).
   The CRQ – SR is a self administered measure of the health related quality of life of COPD patients. The questionnaire has 20 items in total and has been estimated to take 5-10 minutes to complete (Willams et al. 2003). See page 18-23 of the attached questionnaire 'COPD PhD Questionnaire FU_Version 1_06.05.2011.'

The aim of this PhD project is to identify the psychosocial predictors of health related quality of life in COPD patients. The proposed 24 month follow up will allow us to look at the effect of each variable on health related quality of life over time. This 24mth follow-up questionnaire for COPD patients will include the measures outlined above, as well as the following 2 measures which were included in the initial CHOICE questionnaire and 12 month follow-up questionnaire:

1) **Hospital Anxiety and Depression Scale** (Zigmond and Snaith, 1983)
2) **Medical Outcomes Short Form 12** (SF-I2, Ware, 1996)

As with the mailing for the previous CHOICE questionnaires and forthcoming questionnaires we would like to send a reminder letter to anybody who has not returned a questionnaire 3 weeks after the initial mailing (see attached 12 month COPD FU reminder letter version 1_14.04.2011).

Participants have already been identified from the GP practices' using the Quality and Outcomes Framework (QOF) registers. They have also completed the initial CHOICE questionnaire and consented to be followed up at 12 months. However, in the original patient information sheet we did not mention that we may want to follow-up the COPD respondents at 24 months.

Therefore we will now include a new patient information sheet and consent form for COPD patients to consent to be followed up at 24 months (see attached patient information sheet version 1_05.05.2011_ and Consent form version 1_14.04.2011). Furthermore dependent on the outcomes from the questionnaire data, Amy may wish to invite a sample of the COPD patients for in-depth interview. This has been clearly stated on page 3 of the patient information sheet and is made clear on the consent form, where patients have been invited to opt in for interview.

It will be the CHOICE team and not network/GP staff that will be sending the 12 month and 24 month follow-up questionnaires directly to the COPD patients. Before the questionnaires are sent the CHOICE team will contact the practice to enquire whether any of the patients have died and if other exclusion criteria apply since the completion of the initial questionnaire.

We anticipate very few potential problems with the inclusion of these additional measures for COPD patients. The additional measures contain general questions about physical status and psychological variables and they are all validated measures. The telephone number of the Senior Research Assistant will be provided for patients to make contact if they require any further information or clarification before deciding to take part.

In summary, we are seeking a favourable ethics opinion to include 2 additional measures at 12 month follow-up for COPD respondents only and also to add an additional brief follow up questionnaire at 24 months.

References

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Newman MG. Holmes M. Zuellig AR. Kachin KE. Behar E. (2006). The reliability and validity of the panic disorder self report: a new diagnostic screening measure of panic disorder.

Ware JE. (1996). A 12-item short form health survey (SF-12): construction of scales and preliminary tests of reliability and validity. Medical Care, 32, 220–33.

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Zigmond AS. & Snaith RP. (1983). The hospital anxiety and depression scale. Acta Psychiatrica Scandinavica, 67(6), 361-370.

Any other relevant information

Applicants may indicate any specific ethical issues relating to the amendment, on which the opinion of the REC is sought.

List of enclosed documents

Document	*Version*	*Date*
Follow-up Questionnaire PhD	1	06.05.2011
Patient Information Sheet	1	05.05.2011
Consent Form	1	14.04.2011
12 Month COPD FU Letter	1	14.04.2011
12 Month COPD FU Reminder Letter	1	14.04.2011
24 Month COPD FU Letter	1	14.04.2011
24 Month COPD Reminder FU Letter	1	14.04.2011

Declaration

- I confirm that the information in this form is accurate to the best of my knowledge and I take full responsibility for it.
- I consider that it would be reasonable for the proposed amendment to be implemented.

Signature of Chief Investigator: .....

Print name: .....

Date of submission: .....

9.4 Methodological Appendix B – Participant Information Sheet

Participant information sheet for PhD study

MANCHESTER 1824
The University of Manchester

NHS
National Institute for
Health Research

UNIVERSITY OF LIVERPOOL

Quality of Life Study - Participant Information Sheet

Please take time to read this information sheet carefully before you decide whether or not to complete the enclosed questionnaire. If you have any further questions please ask, contact details are given on page 4.

What is the purpose of the study?

You may remember that 12 months ago you completed a questionnaire which asked questions about your use of health care services. The purpose of this questionnaire was to find out which factors lead people with chronic long term physical illnesses to access out of hours care and emergency services. We are now inviting you to complete a follow-up questionnaire so that we can look at your use and experience of health care over the last 12 months.

In addition a PhD researcher who is a part of the CHOICE research team is interested in finding out which factors impact on the quality of life of people with breathing difficulties. She is particularly interested in how stress, which is caused by physical illness, can affect people's quality of life. For the purpose of this project we have included some additional questions at the end of the questionnaire; we hope that you will complete these questions.

We hope that all of this information might help to improve services for people with chronic illness, by making sure that they are able to receive the services they want and need, and by developing new ways of helping people, or organising services, so they have less need to use emergency or out of hours services.

MANCHESTER CITY COUNCIL

Manchester Mental Health and Social Care Trust NHS

Page 1 of 4

V 3 05.07.2011

Who is doing the study and who has approved it?

The project is being funded by the National Institute of Health Research and is being run by a team of researchers, clinicians and senior staff from Manchester Primary Care Trust, Manchester Mental Health and Social Care Trust and the Universities of Manchester and Liverpool.

The PhD researcher whose additional questions are included in this questionnaire is also a Senior Research Assistant who is employed to work on the project and is completing a PhD at the University of Manchester. The PhD project will be completed in October 2013. It has been approved by the Local Research Ethics Committee (North West 8 Research Ethics Committee, Ref 09/H1013/80).

Why have I been chosen?

You were asked to complete the original questionnaire last year, because you have at least one of four chronic illnesses: diabetes, chronic obstructive pulmonary disease (chest problems), coronary heart disease and asthma. You have been invited to complete the additional questions for the PhD researcher as you indicated in the initial questionnaire that you sometimes have breathing difficulties.

What will taking part involve?

If you would like to take part then this involves completing the follow-up questionnaire which has been included with this information sheet. We estimate that it will take you about 30 minutes to complete. For the purpose of the PhD research project described above, we will also send you a much briefer final follow-up questionnaire in 12 months time.

Do I have to take part in the study?

No, it is voluntary. It is up to you to decide whether or not to take part. If you decline this will not affect the care you receive. After completion and return of the questionnaire, should you decide to change your mind, we will withdraw your details from the study. The contact details of the research team are given on page 4.

Will my taking part in the study be kept confidential?

Yes. Everything you complete on the questionnaire is completely confidential. You have been allocated a number which appears on the questionnaire but your name and any identifiers are kept separate. All questionnaires will be kept in a locked filing cabinet. Data will be stored on a password-protected computer within a locked office at the Department of Research and Development, Rawnsley Building, Manchester Royal Infirmary under the supervision of Professor Else Guthrie. Notes and computer files will not be shown to anyone outside the research team, or individuals representing the Research Sponsor or Regulatory authorities (for the purpose of monitoring or auditing the study). We have to keep these files for 15 years so that research reports can be made and so that the accuracy of information can be checked. After 15 years, all information will be destroyed.

Are there any benefits in taking part?

Although there may be no direct benefits to you personally, we hope that you find participation an interesting and useful experience. Taking part will give us a better idea of how people using services feel about the way their care is provided and the kind of stress that is caused by long term physical illness. It is anticipated that the findings of this study will help us to develop improved services for people with chronic long term illness. We will write to you with the results of the study when it complete.

Are there any disadvantages to taking part in this research?

The main disadvantage is the time it will take. Completion of the questionnaire takes about 30 minutes. Some of the questions ask about symptoms of anxiety or depression but most people usually do not find these questions distressing.

Will I be paid for participation?

We will not be able to offer any payment for helping with this study.

Future Research

In addition to completion of the questionnaires, we would also like to interview a small number of people about their experience of illness and experiences of the services that are currently provided for them. This will only involve a small number of people and we are asking at this stage for you to indicate on the enclosed consent form whether or not you would be interested in taking part in this separate but linked study. Unless you have expressed an interest you will

not have to take part in any future research. However if you do want to be considered for this separate interview study then you may be contacted by one of the research team.

What do I need to do next?

If you are happy to help with the research, please complete the consent form and questionnaire and return it to us in the pre-paid stamped address envelope.

Further information

If you would like more information or want to ask some questions about this research you can contact the PhD researcher, her name and contact details are given below:

- **Miss Amy Blakemore, Senior Research Assistant, Tel: 0161 276 5380**

Email: CHOICE@mhsc.nhs.uk

Address:
Manchester Mental Health & Social Care Trust
Rawnsley Building, 3rd floor
Manchester Royal Infirmary
Oxford Road
Manchester
M13 9WL

For independent advice about taking part in research you can contact, the local Patient Advice and Liaison Service (PALS) on 0161 918 4047.

Thank you for taking the time to read this

Please keep this information sheet for future reference

9.5 Methodological Appendix C – Recruitment Letter

Invitation letter to take part in COPD study

INSERT PRACTICE LETTER HEAD

«address_line1»
«address_line2»
«address_line3»
«address_line4»
«PostCode»

«Title» «forenames» «family_name»
«address_line1»
«address_line2»
«address_line4»
«PostCode»

«study_id»
«mailing-date»

CHOICE (Choosing health options in chronic care emergency)
Health Survey

Dear «Title» «family_name»,

You may remember that 12 months ago you completed a questionnaire from the CHOICE Health Survey, a research project funded by the National Institute for Health Research.

We are very grateful that you took the time to complete this questionnaire. We are now asking you to complete a brief follow-up questionnaire to find out how you are managing with your illness, and if you have needed to use emergency services in the last year. We have also included two sets of questions at the end of the questionnaire to ask you about how your illness affects your quality of life. These questions are for the purpose of a PhD research project which is being completed as part of the CHOICE programme. Please could you fill in the enclosed questionnaire, which should only take a short time to complete, and return it in the pre-paid envelope provided. **No stamp is required.**

For the study to be successful, it would be helpful if as many people as possible complete and return their questionnaire. However, it is up to you if you decide to take part. If you decide not to take part you may return the questionnaire blank and we will not trouble you again, this will have no effect on your future medical care.

