An investigation into the nature, prevalence and severity of anxiety in heart failure patients: The association between anxiety and patient' health outcomes

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Contents

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LIST OF ABBREVIATIONS

ADL	Activities of Daily Living
AF	Atrial Fibrillation
ASD	Acute Stress Disorder
BDI	Beck Depression Inventory
BNI	British Nursing Index
BSI-A	Brief Symptom Inventory-Anxiety
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CASI	Computer Assisted Self Interviewing
CBT	Cognitive Behavioural Therapy
CCM	Chronic Care Model
CED-D	Centre for Epidemiological Studies Depression Scale
COPD	Chronic Obstructive Pulmonary Disease
CI	Confidence Interval
CRD	Centre for Reviews and Dissemination
CRT	Coronary Resynchronisation Therapy
DALY	Disability Adjusted Life Years
DH	Department of Health
DM	Diabetes
DSM-IV	Diagnostic and Statistical Manual
EBM	Evidence Based Medicine
EID	English Indices of Deprivation
ESSI	ENRICHD Social Support Therapy
GAD	Generalised Anxiety Disorder
GAI	Geriatric Anxiety Inventory
HADS	Hospital Anxiety and Depression Scale

HARS	Hamilton Anxiety Rating Scale
HF	Heart Failure
HFPEF	Heart Failure with Preserved Ejection Fraction
HRQoL	Health-Related Quality of Life
IAPTs	Increasing Access to Psycholigic Therapies
IHD	Ischaemic Heart Disease
ICD	Implantable Cardioverter Defibrillator
IMD	Index of Multiple Deprivation
JRULM	John Rylands University of Manchester Library
KCCQ	Kansas City Cardiomyopathy Questionnaire
LSOA	Lower layer Super Output Areas
LTC	Long Term Condition
LV	Left Ventricle/Ventricular
LVEF	Left Ventricular Ejection Fraction
LVSD	Left Ventricular Systolic Disfunction
MAACL	Multiple Adjective Affect Checklist
MI	Myocardial Infarction
MLHFQ	Minnesota Living with HF Questionnaire
MOOSE	Meta-analysis Of Observational Studies in Epidemiology
MOS	Medical Outcomes Study
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NRES	National Research Ethics Service
NSF	National Service Framework
NYHA	New York Heart Association
ONS	Office of National Statistics
PCI	Purcutaneous Coronary Intervention
PCT	Primary Care Trust

PICO	Population, Intervention, Control, Outcome
PIN	Patient Identification Number
PNSD	Paroxysmal Nocturnal Dyspnoea
POMS	Profile of Mood States
PPI	Patient and Public Involvement
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-analyses
PTSD	Post-Traumatic Stress Disorder
QoL	Quality of Life
QUORM	Quality of Reporting of Meta-analyses
RCTs	Randomised Controlled Trials
RfPB	Research for Patient Benefit
rPSIDS	revised Physical Incidence and Distress Scale
RV	Right Ventricle/Ventricular
SCID-I	Structured Clinical Interview for DSM-IV
SF	Short Form
SHA	Strategic Health Authority
SSQ	Social Support Questionnaire
STAI	State Trait Anxiety Inventory
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
VoIP	Voice-over Internet Protocol
WHO	World Health Organisation

ABSTRACT

The University of Manchester

Abstract of Thesis

'The relationship between anxiety and health-related quality of life in adult out-patients with a diagnosis of heart failure'

Submitted by Katherine Easton for the degree of Doctor of Philosophy in September 2012

Long Term Conditions (LTCs) with co-morbid common mental health conditions of anxiety and depression present a significant challenge for UK health and social care services. Depression and anxiety are common in heart failure (HF) patient populations and research suggests depression has a detrimental effect on a range of health outcomes, including Health related Quality of Life (HRQoL). The impact of anxiety is relatively under-researched in this patient group. In this doctoral study a systematic review was conducted to consolidate the evidence base for the prevalence and variance of rates of anxiety in HF patients. Importantly, the relative contribution of anxiety symptoms, measured using the Hospital Anxiety and Depression Scale (HADS), to reported HRQoL , measured using the Kansas City Cardiomyopathy Questionnarie (KCCQ) was examined in a cross-sectional survey of 158 HF patients attending specialist HF outpatient clinics. The systematic review identified 72 studies, with reported rates of anxiety varying dramatically, ranging from 6.2% to 72.3%. The random effects pooled prevalence estimate for anxiety disorders was 13.01% (95% CI 9.3% - 16.9%), for probable clinically significant anxiety was 28.8% (95% CI 23.3% - 34.3%) and the random effects pooled prevalence estimate for elevated symptoms of anxiety was 55.5% (95% CI 48.1% - 62.8%). Not all tools used to assess anxiety were population appropriate. In the survey multivariate analysis found that anxiety symptoms, did not account for a significant proportion of unique variance in HRQoL scores. Higher levels of physical symptom burden, depression and an increased number of physical co-morbidities predominantly account for 69% of the variance in HRQoL ($F_{13,125}$ = p <0.0005). The findings highlight the need for accurate and valid measurement of anxiety and depression within the context of a physical LTC. Anxiety and depression are common in HF patients and the evidence suggests depression in particular predicts reported HRQoL. Further research is required to understand more about the role of anxiety in influencing patient's health outcomes.

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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One engagement, four house moves, two babies, one driving test, a new job and a house renovation later...

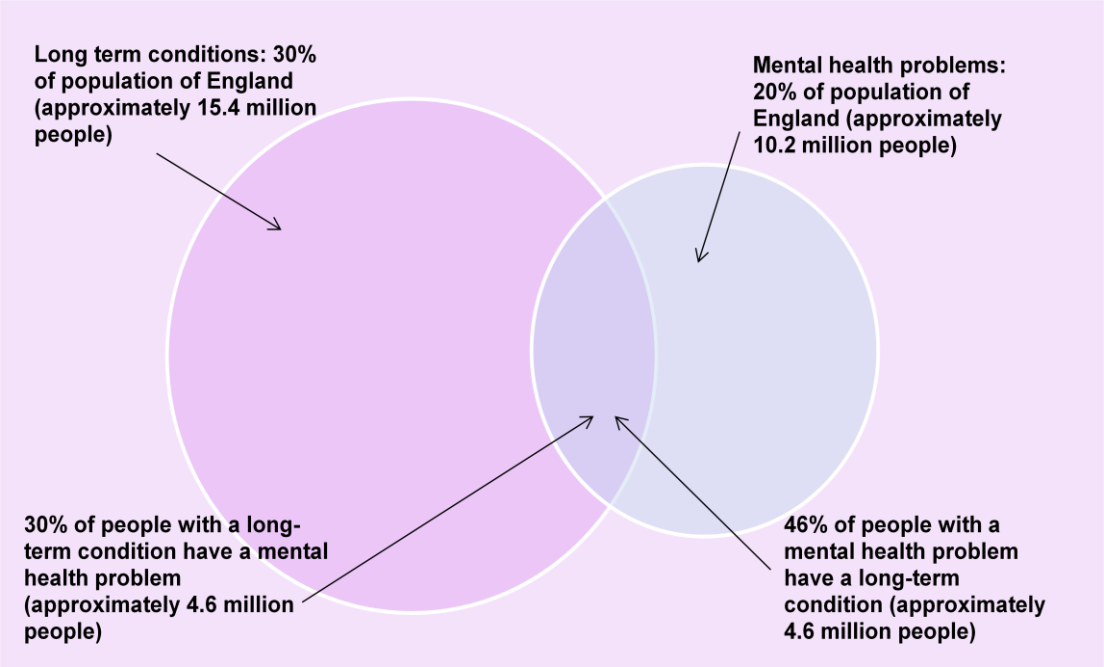
INTRODUCTION

Long Term Conditions (LTCs) can be defined as conditions that cannot, at present, be cured, but can be controlled by medication and other therapies (Department of Health (DH), 2010a). Long Term Conditions such as cardiovascular diseases, diabetes, cancers and respiratory conditions have a poor prognosis and account for almost two thirds of deaths globally World Health Organisation (WHO, 2011), and 70% of all deaths in the United States of America (USA) each year (Kung, Hoyert, Xu and Murphy, 2008). In the United Kingdom (UK) LTCs are highly prevalent and present a significant challenge to health and social care policy and practice (DH, 2012). In England over 15 million people, nearly one in three, have one or more LTC (DH, 2011a).

The impact of LTCs on society, communities, for families and for the individual is substantial. Individuals with one or more LTCs are intensive users of health and social care resources; accounting for 31% of the UK population, but consuming 70% of the total health spend (DH, 2012). Many people with LTCs find it hard to remain in employment and may therefore experience social deprivation (Naylor et al, 2012). On an individual level people with a LTC experience physical and emotional symptoms that can cause significant distress and often experience impaired quality of life compared with healthy peers (DH, 2012). As LTCs cannot be cured, treatment is focused on alleviating the individual's physical symptoms and improving their quality of life. As the burden of LTCs increases, a shift in care from hospital-based acute reactive care to home-based pro-active self-management is required by the patient themselves in order to manage their condition and exacerbation of symptoms (DH, 2010b).

In the past few years it has been acknowledged from research (Naylor et al, 2012), government policy (*No Health without Mental Health*, DH, 2011b) and clinical practice (NICE, 2009 a, b) that people with LTCs are at higher risk of mental health conditions such as anxiety and depression compared to the general population. Evidence suggests that over 30% of those with LTCs will have a co-morbid mental health condition (Cimpean and Drake, 2011). Figure 1 illustrates the overlap in the presence of LTCs and mental health conditions.

Figure 1: The overlap between LTCs and Mental Health Conditions (Naylor et al, 2012)



The total health care costs of treating a person with both a LTC and interacting mental health condition rise by at least 45% (Naylor et al, 2012). The presence of a mental health condition for people with a long-term physical health condition can markedly affect not only a person's emotional health, but also contributes to a decline in physical health (Naylor et al, 2012). Mental health conditions can significantly impair the health-related quality of life (HRQOL) of patients with one or more LTCs (Moussavi et al, 2007).

The mental health of individuals with one particular LTC, heart failure (HF), has until recently received relatively little research attention. As a person's mental health has been found to impact not only on their physical health, use of health services, and HRQoL it is important to investigate the scope of common mental health conditions in a HF population and consider the associations between poor mental health and a range of health outcomes, including HRQoL (Naylor et al, 2012). Research in this area is heterogeneous with respect to variable conceptualisation and measurement, making interpretation of the research available difficult. In addition, relatively little research has been conducted in HF patient samples to examine whether anxiety, independent of depression, has the potential to determine patient reported HRQoL whilst controlling for known socio-demographic and clinical co-variates.

The aims of this doctoral research are to explore the published prevalence and variations of anxiety in HF patient samples and measure the contribution anxiety makes to HRQoL scores in a sample of outpatients with a HF diagnosis.

The research questions are presented in figure 2 below.

Figure 2:Phases of research

Phase One

1. What is the aggregated prevalence of anxiety disorders and symptoms of anxiety among people with a diagnosis of heart failure?
2. What factors are associated with potential heterogeneity in reported prevalence and severity of anxiety?

Phase Two

1. The prevalence and variance of anxiety symptoms in a sample of individuals with a diagnosis of HF attending specialist out-patient HF clinics.
2. What amount of variance do anxiety symptoms account for in HF patients self reported HRQoL whilst controlling for functional status, physical symptom severity, age, gender, levels of depression and social deprivation?

Chapter one covers the background for this thesis and provides the rationale for the research. The chapter contains four parts which discuss the prevalence, impact and management of LTCs; mental health co-morbid to LTCs; heart failure with co-morbid depression and anxiety; and examines research that has sought to understand HRQoL in HF patients.

Chapter two reports the methodological and philosophical approaches adopted in this study, the aims of the research are presented, as is a discussion of the research methods selected; systematic review and cross-sectional survey.

In chapter three the methods and results from a systematic review will be presented. The review identified the prevalence and variations of anxiety in HF samples. The discussion highlights issues with the measurement of anxiety in patient samples.

Chapter Four will present the methods, results and discussion arising from the second phase of research; the cross-sectional survey. The contribution of anxiety toward determining HRQoL scores in a sample of HF patients will be reported.

Finally chapter five will summarise the main findings from the research. The methodological and clinical implications of the findings from this research and potential extensions of this research will be considered.

CHAPTER ONE: BACKGROUND & RATONALE

This chapter will present background research and policy relating to the growing burden of LTCs. The chapter will examine how the UK health and social care services currently care for this patient population.

Common mental health conditions are common, both nationally and globally. Depression and anxiety will be conceptualised and the prevalence and impact of these conditions will be considered. The PhD study was initiated prior to increasing awareness and recognition from the UK government of the association between LTCs and co-morbid mental health conditions. The impact of such associations will be considered.

The mental health of one LTC in particular, heart failure, has received relatively little research attention. Evidence to support the prevalence and impact of two common mental health conditions, anxiety and depression, in HF patient samples will be discussed.

The HRQoL of patients with HF will be explored and the evidence to determine predictors of quality of life in this patient sample will be discussed.

Part One: Long Term Conditions

The World Health Organisation (WHO) defines LTCs as health problems that require ongoing management over a period of years or decades. The term refers to a variety of conditions ranging from physical disabilities, mental health conditions, non communicable diseases (cancer, respiratory diseases, diabetes and cardiovascular conditions) and communicable conditions (HIV/AIDS).

Prevalence of long term conditions

Globally it is difficult to estimate the prevalence of LTCs as no reliable data exist in many countries (WHO, 2010). There are however data to indicate that LTCs are the leading cause of death on a global scale, with almost two thirds of deaths (36 million annually) attributable to LTCs, mainly cardiovascular disease, cancers, diabetes and chronic lung disease in 2008 (WHO, 2010). Cardiovascular disease in particular is the leading cause of death in high-income countries, followed by stroke, lung cancer, pneumonia and asthma/ bronchitis (WHO, 2010). Projections for 2030 suggest that ischemic heart disease and chronic obstructive pulmonary disease will continue to be two of the main causes of death on a global scale (WHO, 2010).

In other high income countries such as the USA LTCs impair the health of over 50% of the population as a result of widespread adverse health behaviours including smoking, a lack of physical activity, poor diet and excessive alcohol consumption (Kung et al, 2008). In England it is estimated that around 30% of the population, nearly 16 million people live with one or more LTCs (DH, 2011a). Of patients seen in primary care alone from 2010 to 2011, 1,877,518 people had a diagnosis of coronary heart disease, 7,46 0,497 hypertension, 2, 455,937 diabetes and 392,852 have a diagnosis of heart failure (The Health and Social Care Information Centre, 2011), at least this many again are seen in secondary care services. The prevalence of LTCs rises with age. The Department of Health states that that 58 % of people aged over 60 years suffer from a LTC rising to 75 % in those over 75 years of age (Department of Health, 2012).

Globally the prevalence of LTCs is increasing, particularly in low and middle income countries where poverty increases individuals' exposure to a number of behavioural risk factors that are known to cause a range of LTCs: tobacco use, unhealthy diet, alcohol consumption and reduced physical activity (WHO, 2010). Rates of LTCs in higher income countries, including England are anticipated to remain relatively steady for the time being, however, in the longer-term rates of LTCs in England are projected to rise by 25% in the next 25 years (DH, 2010). The rise in prevalence of LTCs and multiple LTC morbidity is due to a number of factors including:

1. A reduction in overall mortality rates as more people are living longer, in part due to improvements in the medical treatment of a range of conditions. In the UK 16 % of the population are over 65 years, with over 1 million of this group over the age of 85 years (Cowie & Kirby, 2003). This figure is set to increase within society (Emmerson, Frayne & Goodman, 2000). Many individuals from this increasing older population will live healthy, extended lives; however, as the burden of disease shifts from premature death from acute illness the rates of cardiovascular conditions and cancers, and other LTCs such as heart failure (HF), chronic obstructive pulmonary disease (COPD), diabetes (DM) and dementia have become more prevalent, particularly in older populations (WHO, 2009).

2. The increase in the aging population is coupled with an increase in behavioural risk factors that play a role in the development of LTCs, such as obesity, smoking, and a sedentary lifestyle. Globally and nationally lifestyle factors that contribute to the rising prevalence of LTCs are reported to be the highest risk to mortality, affecting countries across all income groups: high, middle and low (WHO, 2010).

Impact of Long Term Conditions for patients

People who have been diagnosed with a LTC experience a number of physical symptoms which may progress steadily, come and go and vary with regards to the distress and interference they cause on people's lives. Almost half of people with a LTC report feeling moderate to extreme pain, increasing to 80% of people who experience three or more LTCs (DH, 2012). Many symptoms of a range of LTCs such as breathing problems, pain and extreme tiredness (fatigue) may be controlled to an extent with medications, therapies, interventions, or lifestyle alteration. The treatment regimen for patients with a LTC can be

complex and require individuals to manage their condition effectively (self-care) (DH, 2012). Many medications can have side-effects for patients that in turn may need to be treated with further medication. Younger patients with a LTC may need to maintain employment and sustain an income for their families (DH, 2012). The presence of a LTC may make this difficult and lead to financial difficulties and social deprivation (Naylor et al, 2012). The impact of a LTC can compromise patient's psychological well-being and ultimately their quality of life including social functioning (DH, 2012; DH, 2010).

Consumption of health care services and financial costs from Long Term Conditions

Persons with one or more LTCs represent approximately 30% of the English population and account for 52 % of all general practitioner (GP) appointments, 65 % of all outpatient appointments and 72 % of all in-patient bed days (DH, 2012). The UK National Health Service (NHS) provides free healthcare to over 61, 838 million people (World Bank, World Development Indictors, 2011)[1], at a cost in excess of £100 billion a year (Ham, Imison, Goodwin, Dixon & South, 2011). The Department of Health estimates that LTCs account for around 70 % of total health spend (DH, 2010). The increasing prevalence of LTCs has, and will continue to have, a dramatic impact on the economy. Estimates suggest that by 2022 public expenditure on LTCs will rise by 94 % to sterling15. 9 billion in light of the increasing aging population trend (Department of Health, 2012). This has led to the search for effective LTC policies and management strategies to be one of the most pressing healthcare challenges facing modern society.

Long Term Condition Management

As LTCs cannot currently be cured, only managed, clinicians use a combination of life-style changes, medications, surgery and devices in order to alleviate patients' physical symptom burden, stabilise their condition/s and improve patient's quality of life as related to their health (HRQoL). This in turn can reduce healthcare utilisation by these patient groups, specifically rates of emergency hospital readmissions (DH, 2010). In the current

[1] http://issuu.com/world.bank.publications/docs/9780821387092

financial climate the UK National Health Service must continue to improve patient care whilst facing a number of key challenges.

These challenges include the increasing aging population and a shifting burden of disease to LTCs (Ham 2010). In addition a shift in social structure has seen fewer people living with, or being cared for, by their extended family, which places additional demands on paid for/statutory support (Ham et al, 2011).

UK Long Term Condition Model

The care of individuals with one or more Long Term Conditions (LTCs) is guided by the National Health Service (NHS) and Social Care Long Term Conditions Model, as presented in the previous government's document '*Supporting people with Long Term Conditions'* (DH, 2005a). The model outlined how individuals with LTCs would be identified, receive care according to their needs and be encouraged to self-manage. See figure 3 for characteristics of the model. The UK LTC Model was developed based on examples of good practice in the UK and internationally, drawing heavily, although not exclusively on the Chronic Care Model (CCM) from the USA which emphasises a spread of care across a range of services including hospital, community and social care organisations, encouraging the development of patient support groups and effective self-management strategies (Bodenheimer, Wagner & Grumbach, 2002a, b; Wagner, et al, 2002).

Figure 3:Characteristics of the UK NHS and Social Care LTC model

- **Identify** all LTC patients in a health community

- **Stratify** patients so that their care matches their needs based on the Kaiser Permanente Pyramid (see figure 4)

  - *Level 3:* Case management: for patients requiring intensive specialist management, coping with co-morbid conditions or at risk of their condition deteriorating.

  - *Level 2:* Disease-specific management: for patients requiring regular contact with a multidisciplinary team to ensure effective management of their disease

  - Level 1: Supported self care: patients requiring usual care supported to self-manage.

  - *Prevention and health promotion*: at risk populations

- Initial focus on very **high intensity users** of secondary care services through **case management**

- Appoint **community matrons** to spearhead case management

- Identify **prospective** high intensity users

- Establish **multi-professional teams** based in primary and community care to manage care across settings

- Develop strategy for comprehensive **self care**

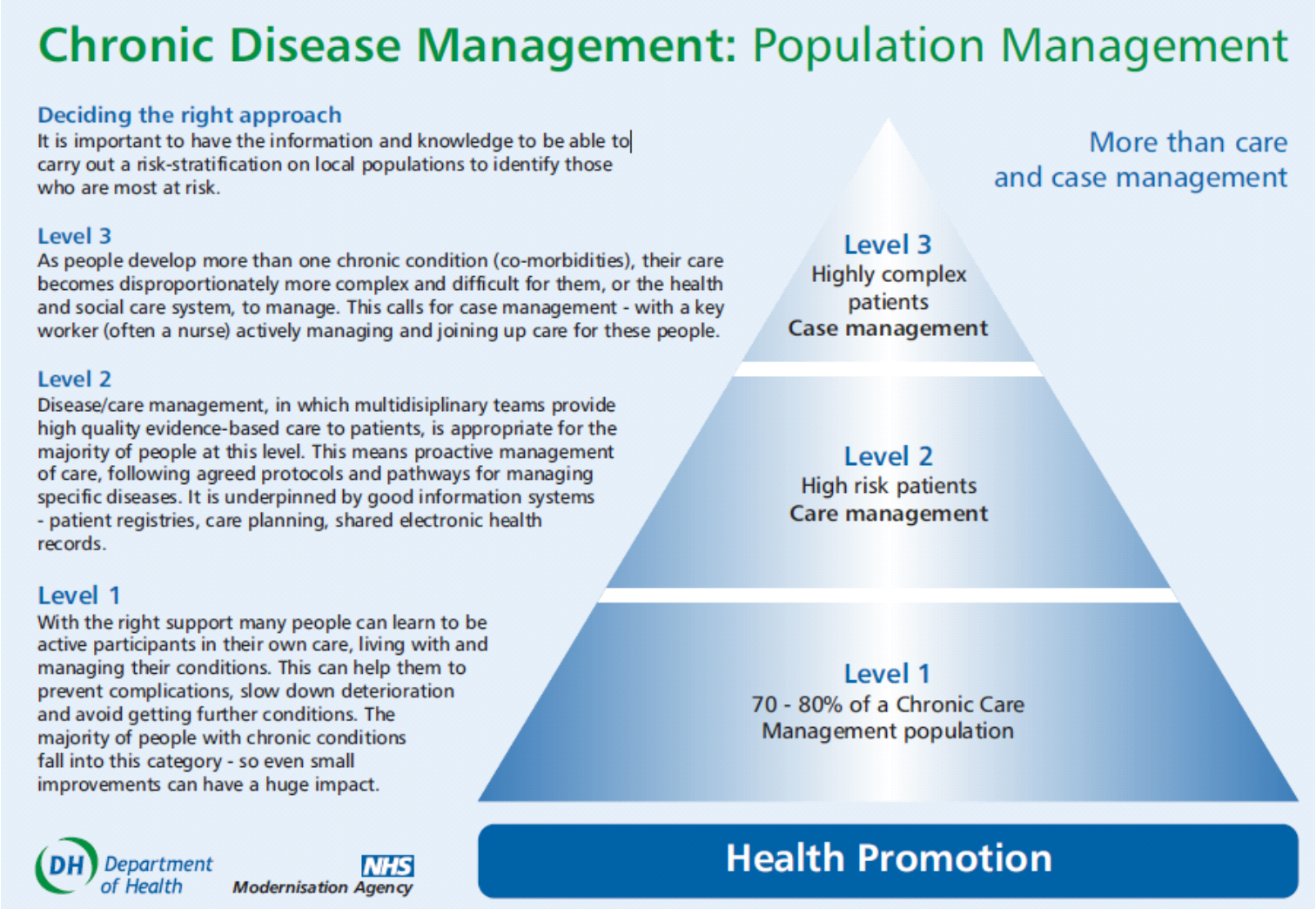
- Implement the **Expert Patient Programme**

- Use **tools** and techniques available to make an impact (e.g. telehealth and telecare).

The UK NHS and Social Care LTC model acknowledges that the largest increases in LTCs will be in the number of people experiencing co-morbidities (DH, 2012). A holistic, coordinated approach to care is proposed with patients' care transcending primary and secondary care service divides. The model also proposes the most intensive care in the least intensive setting. Patients are to be treated sooner and earlier in their disease course as a result of earlier detection of LTCs, through the integration of primary and specialist services and promotion of self-management (Singh & Ham, 2006). An illustration of the stratified approach to care can be seen in figure 4, the Kaiser Permanente Pyramid.

Currently a disproportionate number of patients with a LTC are managed at level three; case management for highly complex patients (DH, 2010a). A patient presenting at this level should represent three or four per cent of patients with LTCs who have a mix of medical and social problems requiring a holistic approach to care. This patient group pose the biggest burden to resources and many initiatives are targeted at this group with the aim of maximising function and increasing quality of life (Wilson, 2005). The majority of LTC care can be managed in Level One of the Kaiser Permanente pyramid, self-managed care. This level of care is neglected with regards to resources; however care delivered at level one can considerably reduce the demand on resources by enabling patients to monitor their own condition (Wilson, 2005).

Figure 4: Kaiser Permanente Pyramid of service delivery as applied in the UK LTC model (DH, 2005)



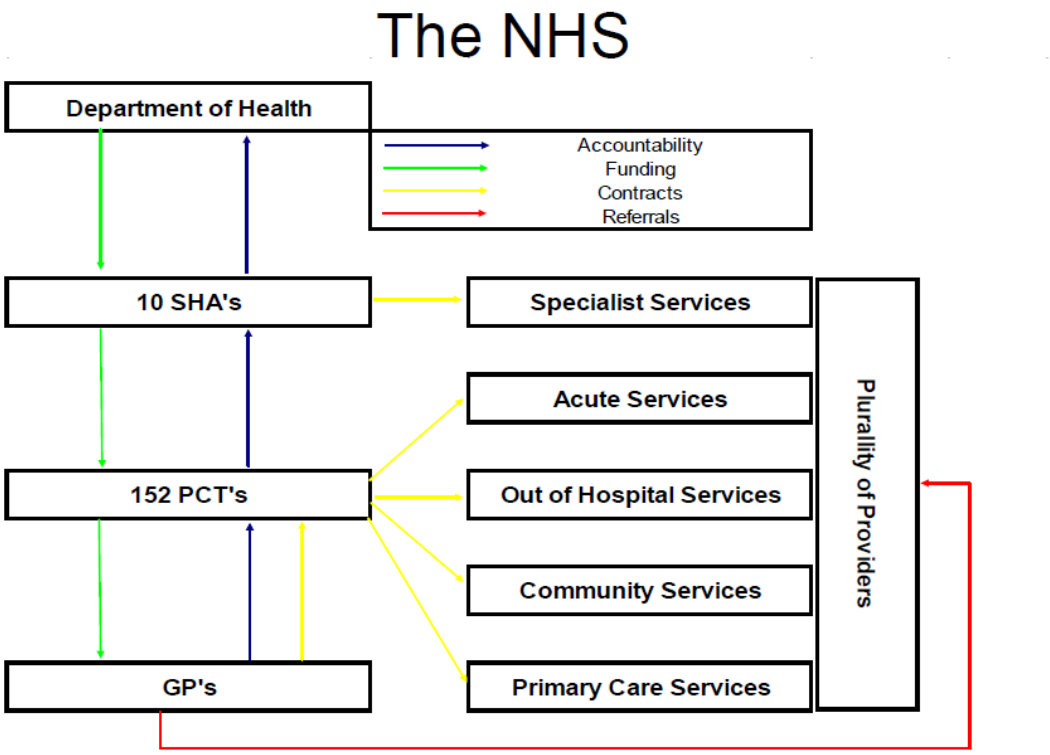
If HF patients are to self-manage their condition effectively in the community with support from health and social care organisations, they must be able to adhere to complex treatment regimens and identify exacerbation of symptoms and react to any exacerbations appropriately. For patients to actively engage in self-care behaviours they must be motivated and feel they have the abilities to manage their own health (Jerant et al, 2005; Bodenheimer et al, 2002c).

The UK NHS

Within England, the entire system of health and social care is in a state of flux following the election of a new Coalition Government in May 2010 and the passing of the Health and Social Care Act 2012. In particular, the way in which responsibility and authority is delegated from national government and from the national NHS executive to regional commissioning, policy and governance bodies such as the current Strategic Health Authorities, and Primary Care Trusts, has been radically changed (Easton, Brownsell, Hawley & Mawson, 2011).

The NHS pre Health and Social Care ACT 2012 can be summarised by the diagram below (figure 5).

Figure 5:The NHS structure (Easton, Brownsell, Hawley & Mawson, , 2011).



United Kingdom health and social care provisions based on this NHS structure were not suited to meet the needs of the growing number of people with one or more LTC based on the LTC model of care outlined above (Ham et al, 2011). National Health Service funding was allocated based on a formula that determined the level of need in a given geographical region, or Primary Care Trusts (PCTs); with younger, deprived, urban areas receiving a far greater proportion of funding in order to tackle 'health inequalities' (Asthana, 2011). Subsequently funding was lacking in areas where LTCs are most prevalent; demographically older regions. A main target for increasing NHS efficiency and savings is to encourage patients to self-care at home and better manage their condition to prevent costly acute, unplanned appointments and reduce the need for bed days taken to manage acute, unexpected exacerbations (Department of Health, 2011). Currently UK health care is primarily a hospital-based model of acute care, which sees individuals with LTCs managed poorly in the community and frequently admitted to hospital (Ham et al, 2011; Thorlby & Maybin, 2010). The King's Fund, a UK health charity that aims to shape health policy and practice, have stated that any models of LTC care should be less orientated towards treating acute illness and more focused on prevention, accompanied by a shift in resources away from acute hospitals to providing more care in the community (Ham et al, 2011).

Both Strategic Health Authorities' (SHA's) and PCT bodies have been abolished with devolution of budgetary responsibility to GP clinical commissioning groups. Since the beginning of 2013 Primary Care Trusts (PCTs) have been replaced by General Practitioner (GP) led commissioning consortia (Clinical Commission Groups - CCGs) in a bid to deliver efficiency savings of 20bn by 2015 (Smith & Mays, 2012). GP led commissioning is seen as being a key component in the government's plans to deliver efficiency savings as GP's are thought to be best placed to purchase health services for the local population due to their role as gatekeepers to expensive secondary care and diagnostics, and their knowledge of the patients on their practice list. As the budget holders for referrals and treatment decisions, GP's are predicted to be the drivers for the development of community care. As the focus of care shifts to the community an emphasis on collaborative care between social care services and health services may lead to greater resources for prevention of LTCs and more proactive care.

Summary

- Rates of LTCs are high and will increase over the coming years due to an expanding aging population.

- The personal and financial impact of LTCs is significant.

- Treatment for LTCs focuses on stabalising patients' condition/s, alleviating physical symptom burden and improving quality of life.

- The LTC model of care proposes that care of patients with one or more LTCs should be holistic and coordinated across primary and secondary care services.

- The majority of patients can be cared for at level 3: supported self-care.

- However the current NHS structure is focused on hospital-based acute management.

- The formation of GP clinical commissioning groups may provide more integrated care between health and social care services and target provisions at level 3 care; self-management.

- In the coming years patients with one or more LTCs are going to be expected to take more responsibility for their health and well-being. It can be argued that a patient's ability to adequately self-care will be determined, to a degree, by their HRQoL.

The following section considers another significant concern for glaboal and national health and social care; common mental health conditions. The prevalence and treatment of both depression and anxiety are discussed, along with issues associated with the conceptualisation and measurement of these common mental health conditions.

Part Two: Mental Health Conditions

Mental health conditions are common in both the UK and internationally. Globally at least one in four people will experience a mental health condition in their lifetime (Murray & Lopez, 1996). In a recent psychiatric morbidity survey of England, 23 % of adults were identified with one or more mental health conditions (McManus et al, 2009). Mental health conditions are the largest single cause of disability in the UK (DH, 2011b). The cost of mental health problems accounts for 11 % of the NHS secondary health care budget (DH, 2011b) and costs the English economy £105 billion (DH, 2011b), of which £30 billion is work related as a result of unemployment and incapacity benefit (Naylor et al, 2012).

The personal cost of mental health conditions is high. The presence of mental health conditions can significantly impacting on individuals' and families' education, work life, social life, family life, functioning and ultimately their quality of life (DH, 2011b).

When we speak of common mental health conditions we are referring primarily to conditions of depression and anxiety, which are highly prevalent both internationally and in the UK, accounting for approximately 97% of all people experiencing an episode of mental ill- health (Richards & Suckling, 2008). The National Institute for Health and Care Excellence (NICE) has produced a set of guideleines for the identification and pathways to care for common mental health disorders (NICE guideline 123) (NICE, 2011).The guidelines identify common mental health disorders as depression, generalised anxiety disorder, panic disorder, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD) and social anxiety disorder, all of which can have a life-time course of relapse and remission and vary in severity. (NICE 2011)

Defining Depression and Anxiety

Depression and anxiety can be characterised by the signs and symptoms experienced and displayed by individuals, that present at varying degrees and impact on individual's mental health, their physical health, quality of life and social and economic situation (First et al, 1995). The use of signs and symptoms to diagnose depression and anxiety is informed by a conventional medical model approach, which traditionally assumes that mental illness is a

result of physical problems and should be treated medically. The advantage of using a conventional medical model classification approach to diagnosing depression and anxiety is that diagnostic patterns can be established, informing health care providers on the course of a condition, underlying causes and treatments.

The medical model has strong clinical applications. Two significant diagnostic systems for mental health are the Diagnostic and Statistical Manual - IV (DSM-IV) (APA, 2004) system and the International Classification for Diseases - 10 (ICD- 10) (WHO, 2010) classification system. Both systems identify a range of symptoms of depression and anxiety, including sub-types and severities, indicating the duration of time key symptoms should be present for in order for diagnosis (NICE, 2009). Although within the UK clinicans are free to use any diagnostic classification system, such as DSM or ICD, the National Institute for Health and Care Excellence (NICE) adopt DSM-IV criteria in much of their clinical guidance for the identification and treatment of mental health conditions. They state this is due to the fact that much of the empirical evidence draws on this classification system. In addition, DSM systems incorporate functional impairment resulting from symptoms into their diagnoses, making the targeting of treatment at specific levels of severity possible (NICE, 2009).

It has to be acknowledged however (and the NICE guidelines do this) that the medical model is not without its critics. The medical model places the doctor or physician as the expert in patient care and sees the patient as a passive actor in medical interactions. However, there has in recent years been a move towards patient-centred care, seeing the patient as more active and responsible for their own health (ref). Within the developing chronic care model presented on page 27 patients are expected to increasingly self-manage their own health more in the community, with a range of health professionals collaborating to provide holistic care for patients, addressing medical, psychological and social needs.

Other models are available to define common mental health problems such as the biopsychosocial model, which identifies not only biological but also psychological and social factors as key to determining health and illness in humans; which ultimately requires a health care team to tackle biological, psychological and social influences on a patient's health. The model is increasingly useful in the area of LTC care as empirical research highlights not only biological causes of illness but also psychological and social factors that can influence a persons engagement with risky health behaviours such as smoking,

alcohol consumption, diet and participation in health-promotion behaviours such as engaging in physical activity and adherence to treatment regimens (DiMatteo, Haskard & Williams, 2007). Common mental health conditions can alternatively be conceptualised as socially constructed. From this perspective, diagnosis based on the traditional medical model is considered mere deviations from societal norms, with consequential treatment viewed as an attempt to make individuals conform to normative values (Paley, 2002). The World Health Organisation does highlight the importance of taking a holistic approach to health care (WHO, 2008), however, the current mental health system promotes guidance and management of depression and anxiety using the former approach, the medical model, to identify people and assign them a diagnositic label that will inform treatment.

In the current thesis, anxiety and depression have been conceptualised using a medical model approach to identify signs and symptoms of both conditions, however, biopsychosocial models of health are ultimately guiding this research as the additive influence of clinical, psychological, environmental and social factors are considered important in determining both patients physical and mental health.

Symptoms, Severity and Diagnoses

Both depression and anxiety are thought to comprise of physiological, cognitive and emotional, and behavioural components; some of which are thought to be general to both conditions, such as distress, others are specific to either depression or anxiety (Simms et al, 2008).

The severity of an individual's anxiety and/or depression can be, and with respect to this thesis has been viewed as existing along a continuum of severity ranging from normal/mild to severe and culminating in cut-off points or thresholds that indicate the presence of clinically significant disorders. The severity of a person's depression and/or anxiety is determined by the number and severity of symptoms, as well as the degree of functional impairment. The symptoms experienced by an individual and the severity of those symptoms have implications for their management and treatment.

Depression

Depression is a mood disorder, characterised essentially by low mood and the inability to experience pleasure. Symptoms include:

- *Physiological*: Insomnia, hypersomnia, fatigue, headaches, digestive problems, decreased appetite, occasional increased appetite.
- *Cognitive and Emotional:* Distress, low mood, loss of pleasure or interest in activities, poor concentration and memory, rumination, feelings of worthlessness, inappropriate guilt or regret, helplessness, hopelessness, indecisiveness, self-hatred, recurrent thoughts of suicide, death or self-harm; with or without a specific plan.
- *Behavioural*: Withdrawal, reduced sex drive, agitated, lethargic, irritable, self-harm, attempted suicide.

For a formal diagnosis of clinical Major Depression at least five out of nine (DSM-IV) (American Psychiatric Association (APA), 2000) and four out of ten (ICD-10) symptoms should be present for at least two weeks on most days; to include one (DSM-IV) or two (ICD-10) key symptoms of low mood, loss of interest of pleasure or loss of energy. Sub-threshold depression has also been recently identified as distressing to individuals, with diagnosis defined as at least one key symptom of depression but with insufficient other symptoms to warrant criteria for full diagnosis (NICE, 2009).