The information you provide will be used only for research purposes and all your answers will be treated in the **strictest confidence**. If you have any questions about the survey, contact details for the research staff are given below and at the beginning of the questionnaire.

Thank you for your help.

Yours sincerely,

Dr XXXXXX

Study Contact details:

Miss Amy Blakemore, Senior Research Assistant	Tel: 0161 276 5380
Mrs Jennifer Watson, Senior Research Assistant	Tel: 0161 701 1948
Prof Elspeth Guthrie, Programme Director	Tel: 0161 276 5389
Email: CHOICE@mhsc.nhs.uk	**Website:**http://choice.mhsc.nhs.uk

12 MONTH COPD FU LETTER V1. 14.04.2011

9.6 Methodological Appendix D - Questionnaire

CHOICE 12 month follow-up questionnaire, including the measures for this PhD study

MANCHESTER 1824
The University of Manchester

NHS
National Institute for Health Research

UNIVERSITY OF LIVERPOOL

CHOICE

12 month Follow-up (including quality of life study)

Health Survey

This is a follow-up questionnaire from the Choice Health Survey which you kindly completed 12 months ago. We hope you can spare a few minutes to complete this questionnaire to let us know how you are doing. The questionnaire contains questions about your physical health, use of emergency services over the last 12 months and anxiety and stress. Please return it to your GP in the enclosed stamped addressed envelope.

Rawnsley Building,
Manchester Royal Infirmary,
Oxford Road, Manchester M13 9WL
Tel: 0161 276 5331 Fax: 0161 273 2135

If you have any questions or queries, please contact:

Amy Blakemore Tel: 0161 276 5380

Jennifer Watson Tel: 0161 701 1948

Prof Else Guthrie Tel: 0161 276 5389

or email CHOICE@mhsc.nhs.uk

MANCHESTER CITY COUNCIL

Manchester Mental Health and Social Care Trust NHS

Firstly, we would like to gather some background details...

A1a Today's date

A1b Date of birth

A2 Are you? (please tick) Male ☐ Female ☐

A3 Do you live alone? (please tick) Yes ☐ No ☐

If yes please tell us for how long you have lived alone ☐ Years ☐ Months

B1 Do you have any of the following conditions?

Please tick all that apply

Heart disease	☐ 1	Cancer	☐ 5
Asthma	☐ 2	Stomach or bowel problem	☐ 6
Diabetes	☐ 3	High blood pressure	☐ 7
Chronic obstructive pulmonary disease	☐ 4	Arthritis or other joint problems	☐ 8

Do you have any other conditions? (please specify) _____

Please answer the following questions by circling the number which best corresponds to your views.

B2 How much does your physical ill health affect your life?

0	1	2	3	4	5	6	7	8	9	10
No effect at all										Severely affects my life

B3 How long do you think your physical health problems will continue?

0	1	2	3	4	5	6	7	8	9	10
A very short time										Forever

B4 How much control do you feel you have over your physical health problems?

0	1	2	3	4	5	6	7	8	9	10
Absolutely no control										Extreme amount of control

B5 How much do you think your treatment can help your overall physical health?

0	1	2	3	4	5	6	7	8	9	10
Not at all										Extremely helpful

B6 How much do you experience symptoms from your physical health problems?

0	1	2	3	4	5	6	7	8	9	10
No symptoms at all										Many severe symptoms

B7 How concerned are you about your physical ill health?

0	1	2	3	4	5	6	7	8	9	10
Not concerned at all										Extremely concerned

B8 How well do you feel you understand your physical ill health?

0	1	2	3	4	5	6	7	8	9	10
Don't understand at all										Understand very clearly

B9 How much does your physical ill health affect you emotionally? (e.g. does it make you irritable, scared, upset, low, stressed etc?)

0	1	2	3	4	5	6	7	8	9	10
Not at all affected emotionally										Extremely affected emotionally

B10 Please list in rank-order the three most important factors that you believe caused your physical health problems. The most important causes for me are:-

1. _____
2. _____
3. _____

Please continue on page 4.

We would like to ask about your use of GP and Hospital Care over the last 12 months.

C1 In the last 12 months, how often have you visited your GP for a non-emergency appointment?

By this we mean an appointment you have booked at least one day before being seen.

☐☐ No of times

C2 In the last 12 months, how often have you asked for an emergency visit at home from your GP or GP out of hours service?

☐☐ No of times

C3 In the last 12 months, how often have you attended a hospital out-patient appointment?

☐☐ No of times

C4 In the last 12 months, how often have you had to dial 999 and call an ambulance?

☐☐ No of times

C5 In the last 12 months, how often have you attended an emergency department/casualty because of an emergency health problem?

☐☐ No of times

In the last 12 months, how often have you attended some other department or agency for an emergency health problem (e.g. walk in centre) ?

☐☐ No of times

Please tell us what kind of emergency department or service you used.

_____

C6 In the last 12 months, how often have you been admitted to hospital due to an emergency health problem?

☐☐ No of times

We would like know if you have sought help for an emergency health problem in the last 3 months (by this we mean had to call a 999 ambulance, use casualty or a walk-in centre or call an emergency GP out to see you). Please think about the most recent time that help was needed.

D1 Thinking about the most recent time help was needed in an emergency, how many weeks ago was that?

☐☐ Number of weeks

D2 Again thinking about the most recent time, how long after thinking this health problem was an emergency was help sought?

- Immediately ☐ 1
- Less than 2 hours ☐ 2
- Between 2 and 12 hours ☐ 3
- Between 12 and 24 hours ☐ 4
- More than 24 hours ☐ 5

D3 What type of health problem was it?
Please tick one

- Exacerbation of one or more of the following illnesses (either diabetes, heart disease, asthma or lung disease) ☐ 1
- Exacerbation of a different illness to the above ☐ 2
- Injury or other reason ☐ 3

D4 Still thinking about the most recent health problem, please tick the services that were involved in giving help or advice. Include all those you tried to contact, even if this was not successful.

- GP from my usual practice ☐
- Someone at my GPs but not a GP ☐
- GP out of hours/emergency GP ☐
- Minor Injuries Unit ☐
- Walk-in centre ☐
- Hospital A&E department ☐
- Hospital clinic or day ward ☐
- Admission to A&E overnight ☐
- 999 emergency ambulance ☐
- Mental health crisis team ☐
- Admission to hospital overnight ☐
- Admission to hospital for more than 24 hours ☐

If you accessed some other service that is not listed above, please write them below:

_____

These questions ask you for your views about your health, how you feel, and how well you are able to do your usual activities.

Please answer every question by ticking one box. If you are unsure about how to answer, please give the best answer you can.

E1 In general would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

		Yes, limited a lot	Yes, limited a little	No, not limited at all
E2	Moderate activities such as moving a table, pushing a vacuum cleaner, bowling or playing golf	☐ 1	☐ 2	☐ 3
E3	Climbing several flights of stairs	☐ 1	☐ 2	☐ 3

During the past 4 weeks, have you had any of the following problems with your work or other daily activities as a result of your physical health?

E4	Accomplished less than you would like	Yes ☐ 1	No ☐ 2
E5	Were limited in the kind of work or other activity	Yes ☐ 1	No ☐ 2

During the past 4 weeks, have you had any of the following problems with your work or other daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

E6	Accomplished less than you would like	Yes ☐ 1	No ☐ 2
E7	Didn't do work or other activities as carefully as usual	Yes ☐ 1	No ☐ 2

You have just answered questions regarding the last 4 weeks, we would now like to ask you some questions about today

Please place a tick in at least one box in each group below, please indicate which statements best describe your own health state today

F1	Mobility	I have no problem in walking about	1
		I have some problem in walking about	2
		I am confined to bed	3
F2	Self-care	I have no problem with self-care	1
		I have some problem with washing or dressing myself	2
		I am unable to wash or dress myself	3
F3	Usual activities (e.g. work, study, housework, family, or leisure activities)	I have no problem with performing my usual activities	1
		I have some problem with performing my usual activities	2
		I am unable to perform my usual activities	3
F4	Pain/Discomfort	I have no pain or discomfort	1
		I have moderate pain or discomfort	2
		I am in extreme pain or discomfort	3
F5	Anxiety/Depression	I am not anxious or depressed	1
		I am moderately anxious or depressed	2
		I am extremely anxious or depressed	3
F6	Compared with my general level of health over the past 12 months, my health state today is:	Better	1
		Much the same	2
		Worse	3

al work (including both

2

Extremely

ave been with you
e the one answer
elling.

f None of the time 6

f None of the time 6

E11 Have you felt downhearted and low?

1	2	3	4	5	6
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time

E12 During the past 4 weeks, how much has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives etc)?

1	2	3	4	5	6
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time

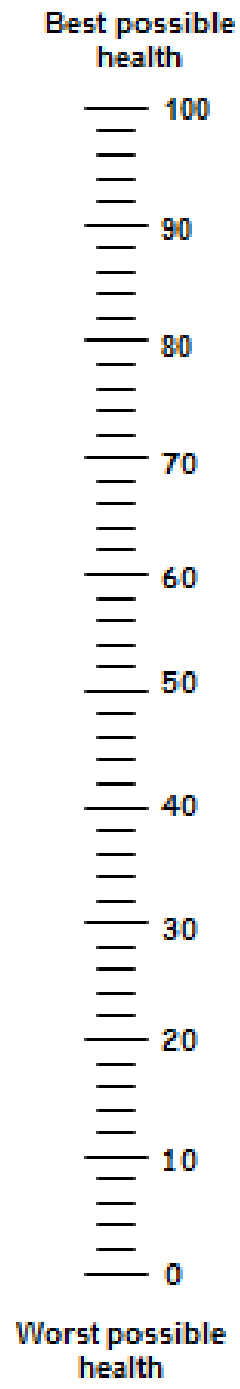
F7

To help people say how good or bad their health is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked by 100 and the worst state is marked by 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion.

Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is.

Your own health state today



This section is concerned with feelings and emotions.