Anxiety

Anxiety is a complex and multi-faceted construct. From a medical model perspective anxiety has been defined as apprehensive anticipation of future danger or misfortune accompanied by a feeling of dysphoria or somatic symptoms of tension (APA, 2004). Anxiety is an umbrella term used to describe a range of subtypes of abnormal, pathological fears, anxiety and phobias. Anxiety is an unpleasant emotional state with exhausting physiological components, the source of which is not always readily available. Anxiety is considered separate to fear for a number of reasons; specifically anxiety is often experienced for a longer duration than fear, is future-orientated, may not relate to a specific threat and often involves individuals perceiving the threat as uncontrollable and unavoidable (Sylvers, Lilienfeld, & LaPrairie; 2011). Anxiety or worry is a common experience for many people as a response to a multitude of life events. However, it is abnormal, irrational worry, experienced more often than not, continued for an extended,

chronic period of time that distinguishes normal from pathological anxiety. Symptoms of anxiety can include:

- *Physiological*: Heart palpitations, muscle tension, nausea, chest pains, shortness of breath, headaches, increased blood pressure as blood flow increases to major organs, whilst immune and digestive functions are inhibited. These reactions are considered part of the fight or flight reaction to danger/threat. External signs of anxiety can include sweating and trembling. Panic attacks, although not experienced by all individuals who have anxiety, are a common symptom. Panic attacks can come without warning as a result of irrational fear and are characterised by a subjective perception of fear or discomfort in which some of the following symptoms develops abruptly and reach a peak within 10 minutes (but can remain for hours) (DSM –IV): palpitations, sweating, trembling/shaking, shortness of breath, feeling of choking, chest pain, nausea, light-headed/dizzy, fear of dying, chills/hot flushes, fear of losing control, numbness/tingling sensation, derealisation (detachment from reality).
- *Cognitive and Emotional:* Distress, confusion, memory problems, and fearful thoughts, feelings of apprehension or dread, trouble concentrating, feeling tense or jumpy, anticipating the worst, irritability, restlessness, watching (and waiting) for signs (and occurrences) of danger.
- Behavioural: pacing, wringing hands, withdrawal and changes in sleep patterns.

Clinical Anxiety disorders can be broken down into different types, the most common of which are Generalised Anxiety Disorders (GAD), Phobic Disorders, Panic Disorders, Obsessive Compulsive Disorders (OCD), Agoraphobia, Social Anxiety Disorder, and Post Traumatic Stress Disorder (PTSD). These disorders share common features, including panic attacks. For a formal diagnosis of GAD using DSM-IV criteria three of more of the following six symptoms, associated with multiple events/activities should be present on more days than not for at least 6 months, with the patient unable to control the worry. (APA, 2004);

- Restlessness
- Easily fatigued
- Difficultly concentrating
- Irritability
- Muscle tension

- Sleep disturbances

Using ICD 10 criteria at least four symptoms, from an extensive list[2] of predominantly physiological symptoms under the headings listed below should be present for at least six months with prominent worry, tension and feelings of apprehension about every day events:

- Autonomic arousal symptoms
- Symptoms involving the chest or abdomen
- Symptoms involving mental state
- General somatic symptoms
- Symptoms of tension
- Other non-specific symptoms

Differences in the core symptoms used by the two classification systems are evident. DSM –IV core symptoms focus more on vigilance and scanning, whilst ICD criteria are predominantly focused around physiological arousal (Slade & Andrews, 2001). In additon DSM-IV criteria state that worry should be difficult to control or perceived as difficult to control to warrant clinical diagosis of GAD (Slade & Andrews, 2001).

As stated, in the current thesis, depression and anxiety have been conceptualised using a medical model approach, which suggests that conditions can be identified by looking for and measuring the severity and frequency of particular signs and symptoms. To this end it is accepted that both depression and anxiety can be identified in individuals using measurement tools that assess both the frequency and severity of key symptoms.

Measuring common mental health conditions

Clinically significant depression and anxiety can be identified using clinical interviews, administered by persons trained to identify the aforementioned sign and symptoms of both conditions. The Structured Clinical Interview for DSM IV for Axis I disorder (SCID - I) (first et al, 1996) based on DSM criteria for depression and anxiety and the WHO Composite International Diagnostic Interview (CIDI) (WHO, 1996) based on both DSM-IV and ICD-10 classification systems are examples of two such diagnostic interviews.

[2] http://www.who.int/classifications/icd/en/GRNBOOK.pdf

Both interviews must be administered by a trained individual and can be lengthy, taking between 30 minutes to two hours to complete depending on the patient's history and complexity of signs and symptoms (First et al, 1996). When considering the screening of common mental health conditions in busy clinical primary or secondary care settings, a brief, self-administered tool would be advantageous.

Questionnaires have been developed to measure symptoms of depression and/or anxiety such as the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983), the Back Depression Inventory (Beck, 1961), the Self-Rating Depression scale (Zung, 1965), the Geriatric Depression (Brink & Yesavage, 1982) and Anxiety scales (GAI) (Pachana et al, 2007), the State-Trait Anxiety Inventory (STAI) (Spielberger, 1977), the Generalised Anxiety Disorder -7 (GAD-7) (Spitzer et al, 2006), the PHQ-9 (Kroenke, Spitzer & Williams, 2001) and the Brief Symptom Inventory (BSI) (Derogartis, 1983), to name a few. Each of these tools takes less time to complete than a clinical interview, with some taking a matter of minutes to complete, and can be self-administered by a patient. All of the aforementioned tools have been found to be reliable and valid, to varying degrees, in identifying the potential presence of depression and anxiety in individuals (McDowell, 2006).

The accurate measurement and identification of depression and anxiety is complicated by the frequent co-occurrence of these conditions (Singleton et al, 2001, cited in NICE, 2011). Research indicates that anxiety and depression can co-occur in approximately 70% of cases, and to date it appears that the likelihood of anxiety proceding depression is more likely than the reverse (Merikangas et al, 2003; Hagnell & Grasbeck, 1990). The challenge of identifying and treating anxiety and depression is further exacerbated by an overlap in symptoms, particularly those of a physiological nature. Anxiety and depression share symptoms of fatigue, sleep disturbance, changes in appetite, restlessness, distress, confusion, memory problems, irritability and withdrawal amongst others. Individuals who experience either anxiety and/or depression will share a tendency of overestimating the risk in a situation, underestimating personal resources for coping and share an avoidant coping style (Marano, 2003). One reason the two conditions share features in common and can contribute to the development of each other may be due to the fact that both anxiety and depression can cause changes in neurotransmitter function, particularly serotonin (Gulley & Nemeroff, 1993). Table 1 summarises key neurotransmitters thought to be involved in both anxiety and depression.

Table 1: A table to summarise key neurotransmitters associates with common mental health conditions.

Neurotransmiter	Actions	High levels	Low levels
GABA (Gamma-aminobutyric acid)	Inhibatory. Regulates anxiety and reduces stress. Primary function is to prevent over stimulation. Regulates excitatory neurotransmitters such as norepinephrine, epinephrine and also serotonin. Mood moderator.	Excessive relaxation and sedation.	Anxiety, instrusive, worrying thoughts. Correct regulation of GABA is required to prevent over stimulation and regulate sleep.
Serotonin	Inhibitory. Regulates mood, anxiety, sleep, appetite, cardiovascular function, muscle contraction.	Sedation, decreased sexual drive.	Depressed mood, anxiety, panic attacks, fatigue, feeling tense, irritatable, sleep problems, obsessions/compulsions.
Epinephrine (derived from Norepinephrine)	Excitatory. Regulates arousal, mental focus. Used as vasoconstrictor in cardiac arrest.	Acute, stress, sleep problems, irritability, increased blood pressure and heart rate.	Fatigue, weight gain, poor concentration.
Norepinephrine (synthesied from dopamine)	Excitatory. Reguates 'fight or flight' and signals other stress hormones to act. Rises blood pressure and heart rate.	Contribute to anxiety. Increased alertness – leading to high blood pressure, heart rate, fear, sense of dread, irritability & insomnia.	Lack of energy, loss of alertness, poor memory.

Treatment and Management

Although anxiety and depression often co-occur and share some similar features current prevailing opinion postulates that the two conditions are discrete disease entities (NICE, 2011) and are treated as such in their treatment and management. The majority of depression and anxiety is diagnosed and treated in primary care settings (up to 90%) (NICE, 2011). In the UK, care pathways operate on a stepped care approach, which sees patients receiving the lowest appropriate service tier in the first instance, with a 'stepping up' to more intensive or specialist treatments only occurring when necessary. Most patients with anxiety and/or depression are treated with psychotropic medication. Patients with anxiety may be prescribed antidepressents in the long-term including Selective Serotonin Reuptake Inhibitors (SSRIs) which increase the levels of serotonin in the brain, and in the short-term, Benzodiazepines, which have a sedatory effect. In general it is reported that patient's prefer to receive psychological treatment options although the availability of these types of therapies often means that patient's do not have access to them immediately (NICE, 2011). Patients with mild or lower levels of depression or anxiety may be offered individual facilitated self-help or computerised self-help based on the principles of cognitive-behavioural therapy (CBT), group-based peer support or non-directive counselling delivered at home (NICE, 2011). If patients with mild depression and/or anxiety are non-responsive to these initial treatments then medication and psychological therapies may be offered (NICE, 2011).

As anxiety and depression often co-exist and share similar features there has been increasing interest in treating both conditions simultaneously and CBT has an evidence-base and applications for both conditions (NICE, 2011). Treatment of co-existing anxiety and depression seldom hinges on which disorder came first, however depression can be so incapacitating that it may be necessary to be treated first so that patients can engage better with therapy for anxiety (NICE, 2011).

Prevalence of depression and anxiety

Prevalence rates of major depression have been found at around 2.5 % to 3 % both in the UK and globally (Singleton et al, 2001, cited in NICE 2009a; Moussavi et al, 2007). In the UK over 15 % of the population will experience an episode of depression in their lifetime,

with around two-thirds of the population experiencing low mood sufficient to interfere with their daily lives (NICE, 2009a). Females experience depression at higher rates than males, with one in four females requiring treatment for depression compared with one in ten males (NICE, 2009a). Depression is the third leading cause of disease-burden globally as calculated by Disability Adjusted Life Years (DALYs) which calculate the years of life lost due to premature mortality and productive life lost due to disability (WHO, 2010). Depression is predicted to be the leading cause of disease burden globally by 2030 (WHO, 2010).

Anxiety is thought to be more prevalent than depression. The one-week prevalence rates from the Office of National Statistics 2007 household survey were 4.4 % for generalised anxiety disorder, compared with 2.3 % for depression (National Centre for Social Research, 2009). Rates of PTSD (3.0%), phobias (1.4%), OCD (1.1%) and panic disorder (1.1%) are lower than those for GAD. Females are at higher risk of experiencing Generalised Anxiety Disorder (GAD) than males, with a 2:1 ratio often found in prevalence studies (Brown, O'Leary, and Barlow, 2001). The same authors also highlight that anxiety increases with age, with up to 17 % of elderly men and 21.5 % of elderly women experiencing severe anxiety, although the term elderly is not defined. A recent systematic literature review of the prevalence of anxiety in older adults aged > 60 years both in the community and clinical settings (Bryant, Jackson & Ames, 2007) found that anxiety symptoms such as feeling fearful, tense and nervous were experienced ‘a little’ or ‘quite a bit’ and have been reported in 20 % to 26 % of healthy older adults (Flint, 1994; Mehta et al, 2003).

As stated previously, anxiety can occur in isolation but is thought to be more commonly found alongside depression or other mental health conditions, which can make accurate diagnosis problematic (NICE, 2011; Wittchen et al., 2002). The presence of both co-existing anxiety and depression is higher than either condition in isolation (Merikangas ert al, 2003) and has been recorded at a prevelence rate of 11.4 % in the UK population (Singleton et al, 2001, cited in NICE, 2011). A range of studies have found that the emergence of depression among patients with anxiety is more common than the reverse (Merikangas et al, 2003; Hagnell & Grasbeck, 1990). Interestingly, research suggests that the course of co-morbid anxiety and depression, the duration and severity, is worse than that of both anxiety and depression in isolation (Penninx et al, 2011). The significance of co- morbid anxiety and depression has been acknowledged in ICD-10 revisions, with the

addition of ‘mixed anxiety-depression’ diagnosis for patients whose levels of anxiety and depression do not meet criteria for diagnosis of one condition in isolation over the other (WHO, 2010).

It is clear from examining the literature pertaining to common mental health conditions of depression and anxiety that the conditions manifest in physiological, cognitive, emotional and behavioural ways. As both conditions share some common features and symptoms the accurate and valid measurement of both conditions can be challenging and is an area of continual research and development. What is certain is that chronic and severe depression and/or anxiety places a significant burden on patients physical, emotional, social and financial well-being, in addition to being a costly health and social care problem.

Summary

- Mental health conditions, particularly depression and anxiety, are common both globally and nationally within the UK and have a significant impact on patient's lives and the economy.

- Common mental health conditions have been conceptualised using a medical model that postulated signs and symptoms of health conditions act as markers to identify the severity and presence of particular medical conditions in patients.

- Difficulties arise when identifying depression and anxiety. Although anxiety and depression are currently thought to be discrete conditions, they share some common signs and symptoms and can be managed in similar ways.

In part three of chapter one the mental health of patients with LTCs will be considered. The issue of accurately separating out, not only anxiety and depression from each other but in disentangling common mental health conditions from physical disease processes is considered. The added implications of co- morbid mental and physical health conditions on the economy, patients' physical health and well-being are considered. Finally, the governmental response to this increasingly acknowledged health and social care concern is presented.

Part Three: Mental health conditions co-morbid to long term physical health conditions

People with LTCs, as defined in part one of this chapter, are reported to be at higher risk of experiencing or developing a common mental health problem than the general population (Naylor et al, 2012), particularly those patients with multiple LTCs (Moussavi et al, 2007; Mercer and Watt, 2007). Depression is reported to be three times more common in populations with cardiovascular conditions including coronary artery disease, angina, HF and following a myocardial infarction (MI) compared with the general population (Fenton and Strover, 2006; Benton, Staab & Evans, 2007; Gunn et al, 2010). The prevalence of anxiety symptoms (not specific anxiety disorders) in patients with Coronary Artery Disease (CAD) has been found at around 20 to 25 % in those who have not experienced an acute cardiac event, and rises to 70 to 80 % in patients following an acute cardiac event, such an MI or cardiac arrest (Januzzi et al, 2000).

Patients with a diagnosis of COPD are three times more likely than the general population to experience mental health problems (NICE, 2010), particularly anxiety (Livermore et al, 2010). In a recent review on this subject the rates of depression in COPD were found to range between 7 % to 79 % depending on the measures used to assess the condition (Yohannes et al, 2010). Aggregated rates of clinical anxiety and of depressive symptoms were found at 55% and 24.6% respectively in the review (Yohannes et al, 2010), over twice the rate found in controls without a COPD diagnosis (11.7%) (Zhang et al, 2011).

With the presence of any LTC a certain amount of low mood and worry relating to diagnosis, the occurrence of unpleasant symptoms, lifestyle restriction, complicated treatment regimens or a sense of one's own mortality is to be expected. However, chronic and intense low mood and/or worry are not a normal reaction for such patient groups and should be a cause for concern to clinicians (McDowell, 2006; Barlow, 2002).

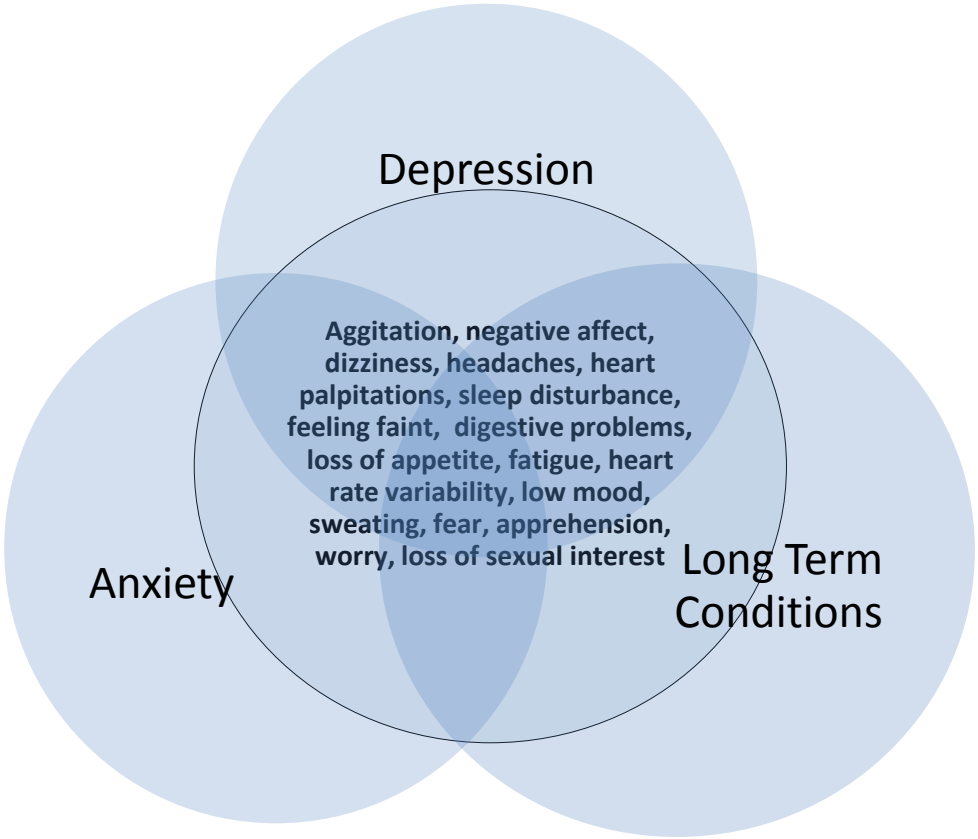
Issues with measurement and identification

Worryingly, it is difficult to know whether the prevalence data for common mental health conditions in samples with physical long term conditions are accurate. Not only is it challenging to separate out symptoms of anxiety and depression from one another as

previously highlighted, but the addition of a physical disease process can compound the issue of overlapping and co-occuring symptoms already existing. Many symptoms of depression and/or anxiety overlap with those of a range of LTCs, as the ven diagram below highlights (figure 6). Considering a range of signs and symptoms that span a number of LTCs, particularly cardiovascular conditions, it can be seen that disentangling a physical disease process from a mental health condition can be problematic.

To further add to the challenge of accurately identifying common mental health conditions in the context of a physical disease process, many medications used to treat anxiety, depression and some cardiovascular conditions, such as Selective Serotonin Reuptake Inhibitors's (SSRI's) and Beta Blockers have common side effects that mirror symptoms found with anxiety, depression and many physical disease process (figure 6) [3].

Figure 6: A Venn diagram to illustrate the overlap between common mental and physical health conditions.



[3] http://www.nhs.uk/Pages/HomePage.aspx

As highlighted in figure 6 many physical signs and symptoms of physical LTCs also manifest as somatic symptoms in the conditions of anxiety and depression.

As a result of this overlap in symptoms between physical and mental health conditions the accurate identification of anxiety and depression in these patient populations and the monitoring of treatment effects on such outcomes can be challenging. Evidence suggests that detection of mental health conditions in this patient population during primary care consultation could be improved (Naylor et al, 2012). Research has indicated that depression, for example, is only detected in a small percentage of patients presenting at primary care services with LTCs (Cepoiu et al, 2008; Katon 2003). Qualitative research conducted in primary care settings suggests that during consultation both clinicians and patients focus more on physical symptoms of their conditions than emotional symptoms and well-being across a range of LTCs (Coventry et al, 2011). Sixty-nine per cent of patients experiencing depression initially present to primary care services with physical symptoms (Simon et al, 1999) and 25% of emergency room visits for acute chest pain turn out to be panic disorder (Hoffman and Pollock, 2003); suggesting that patients themselves focus on the physical manifestation of mental health conditions when reporting them. Less is known about the detection of common mental health conditions, co-morbid to LTCs in secondary care settings, however recent research from the Netherlands has found that only a minority of HF patients attending outpatient clinics are routinely screened for anxiety and depression (Saskia, Pasteuning & Walpot, 2012).

A number of reasons have been suggested for a lack of identification and management of psychological factors in clinical practice.

1. As mentioned, the presence of physical LTCs can make the detection of depression and anxiety problematic, as many somatic symptoms that form part of diagnosis for mental health conditions are often also features of a number of LTCs (Naylor et al, 2012). Clinicians may be unsure of how best to assess common mental health conditions.
2. In addition, time constraints may prevent health professionals from identifying mental health complaints (Moser, 2002).
3. Clinicians may believe that anxiety and depression are natural responses to a LTC (Coventry et al, 2011).
4. Clinicians may place the treatment of physical health problems at a higher priority than patient's mental health.

Or

5. They may be unaware that anxiety and depression can be effectively treated by psychological therapies or other treatment (IAPT, 2008).

Importantly, not all measurement tools developed to screen for depression and/or anxiety mentioned previously omit somatic items which may lead to inaccurate reporting of rates of depression and anxiety in HF literature and in screening of both conditions in clinical practice. The selection of appropriate measures in this research area is crucial to accurately identifying rates of depression and anxiety and will be discussed at length in the methods sections of chapters two and three of the thesis and in the discussion sections.

Implications of co-morbid mental and physical health conditions

If patients with LTCs are to manage their condition effectively in the community with support from health and social care organisations as highlighted in part one of chapter one they must be able to adhere to complex treatment regimens and identify exacerbation of symptoms and react to any exacerbations appropriately (Bodenheimer et al, 2002c). For patients to actively engage in self-care behaviours they must be motivated and feel they have the abilities to manage their own health. However the presence of a co-morbid mental health condition has been found to reduced patient's abilities to self-care, lower quality of life, increase exacerbations and rates of mortality; which in turn impacts on the heath care use of this patient group and health and social care costs (Naylot et al, 2012).

Physical health

Clinically patients with a range of physical LTCs and co-morbid mental health conditions experience poorer functional ability than those without a mental health diagnosis (Molosankwe et al, unpublished, cited in Naylor et al, 2012). Individuals with cardiovascular conditions and chronic lung conditions with co-morbid mental health problems experience 50 % more exacerbations of their condition a year (Whooley et al, 2008; Laurin et al, 2009). Heart failure patients are eight times more likely to die within 30 months if they have depression (Junger et al, 2005). These trends have also been found in patients with a diagnosis of diabetes and COPD (Naylor et al, 2012). The potential

mechanisms that link common mental health conditions with poorer health outcomes for patients with LTCs will be considered further in part four of this chapter within the specific context of heart failure.

Quality of life

With regards to a patient's well-being, having a physical LTC or mental health diagnosis in isolation has been found to impair quality of life to a significant degree (DH, 2010a) and so it is no surprise that the combination of conditions further impairs an individual's perceptions of their quality of life. In the most recent World Health Survey co-morbid depression was found to lower quality of life for individuals with a range of physical LTCs to a greater degree than having multiple physical LTCs alone (Moussavi et al, 2007). Interestingly it has been found in some studies that the presence of anxiety or depression in patients with COPD and some cardiovascular conditions can have a larger impact on patient's perceptions of their quality of life than disease severity or functional status such as lung function (Yohannes et al, 2010; Cully et al, 2006; de Jong et al, 2006).

Financial impact

Poorer functional status, an increased rate of HF symptom exacerbations, a reduced ability to adequately self-care and impaired quality of life in turn lead to increased health service use and costs (Naylor et al, 2012). The presence of depression increases rates of hospital readmission for patients with cardiovascular conditions, with rates two to three times higher for patients with HF (Jiang et al, 2001; Fenton and Stower, 2006). In a recent King's Fund document Naylor et al (2012) examined international data on health care costs from a number of studies. They concluded that the increase in healthcare provisions resulting from co-morbid mental health conditions leads to an associated increase in cost of up to 45-75 % for patients with a physical LTC, even after adjusting for disease severity (Naylor et al, 2012). The authors state that between 12 % and 18 % of all expenditure of LTC care is linked to poor mental health and well being; that is between £8 and £13 billion of NHS spending (Naylor et al, 2012). This cost to the economy is increased further when unemployment and absence from work as a result of illness is considered (Naylor et al, 2012; Druss et al, 2000).

Response to need for improved care of patients with LTCs and co-morbid mental health conditions

The association between mental health and LTCs has been highlighted in a number of published reports and government guidelines including:

- The National Institute for Health and Clinical Excellence (NICE) guidelines for depression (NICE, 2009a) which specifically indicate that clinicians should use the guidelines for patients both with and without a chronic physical condition.
- Similarly updated NICE guidelines for Generalised Anxiety Disorder and Panic Disorder (NICE, 2011) now suggest that the presence of anxiety should be considered for all patients presenting at primary care with a diagnosis of a LTC.
- From a LTC angle the National Service Framework (NSF) for LTCs (2005) highlights the need for community rehabilitation and support in an attempt to address psychosocial problems, in particular anxiety and depression (DoH, 2005a). It states that intensive rehabilitation should be delivered for cognitive, behavioural and emotional problems, and that counselling and psychological support should be offered to help people adjust to their life situations.
- More recently a report was published by the Healthcare Commission during the consultation phase of the NSF for COPD[4] (NICE, 2010; Commission for Health Care Audit and Inspection, 2006). The Healthcare Commission paper details how current mental health services (e.g. cognitive behavioural therapy (CBT) may be used in the context of care for LTCs, illustrated through the use of case studies. The case studies highlight how CBT techniques may be useful in increasing coping skills and patient's ability to manage their condition.

Recently the current UK government has given equal weight to mental health conditions and physical conditions in the recent public health White Paper '*Healthy Lives, Healthy People'* (DH, 2010) and highlighted the problem of mental health conditions in '*No Health without Mental Health'* (DH, 2011b), stating that over the next four years 400 million pounds will be invested in England into initiatives such as Increasing Access to Psychological Therapies (IAPTs) and expanding provisions for young people, older

[4] http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_113279.pdf

people, those with LTCs and those with severe and enduring mental health conditions (DH, 2011b).

The increased government interest in association between mental health conditions and LTCs is promising and research evidence suggests that the mental health of a range of LTCs is under investigation, however the mental health of one LTC in particular, heart failure, has been relatively under-researched until recently.

Summary

- Recently research has highlighted that individuals with one or more physical LTCs are vulnerable to experiencing common mental health problems.

- The issues of accurately measuring depression and anxiety are compounded by the presence of a physical disease process. This is reflected in a lack of clinical attention in this area, with evidence from primary and secondary care settings suggesting common mental health conditions and well-being in general are often under-assessed during consultation.

- Patients with physical LTCs and co-morbid mental health conditions, particularly depression have been found to experience poorer functional health, higher rates of mortality and engage in more risky health behaviours than patients with one or more LTCs alone.

- Patients' HRQoL suffers to a higher degree when mental health conditions are experienced, with some research indicating that a person's mental health contributes more to determining patients satisfaction with life and their health than the severity of their physical condition.

- Government and clinical guidelines acknowledge the importance of identifying and treating mental health conditions particularly when they are co-morbid to a physical LTC.

The following section focuses on one LTC in particular, heart failure. The condition of HF is presented and the research evidence for the prevalence and impact of depression and anxiety in this physical LTC is considered. The problems arising in accurately measuring depression and anxiety in this patient population are further explored and heterogeneity in reported rates of anxiety is discussed.The first phase of research from the study will be presented.

Part Four: Heart failure and co-morbid depression and anxiety

Heart failure is a '*complex clinical syndrome of symptoms and signs that suggest the efficiency of the heart as a pump is impaired. It is caused by structural or functional abnormalities of the heart'* (NICE, 2010, pp 4), which requires complex and timely management.

Types of HF

Heart failure can be located structurally, either in the left ventricle (left-sided), right ventricle (right-sided), or both (biventricular). Left ventricular (LV) heart failure is more common than right ventricular (RV) failure, which often but not always occurs as a result of left-sided failure. Damage to the left ventricle often results from a myocardial infarction (MI) (NICE, 2010). Heart failure can also be defined according to whether there is diastolic or systolic dysfunction. Systolic dysfunction refers to impairment in the heart's ability to contract effectively and results in a decreased proportion of blood being ejected during systole (reduced ejection fraction). Often when the term HF is used it is synonymous with left ventricular systolic dysfunction (LVSD), and it is the most common form of failure in the heart.

However, some patients (primarily older patients) may present with symptoms of HF with a preserved EF (HFPEF). Many will have evidence of diastolic dysfunction, which is the inability of the heart to relax and fill properly following systole. HFPEF and diastolic HF are controversial, due in part to difficulties in diagnosis (Nicolson, 2007; ESC 2012 Clinical Guidelines).

Symptoms of heart failure

Common symptoms of HF can be distressing and include shortness of breath (dyspnoea), with some patients short of breath at rest, or when lying down (orthopnoea). Some patients experience sudden breathlessness at night (paroxysmal nocturnal dyspnoea (PNSD) which can be confused with panic attacks. Some patients experience fluid retention manifesting as peripheral oedema (swelling of ankles or legs) as the body attempts to compensate for poor cardiac output (Funk & Winkler, 2008). Many patients experience fatigue, commonly

as a result of a reduction in blood supply to muscles; however other causes include depression and anaemia.

Classification of HF severity or functional status

Although the onset of heart failure can be acute as a result of MI or viral myocarditis for example, it is more common for the syndrome to have developed over a period of time, with the heart incurring assaults or weakening progressively. During this time an individual may be asymptomatic or be defined as pre-clinical, but be identified as being at a high risk of developing heart failure in the future. It is increasingly common for individuals to be identified at this stage; and as expected outcomes improve the earlier a patient is detected and managed. On average asymptomatic patients will receive fewer hospitalisations, show slower decline and have higher overall survival rates than an individual diagnosed with advanced heart failure (Silver, 2006). Patients at this stage are usually identified from health histories and risk factors identified in medical notes and are treated with risk factor management (Funk & Wikler, in Moser eds, 2008). With regards to the governments policy on the management of LTC it would be beneficial to identify people at pre-clinical stages of heart failure. Preventative and early self-care management at level three of the 'stepped care approach' would be cost-effective in the long-term as a large amount of people could be treated with minimal resources, as opposed to more costly and intensive care for those with advanced and unstable heart failure.

The most widely used system of classifying the functional status of the patient in HF is the New York Heart Association (NYHA) classification[5]. Heart failure is separated in four distinct stages based on patient's symptoms.

Class I:	Asymptomatic. No limitation from ordinary activity
Class II:	Slight, mild limitation with moderate activity (two flights of stairs), comfortable at rest or mild exertion
Class III:	Marked limitation from very mild exertion (walking across a room), comfortable only at rest
Class IV:	Any activity brings discomfort and symptoms, even at rest (lying or sitting)

[5] http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp

The scoring system is easy to remember and simple to use, and many clinicians have indicated its use as one of the best early predictors for mortality in this patient group (Nicholson, 2008). However, this test reliance on self-reporting by the patient and subjective scoring by providers has led some to question its reliability (Raphael et al, 2006). Clinicians and researchers often do not report the specific questions they ask patientsin order to assess their functional class, meaning that it can be difficult to produce replicable assessments using this measure (Raphael et al, 2006). The stage a patient is assigned to can vary depending on the line of questioning used or the context in which patients are asked to place their functioning. Also clinicians may often ask a patient 'how far can you walk before getting out of breath?' to assign people, but research suggests there is little value in this form of questioning as estimates bear little resemblance to actual exercise capacity, even when correcting for patients poor perception of distance (Enright, 2003). When self reported distance is compared to peak oxygen consumption correlation have been shown to be non-significant (Raphael et al, 2006). Despite these concerns the system is shown to be a reliable predictor of mortality in heart failure and an easily applied assessment, meaning many if not all heart failure will have a NYHA classification assigned to them at some stage in their assessment.

Causes of heart failure

Although the onset of heart failure can be acute as a result of an MI or viral myocarditis for example, it is more common for the syndrome to be chronic, developing over a period of time, with the heart incurring assaults or weakening progressively. The main causes of HF in the western world are coronary artery disease (CAD), hypertension, valve disease and arrhythmias, particularly atrial fibrillation (AF) (Nicolson, 2007). Coronary artery disease or ischaemic heart disease (IHD) is the main cause of LVSD. Hypertension is a risk factor for CAD and the two often co-exist, which makes the direct contribution of hypertension to the development of HF difficult to establish. In the Hillingdon Heart Study, a population sample of urban West London PCT from 1995-1996, CAD was the single most common cause of heart failure (in 36 % of cases), with over 44 % of these patients also presenting with hypertension (Cowie et al, 1999).

Arrhythmias (abnormal heart rhythms) are a cause and consequence of HF. Chronic atrial fibrillation is common in older adults, affecting 10 % of those over 75 years and up to 30

% of chronic HF patients (Cowie et al, 1999). The loss of the contribution of atrial contraction to ventricular filling can reduce cardiac output by 10 to 30 %, impacting the efficiency of the heart, activity tolerance, and prognosis (Cowie & Kriby, 2003).

Other less common causes of HF include; alcohol abuse, diabetes, infections, genetic mutations/congenital heart disease, valvular heart disease and dilated cardiomyopathies.

Incidence and prevalence trends

As the diagnosis of HF can be problematic, at times open to subjective interpretation by clinicians it is difficult to ascertain accurate rates of HF. In addition the detection of HF has improved over the years, which means increased rates of HF may reflect improvements in medical science rather than actual increases in the condition.

Incidence refers to the number of new cases of a condition over a specified period of time. Using only the number of new cases of acute hospital admissions for HF diagnosed using echocardiography over a 20 month period in Hillingdon, West London Cowie et al (1999) found that in persons aged 45-54 years the incidence rate of HF was 0.2 %, with rates rising steadily to 7.5 % in those 75-84 years old to 11.6 % in persons over 85 years. Rates are found to increase with age, doubling with every decade (Kannel, 2000) and to be higher in males (Cowie et al, 1999). Overall evidence suggests that the rate of new HF diagnoses are stable, similar to new rates of LTCs in general (DH, 2010).
The prevalence of HF or LVSD, the total number of cases in a given population is reported as 3-20 per 1000 (0.3 -2 %) in people under 75 years, rising to 3-130 per 1000 (0.3-13 %) in people over 75 years (NICE, 2010). Although not the most prevalent LTC in the UK today, nearly 400,000 persons with a documented HF diagnosis were seen in UK primary care services in 2010/2011 (The Health and Social Care Information Centre, 2011). In total around 900,000 people in the UK have been diagnosed with HF, with almost as many individuals estimated to have damaged hearts but, as yet, no symptoms of HF (NICE, 2010). A table in appendix 1 presents the findings from a number of large scale studies that have examined the rates of HF or LVSD (Appendix 1). Findings suggest that estimates of HF prevalence may be conservative as a result of:

- Assessment based on signs and symptoms of HF. Over half of individuals diagnosed with LVSD have been found to be asymptomatic.

- Selective samples.
- The omission of HFPEF from the majority of large scale studies as it is difficult to screen for using only clinician rating measures.

The prevalence of HF is found at increased rates in males, with more cases of males (67 %) than females (33 %) seen in UK primary care services until the age of 75yrs (NHS information centre, 2010). The increased rate of HF in males is likely to be the result of higher rates of CAD in the male population, a leading cause of HF (British Heart Foundation, 2010). The prevalence of HF increases steadily with age and overall temporally. The average age at first diagnosis is 76 years, with approximately 1 in 7 people over 85 years and older living with the condition (NICE, 2010).

Management of HF patients

The diagnosis and grading of HF can be complicated and often open to subjectivity. Suspected HF based on signs and symptoms is usually identified in primary care services, unless patients experience an acute cardiac event, and present at emergency departments (secondary care). Clinical management of HF focuses on alleviating physical symptom burden, slowing disease progression, improving patient's health related quality of life (HRQoL), and reducing healthcare utilisation (specifically rates of hospital readmissions) through a combination of life style changes, medications, surgery and the use of devices (National Health Service, 2011). The assessment, diagnosis, and management of HF have advanced dramatically in the last three decades with the development of drug therapies and interventional treatments, such as implantable devices and heart transplants (DH, 2010).

Prognosis

Even though the management of HF patients has improved in recent decades the prognosis for patients with a diagnosis of HF is poorer than that of many cancers including breast, prostate and bladder cancer and similar to those diagnosed with cancer of the colon (Cowie & Kirby, 2003). Globally, cardiovascular diseases such as CAD and hypertension are classified as the leading cause of death for many HF patients (WHO, 2011). Doctors are

actively discouraged from recoding HF as a cause rather than a mode of death; therefore it is difficult to determine accurate mortality rates (Nicholson, 2007).

A large scale prospective study of thousands of Americans found one year survival rates following diagnosis of 64 % for females and 57 % for males; and five year survival rates of 38 % and 25 % for females and males respectively (Ho et al, 1993). However, some of these patients were recruited for the longitudinal study a long time ago and so may not have had the benefits of modern medicine to improve outcomes. The Hillingdon Heart study found lower, albeit still poor one year mortality rates of 38 % in the first 12 months of HF diagnosis (Cowie et al, 1999).

Mortality correlates highly with presence of co-morbid conditions, older age and a history of recurrent hospitalisations, particularly after the first month of diagnosis. Recently the UK National HF Audit for 2009/2010 found that within a year of admission to hospital for HF, 32 % of patients died (NHS Information Centre, 2010). Those hospitalised for acute HF who had access to specialist care, those seen by HF nurses and cardiologists have lower mortality rates than those discharged to primary care (23% versus 32 %) (NHS Information Centre, 2010).

Health-related Quality of life

Health-related quality of life is a multi-dimensional and subjective concept (Franzen, 2007) that refers to an individual's satisfaction or happiness with domains of life that are affected by their 'health', such as physical, psychological, social functioning and well-being (Wilson & Cleary, 1995). Health being defined in line with the WHO definition (1946) "*Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (p2)*

Health-related quality of life is an important outcome in HF research where it is often included in composite endpoints along with HF functional class and the frequency of cardiac events/healthcare use (Peters-Klimm et al, 2010). The use of HRQoL as an outcome in clinical practice can facilitate communication, help patients estimate the impact of a disease on their daily lives, and help clinicians monitor responses to treatment (Higginson & Car, 2001). The concept is of particular use in patients with a physical LTC as the possibilities of a cure are few and patients must manage a range of complex and

debilitating symptoms and treatment regimens on a daily basis (Franzen 2007). Health-related quality of life is also a useful concept for measuring the effectiveness of various therapies and interventions on individual's lives (Shively and Wilson, 2001). Moreover, a substantial number of patients have been found to prioritise improvements in HRQoL over survival (Lewis et al, 2001; Rector et al, 1995), making this patient-centred health outcome a key feature of HF treatment and subsequently, HF research.