Read each item and place a tick in the box opposite the reply which comes closest to how you have been feeling in the past week:

G1	I feel tense or 'wound up':	Most of the time	☐ 3
		A lot of the time	☐ 2
		Time to time, occasionally	☐ 1
		Not at all	☐ 0
G2	I still enjoy the things I used to enjoy:	Definitely as much	☐ 0
		Not quite so much	☐ 1
		Only a little	☐ 2
		Hardly at all	☐ 3
G3	I get a sort of frightened feeling as if something awful is about to happen:	Very definitely and quite badly	☐ 3
		Yes, but not too badly	☐ 2
		A little, but it doesn't worry me	☐ 1
		Not at all	☐ 0
G4	I can laugh and see the funny side of things:	As much as I always could	☐ 0
		Not quite so much now	☐ 1
		Definitely not so much now	☐ 2
		Not at all	☐ 3
G5	Worrying thoughts go through my mind:	A great deal of the time	☐ 3
		A lot of the time	☐ 2
		From time to time but not too often	☐ 1
		Only occasionally	☐ 0

G6	I feel cheerful:	Not at all	0
		Not often	1
		Sometimes	2
		Most of the time	3
G7	I can sit at ease and feel relaxed:	Definitely	0
		Usually	1
		Not often	2
		Not at all	3
G8	I feel as if I am slowed down:	Nearly all the time	3
		Very often	2
		Sometimes	1
		Not at all	0
G9	I get a sort of frightened feeling like 'butterflies' in the stomach:	Not at all	0
		Occasionally	1
		Quite often	2
		Very often	3
G10	I have lost interest in my appearance:	Definitely	3
		I don't take so much care as I should	2
		I may not take quite as much care	1
		I take just as much care as ever	0
G11	I feel restless as if I have to be on the move:	Very much indeed	3
		Quite a lot	2
		Not very much	1
		Not at all	0

G12	I look forward with enjoyment to things:	As much as I ever did	☐
		Rather less than I used to	☐
		Definitely less than I used to	☐
		Hardly at all	☐
G13	I get sudden feelings of panic:	Very often indeed	☐
		Quite often	☐
		Not very often	☐
		Not at all	☐
G14	I can enjoy a good book or radio or TV programme:	Often	☐
		Sometimes	☐
		Not often	☐
		Very seldom	☐

The following questions ask about recent events in your life.

We would like to ask you some questions about personal situations that you may have encountered during the last six months. Although some of these things are personal and of a sensitive nature, it would help a great deal if you could answer all of them.

Please answer all questions by ticking ☑ the box you think most closely applies:

All answers will be kept strictly confidential

During the last 6 months, have you experienced any of the following:

H1	Serious illness or injury to yourself?	Yes ☐	No ☐
H2	Serious illness or injury to a close relative?	Yes ☐	No ☐
H3	The death of a first-degree relative, including child or spouse?	Yes ☐	No ☐

H4	The death of a close family friend or second-degree relative?	Yes ☐	No ☐
H5	Separation due to marital difficulties?	Yes ☐	No ☐
H6	Broken off a steady relationship?	Yes ☐	No ☐
H7	A serious problem with a close friend, neighbour or relative?	Yes ☐	No ☐
H8	Been unemployed/seeking work for more than one month?	Yes ☐	No ☐
H9	Been sacked from your job?	Yes ☐	No ☐
H10	A major financial crisis?	Yes ☐	No ☐
H11	Problems with the Police or a Court appearance?	Yes ☐	No ☐
H12	Had something valuable lost or stolen?	Yes ☐	No ☐

The next section (I) on page 14 is concerned with panic attacks. Previous research has shown that panic attacks are commonly experienced by people who have breathing difficulties and we would like to know more about how they may affect people's quality of life.

Panic attacks are discrete episodes of intense fear, apprehension or terror that come on very quickly and are accompanied by a number of physical symptoms. Panic attacks can appear for no apparent reason (spontaneously) or they can occur in situations which have become associated with them (e.g. a long queue in a shop, closed spaces, or driving over bridges).

Do not consider fear to be a panic attack if it lasts several hours or most of the day.

I1 During the last six months, have you had a panic attack or a sudden rush of intense fear or anxiety? (please tick one)

☐ Yes ☐ No

If 'Yes' when was the most recent time this occurred? ☐ Enter date

If you answered 'No' to question I1 (you HAVE NOT experienced a panic attack) please leave the remainder of this section blank and move on to section J on page 17

If you answered 'Yes' (you HAVE experienced a panic attack) please continue with question I2 on this page.

I2 Was at least one panic attack unexpected, as if it came out of the blue?

☐ Yes ☐ No

I3 Did it happen more than once?

☐ Yes ☐ No

If 'Yes' approximately how many panic attacks have you had in your lifetime? ☐ Enter number

If you answered 'No' to question I2 & I3 please leave the remainder of this section blank and move on to section J on page 17, otherwise please continue with question I4 on page 15.

I4 Have you ever worried a lot (for at least one month) about having another panic attack?

☐ Yes ☐ No

I5 Have you ever worried a lot (for at least one month) that having the attacks meant you were losing control, going crazy, having a heart attack, seriously ill, etc?

☐ Yes ☐ No

I6 Did you ever change your behaviour or do something different (for at least one month) because of the panic attacks?

☐ Yes ☐ No

I7 Think back to your most severe or recent panic attack. Did you ever experience any of the following symptoms? (please tick yes or no for each symptom)

	Yes	No
a. Shortness of breath or smothering sensations?	☐	☐
b. Feeling dizzy, unsteady, lightheaded or faint?	☐	☐
c. Palpitations, pounding heart or rapid heart rate?	☐	☐
d. Trembling or shaking?	☐	☐
e. Sweating?	☐	☐
f. Feelings of choking?	☐	☐
g. Nausea or abdominal distress?	☐	☐
h. Numbness or tingling sensations?	☐	☐
i. Flushes (hot flashes) or chills?	☐	☐
j. Chest pain or discomfort?	☐	☐
k. Fear of dying?	☐	☐
l. Fear of going crazy or doing something uncontrolled?	☐	☐

I8 How much do these symptoms interfere with your daily functioning? (tick one box)

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Not at all	Mildly	Moderately	Severely	Very severely/ Disabling

I9 How distressing do you find these symptoms? (tick one box)

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
No distress	Mild distress	Moderate distress	Severe distress	Very severe distress

I10 When you have had panic attacks, does it often take **less than ten minutes** from the point at which the attack begins, to the point at which it reaches a peak or becomes most intense?

☐ Yes ☐ No

I11 Just before you began having panic attacks, were you taking any drugs or excessive amounts (more than 4 cups daily) of stimulants (e.g. coffee, tea or cola with caffeine)?

☐ Yes ☐ No

a. If 'Yes' what was it that you were taking? ☐

b. How much of it were you taking? ☐

Enter number of cups etc.

I12 Have you ever been diagnosed with a medical problem (hyperthyroidism, a seizure or cardiac condition, etc.) that could have caused your panic symptoms?

☐ Yes ☐ No

This section is concerned with how you have been feeling during the last 2 weeks.

Below is a list of activities which make some people feel short of breath. For each of the activities below, tick the box that best describes how much shortness of breath you have had whilst doing that activity in the last 2 weeks.

The last box has been provided for you to indicate if you have NOT DONE an activity during the last 2 weeks.

	Activities	Extremely short of breath	Very	Quite a bit	Moderate shortness of breath	Some	A little	Not at all short of breath	Not done
J1	Feeling emotional such as angry or upset	☐	☐	☐	☐	☐	☐	☐	☐
J2	Taking care of your basic needs (bathing, showering, eating or dressing	☐	☐	☐	☐	☐	☐	☐	☐
J3	Walking	☐	☐	☐	☐	☐	☐	☐	☐
J4	Performing chores (such as housework or shopping for groceries)	☐	☐	☐	☐	☐	☐	☐	☐
J5	Participating in social activities	☐	☐	☐	☐	☐	☐	☐	☐

These next questions ask you about your energy in general and how your mood has been during the last 2 weeks.

J6 In general, how much of the time during the last 2 weeks have you felt frustrated or impatient?

- All of the time ☐
- Most of the time ☐
- A good bit of the time ☐
- Some of the time ☐
- A little of the time ☐
- Hardly any of the time ☐
- None of the time ☐

J7 How often during the last 2 weeks did you have a feeling of fear or panic when you had difficulty getting your breath?

- All of the time ☐
- Most of the time ☐
- A good bit of the time ☐
- Some of the time ☐
- A little of the time ☐
- Hardly any of the time ☐
- None of the time ☐

J8 What about fatigue? How tired have you felt over the last 2 weeks?

- Extremely tired ☐
- Very tired ☐
- Quite a bit of tiredness ☐
- Moderately tired ☐
- Somewhat tired ☐
- A little tired ☐
- Not at all tired ☐

J9 How often during the last 2 weeks have you felt embarrassed by your coughing or heavy breathing?

- All of the time ☐
- Most of the time ☐
- A good bit of the time ☐
- Some of the time ☐
- A little of the time ☐
- Hardly any of the time ☐
- None of the time ☐

J10 In the **last 2 weeks**, how much of the time did you feel very confident and sure that you could deal with your illness?

- None of the time ☐
- A little of the time ☐
- Some of the time ☐
- A good bit of the time ☐
- Most of the time ☐
- Almost all of the time ☐
- All of the time ☐

J11 How much energy have you had in the **last 2 weeks**?

- No energy at all ☐
- A little energy ☐
- Some energy ☐
- Moderately energetic ☐
- Quite a bit of energy ☐
- Very energetic ☐
- Full of energy ☐

J12 In general, how much of the time did you feel upset, worried or depressed during the **last 2 weeks**?

- All of the time ☐
- Most of the time ☐
- A good bit of the time ☐
- Some of the time ☐
- A little of the time ☐
- Hardly any of the time ☐
- None of the time ☐

J13 How often during the last 2 weeks did you feel you had complete control of your breathing problems?

- None of the time ☐
- A little of the time ☐
- Some of the time ☐
- A good bit of the time ☐
- Most of the time ☐
- Almost all of the time ☐
- All of the time ☐

J14 How much of the time during the last 2 weeks did you feel relaxed and free of tension?

- None of the time ☐
- A little of the time ☐
- Some of the time ☐
- A good bit of the time ☐
- Most of the time ☐
- Almost all of the time ☐
- All of the time ☐

J15 How often during the last 2 weeks have you felt low in energy?

- All of the time ☐
- Most of the time ☐
- A good bit of the time ☐
- Some of the time ☐
- A little of the time ☐
- Hardly any of the time ☐
- None of the time ☐

J16 In general, how often during the last 2 weeks have you felt discouraged or down in the dumps?

- All of the time ☐
- Most of the time ☐
- A good bit of the time ☐
- Some of the time ☐
- A little of the time ☐
- Hardly any of the time ☐
- None of the time ☐

J17 How often during the last 2 weeks have you felt worn out or sluggish?

- All of the time ☐
- Most of the time ☐
- A good bit of the time ☐
- Some of the time ☐
- A little of the time ☐
- Hardly any of the time ☐
- None of the time ☐

J18 How happy, satisfied or pleased have you been with your personal life during the last 2 weeks?

- Very dissatisfied, unhappy most of the time ☐
- Generally dissatisfied ☐
- Somewhat dissatisfied, unhappy ☐
- Generally satisfied, pleased ☐
- Happy most of the time ☐
- Very happy most of the time ☐
- Extremely happy could not be more satisfied or pleased ☐

J19 How often during the last 2 weeks did you feel upset or scared when you had difficulty getting your breath?

- All of the time ☐
- Most of the time ☐
- A good bit of the time ☐
- Some of the time ☐
- A little of the time ☐
- Hardly any of the time ☐
- None of the time ☐

J20 In general, how often during the last 2 weeks have you felt restless, tense or uptight?

- All of the time ☐
- Most of the time ☐
- A good bit of the time ☐
- Some of the time ☐
- A little of the time ☐
- Hardly any of the time ☐
- None of the time ☐

Thank you very much for helping us with this Health Survey.
Please check carefully that you have completed ALL the relevant sections of the questionnaire.
Please return the questionnaire in the pre-paid envelope provided.

Research team contact address:
CHOICE Project
Rawnsley Building,
Manchester Royal Infirmary,
Oxford Road, Manchester M13 9WL

Amy Blakemore	Tel: 0161 276 5380
Jennifer Watson	Tel: 0161 701 1948
Prof Else Guthrie	Tel: 0161 276 5389
Or email us at	CHOICE@mhsc.nhs.uk

9.7 Methodological Appendix E – Reminder Letter Baseline

Reminder letter sent to those who did not return their questionnaire within 2 weeks

INSERT PRACTICE LETTER HEAD

«address_line1»
«address_line2»
«address_line3»
«address_line4»
«PostCode»

«Title» «forenames» «family_name»
«address_line1»
«address_line2»
«address_line4»
«PostCode»

«study_id»
«mailing-date»

CHOICE (Choosing health options in chronic care emergency)
Health Survey

Dear «Title» «family_name»,

As you may recall, you were recently sent a brief follow-up questionnaire from the CHOICE Health Survey team. It would be helpful if as many people as possible complete and return their questionnaire. As we do not appear to have received a reply, we would be grateful if you would consider taking a little time to fill in the enclosed brief questionnaire. If you do not wish to participate, please return the blank questionnaire in the pre-paid envelope provided, and we will not trouble you again.

The information you provide will be used only for research purposes and all your answers will be treated in the strictest confidence. If you have any questions about the survey, contact details are given below and at the beginning of the questionnaire.

Thank you for your help.

Yours sincerely,

Dr XXXXXX

Study Contact details:
Miss Amy Blakemore, Senior Research Assistant — Tel: 0161 276 5380
Mrs Jennifer Watson, Senior Research Assistant — Tel: 0161 701 1948
Prof Elspeth Guthrie, Programme Director — Tel: 0161 276 5389

Email: CHOICE@mhsc.nhs.uk

Website:http://choice.mhsc.nhs.uk

12 MONTH COPD Reminder FU LETTER V1. 14.04.2011

9.8 Methodological Appendix F – NHS Ethics Amendment 2

Substantial amendment to request permission to make reminder calls at follow-up

NHS
National Patient Safety Agency

National Research Ethics Service

NOTICE OF SUBSTANTIAL AMENDMENT

For use in the case of all research other than clinical trials of investigational medicinal products (CTIMPs). For substantial amendments to CTIMPs, please use the EU-approved notice of amendment form (Annex 2 to ENTR/CT1) at http://eudract.emea.eu.int/document.html#guidance.

To be completed in typescript by the Chief Investigator in language comprehensible to a lay person and submitted to the Research Ethics Committee that gave a favourable opinion of the research ("the main REC"). In the case of multi-site studies, there is no need to send copies to other RECs unless specifically required by the main REC.

Further guidance is available at http://www.nres.npsa.nhs.uk/applicants/review/after/amendments.htm.

Details of Chief Investigator:	
Name:	Professor Elspeth Guthrie
Address:	Rawnsley Building, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL
Telephone:	0161 276 5331 (Secretary: Wendy Clarke)
Email:	elspeth.a.guthrie@manchester.ac.uk
Fax:	0161 273 2135

Full title of study:	CHOICE (Choosing Health Options in Chronic Care Emergencies) quantitative study - Developing effective strategies to reduce unscheduled care in chronic disease.
Name of main REC:	North West 8 Research Ethics Committee – Greater Manchester East Street
REC reference number:	09/H1013/80
Date study commenced:	GP recruitment commenced May 2010
Protocol reference *(if applicable)*, current version and date:	0904
Amendment number and date:	Substantial amendment 8, May 2012

Type of amendment (indicate all that apply in bold)

(a) Amendment to information previously given on the NRES Application Form

Yes **No**

If yes, please refer to relevant sections of the REC application in the "summary of changes" below.

(b) Amendment to the protocol

Yes **No**

If yes, please submit either the revised protocol with a new version number and date, highlighting changes in bold, or a document listing the changes and giving both the previous and revised text.

(c) Amendment to the information sheet(s) and consent form(s) for participants, or to any other supporting documentation for the study

Yes **No**

If yes, please submit all revised documents with new version numbers and dates, highlighting new text in bold.

Is this a modified version of an amendment previously notified to the REC and given an unfavourable opinion?

Yes **No**

Summary of changes

Briefly summarise the main changes proposed in this amendment using language comprehensible to a lay person. Explain the purpose of the changes and their significance for the study. In the case of a modified amendment, highlight the modifications that have been made.

If the amendment significantly alters the research design or methodology, or could otherwise affect the scientific value of the study, supporting scientific information should be given (or enclosed separately). Indicate whether or not additional scientific critique has been obtained.

What is the purpose of the proposed changes?

The purpose of this amendment is to request the addition of follow up phone calls for patients who are taking part in the PhD project which is linked to the CHOICE Study 2a [ref: 09/H1013/80] which received a favourable ethical opinion on the 16 May 2011 (ethics amendment number 06).

272 COPD patients who returned initial questionnaires in July 2011 are scheduled to be followed up in July 2012 (see *Figure 1 below for an illustration of the timelines*). In order to maximise the response rates and strengthen the scientific quality of the study, ensuring that the results of this study can be generalised to the wider COPD patient population **we would like to request permission to make a telephone reminder call to patients who do not return this final questionnaire.**

The telephone calls will be for the purpose of reminding patients to return the questionnaire. The call will be made for all patients who have not returned the questionnaire 2 weeks after the reminder letter is sent out (*please see attached Follow Up Mailing Flowchart*). For those patients who have received the questionnaire but are having difficulties completing it the PhD student can help them with this over the phone.

Who will carry out the calls?
The telephone calls will be carried out by Miss Amy Blakemore (Senior Research Assistant / PhD student).

What amends have been made to the documentation?
The letter which accompanies the reminder questionnaire has been amended to make participants aware that they may receive a telephone call if they do not return the questionnaire. The amended letter is attached.

Do we foresee any ethical issues/risks with this amendment?
We feel that there are no major risks or ethical issues with making reminder follow-up calls,

Prior to making the reminder call, checks will be made with the GP practice to ensure that the patient has not passed away or that there is no other reason why the patient should not be called.

During the call if a patient raises any concerns about their physical or mental health Amy will encourage the patients to discuss any issues with their GP. If there is any immediate risk to the patient Amy will discuss these with me as the chief investigator, and where thought necessary appropriate action will be taken, such as further discussion with the patient and/or GP.

9.9 Methodological Appendix G – Reminder Letter Follow-up

Amended reminder letter for follow-up

INSERT PRACTICE LETTER HEAD

«address_line1»
«address_line2»
«address_line3»
«address_line4»
«PostCode»

«Title» «forenames» «family_name»
«address_line1»
«address_line2»
«address_line4»
«PostCode»

«study_id»
«mailing-date»

CHOICE (Choosing health options in chronic care emergency) Health Survey

Dear «Title» «family_name»,

As you may recall, you were recently sent a brief follow-up questionnaire for the PhD research project which is part of the CHOICE Health Survey. It would be helpful if as many people as possible complete and return their questionnaire. As we do not appear to have received a reply, we would be grateful if you would consider taking a little time to fill in the enclosed brief questionnaire.

Please note, if we don't hear from you within the next two weeks, you may receive a reminder phone call from the PhD Student, Miss Amy Blakemore, to check that you have received this questionnaire.

If you do not wish to participate, please return the blank questionnaire in the pre-paid envelope provided, and we will not trouble you again.

The information you provide will be used only for research purposes and all your answers will be treated in the strictest confidence. If you have any questions about the survey, contact details are given below and at the beginning of the questionnaire.

Thank you for your help.