Poorer HRQoL in HF patients has been linked to adverse health outcomes such as poorer physical functioning and perceived symptom burden (Laederach–Hofmann et al, 2007), higher rates of unscheduled outpatient appointments, diminished self-care (Buck et al, 2012), and higher rates of hospital readmission and ultimately mortality (O'Loughlin et al, 2010; Clemencia Zuluaga et al, 2010; Iqbal et al, 2010; Rodriguez-Artalejo et al, 2005; Bennett et al, 1997; Konstam et al, 1996).

Health-Related QoL (HRQoL) has been shown to be severely compromised in individuals with HF (Jeunger et al, 2002; Lesman – Leegte et al, 2009; Hobb et al, 2002). Patients with HF report greater impairment in their HRQoL compared to aged and gender matched healthy populations (Heo et al, 2007b; Brostrom et al, 2004; Hobbs et al, 2002; Ekman, Fagerberg & Lundman, 2002; Van Jaarsveld et al, 2001; Steptoe et al, 2000; Cline et al, 1999) and to patients with other medical conditions including those with angina, hypertension, previous MI, arthritis and COPD (Johansson et al, 2006; Jeunger et al, 2008; Jeunger et al, 2002; Steptoe et al, 2000).

As the HRQoL of HF patients is particularly compromised and research has indicated that a person's self-rated HRQoL is a significant predictor of a range of health outcomes including hospital readmissions and mortality, it is important to accurately and comprehensively identify factors that predict variance in HRQoL in order to focus interventions to improve patients well-being. Research investigating factors associated with HRQoL in HF patients will be considered in part four of this chapter.

Co-morbid depression and anxiety in heart failure samples

The presence and impact of depression and anxiety in HF patient populations is a relatively new area of research interest, with published papers appearing increasingly in the past

decade. In NHS guidance related to the management and treatment of patients with LTCs and HF in particular, health professionals are advised to be aware of, and screen for potential depression. Anxiety, although often co-morbid to depression, usually proceeds depression and is as distressing and often more prevalent than depression, has previously been neglected (Konstam, 2005; Merikangas et al, 2003; MacMahon, 2002).

Anxiety and depression can preceed the onset of HF in patients and research does suggest that anxiety and depression can have a significant negative impact on the development of cardiovascular abnormalities (Rozanski et al, 1999). Whether the pathophysiology mechanisms linking depression and anxiety with cardiac events are behavioural, with an increased tendency towards adverse health behaviours such as smoking, poor diet and lack of exercise, or physiological, with direct pathophysiological impact from anxiety and depression placing strain on the heart and associated systems; is still to be determined (Doering & Cross, 2008; de Jong, 2008; Rozanski et al, 1999).

It can also be the case the anxiety and/or depression develop following the diagnosis of HF. Patients with a diagnosis of HF are required to manage a progressive and debilitating condition that places limits on physical activity, requires a multifaceted treatment regimen, and may include periods of hospitalisation, loss of control, isolation, worry, frustration, financial worries, fear of death and a need to reassess ones life situation (Mayou et al, 2000). It is unsurprising that depression and anxiety are reported to be high in this patient population. Interestingly, low levels of anxiety may aid adherence to medication regimens, exercise and lifestyle routines and more prompt consultation with professionals with regards to health (de Jong et al, 2005). However, when anxiety and depression becomes persistent and prolonged they can become harmful and counter productive for patients leading to increased symptom burden and reduced ability to self-care, work and socialise, lower HRQoL, and poorer adherence to treatment plans (Clarke et al, 2000).

Impact of depression and anxiety for heart failure patients

Research indicates that higher levels of depression lead to poorer outcomes for patients with regards to HRQoL, rates of hospital readmission and mortality. Depression in HF samples has been associated with poorer functional capacity (Shen et al, 2011; Clarke et al, 2000), an increase in hospital readmissions, an increase in co-morbid conditions, poorer HRQoL (Hallas et al, 2011; Cully et al, 2010; Faller et al, 2010; Peters-Klimm et al, 2010)

and mortality (Rutledge et al, 2006; Vaccarino et al, 2001; Jiang et al 2001; Murberg et al, 1999; Konstam et al, 1996) in numerous studies and meta-analysis, using a range of assessment methods. However, not all studies have found that depression leads to poorer outcomes for HF patients once the severity of their physical illness was controlled for (Koenig et al, 1998; Krumholz et al, 1998). Research has found that pre-morbid depression is a significant predictor of worse cardiac failure in patients following an MI (Dickens, Mcgowan, Percival et al, et al, 2005). Interestingly however, recent research with patients who have experienced an MI suggests that depression that develops for the first time following a cardiac event is far more deleterious on patient health outcomes than is pre-existing depression (Dickens, McGowan, Percival et al, 2008; de Jong et al, 2006). It is currently unclear whether this is a result of depression manifesting in different ways pre/post cardiac events (Dickens et al, 2008). Research investigating the temporal importance of the onset of depression and its links with poor health outcomes has yet to be conducted using HF samples.

Anxiety in HF patient samples has been associated with poorer functional status (Shen et al, 2011; Juenger et al, 2005; Heo et al, 2007b; Clarke et al, 2000), poorer adherence to medication (de Jong et al, 2011) and higher rates of hospital admissions compared to HF patients without mental health comorbidities (Volz et al, 2011; Song et al, 2009; Tsuchihashi-Makaya, 2009; Konstam et al, 2005; Jiang et al, 2001; Rutledge et al, 2006). A direct link between anxiety and mortality is yet to be established when demographic, clinical and treatment factors are controlled (Juenger et al, 2005; Friedmann et al, 2006; Jiang et al, 2006; Krumholtz et al, 1998). As with depression, the timing of the development of anxiety and the consequent relationship between anxiety and health outcomes has yet to be considered in research using HF patient populations.

The mechanisms by which anxiety and depression impact on individuals physical health, prognosis and well being are an area of active research, although it is suggested that both physiological and behavioural pathways may be invovled (de Jong et al, 2011). From a behavioural perspective the presence of anxiety and/or depression in patients with one or more LTCs may increase the propensity towards engaging in risky behaviours including poor diet, smoking, alcohol consumption and inactivity. Patient's ability to adequately self-care and adhere to treatment regimens may become impaired (de Jong et al, 2011; Konstam et al, 2005). Poorer treatment concordance has been shown to be implicated in

42–64 % of HF hospital readmissions (Horwitz et al, 1990) and has been found to mediate the relationship between anxiety and event-free survival (de Jong et al, 2011).

Interestingly, research conducted with heart failure patient samples has found that a number of physiological mechanisms may explain the links between depression and anxiety and poor physical health outcomes, including mortality (York, Hassan & Sheps, 2009; Jiang et al, 2004; Joynt, Whellen & O'Conner, 2004). Persuasive evidence exists suggesting that autonomic nervous system dysfunction links common mental health conditions and poorer prognosis in cardiovascular disease (York, Hassan & Sheps, 2009). Decreased parasympathetic actitivty and/or increased sympathetic activation increase the risk of acute cardiac events including arrhythmias, ventricular fibrillation and sudden death in cardiovascular samples (York, Hussan & Sheps, 2009; Carney et al, 2002). For example, research has found increased levels of norepinephrine (NE) in HF samples compared with healthy comparisons, combined with a decreased clearance of (NE) due to poor cardiac output, which, when combined with autonomic nervous system abnormalities associated with depression could accelerate the progression of cardiovascular diseases and increase negative outcomes for HF patients (Carney et al, 2002; Cohn et al, 1984).

In addition a link has been found between increased reduced heart rate variability (HRV) and both depression and anxiety in HF patient samples, suggesting this patient group will be more vulnerable to arrhythmias compared with medically compared non-psychiatric samples (Jiang et al, 2007; Joynt, Whellen & O'Conner, 2004; Jiang, Krishnan & O'Conner, 2002). Furthermore, evidence suggests that depression in particular can contribute to the onset and maintainence of inflammation of the vascular endothelium in cardiac patients, through engaging in smoking, triggering dysregulation of the neurohormonal systems responsible for cortisol and catecholamine secretion or by increasing susceptibility to infection; thereby contributing to the progression of atherosclerosis (Carney et al, 2002). Research into the physiological mechanisms that may potentially link common mental health conditions and poorer heath outcomes in patients with LTCs and cardiac populations in particular is in its infancy and further research is required to test these potential mechanisms explicitly (Jiang et al, 2009).

Prevalence rates of depression and anxiety

Establishing accurate rates of depression and anxiety in HF samples is difficult, primarily as studies vary widely with respect to sample composition (hospitalised/community, age, gender, geographical location), the classification of depression and anxiety and the method used to assess them (self-report symptom scales or clinically administered psychiatric interviews). As reported previously have been developed to assess depression and/or anxiety such as the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983), the Back Depression Inventory (Beck, 1961), the Self-Rating Depression scale (Zung, 1965), the Geriatric Depression (Brink & Yesavage, 1982) and Anxiety scales (GAI) (Pachana et al, 2007), the State-Trait Anxiety Inventory (STAI) (Spielberger, 1977), the Generalised Anxiety Disorder -7 (GAD-7) (Spitzer et al, 2006), the PHQ-9 (Kroenke, Spitzer & Williams, 2001) and the Brief Symptom Inventory (BSI) (Derogartis, 1983). The majority of measures have been shown to be reliable and valid tools to assess depression and anxiety (McDowell, 2006). However, not all of the tools are suitable for use in HF samples as they have not been tested in older populations or those with LTCs.

Of particular importance when assessing common mental health conditions in a clinical population is the issue of overlapping and converging signs and symptoms which makes research in this area challenging, as highlighted in parts two and three of this chapter (DoH, 2012). Both HF and depression can produce symptoms of fatigue, loss of energy, poor appetite, sleep disturbances, and concentration deficits in patients (Simon, et al 2006). With regards to anxiety the overlap in somatic symptoms with HF could be considered even greater with both conditions able to generate heart palpitations, shortness of breath, chest pains, sweating, shaking and tiredness (refer to figure 6, pp 42). When interpreting prevalence rates in this area consideration must be given to the tools used to screen for and identify both anxiety and depression. Further discussion of measures used to assess anxiety and depression in HF samples is reported in the methods sections of both phases of research in this thesis.

Finally, in addition to challenges in assessment of common mental health problems within a physical health condition, establishing accurate rates of anxiety and depression is also affected by selection and reporting bias in research. Participants taking part in research in this area in general are likely to be more healthy and less depressed and anxious than those who decline to participate or those who do not meet inclusion criteria for studies; which may lead to an underestimation of rates of depression and anxiety (Konstam et al, 2005).

Depression in Heart Failure samples

Yohannes et al (2010) recently conducted a review of the literature and identified 33 studies that reported the prevalence of depressive symptoms in HF samples in a range of clinical samples using 12 different assessment methods; the majority of which do not omit somatic symptoms. Rates of depression varied from 10 % to 60 % depending on the tools selected. Meta-analysis of the prevalence of clinically significant depression in HF patients found an aggregated prevalence of 21.5 %, which varied by the use of questionnaires versus diagnostic interview (33.6 % and 19.3 % respectively) (Rutledge et al, 2006). These rates far exceed the rates of clinical depression found in the general population (Singleton et al, 2001, cited in NICE 2011c; Moussavi et al, 2007). Rates of depression are found to increase in females compared with males, in younger patients, patients of Caucasian ethnicity (Rutledge et al 2006), hospitalised patients compared with outpatients, patients with increased physical symptoms and those with a higher NYHA functional class (Konstam et al, 2005). A large degree of heterogeneity in measurement and sample composition makes interpretation of prevalence rates difficult. However, the high prevalence rates, irrespective of sample composition, measurement method and setting indicate that depression is common in HF patients.

Anxiety in Heart Failure samples

Anxiety in HF patient populations and its potential impact on health outcomes has received far less research attention than depression (Yohannes et al, 2010)**.** Relatively little work exists investigating co-morbid anxiety in HF samples when compared to other cardiac conditions such as CAD, however, research suggests rates of anxiety are higher in HF patient samples than patients with CAD (Stauber et al, 2012). Research into the prevalence and impact of anxiety on health outcomes in HF patient samples has so far produced inconsistent findings (Carroll & Reiger, 2008).

A recent review identified only eight studies to measure the prevalence of anxiety in HF samples and found rates of anxiety ranging between 11 % and 45 % (Yohannes et al, 2010). The review found that six different measurement tools were used to assess anxiety, only three of which are valid anxiety measurement tools (Structured Clinical Interview for DSM-IV (SCID—I), Hospital Anxiety and Depression Scale, State Trait Anxiety Inventory). The search for papers was not reported in this review and so it is impossible to know if this is the full extent of the literature available measuring anxiety in HF patient

samples. In addition, the review did not report the way in which anxiety had been conceptualised in the identified papers. It is unclear whether the rates of anxiety relate to anxiety symptoms, clinical anxiety or specific anxiety disorders, although some of the tools used to measure anxiety in the identified studies assess only anxious mood and therefore the rates of anxiety identified in this review must be interpreted with caution

When anxiety has been assessed in HF patients using standardised clinical interviews (SCID-II) (First et al, 1997) to report clinical anxiety disorders and specific anxiety disorders, rates are high. Haworth et al (2005) assessed 100 out-patients and found 18.4 % met the criteria for at least one anxiety disorder, with 11 % experiencing GAD and 8 % meeting criteria for panic disorder diagnosis. The sample used in this study was relatively young (mean age 67 years, sd = 11) and stable (majority had not been hospitalised in past seven months). Older patients, those with unstable HF and those whose HF may not be managed effectively were not represented.

When symptoms of anxiety as opposed to clinical disorders have been assessed in HF samples' a wide range of questionnaire and interview measures have been used with corresponding varying results depending on the cut-offs or thresholds used to identify anxiety.

Clinically significant anxiety has been found at rates of 28 % and 45 % in community samples using the State Trait Anxiety Inventory (STAI) (Jiang et al, 2004; Freidmann et al, 2006) and 11 % as measured by the Hamilton Anxiety Interview (Schiffer et al, 2008). When the Hospital Anxiety and Depression Scale (HADS) has been used to assess clinical anxiety in HF populations a range of versions have been used, applying a variety of cut-offs to identify anxiety and have produced disparate findings. For example some studies identify anxiety as suspected clinical anxiety (Juenger et al, 2005), mild, moderate and severe anxiety (Volz et al (2011), or border line and severe anxiety (Shen et al, 2011). Rates of reported anxiety vary between 17 % and 28.8 % depending largely on the cut-off values used to identify anxiety 'caseness' (Shen et al, 2011; Volz et al, 2011; Juenger et al, 2005; Haworth et al, 2007). More recently rates of 56% (using a cut-off of 8>) have been reported (Hallas et al, 2011). The reason for such high levels of anxiety in this sample is unclear, however the average age of participants was relatively young (48.6 yrs, sd 9.45) which may explain the high rates to a certain degree. Yu et al (2004; 2006; 2007) and Lee et al (2005) used the Chinese version of the HADS and found mean scores well below the

recommended cut-off point of 8 or more (Bjelland et al, 2002) to indicate possible clinical anxiety or mild anxiety as defined by the test authors (Snaith and Zigmond, 1994). However data on the percentage of patients considered as being anxious was not presented in the paper making the interpretation of data difficult.

Rates of anxiety in HF patient populations are higher still when measured using the Brief Symptom Inventory (BSI) to identify 'anxious' individuals who score higher than general population normative values. Rates of 40 % (Evangelista et al, 2009), 63 % (de Jong et al, 2004) and 72 % (Heo et al, 2007a) have been identified. However, these rates have been determined using differing normative values used to classify individuals as anxious.

Variations in reported rates of anxiety

Few studies have attempted to identify modifiable factors that predict anxiety whilst controlling for known covariates. Identifying modifiable factors that increase rates of anxiety in HF patients can help to structure and improve interventions to decrease anxiety. Known covariates of increased anxiety have been proposed including female gender (Heo et al, 2007), younger age (Heo et al, 2007b), increased HF physical symptom severity (Heo et al, 2007a), an increase in co-morbid medical conditions (Haworth et al, 2005), higher NYHA functional class (Heo et al, 2007a; Haworth et al, 2005), and non-Hispanic black ethnicity (Evangelista et al, 2009). In addition, the influence of perceived social support on levels of anxiety has also been investigated in HF samples with inconsistent findings (Heo et al, 2012; Gallagher et al, 2011; Tsuchihashi-Makaya, 2009; Westlake et al, 2002; Bennett et al, 1998, 2001).

Rationale

The first phase of research for this study will identify the published prevalence of anxiety in HF patient populations. The research has been conducted for two reasons. The first is that a number of new studies have appeared in the past decade investigating the prevalence and impact of mental health conditions on health outcomes in HF patient populations. The review by Yohannes et al (2010) does not appear to present a comprehensive review of available literature and so it is appropriate and timely to consolidate the knowledge base on the prevalence of anxiety in HF patient populations. Secondly, the heterogeneity in

measurement methods of anxiety makes the interpretation of prevalence data difficult and rates vary widely in the literature. Studies conceptualise anxiety in different ways, often making no reference to the way in which anxiety has been defined in their research. Studies use a multitude of assessment methods and various cut-off points to identify anxiety. Variations in reported prevalence will be investigated.

Accurately identifying the rates of anxiety and variations in reported rates will improve our knowledge of anxiety in HF patient populations.

Phase one research questions are as follows:

1. **What the aggregated prevalence of anxiety disorders and symptoms of anxiety are among people with a diagnosis heart failure?**

2. **Which factors are associated with heterogeneity in reported prevalence rates of anxiety in HF patient populations? Specifically, is the way in which anxiety is conceptualised and measured associated with potential heterogeneity in reported prevalence of anxiety?**

Summary

- Heart Failure is a common condition with devastating consequences for individuals and their families. Individuals with HF usually have a poor prognosis and often have significantly impaired HRQoL.

- The prevalence of depression in this patient group is high. The presence of depression has been linked with a number of adverse health outcomes in HF patient samples and has been widely investigated.

- Government guidelines and clinical recommendations make reference to depression and its identification and treatment in HF patient populations.

- Anxiety, although often co-morbid to depression and as prevalent, if not more so, is under researched in HF patient samples.

- Anxiety is difficult to assess in HF patients as the condition shares many similar somatic features with HF and no standardised measurement method exists with which to identify and quantify anxiety.

- It is hard to establish accurate prevalence rates of anxiety in this patient group due to the heterogeneous nature of the research, with regards to sample and measurement methods.

The following section will explore the concept of HRQoL, in particular in heart failure patient populations. Theoretical models of HRQoL will be presented and evaluated with a view to using a theoretical model to better understand the HRQoL of HF patients and specifically consider the potential role that anxiety, and to lesser extent, depression may play in determining perceived HRQoL. The second phase of research for this study will be presented.

Part Five: The association between anxiety and Health-related Quality of Life

As reported in part four of this chapter, patients with a diagnosis of HF report poor HRQoL which has been found to impact on health outcomes including functional status, adherence to treatment regimens, rates of hospital admissions, and mortality. The term health-related quality of life has to an extent become synonymous with health staus and functional staus, but it is a distinct construct from patient's physical health and functional ability. It is also distinct from general quality of life, in that it refers specifically to changes in the quality of a person's life, or at least important areas of life, as a result of medical interventions or conditions (Shively & Wilson, 2001). Health-related quality of life is a multi-dimensional and subjective concept (Franzen, 2007) that refers to an individual's satisfaction or happiness with domains of life that are affected by their 'health', such as physical, psychological, social functioning and well-being (Wilson & Cleary, 1995). It is important for clinicians and researchers to understand which factors contribute to determining patients reported HRQoL in order to direct research appropriately and develop effective interventions that will ultimately improve patients' well-being (Heo et al, 2005; Shively and Wilson, 2001).

Measuring HRQoL

Health-related quality of life can be measured using a single global item, for example with Cantril's Ladder of Life (Testa & Simonson, 1996), however, as HRQoL is considered a multi-dimensional concept multi-item scales are more appropriate (Fayers & Machin, 2000). HRQoL has been assessed using objective measures of functional status or health for example some studies have used NYHA functional class, physical activity or the HF Functional Status Inventory as a proxy for HRQoL (Freidman, 2003; Jaarsma et al, 1999). However, research has shown that individuals with the same objectively assessed health status vary with regards to their subjectively rated HRQoL (Yohannes et al, 2010). Therefore, it is more likely that HRQoL is dependent on a person's interpretations of their health/symptoms, expectations of their health and their coping abilities (Franzen, 2007). That being the case it is more appropriate to measure the concept using subjectively rated tools.

A large number of tools exist to measure HRQoL. A ten year review found over 47 different generic, health-related, condition specific and utility measures used in HF research , with the majority of studies opting for a condition specific HRQoL to measure the concept (Morgan, McGee & Shelley, 2007). Fewer disease-specific tools have been developed. Only five commonly used tools for assessing HRQoL in HF patient populations were identified in a recent systematic review and meta-analysis (Garin et al, 2009).

Generic measures allow for comparisons of data across diseases and can present a broader picture of threats to HRQoL, but may be unresponsive to disease-specific conditions (Fayers and Machin, 2000). This, in one sense, makes their use in clinical practice limited as it is difficult to identify specific areas of improvement or deterioration in HRQoL as a result of interventions. However, as research indicates that co-morbidity is a growing concern in LTCs and HF patient populations the utility of generic HRQoL increases, particularly when health and social care provisions are focusing on collaborative care for LTCs.

Disease specific instruments are designed to be responsive to specific disease related burden and symptoms (Johansson et al, 2004). As a result they have better content validity, sensitivity and responsiveness than generic instruments (Fayers and Machin, 2000). Compared to generic HRQoL tools, few disease specific HRQoL tools have been developed for use with HF patient populations, however, this does increase the potential for comparison of data across a range of HF samples.

Guyatt (1993) recommends that in order to measure HRQoL comprehensively in LTCs both a generic and disease specific measure of HRQoL should be administered. Using two measures in combination increases the application of findings from research (Bowling, 2005).

Models of HRQoL

Conceptual models of HRQoL have been proposed to examine the relationships among variables thought to contribute to determining HRQoL (Bakas et al, 2012; Franzen et al, 2007; Ferrans et al, 2005; Rector, 2005; Shively and Wilson, 2001; Raeburn & Rootman, 1996; Cowen et al, 1992; Patrick & Bergner, 1990; Ware, 1984; George & Bearson, 1980).

See table 2 for an overview of the models content. The models in table 2 are comprehensive; however they are of limited value when trying to identify how clinical variables such as physical symptoms may be related to HRQoL. This is of importance to clinicians who are trained to focus on clinical variables but also to patients who often want to know how a given treatment will impact on both physical and emotional symptoms and social functioning (Shively and Wilson, 2001).

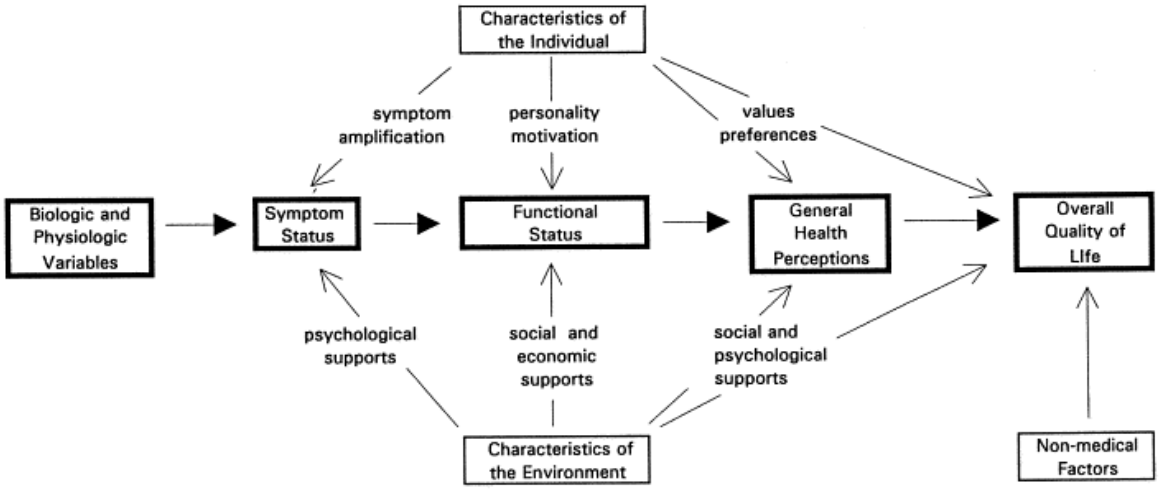
Table 2 Table to summarise available models of HRQoL (Shivley & Wilson, 2001)

Model of HRQoL	Content/Components
George & Bearson, (1980)	Subjective (life satisfaction and self-esteem) and objective (health and functional status, socio-economic status) dimensions of HRQoL for older adults.
Ware (1984)	Disease influences: - personal functioning, - psychological distress/well-being - health perceptions - social/role functioning Characteristics of the individual and the wider social environment are thought to influence the above components.
Patrick & Bergner (1990)	Causal model starting with disease – impairments – functioning – health perceptions – opportunity/capacity for health – HRQoL. Environment and prognosis influence all concepts within the model.
Cowen et al (1992)	Severity of disease, treatment aggressiveness, and socio-economic status influence perceived quality of life for patients with LTCs. This relationship is mediated by symptom distress, functional alterations, and cognitive adaption.
Raeburn & Rootman (1996)	Inter-relationship between quality of life, health (physical being, psychological being, social belonging) and health promotion.

Rector et al (2005) proposed a conceptual model of HRQoL in HF patients whereby physical symptoms (dyspnoea, fatigue, ankle swelling) mediate all the effects of HF on patient's quality of life. The influence of functional limitations and psychological distress are acknowledged, although they are seen to be mediators in the relationship between symptoms of HF and HRQoL. The authors did not find direct evidence to support their model however Rector et al (2006) suggest that other factors independent of physical symptoms determine how HF affects patient's quality of life. Interactive relationships between pathophysiology, symptoms of HF such as dyspnoea, fatigue, ankle swelling, functional limitations and psychological distress have been proposed (Peters-Klimm et al, 2011).

The Wilson and Cleary model of HRQoL (figure 7) is well-established and is the most frequently used model of HRQoL (Bakas et al, 2012). The model proposes that physical and biological alterations result in a patient's perceived symptoms, both physical and emotional, which in turn determines functional status. Functional status, referring to a person's physical, social, emotional, role and cognitive functioning, affects a person's general health perceptions which in turn impacts on HRQoL. Non-medical factors are also proposed to impact on HRQoL although these are not explained. Wilson and Cleary also state that the relationships within the model are affected by characteristics of the individual and environment, although these variables are not described extensively in their work and are left open to interpretation.

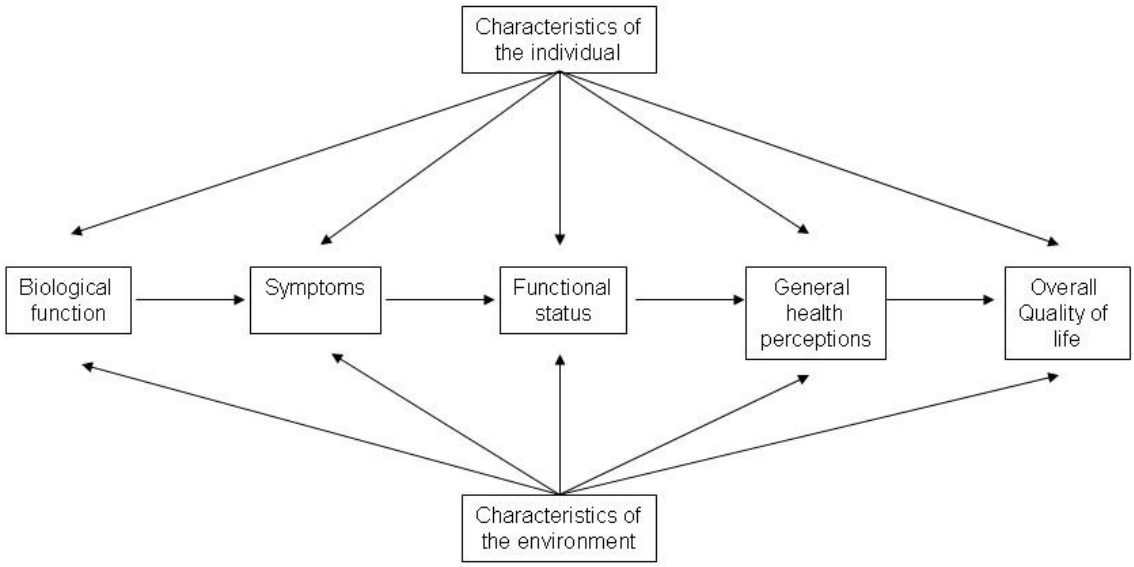
Figure 7: Original Wilson and Cleary Model of HRQoL (1996) (Shively and Wilson, 2001)



Many categories and concepts within the Wilson & Cleary model have not been explicitly explained and are open to interpretation. For example, depression and anxiety could be considered emotional symptoms within perceived symptoms; a characteristic of the individual; or a factor within functional status. Functional status could be conceptualised as disease severity and measured using NYHA functional class or could be measured using another HRQoL tool that assesses a range of functions such as health, social and emotional functioning.

Ferrans and colleagues (Ferrans et al, 2005) have subsequently revised the Wilson and Cleary HRQoL model (figure 8) and described the theoretical grounding of the characteristics of the individual and environment; additional factors believed to be of importance in the construction of patients' perceptions of HRQoL. Characteristics of the individual are categorised as demographic, developmental, biological and psychological; subdivided into cognitive appraisal, affective response, including depression and anxiety and motivation; influencing health outcomes. Characteristics of the environment consist of both social and physical components, social being support of family, friends and healthcare providers and physical aspects relating to characteristics of the environment such as home, neighbourhood or work. Non-medical factors, from the original model have been incorporated into the individual and environmental factors as they have never been fully explained and some suggest may be an attempt to explicate unpredicted influences on HRQoL (Kaprana, 2009). The revised Ferrans model is the second most frequently applied model of HRQoL, as identified in a recent systematic review that sought to identify and critique the most frequency used HRQoL models (Bakas et al, 2012).

Figure 8:A revised version of the Wilson & Cleary (1995) HRQoL theoretical model (Ferrens et al (2005)



The Ferrans model is currently thought to be the most appropriate and comprehensive HRQoL model for use in clinical settings and can be applied to disease-specific populations (Bakas et al, 2012).

In the current thesis the Ferrans model of HRQoL has been drawn on to guide a review of variables thought to be important in determining or influencing HF patient's perceived HRQoL. As previously stated, it is important for policy makers, clinicians and researchers to understand, in as much detail as possible, the factors that influence HF patients HQRoL, in order to inform patient care and align service provisions, care and research with patients and their families needs (Baras et al, 2012).

Research into HRQoL in HF samples

Drawing on the theoretical model proposed by Wilson and Cleary (1996) and revised by Ferrans et al (2005) research evidence pertinent to HRQoL in HF patient samples has been identified and examined. Variables considered potentially relevant to the formation of perceived HRQoL are now discussed.

Functional status

Disease severity when measured using NYHA functional class could be considered a proxy of HF patient's symptom burden as the measurement assess the impact of symptoms on patients functional abilities. NYHA class has been shown to independently predict HRQoL in HF patients in a number of studies (Volz et al, 2011; Shen et al, 2011; Peters-Klimm et al, 2010; Pedrosa et al, 2010; Huang et al, 2010; Iqbal et al, 2010; Faller et al, 2010; Heo et al, 2007; Gott et al, 2006; Lee et al, 2005; Zambroski et al, 2005; Yu, Lee & Woo, 2004; Hobbs et al, 2002; Juenger et al, 2002; Reigel et al, 2002; Cline et al, 1999). Although issues have been associated with the validity and reliability of NYHA functional class as an indicator of patient's level of physical; functioning, as indicated previously (Raphael et al, 2006).

Biologic factors

More objective measures of HF severity including Left Ventricular Ejection Fraction, N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and the etiology of individuals HF have not been found to explain a significant amount of variance in HRQoL scores when measured using a range of tools, both generic and disease-specific (Volz et al, 2011; Shen et al, 2011; Peters-Klimm et al, 2010; Muller –Tasch et al, 2007; Rector et al, 2006; Heo et al, 2005; Juenger et al, 2002). This suggests that patients biological and physiological functioning does not directly influence their perceptions of HRQoL, as the models outlined previously indicate.

Physical Symptoms

In line with the models of HRQoL proposed previously physical symptoms have been found to consistently predict HRQoL in HF patients. This has been the case when HRQoL is measured using disease specific tools the Minnesota Living with Heart Failure Questionnaire (MLHFQ) (Krethong et al, 2008; Heo et al, 2008, 2007a/b, 2005; Rector et al, 2006; Zambroski et al, 2005) and the Kansas City Cardiomyopathy Questionnaire (KCCQ) (Chen et al, 2010); and generic tools (Liu et al, 2011; Johansson et al, 2010). As patients physical health deteriorates, physical symptoms increase, as does the perception of these symptoms as burdensome; reducing patients perceived HRQoL. However, many studies investigating predictors of HRQoL in HF samples have not assessed the relative contribution of physical symptoms to HRQoL (Peters-Klimm et al, 2010; Iqbal et al, 2010; Cully et al, 2010; Azevedo et al, 2008; Gott et al, 2006). Additionally, much of the research in this patient population has assessed only core symptoms of HF, specifically

dyspnoea and fatigue, with the exception of Krethong et al (2008) and Zambroski et al (2005). However, HF patients experience other symptoms, particularly when they experience additional co-morbid physical conditions. Zambroski et al (2005) identified an average of 15 symptoms per participant, with shortness of breath and fatigue most prevalent but difficulty sleeping proving the most burdensome for HF patients. Assessing a wider range of symptoms and assessing those which patients find the most frequent and burdensome may provide more information about the influence of physical symptoms on HRQoL.

Clinical characteristics

When particular physical co-morbidities are investigated, diabetes and respiratory disease have been found to correlate significantly with poorer HRQoL in HF samples (Franzen et al; 2007). However, cardiac co-morbidities have not been found to predict HRQoL (de Jong et al, 2005). When co-morbidity is conceptualised in an additive manner and measured using an index or summation scale some studies have not found that an increase in the number of physical co-morbidities equates to poorer HRQoL (Pressler et al, 2010; Heo et al, 2005; 2007), whereas Peters-Klimm et al (2010), Muller-Tasch et al (2007) and Gott et al (2006) did find that co-morbidity (defined as multi-morbidity disease frequency and/or burden) predicted HRQoL as measured using the KCCQ and SF36. The presence of additional medical co- morbidities may impact further on HF patients' levels of functional status, increase the frequency of medical appointments and add to the complexity of treatment regimens which may in turn impact on perceived HRQoL.

Other clinical characteristiercs pertinent in this patient population including the presence of previous implanted devices and duration of disease are rarely investigated in research exploring variations and predictors of HRQoL in HF patient samples. The influence of such cardiac history has not been shown to significantly predict HRQoL scores in HF patient samples (Shen et al, 2011; Jeunger et al, 2002).

Although the importance of the severity of an individual's physical condition and their physical symptoms are undoubtably prominent factors influencing their perceptions of HRQoL, they alone do not account for all of the variance in reported HRQoL among patients with a range of LTCs including HF once known covariates are controlled. Therefore, researchers have attempted to identify other factors which determine HF patient's perception of their HRQoL. In addition to the clinical variables discussed above,

characteristics of the individual and environment are also thought to determine perceived HRQoL.

Age

Age has been shown to significantly predict HRQoL (Cully et al, 2010; Heo et al, 2005, 2007), with HRQoL improving with older age in HF patient samples (Cully et al, 2010; Huang et al, 2010; Heo et al, 2005, 2007, 2008; Johansson et al, 2006; Zambroski et al, 2005; Steptoe et al, 2000; Cline et al, 1999). As patients age their expectations of their health, social life and physical functioning may decrease causing them less distress (Heo et al, 2005). However not all research has found a linear association between age and HRQoL (Azevedo et al, 2008; Lee et al, 2005; Juenger et al, 2002; Jaarsma et al, 1999).

Gender

With regards to gender females have been shown to experience poorer overall HRQoL compared with males even after age, marital status and clinical variables have been controlled for (Yu, Lee & Wo, 2004; Riegel et al, 2003; Cline et al, 1999; Chin et al, 1998), particularly in relation to physical HRQoL (Friedman, 2003; Cline et al, 1999). However, gender is not always entered in multivariate analysis (Cully et al, 2010) or has not been shown to remain a significant predictor of physical HRQoL in multivariate analysis in all studies (Volz et al, 2011; Heo et al 2005).

Social deprivation

When social deprivation has been conceptualised as occupational and educational level, income or employment in HF samples some research has found an association with HRQoL scores (Cully et al, 010; Gott et al, 2006) when using the KCCQ but not with the MLHFQ (Heo et al, 2005; 2007). Recently research in the UK has found that social deprivation, as measured using a composite score based on census data of employment status, education and skills, housing, average income, and access to services, independently predicted HRQoL as measured using the MLHFQ in a sample of HF with a mean age of 71 yrs (Iqbal et al, 2010).

Perceived social support

The amount of social support a person receives has been identified in the Wilson & Cleary model of HRQoL as a potential predictor of HRQoL in HF patients (Ferrans et al, 2005).

Social support may influence patients' perceptions of their HRQoL, potentially providing a buffer for negative life events. Research in this area is heterogeneous with regards to the manner in which social support is defined and measured. Little evidence exists to support an association between single item variables such as marital status, cohabitation or social network size and HRQoL, particularly when other factors, such as NYHA functional class are controlled for (Cully et al, 2010; Yu, Lee & Woo, 2004; Westlake, 2002). However, the lack of an informal care giver (Iqbal et al, 2010) or a lack of functional and emotional social support (Bennett et al, 1998, 2001) has been shown to be independently related to poorer HRQoL, although this is not supported by all research (Shen et al, 2011; Volz et al, 2011; Krethong et al, 2008). A review of the literature investigating HRQoL in HF samples concluded that more research is needed to explore the relationship between support and HRQoL in this patient population (Johansson et al, 2006).