Yours sincerely,

Study Contact details:

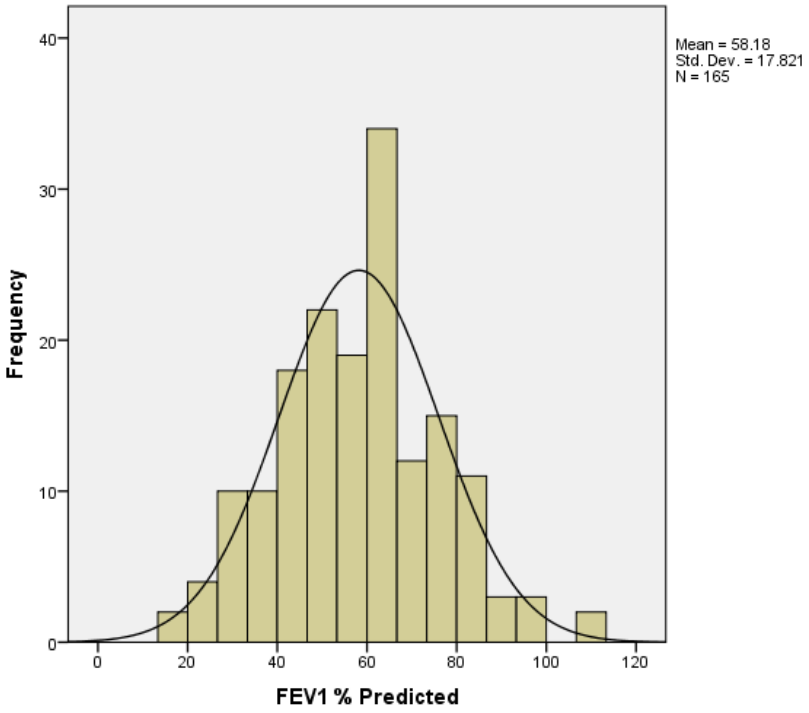
Miss Amy Blakemore, Senior Research Assistant	Tel: 0161 276 5380
Mrs Jennifer Watson, Senior Research Assistant	Tel: 0161 701 1948
Prof Elspeth Guthrie, Programme Director	Tel: 0161 276 5389
Email: CHOICE@mhsc.nhs.uk	**Website**:http://choice.mhsc.nhs.uk

24 MONTH COPD Reminder FU LETTER V2 28.05.2012

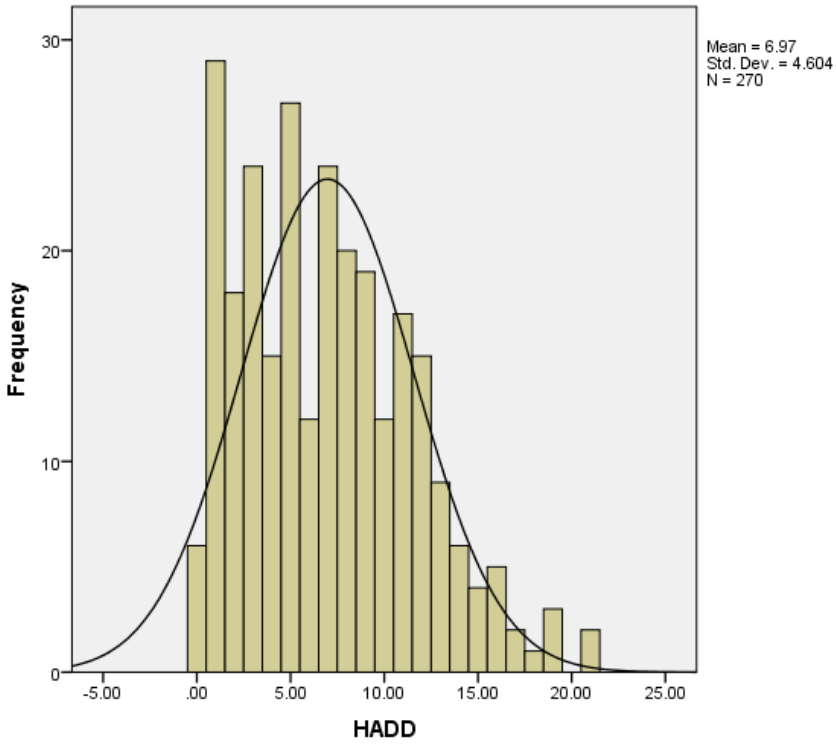
9.10 Statistical Appendix A - Historgrams

Histograms to show the distribution of data

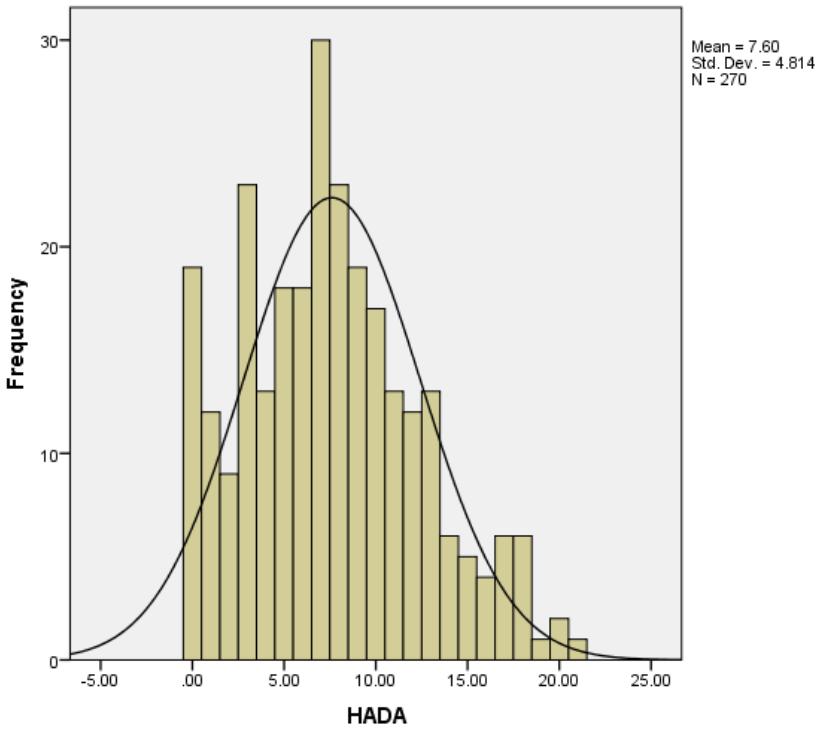
9.10.1 Histogram for COPD severity (FEV_1 % predicted) at baseline



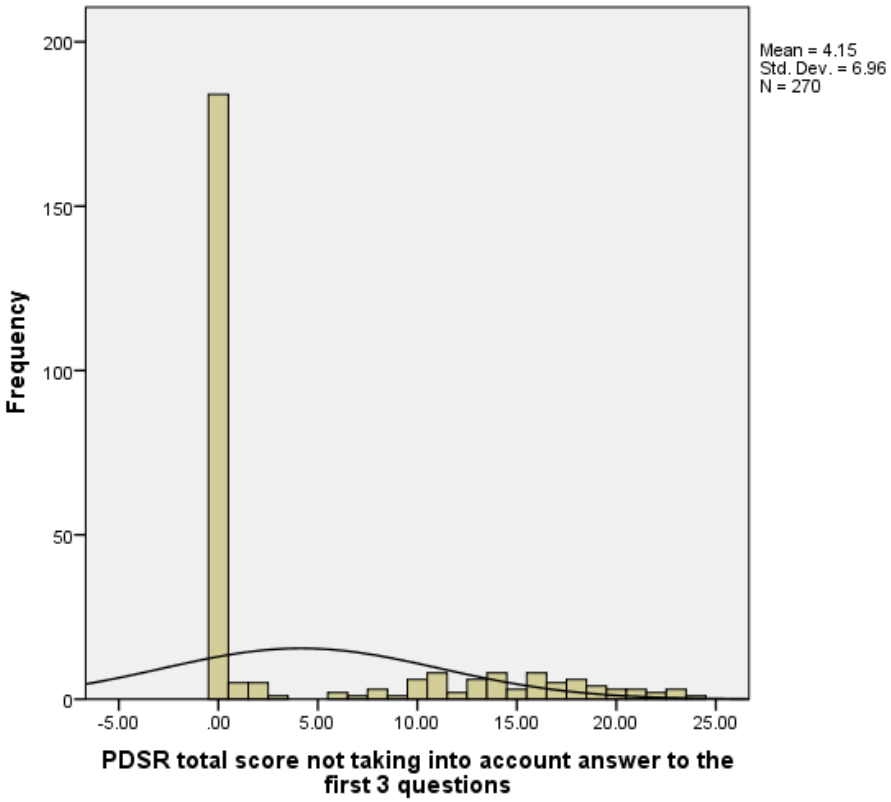
9.10.2 Histogram for depression subscale of HADS (HAD-D) at baseline



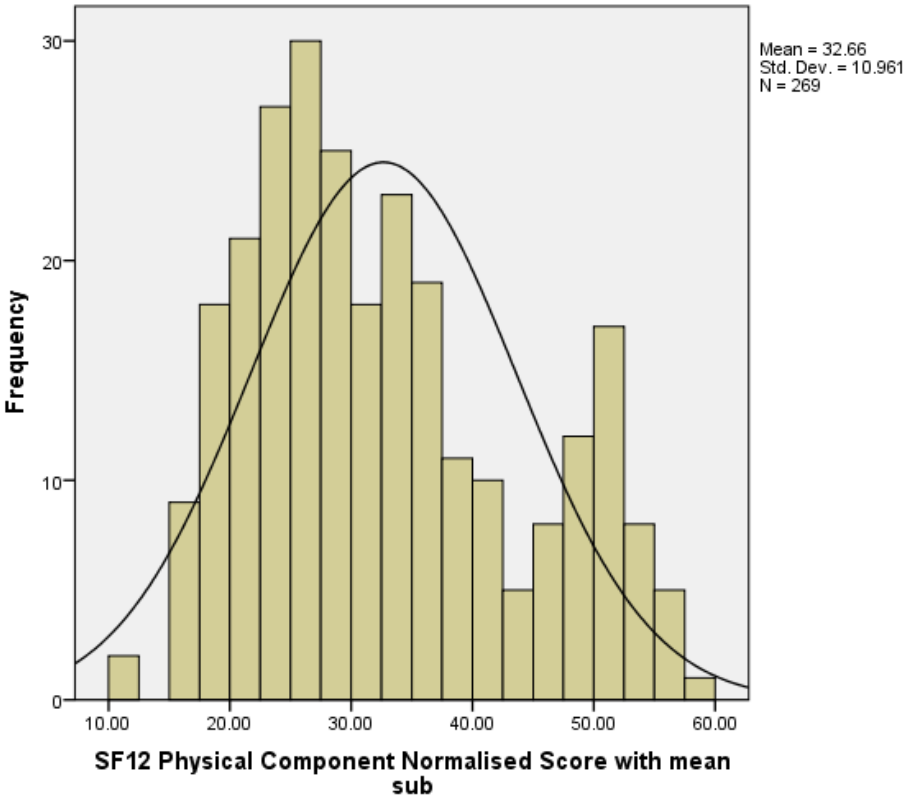
9.10.3 Histogram for anxiety subscale of HADS (HAD-A) at baseline