Mental health/Emotional symptoms

Research has shown that the presence of mental health conditions in general impact on HRQoL to a high degree (Yohannes et al, 2010; Moussavi et al, 2007; de Jong et al, 2006); however until recently the inclusion of emotional symptoms such as depression and particularly anxiety in research investigating HRQoL in HF samples has been scarce (Heo, 2007; 2008). Depression has been found to be a predominant predictor of HRQoL in samples of HF patients (Dekker et al, 2011; Peters-Klimm et al, 2011; Hallas et al, 2011; Cully et al, 2010; Faller et al, 2010; Muller-Tasch et al, 2007), to a significantly higher degree than co- morbid anxiety (Cully et al, 2010). However, none of these studies have assessed physical symptom severity in HRQoL models, which may account for more variance in HRQoL scores or alter the influence of depression in patient's perceptions of their HRQoL.

Some studies have found that HF patients perceptions of their HRQoL, measured using the MLHFQ and Chronic Heart Failure Questionnaire, is influenced in part by anxiety measured using the HADS (Volz et al, 2011; Shen et al, 2011; Lee et al, 2005), and BSI (Heo et al, 2007, 2008). Other researchers have not identified an association between anxiety and HRQoL in multivariate analysis using the KCCQ to measure HRQoL and the Geriatric Anxiety Inventory to measure anxiety (Cully et al, 2010). Yet again none of these studies have examined the influence of physical symptom severity in a comprehensive manner within their HRQoL models.

Other factors proposed to influence HRQoL to a lesser extent include behavioural factors (smoking, alcohol consumption), health perceptions, personality traits (type D personality), cognitions (illness perceptions) and psychological constructs including perceived control and self-efficacy.

Rationale

Still, some variance in HRQoL scores remains unexplained and a comprehensive model of predictors has yet to be identified. As with research conducted into the levels of anxiety in HF patient samples the conceptualisation of variables, the measurement of concepts and sample composition varies so widely in HRQoL research in HF samples. It is difficult to determine why some factors are associated with perceived HRQoL in studies but not in other in any sophisticated or meaningful manner. Working from a conceptual framework for HRQoL, may help overcome some difficulties in interpreting research that arises from significant heterogeneity in variable conceptualisation and measurement.

What is clear from the research is that at present variations in patients self-reported HRQoL are not fully accounted for by physical or medical factors alone, such as physical symptoms, functional status or physical disease severity, across many LTCs including HF (Yohannes et al, 2010; Pelle et al, 2008; Heo et al, 2007a; de Jong et al, 2005, Heo et al, 2005). People with objectively similar health status can subjectively rate their HRQoL differently. Although the Wilson and Cleary and revised Ferrans models of HRQoL position mental health/emotional symptoms on the periphery of the model, within the category of characteristics of the individual, thought to influence patients perceptions of their physical symptoms and functional status, it may be that conditions such as depression and anxiety play a much more significant role in the development of HF patients self-perceived and reported HRQoL.

Depression and anxiety may account for some variation in HRQoL scores and have the advantage in health care of being dynamic, modifiable factors that are responsive to intervention (Ferrans et al, 2007; de Jong et al, 2005). In order to identify the proportion of variance anxiety symptoms account for in HRQoL they must be investigated in a representative sample of HF patients, using appropriate tools validated for use in this population, whilst controlling for known demographic, environmental and medical covariates including physical symptoms.

Phase two research questions are as follows:

1. **What is the prevalence and variance of anxiety symptoms in a sample of individuals with a diagnosis of HF attending specialist out-patient HF clinics?**

2. **What amount of variance in HF patients' self reported HRQoL is accounted for by anxiety symptoms after controlling for physical symptoms, perceived social support, depression and known demographic, environmental and medical covariates?**

Summary

- Health related quality of life is an important outcome in HF research and clinical practice used to demonstrate the effectiveness of treatments and to monitor patient's health and well-being.

- There are a number of factors thought to determine individuals' perceptions of their HRQoL, although a comprehensive understanding of which factors are important and which are not is lacking.

- The evidence to suggest that depression and particularly anxiety may influence HRQoL is sparse and inconsistent.

- A conceptual model of HRQoL may help steer research in this area.

- Research in this area has suffered due to discrepancies in conceptualisation of variables and measurement methods used.

Summary of Chapter One

Part One

- Long term conditions are highly prevalent and represent a significant challenge for health and social care in the UK and worldwide.
- Individuals with LTCs experience, amongst other things an impaired HRQoL as a result of their physical conditions.
- Individuals with one or more LTCs will increasingly be expected to self-manage their condition in order to monitor symptoms and prevent costly exacerbations and emergency hospital readmissions.

Part Two

- Mental health conditions, particularly depression and anxiety are also common in the UK and like all LTCs are costly, both for the individual and society.
- Common mental health conditions have been conceptualised using a medical model that postulated signs and symptoms of health conditions can be used to identify the severity and presence in patients.
- Difficulties arise when identifying depression and anxiety. Although anxiety and depression are currently thought to be discrete conditions, they share some common signs and symptoms and can be managed in similar ways.

Part Three

- Mental health conditions are increasingly co-morbid to physical LTCs; increasing the costs to society dramatically.
- Identifying the presence of a common mental health condition, such as depression and/or anxiety, within the context of a physical condition can be challenging, as many symptoms overlap across conditions.
- The impact of a mental health condition on the health and well-being of a person with a physical LTC is large. A persons physical functioning, symptom burden, rate of readmission to hospital, ability to self care and overall HRQoL are affected as a result.

- The UK government is making the mental health of persons with a physical LTC a priority.

Part Four

- Heart failure is a common LTC with poor prognosis.
- Individuals with HF experience a range of distressing physical symptoms and impaired HRQoL compared with the general population.
- Depression and anxiety are common in HF patient samples. However the lack of standardised assessment of the conditions, the complexity of assessment when coupled with a cardiac condition and the heterogeneity of study samples means that it is difficult to accurately identify the scope and nature, particularly of anxiety in this patient population.

Part Five

- The HRQoL of HF patient's is an important outcome in research and clinical practice.
- HF patients' HRQoL can be affected by a range of factors although improving a patient's physical health does not always increase their perceived HRQoL.
- Research investigating the role that anxiety may play in determining HRQoL in HF patient populations is limited and results are so far inconsistent.
- A conceptual model of HRQoL in this area may help to steer research and increase consistency in conceptualisation and measurement of variables.

It is necessary to accurately identify the extent of anxiety in HF patient samples and variations in rates of anxiety in this patient group. Similarly it is necessary to understand how a person's mental health condition, particularly anxiety, may impact HF patients' perceived HRQoL, in relation to physical factors, as this is increasingly a key health outcome in HF treatment.

CHAPTER TWO**: METHODOLOGY**

Chapter two presents the methodology undertaken in the PhD. The chapter is separated in to three parts.

Part one of chapter two will present the research methodology for the PhD, examining the research objectives, philosophical position of the research and research design.

Part two discusses the systematic review method, selected to address phase one research questions:

1. What is the aggregated prevalence of anxiety disorders and symptoms of anxiety among people with a diagnosis of heart failure?

2. What factors are associated with potential heterogeneity in reported prevalence and severity of anxiety?

The process of systematic reviewing is discussed along with unique challenges presented when conducting a review of prevalence studies.

Part three presents the survey method used to address phase two research questions:

1. What is the prevalence and variance of anxiety symptoms in a sample of individuals with a diagnosis of HF attending specialist out-patient HF clinics?

2. What amount of variance do anxiety symptoms account for in HF patients self reported HRQoL whilst controlling for demographic, environmental and clinical covariates?

Key components of the survey method are considered including variable measurement and data collection. Ethical considerations in health services researcher are addressed by considering the role of patients and public involvement in research conducted with participants.

Part One**: Research Strategy**

Construction of research strategy

The choice of methods used in this thesis was guided predominantly by the research aims but also by methodologies and theoretical perspectives, which are in turn informed by a synthesis of ontological assumptions (about the nature of reality) and epistemological assumptions (relating to how we can understand that reality). A researcher's previous research training and experience with particular methods will also in part influence the approach taken to conducting the research. It is necessary to understand why certain methods are suitable for addressing particular questions, and an understanding of theoretical perspectives and epistemologies associated with certain methods allows the research to be situated contextually and logically (Crotty, 2003).

Research objectives

The objective of this PhD was to explore anxiety in a sample of HF patients, considering the variance in levels of anxiety and the influence anxiety has on patients perceived HRQoL, whilst controlling for a number of demographic, environmental, and medical factors.

Philosophical position

Epistemology is concerned with the nature of knowledge, how the world can be studied and how knowledge can be acquired. The epistemological stance in this PhD is one of post-positivism (Popper, 1959; Kuhn, 1962), adopting the theoretical standpoint of critical or subtle realism (Hammersley, 1992), which postulates that social reality is external and objective to the individual and consists of observable events that exist independently of an individual's beliefs or understanding relating to them but, that this reality is only accessible to us via respondents' interpretations (which may be further interpreted by the researcher) (Trochim, 2006). The existence of multiple realities or different perspectives does not negate the existence of an external reality that can be 'captured' using scientific methods.

Before considering post-positivism it is necessary to explain the positivist approach that preceded an important shift away from the central tenets of positivist enquiry. Prior to the middle part of the 20th century much of social science was studied from an empiricist perspective (positivism). The positivist philosophy attempts to identify patterns and associations in human behaviour through observation and experimentation which can be generalised to a wider population (Durkeim (1974). Basic principles of the scientific theory or knowledge acquisition are determinism, empiricism, parsimony and generality (Cohen et al., 2000). Determinism states that events are caused by other circumstances, therefore understanding causal links and patterns is necessary to predict and control the world. Empiricism is the collection of verifiable evidence to support theories or hypotheses and parsimony refers to the explanation of events in the most economic way. Finally, generality is the process of extrapolating from one set of observations to a wider context (Dash, 2005). A main criticism of positivist philosophy is a rejection of the idea that human behaviour and the social world can be studied objectively, with no regard for the subjectivity of human experience (Trochim, 2006). Additionally the positivist paradigm completely dismisses the subjective state of the individual, labelling human behaviour as passive and determined by the external environment. Positivism does not allow for the interpretation of social reality by individuals (Dash, 2005).

As a reaction to this hard-line position that mirrors that of the natural sciences post-positivism emerged, the most common form of which is critical realism as identified previously. As noted within this paradigm meaningful reality exists external to the individual consciousness and as a result can be quantified, measured and tested applying the methods of the natural sciences. A difference from positivism is that a post-positivist critical realists recognise the concept of constructivism, which postulates that as humans we construct our views of the world based on our experiences within it; it is only through the study of an individual's interpretation can we learn more about external reality. Therefore multiple views of reality can exist, constructed by the individual but ultimately regularities exist and it is these patterns, rather than exceptions that are the focus of scientific enquiry (Shi, 2008).

Another crucial difference from positivism is that observations of reality are subjective, open to error and uncertainty (Trochim, 2006). The search for laws and patterns through observation remains the same, however, the belief that an absolute understanding of social phenomena and reality is possible does not. The aim is to strive for objectivity and

neutrality. However, it is acknowledged that subjectivity and bias may exist, both in an individual's interpretations of reality and in a researchers understanding of respondents interpretations. It is important to be reflexive and consider ways in which bias may impact upon the research findings, being transparent in relation to personal and technical aspects of the research process. The researcher cannot be totally removed from a piece of research, an adequate level of transparency in the research process allows for identification of subjectivism and its acknowledgement, in part, allows readers to consider the impact on research findings (Crotty, 2007). Triangulation is also proposed; data triangulation, the use of multiple measures and investigator triangulation, the use of multiple observations, can be combined in order to reduce the degree of error within research. The knowledge generated from these different enquiries should not be synthesised to produce a definitive answer to questions, but can serve to add breath or depth to an analysis through the use of multiple perspectives as opposed to reliance on one approach alone (Fielding & Fielding, 1986).

Research questions

Blaikie (2006) states there are three main types of research question, What, Why and How questions, each corresponding to three aims in research. What (to describe and provide a detailed account or precise measurement of characteristics of and patterns of phenomena), Why (explain/understand phenomena, establishing causes or reasons behind the existence of a social phenomena, can be based on interpretations from social actors), How (to change, with practical outcomes and interventions). The research in this study will focus on what and why questions, seeking to describe and understand the nature of anxiety in this patient group and its potential relationship with a range of outcomes.

PhD Design

The research was conducted in two distinct, sequential phases using multi-method techniques to achieve two discrete set of questions (figure 9).

Figure 9: Phases of research and research questions.

Phase One

Questions:

1. What is the aggregated prevalence of anxiety disorders and anxiety symptoms among people with a diagnosis of heart failure?

2. What factors are associated with heterogeneity in reported prevalence of anxiety? Specifically, is the way in which anxiety is conceptualised and measured associated with potential heterogeneity in reported prevalence of anxiety?

Epistemology: Post - positivism

Theoretical perspective: Critical Realism

Methodology: Systematic review of secondary data

Methods: Systematic literature search, secondary analysis of research, narrative synthesis, meta-analysis

Phase Two

Questions:

1. What is the prevalence and variance of anxiety symptoms in a sample of individuals with a diagnosis of HF attending specialist out-patient HF clinics?

2. What amount of variance do anxiety symptoms account for in HF patients self reported HRQoL whilst controlling for demographic, environmental and clinical covariates?

Epistemology: Post-positivism

Theoretical perspective: Critical realism

Methodology: Survey Research

Methods: Sampling, measurement, Questionnaires, statistical analysis

Part Two: **Systematic review methodology**

The aims of the first phase of research are to identify the prevalence of anxiety in HF samples and explain the large amount of variance in prevalence. A systematic review has been conducted to meet this aim. Part two of this chapter discusses the systematic review method and the particular challenges that conducting a review of prevalence presents.

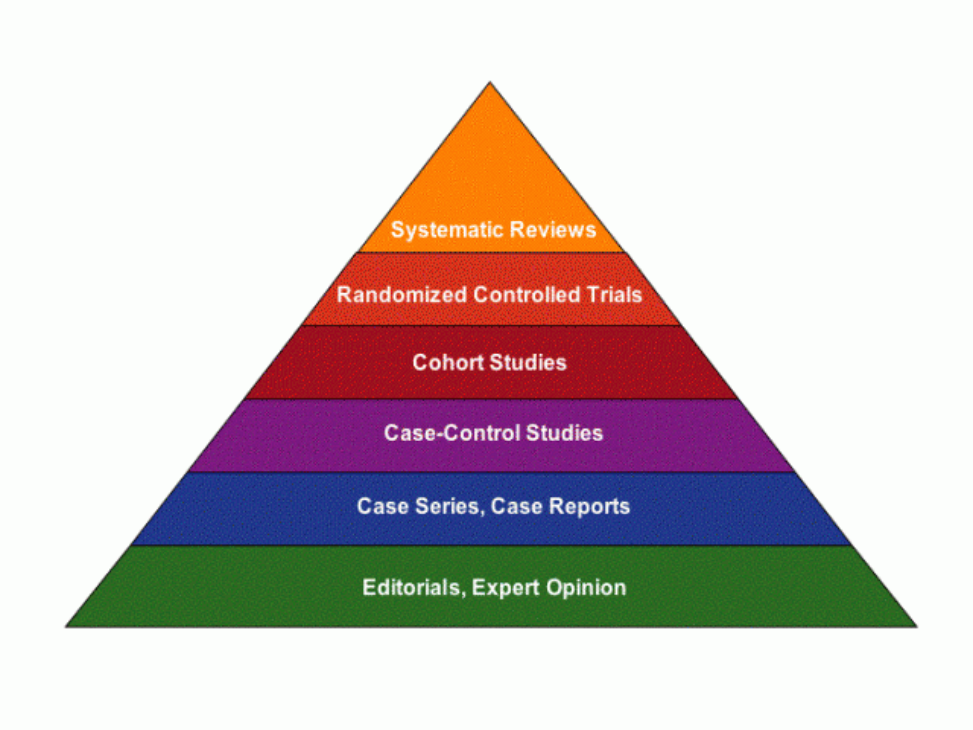
The systematic review method

A systematic review is a scientific research method that attempts to minimise bias and errors to "*identify, evaluate and summarise the findings of all relevant individual studies, thereby making the available evidence more accessible to decision makers. When appropriate, combining the results of several studies gives a more reliable and precise estimate of an intervention's effectiveness than one study alone"* (Centre for Reviews and Dissemination CRD, 2009, pp preface V). Formal approaches and systematic methods for appraising and collating evidence have been developed in recent decades in response to calls from the 'evidence movement' to organise knowledge into a useable and reliable format. In the healthcare arena it was Archie Cochrane's seminal text 'Effectiveness and efficiency' (Cochrane, 1972) which urged health practitioners to practice evidence based medicine (EBM). Evidence based Medicine (EBM) is the use of current best evidence, integrating individual clinical expertise with the best available external clinical evidence from systematic research to make informed decisions about the healthcare of individual patients (Sackett et al., 1996). With respect to external clinical evidence the quality can range from systematic reviews through to case-controlled studies down to single case studies.

Systematic reviews emerged in their first formal guise in 1975 under the term 'meta analysis' (Oakley et al., 2005b). In the late 1970s and early 1980s a group of health service researchers in Oxford began a programme of systematic review research on the effectiveness of health care interventions. The Cochrane Collaboration (http://www.cochrane.org/) was formed in 1992 and is now an international network of researchers, academics, practitioners and users who aim to manage healthcare knowledge and ensure it is quality assured, accessible, and cumulative (Oakley et al., 2005). Systematic reviews are considered the highest level of evidence in EBM (see figure 10),

depicted at the top of the pyramid of hierarchy of evidence. In order to determine whether a particular intervention is effective in a given population high quality evidence is required, free from bias and error. The aim of a systematic review is to combine the results of multiple primary studies to provide a more reliable and precise estimate of effect size for an intervention than a single study alone (CRD, 2009). Often studies are heterogeneous (diverse), in terms of methodology, sample and outcomes. It is therefore necessary to identify differences in studies before combining data to produce an overall effect size. In addition it is not possible to eliminate existing biases in primary studies that may impact on the outcome of an intervention. However it is possible to assess the level of this bias so the impact can be considered in any review conclusion. It is the rigour in which systematic reviews are conducted and the attempts made to reduce bias that distinguishes systematic reviews from traditional literature reviews. All reviews are retrospective and observational; therefore they are open to systematic and random error (Cook et al., 1997). The quality of a review and its contribution to our understanding of a particular issue is determined by the extent to which the research method used can eliminate or minimise error and bias.

Figure 10: Levels of evidence pyramid. (Evidence-Based Practice in the Health Sciences (December 6th 2010) http://ebp.lib.uic.edu/nursing/?q=node/12)



Systematic reviews involve a number of steps to be taken to reduce bias in the selection and inclusion of individual studies, the extraction of data, quality assessment and synthesis of findings and finally reporting of the review that a literature review does not include (Higgins, 2011).