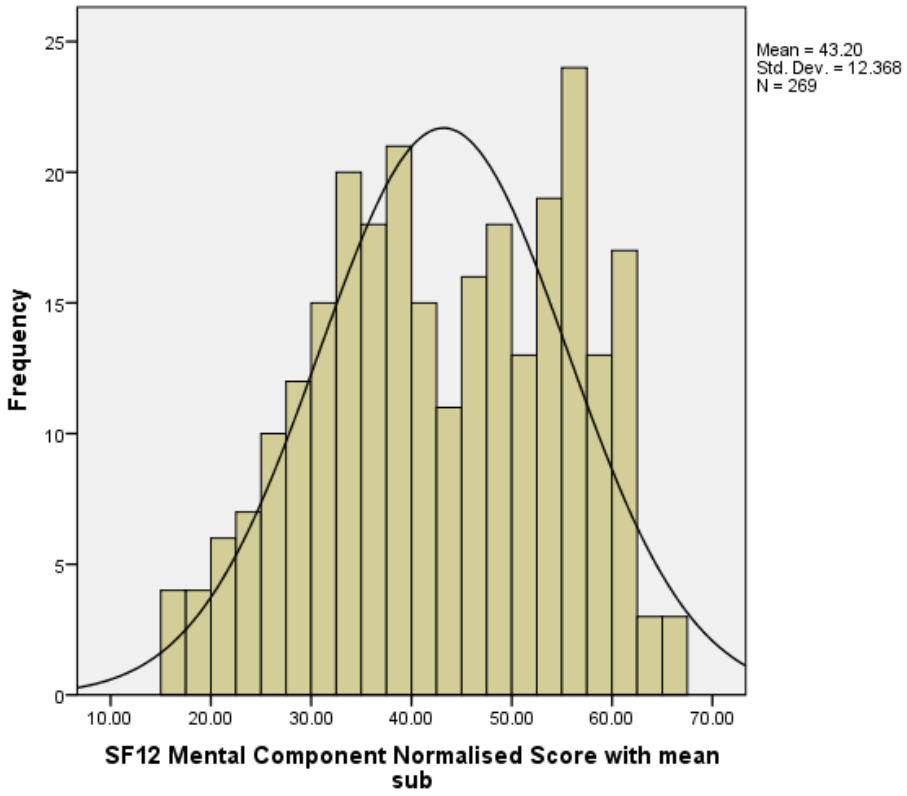
9.10.4 Histogram for panic (PDSR) at baseline



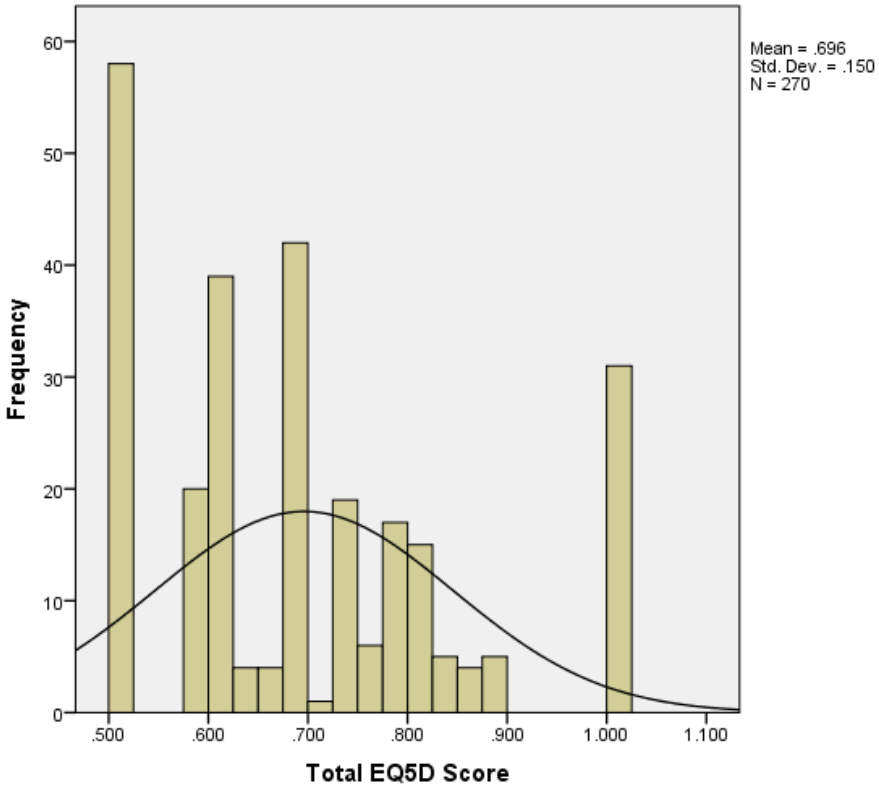
9.10.5 Histogram for general, physical HRQoL (SF-12 physical component score) at baseline



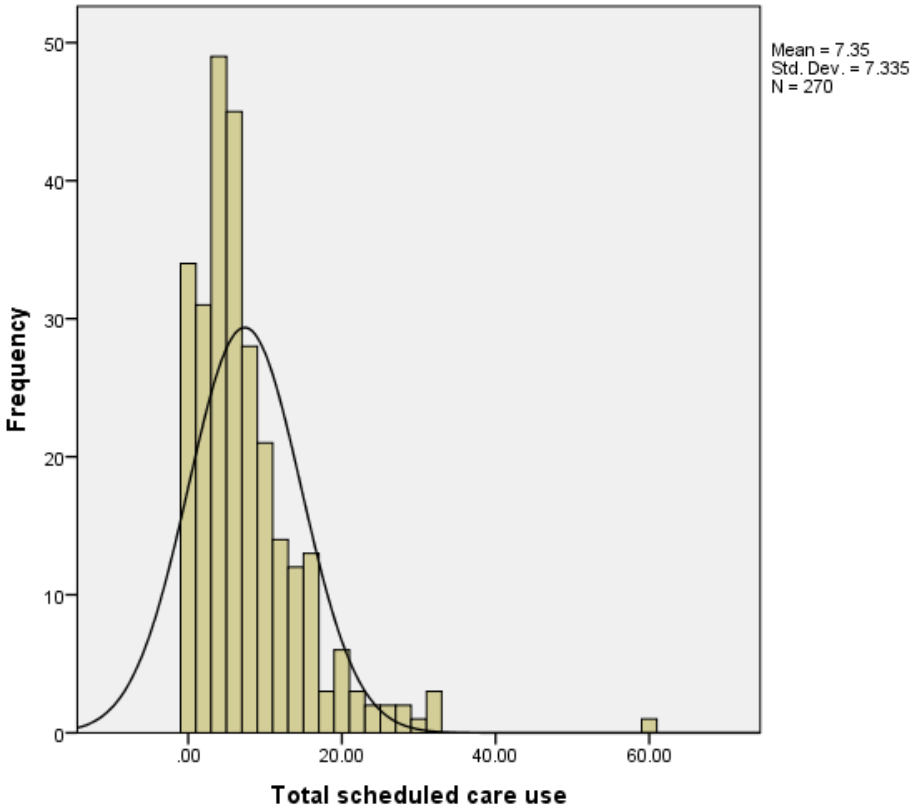
9.10.6 Histogram for general, mental HRQoL (SF-12 mental component score) at baseline



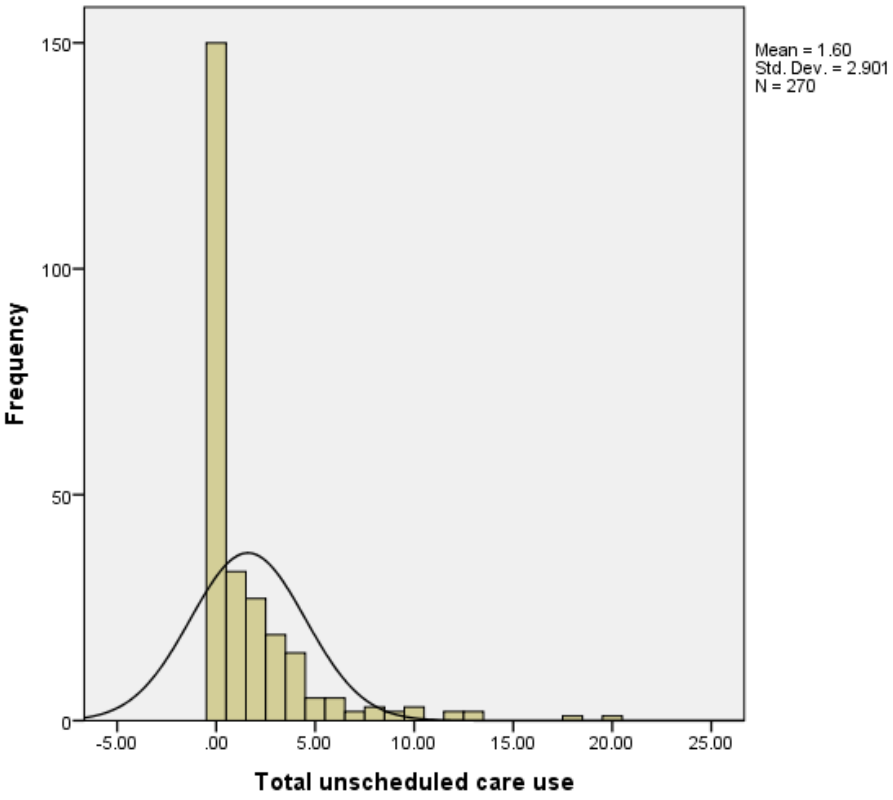
9.10.7 Histogram for total EQ-5D score at baseline



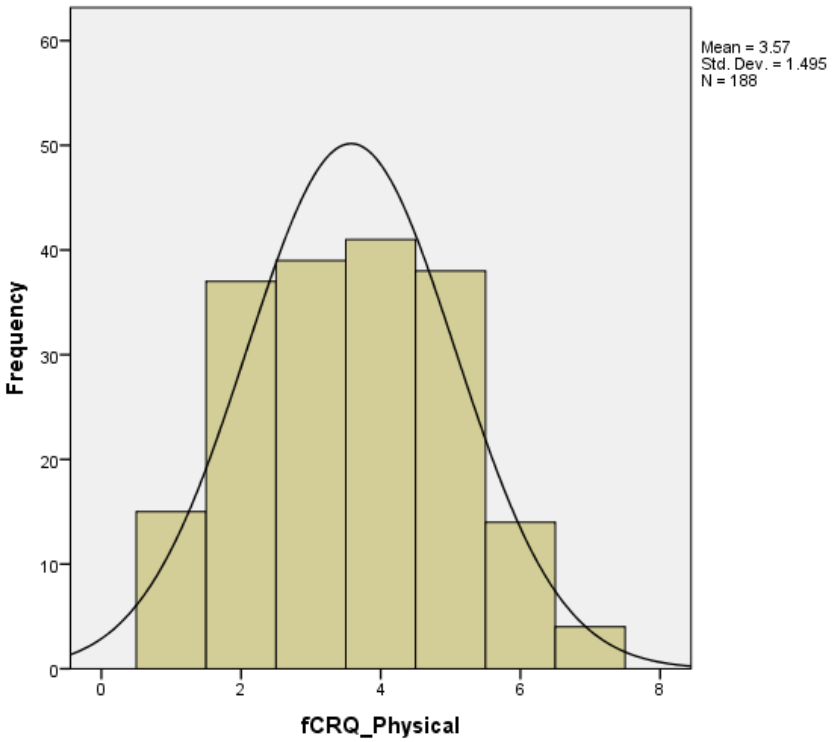
9.10.8 Histogram for total scheduled healthcare use at baseline



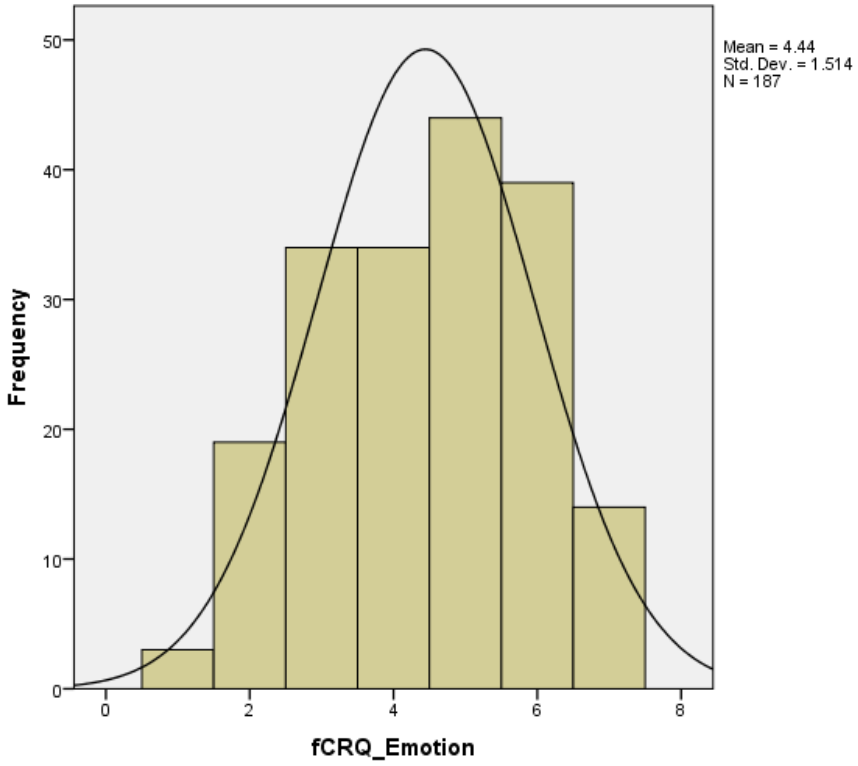
9.10.9 Histogram for total unscheduled healthcare use at baseline



9.10.10 Histogram for respiratory specific, physical HRQoL (CRQ physical) at 12 month-follow up



9.10.11 Histogram for respiratory specific, emotional HRQoL (CRQ emotion subscale) at 12 month follow-up

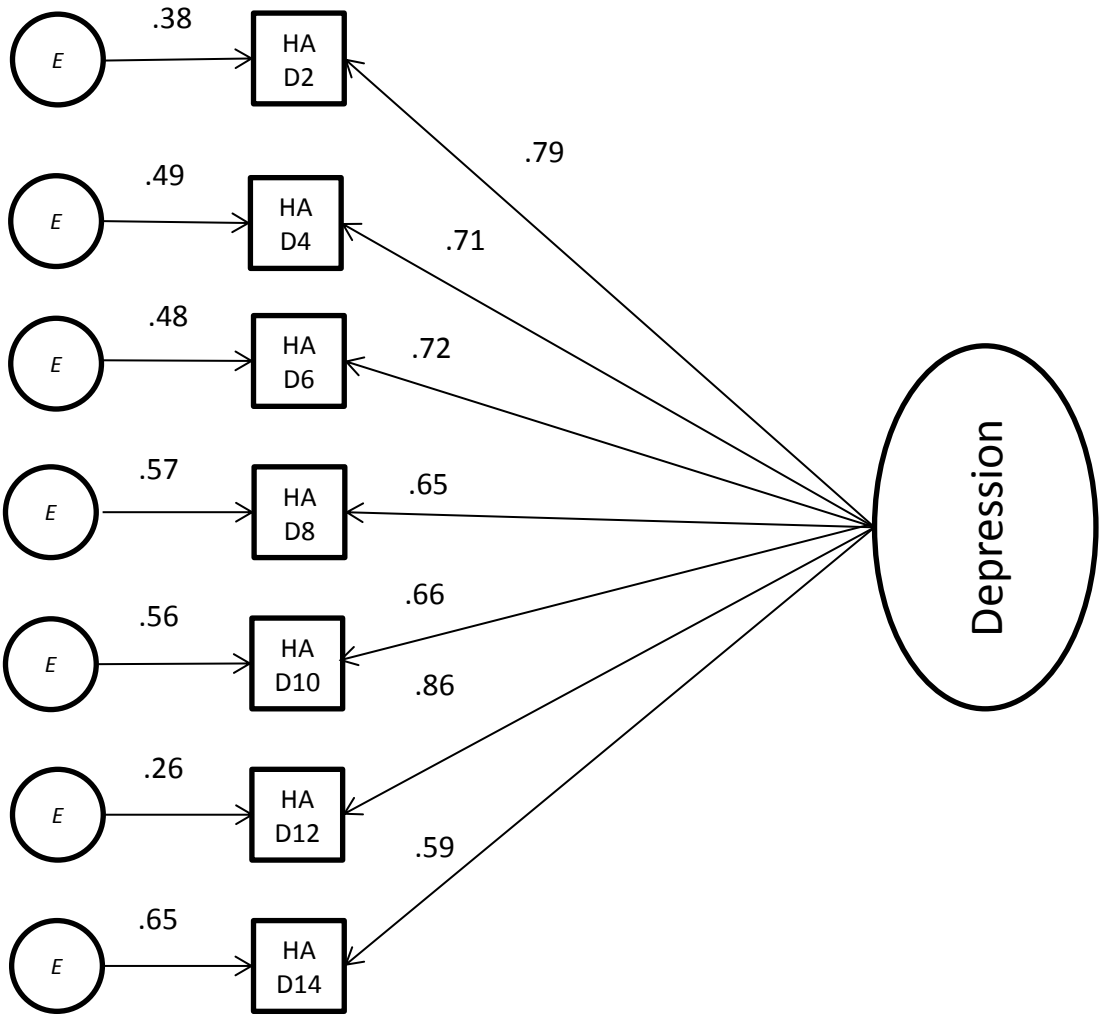


9.11 Statistical Appendix B – Correlation Matrix for Baseline Variables and Respiratory HRQoL at 12 Months

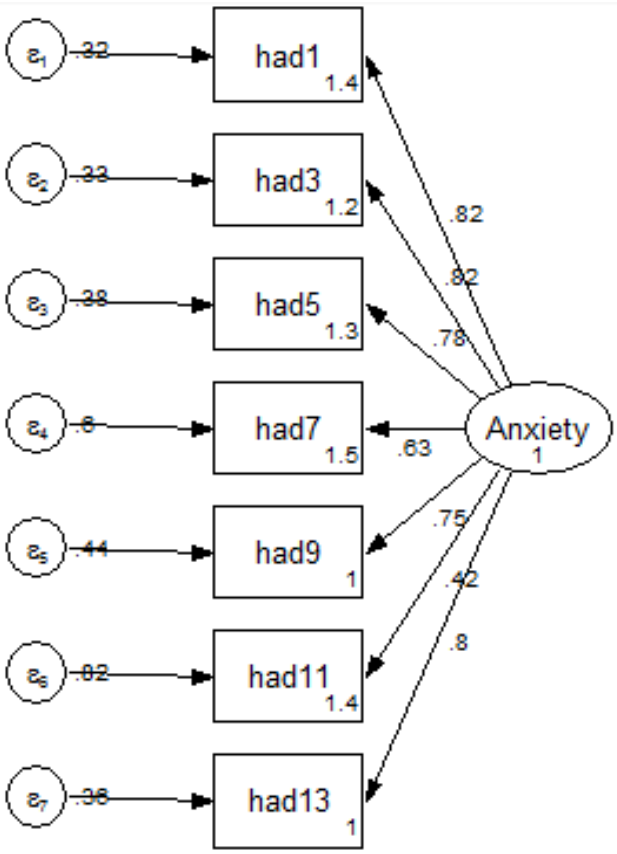
	Spearman's correlation matrix		1	2	3	4	5	6	7	8	9	10	11	12	13	14
1	CRQ Physical at 12 months	rho	1.000	.701**	.034	-.160*	.241**	-.154*	-.611**	-.387**	-.353**	.542**	.561**	.533**	-.324**	-.317**
		n	188	188	188	188	117	188	188	188	188	188	188	188	188	188
2	CRQ Emotion at 12 months	rho	.701**	1.000	.233**	-.194**	.121	-.256**	-.722**	-.675**	-.407**	.469**	.718**	.599**	-.256**	-.242**
		n	188	188	188	188	117	188	188	188	188	188	188	188	188	188
3	Age	rho	.034	.233**	1.000	.027	-.087	-.065	-.204**	-.306**	-.271**	.054	.276**	.187*	-.150*	.021
		n	188	188	188	188	117	188	188	188	188	188	188	188	188	188
4	Comorbidities	rho	-.160*	-.194**	.027	1.000	.145	.097	.223*	.198*	.149*	-.151*	-.162*	-.241*	.417**	.171*
		n	188	188	188	188	117	188	188	188	188	188	188	188	188	188
5	FEV_1 % predicted	rho	.241**	.121	-.087	.145	1.000	.114	-.170	-.072	-.160	.071	.196*	.091	-.020	-.104
		n	117	117	117	117	117	117	117	117	117	117	117	117	117	117
6	Threatening life events	rho	-.154*	-.256**	-.065	.097	.114	1.000	.158*	.348*	.337**	-.105	-.271**	-.222**	.038	.116
		n	188	188	188	188	117	188	188	188	188	188	188	188	188	188
7	Depression	rho	-.611**	-.722**	-.204**	.223**	-.170	.158*	1.000	.650**	.371**	-.655**	-.735**	-.714**	.286**	.190**
		n	188	188	188	188	117	188	188	188	188	188	188	188	188	188
8	Anxiety	rho	-.387**	-.675**	-.306**	.198**	-.072	.348**	.650**	1.000	.533**	-.359**	-.708**	-.551**	.236**	.151*
		n	188	188	188	188	117	188	188	188	188	188	188	188	188	188
9	Panic	rho	-.353**	-.407**	-.271**	.149*	-.160	.337**	.371**	.533**	1.000	-.222**	-.463**	-.353**	.225**	.269**
		n	188	188	188	188	117	188	188	188	188	188	188	188	188	188
10	SF-12 PCS	rho	.542**	.469**	.054	-.151*	.071	-.105	-.655**	-.359**	-.222**	1.000	.373**	.678**	-.237**	-.135
		n	188	188	188	188	117	188	188	188	188	188	188	188	188	188
11	SF-12 MCS	rho	.561**	.718**	.276**	-.162*	.196*	-.271**	-.735**	-.708**	-.463**	.373**	1.000	.609**	-.266**	-.243**
		n	188	188	188	188	117	188	188	188	188	188	188	188	188	188
12	EQ5D	rho	.533**	.599**	.187*	-.241**	.091	-.222**	-.714**	-.551**	-.353**	.678**	.609**	1.000	-.259**	-.197**
		n	188	188	188	188	117	188	188	188	188	188	188	188	188	188
13	Scheduled care use	rho	-.324**	-.256**	-.150*	.417**	-.020	.038	.286**	.236**	.225**	-.237**	-.266**	-.259**	1.000	.302**
		n	188	188	188	188	117	188	188	188	188	188	188	188	188	188
14	Unscheduled care use	rho	-.317**	-.242**	.021	.171*	-.104	.116	.190**	.151*	.269**	-.135	-.243**	.197**	.302**	1.000
		n	188	188	188	188	117	188	188	188	188	188	188	188	188	188

9.12 Statistical Appendix C – Measurement Models

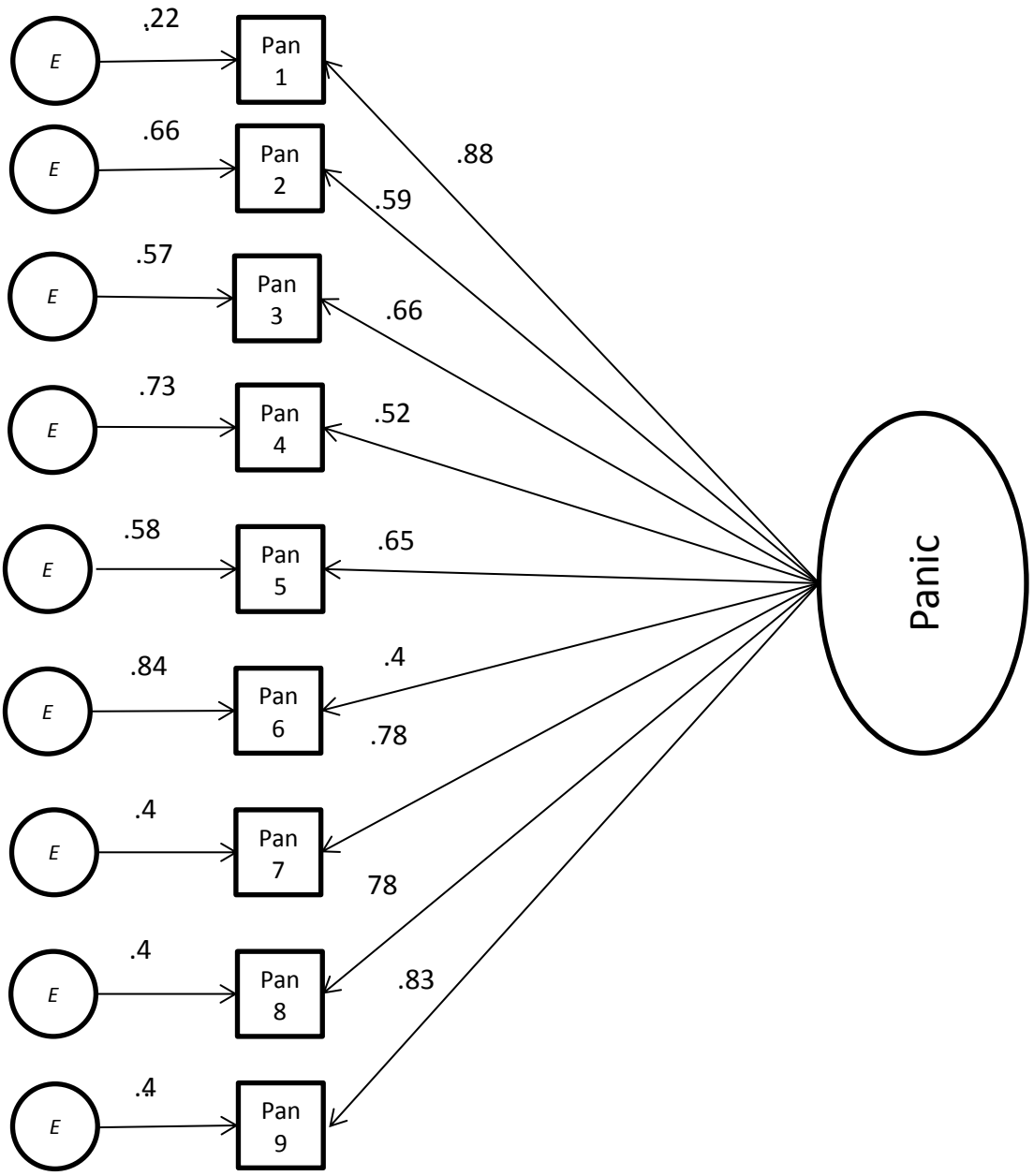
9.11.1 Measurement model for depression – standardised factor loadings



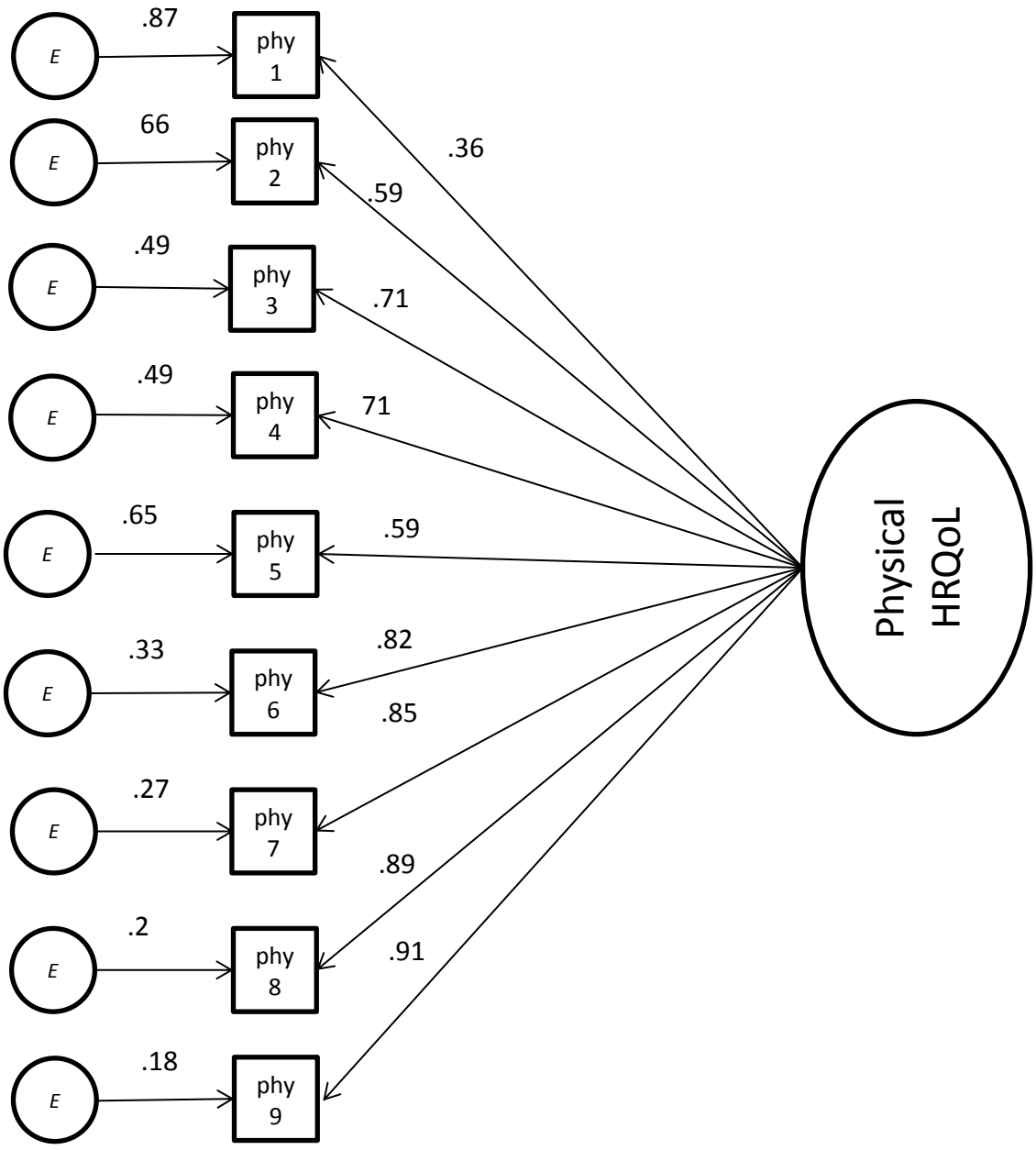
9.11.2 Measurement model for anxiety – standardised factor loadings



9.11.3 Measurement model for panic – standardised factor loadings



9.11.4 Measurement model for respiratory specific physical HRQoL – standardised factor loadings



9.11.5 Measurement model for respiratory specific emotional HRQoL – standardised factor loadings