The key aspects of systematic reviews will now be considered. As the review in this study was not conducted to establish the effectiveness of an intervention, the unique challenges this presents will be discussed, particularly issues relating to the use of observational studies in systematic reviews and the quality assessment of such studies.

Systematic review Questions

Systematic reviews address a specific, often narrow, research question (Cook et al., 1997). Traditionally systematic reviews were conducted to establish the effectiveness of an intervention in order to guide EBM. However, many other question types can be addressed using systematic reviews to guide health care policy and practice including assessing the frequency or rate of a condition; identifying aetiology or risk factors; identifying underlying mechanisms of illness and assessing the economic value of an intervention

(Kitchenham, 2011). The question is typically structured according to a specific population and setting (for example, elderly HF outpatients), the intervention of interest in the case of effectiveness reviews (for example, home-based exercise programme), comparator (usual care) and the outcomes of interest (such as left ventricular ejection fraction); this structure is referred to as a PICO (Sayers, 2007). In addition the study designs relevant to addressing the study question may also be specified. The question structure will guide both the inclusion criteria for the review and the search strategy.

Traditionally, RCT designs are included in systematic reviews, and this is still the case for the majority of Cochrane reviews. However with certain review questions, particularly those addressing the prevalence of conditions or where research in an area is lacking, it may be appropriate to include other research designs, including observational research and qualitative research evidence.

Once the questions for the review have been established a crucial stage is to develop a detailed protocol that will set out *a priori* the search strategies to identify studies; inclusion/exclusion criteria for studies; methods of quality assessment, data extraction strategy and a plan for data synthesis. In detailing the steps of the review process a level of transparency can be achieved. This minimises the opportunity for bias to arise. The protocol is also useful to demonstrate the reliability of a review, as the protocol should document the review process in as much detail as would be required to replicate the study and obtain the same results (robust findings).

Eliminating bias

All available evidence to address a review question is systematically searched for, retrieved, screened and data are extracted. In searching for relevant studies for a systematic review and during the screening process a number of biases must be considered and highlighted if not overcome to ensure all available evidence is identified. When screening studies for inclusion in a systematic review stringent inclusion criterion are identified *a priori* and applied during the screening process by several reviewers working independently to minimise the probability of bias (Greenhalgh, 1997). Extraction conducted by more than one individual is also recommended to ensure errors do not occur in the extraction of data from primary studies. Table 3 highlights some potential sources of bias that may occur during the searching/screening stage of a systematic review.

Table 3 Potential types of bias in the searching and screening process

Bias	Description
Publication bias *(also known as positive results bias)*	Refers to the tendency for investigators, reviewers and editors to favour manuscripts based on the direction or strength of study findings (Dickersin et al.,1994). Trials with less positive findings may also take longer to publish (time-lag bias). Using a systematic review method attempts are made to identify research in progress as well as published studies. Statistical analysis of this bias during data synthesis can estimate the influence this bias has had on the outcome of the review.
Language bias	Refers to the tendency for only English language journals to be searched for relevant studies. Studies may be missed in the searching process, providing less data to synthesis in the review. Additionally significant positive findings from studies conducted in non-English language speaking countries are more likely to be published in English language journals (Egger et al, 1997; CRD 2009) . The review may generate biased results if more positive results are potentially included (CRD, 2009).
Retrieval bias	Refers to database, coding and citation biases, with the indexing and inclusion of publication varying across databases (Zielinski C, 1995). In searching for relevant studies for a systematic review attempts to include all relevant databases should be made and search strategies adjusted in accordance with individual database indexing.
Reviewer bias	A recent concern for the Cochrane Bias Methods Group and refers to subjective bias introduced at the secondary level (Ernst, 1994) Often literature reviews are conducted by experts in the field who may have a hypothesis or position which they would like to see the literature support and may be selective with the studies they choose to include in the review. All attempts should be made to search for and select studies in a transparent and systematic manner, using inter-rater quality assessments.

Quality assessment

The quality of individual studies included in a systematic review should be assessed. It is crucial to critically appraise methodological quality so that data from poor quality studies is not given the same weight as that collected from high quality, robust studies with good internal validity. Internal validity refers to the accurate measurement of variables and external validity refers to the extent to which findings can be said to be generalisable to members of the defined population under investigation. It is not possible to eliminate bias in primary studies, but it is possible to assess this bias so the impact can be removed in data synthesis or addressed in review conclusions. Recently, Moja et al (2005) found that quality assessment was conducted in 93.9% of Cochrane reviews of effectiveness, but in only 60.3% of non-Cochrane systematic reviews published in peer reviewed journals. Furthermore only 51.4% of both Cochrane and peer review published systematic reviews linked quality assessment to the interpretation of results; a finding supported by Moher et al (1999).

Study quality can be considered in relation to external and internal validity, clinical relevance or quality of reporting. Study quality can be assessed using a quality scale, combining information on several features into a single numerical value, or using a component approach to examine dimensions of quality without circulating a score (Juni et al., 2001). The use of composite quality scales is common in medical journals (Moher et al., 1995, 1999). However, composite scales are criticised in systematic review discussion literature as the dimensions assessed can vary widely and the use of a wide variety of scales produces discordant and at times misleading results across reviews. The content of some quality scales often has little evidence to support their association with internal validity and cannot be applied across research designs. The application of quality scores as a weight in the statistical analysis of study data is also not recommended (Juni et al., 2001). The choice of scale will influence the outcome of the review and may lead to a misinterpretation of results. The use of a quality score does little to eliminate bias in the review, as poor quality studies are still included in the synthesis of data. As quality composite scores cannot aide the identification of key quality components involved in associations between quality and effect size, their use in well conducted systematic review is not recommended (Whiting et al., 2005).

The use of a component approach has been found to be preferable in Cochrane reviews (Moher et al., 1995). The importance of individual quality domains can be considered in

the context of a particular review and the direction of potential bias associated with components can be assessed. Categorical data from quality components can be considered in sensitivity analysis to investigate whether key components are associated with pooled estimates or effect sizes (Juni et al., 2001).

Synthesis of findings

Finally, systematic review summarise the results of individual studies objectively. The synthesis of data can take the form of a quantitative synthesis (meta-analysis) when appropriate. Data can be transformed into a common measurement scale and combined using advanced statistical techniques. However, statistical synthesis can occur in reviews without taking into account study quality or heterogeneity in design, sample composition and outcome measurement; subsequently producing biased and at times meaningless summary data (Petticrew, 2001). If studies are significantly heterogeneous it can be misleading to force results into a single summary estimate. In such instances or when the research question does not lend itself to quantitative analysis, for example when looking to synthesise views or experiences of a particular topic, or where quantitative data is not available, a narrative synthesis may be more appropriate (Davies & Crombie, 2009).

Conversely, it has been argued that avoiding quantitative synthesis of outcome data due to statistical, clinical and methodological heterogeneity is too weak an argument alone to avoid its use in systematic reviews (Ioannidis et al., 2008). Many statistical models can accommodate high levels of statistical heterogeneity and on occasions it could be considered appropriate to examine how variables moderate the direction and strength of outcomes using meta-regression techniques, rather than avoid quantitative synthesis based on these factors.

Guidance on conducting and reporting systematic reviews

Guidelines for conducting and reporting reviews of clinical studies of effectiveness exist to aid researchers conducting systematic reviews and encourage higher quality reporting. These include the Cochrane Collaboration, an international initiative that prepares, maintains, and disseminates the results of systematic reviews of health care interventions. The Cochrane Collaboration also produces literature to aid researchers conducting reviews (Higgins, 2011). Additionally the NHS Centre for Reviews and Dissemination produces a regularly updated report to provide practical advice on aspects of undertaking a systematic

review (CRD, 2009). Researchers conducting reviews of effectiveness can refer to a number of statements and checklists to assist them in standardising their review methodology. These include the Quality of Reporting of Meta-analyses (QUORM) (Clarke, 2000), recently replaced by Preferred Reporting Items for systematic reviews and Meta-analyses (PRISMA) (Moher et al., 2009).

Developments in the method

As the techniques of systematic review have developed, its application has increased beyond that of exploring the effectiveness of interventions in medical research for which it was initially developed. The method has increased in scope to summarise not only analytical research of the efficacy of an intervention but also descriptive information relating to disease incidence, prevalence and risk factors (Dickersin et al.,2002; Petticrew, 2001). The focus of the current systematic review is not to assess the effectiveness of an intervention, rather to measure the prevalence of a condition in a specified population.

Outcomes, both health and non-health related, are defined and measured quantitatively and qualitatively in primary research. As a result they can be included in systematic reviews. Systematic reviews are increasingly being used to strengthen the evidence base in epidemiology (Dickersin et al, 2002). As research increases relating to the prevalence of conditions, risk factors and morbidities, efforts are required to assess the quality of this work and synthesise findings in an unbiased manner for use in service planning. Systematic reviews are an efficient technique for hypothesis testing, summarising results of existing studies, and for assessing consistency among previous studies; these procedures are not unique to research testing the efficacy of an intervention, or necessarily to that of healthcare research.

With these developments that have widened the focus and application of systematic reviews, it has been necessary to expand the search for relevant evidence to data generated from research designs other than those of randomised controlled trials (RCTs) (Thomas et al., 2004). Well conducted RCTs are generally considered to offer higher quality evidence than uncontrolled trials, observation studies and qualitative research, as many sources of bias that may affect estimates of treatment outcomes are minimised. However, in many areas of research RCTs do not lend themselves to the area of investigation, this may be due to ethical reasons or it may be that study variables are not appropriate for manipulation. In

new areas of research RCTs may not yet be being conducted and we cannot wait for the trials to be conducted (Sackett et al., 1996). With respect to epidemiological research observational and descriptive designs are far more common and so evidence from 'lower level' designed studies must be considered (Kelly, 2010).

Inclusion of observational studies

The focus of the current systematic review is to establish the prevalence of, and explore variations in anxiety in a heart failure population and consider variations in prevalence based on measurement, population and methodology. Psychological variables are increasingly being used as outcomes in RCTs, however, the majority of research conducted into HF and associated psychological conditions comes in the form of observational studies. The use of observational studies in systematic reviews and meta-analyses is fairly common and has increased noticeably in the last two decades (Dickersin, 2002, Egger, 2001). The inclusion of observational studies in a systematic review, although possible from a methodology standpoint does present additional challenges for the reviewer.

Identifying observational research

Irrespective of the aim of a review or the designs included, the steps involved in conducting a systematic review and its reporting are the same. However, additional consideration must be given to the identification of studies, assessing the quality of evidence included and to the synthesis of data when including studies of differing design (Simunovic, 2009). Far less guidance exists to aid researchers in conducting systematic reviews in epidemiology using observational studies (Dickersin, 2002; Stroup et al., 2000; Wong, 2008), making reviews in this area challenging and open to variation with respect to quality (Wong, 2008). Consensus statements for the reporting of meta-analyses of observational studies do exist such as the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) (Stroup et al., 2000). In essence however, there exists a disparity in available literature for researchers conducting reviews of effectiveness and those measuring epidemiological trends, particularly with respect to quality appraisal (Wong, 2008).

Assessing quality in observational research

Assessing the quality of observational research that does not necessarily test the effectiveness of an intervention or use a controlled design can be problematic (Juni et al.,

2001). Observational studies are less well controlled than RCTs and as a result are subject to more sources of bias. This bias must be assessed and acknowledged in a systematic review so the results can be considered in light of this. The selection of participants, measurement of outcome variables and appropriate use of analytical methods to control for confounding are key components that must be considered to assess the internal validity observational research (Simunovic, 2009). There is no standard quality assessment tool for use with observational studies or for use in reviews that seek to document the presence or prevalence of a condition as opposed to measure the effects of an intervention (Deeks et al, 2003). It is therefore advised that key components be chosen relating to an individual review's context, choice of design inclusion and outcome (Simunovic, 2009). Quality assessment of observational studies should be used to alert reviewers and readers to the extent of bias and the resulting uncertainty in pooled data.

Summary

- Well conducted systematic review will present all available research evidence to date that addresses a specific and defined research question.

- The reader will be able to clearly follow the process of searching, selection and extraction of data from all available evidence.

- The results of the review will present all relevant information from research that addresses aims of the review and the synthesis of findings should be transparent.

- The quality of included studies should be considered and reflected on when interpreting the findings from the review.

- All potential sources of bias should be identified and discussed, in order to appraise the robustness of any conclusions made.

- A systematic review is the most appropriate research method to address the aims of phase one of this research: identify the aggregated prevalence of anxiety disorders and symptoms among people with heart failure and identify factors associated with potential heterogeneity in reported prevalence of anxiety?

The working methods for the systematic review conducted in phase one of this study can be found in chapter four along with the systematic review results and discussion

Part Three**: Survey methodology**

The second phase of research was conducted with the aims of measuring the level of anxiety in a sample of individuals with a diagnosis of HF attending specialist out-patient HF clinics, identifying variables that predict variance in reported rates of anxiety and examining the amount of variance that anxiety accounts for in HF patients self reported HRQoL, whilst controlling for demographic, environmental and medical factors. A survey method is the most appropriate method to meet these aims. The decision to a adopt survey method in phase two of this study was determined mainly by the research aims and ultimately by the epistemological stance taken in the research. Part three of this chapter considers various aspects of survey design including ethical considerations and patient and public involvement in research design.

Survey methods

A survey is a non-experimental data collection method used to record information, specifically prevalence, distribution and interrelationships of variables from a defined population from which the results may be extrapolated to make inferences about a larger population (Polit & Beck, 2010). Survey research is an extremely popular and widely applied investigational method that involves the sampling, collection and analysis of self-report data from individuals or groups (Czaja R & Blair, 1996). Surveys can be conducted in many disciplines and areas of research exploring persons' or groups' actions, knowledge, intentions, opinions, attitudes and values. As surveys rely on respondents to report data to a series of questions posed by the investigator, either in self-administered questionnaire or interview format, the population should have access to the information you require them to provide and have the cognitive abilities to reflect on and report this information (Polit & Beck, 2010).

Both questionnaires and interviews can be administered using a survey method to obtain data on one occasion, generating a snap shot (cross-sectional research), or over time to measure changes in phenomena (longitudinal). Survey data can be collected in a number of ways: face-to-face, through the post, over the telephone or internet, or indeed any interactive communication device that has the facility to present information and record responses (Trochim, 2006).

Phase two design

In phase two of this study a cross-sectional, quantitative, self-administered questionnaire survey has been conducted, with face-to-face recruitment supplement with reminder telephone calls. A cross-sectional design was selected over a longitudinal approach as one aim of the research was to measure the prevalence of anxiety in a HF population and a cross-sectional design is the optimal design for this. In addition the relationships between anxiety, HRQoL and associated variables can be tested using a cross-sectional approach as another aim of the study was to measure associations between variables, rather than identify mechanisms that underlie these associations. Finally a required sample size and time constraints meant that a longitudinal study may have been impractical in this instance; particularly given how comprehensive the systematic review was.

The use of quantitative questionnaire methods has been selected over qualitative interview methods based on philosophical and resource considerations. An epistemological decision was made regarding the way concepts could be understood and investigated. In this study concepts such as anxiety and HRQoL were quantified and measured in a consistent manner. This allows for the identification of patterns, allowing generalisations to be made to the wider HF patient population. Qualitative research techniques, such as interviews or observations of phenomena, whilst providing in-depth information, would not allow for the identification of patterns to the same extent. Quantitative techniques forego depth of data and test the strength of associations between variables (Coolican, 2009).

Variable conceptualisation and measurement

In order to identify patterns in human behaviour variables or constructs were quantified, for example the functional health status of a participant was conceptualised as their NYHA functional class and measured using quantitative techniques. The conceptualisation of variables included in the survey is reported in the working methods section of chapter four of this thesis. It is then necessary to measure these variables in a consistent manner, therefore reducing bias and maximising objectivity in data collection.

In order to ensure quality measurement tools were selected to accurately identify and record phenomena evidence for their validity (accuracy and appropriateness) and reliability (consistency) in this patient population required careful consideration. These considerations are often referred to as a measure's psychometric properties (McDowell,

2006). A measure can be reliable but not valid, valid yet unreliable; ideally a measure should be both valid and reliable.

Validity

The choice of measurement tool used to capture evidence of a particular concept is as crucial as the initial selection of variables and their conceptualisation in determining the validity of research findings. The validation of an instrument is determined by its ability to measure the construct it purports to measure. With respect to the current research a number of types of validity have been determined to be of importance; construct validity, content validity, criterion or convergent validity and diagnostic validity.

- *Construct validity* refers to theoretical congruence between selected operationalised construct/s and the items selected to measure construct/s (Trochim, 2006). In simple terms questionnaires must contain items that measure the construct they purport to measure. Content, criterion and diagnostic validity all contribute to determining the construct validity of a measure.

- *Content validi*ty refers to the extent to which items within a measure are reflective of domains of importance to the construct. For example, an item that is developed to measure physical symptoms in HF patient samples would need to include all symptoms of relevance to that particular population in order for its content to be considered valid. This can be straight-forward for many concepts such as many medical conditions. However constructs such as intelligence or HRQoL present challenges when determining the criteria that constitute the content domain (Trochim, 2006).

- *Criterion or convergent validity* examines the extent to which a measure correlates, or converges on, other measures that theoretically it should be similar to. In the testing and validation of measures the correlation of outcomes is often compared to other well validated and extensively used tools in order to determine evidence of convergent validity.

- *Diagnostic or concurrent validity* refers to a measures ability to discriminate between groups that it should theoretically be able to distinguish between. This type of validity is sometimes referred to as ‘sensitivity’. Diagnostic validity is

undoubtably of importance for tools that aim to screen and identify individuals with a particular condition, such as anxiety disorder, from those who do not meet the criteria/threshold for the condition. Measures are tested on groups of individuals who may or may not have a particular relevant diagnosis/condition in order to determine the extent to which the measurement tool can differential between cases. An additional consideration when determining the diagnostic validity of a measure is the extent to which a measure is responsive to change in a given population/condition.

Reliability

A reliable measure will be consistent and repeatable, generating accurate data on subsequent administrations of the measure in the same population (Trochim, 2006). Reliability is estimated by considering:

- *Inter-rater reliability* (the degree to which different raters/administrators provide consistent estimates of the same phenomenon).
- *Test-retest reliability* (consistency over time).
- *Internal consistency* (homogeneity (similarity) of results across items within a measure) (Trochim, 2006; Higginson & Carr, 2001).

The above types of reliability are measured using correlations; the correlation between different administrator's outcomes, correlations over time and between items. Cronbach's coefficient alpha (α) is a calculation used to calculate the internal reliability of a measure, with cronbach's α higher than 0.70 deemed acceptable (Cronbach, 1951; Deaton et al., 2001). The correlation coefficient is sensitive to the number of items in a scale. Shorter scales with fewer than ten items commonly have lower Chronbach values (e.g .5). Pallant (2007) recommends using the inter-item correlation for such items. Briggs and Cheek (1986) recommend an optimal inter-item correlation range of .2 to .4. The psychometric properties of potentially appropriate questionnaires will be reviewed prior to their inclusion in the current survey to increase validity and reliability of data collected.

Data collection

Surveys using questionnaire methods can be conducted using face-to-face techniques, via post or email, over the telephone or using the internet. Researchers must consider the

population under investigation and available resources, time and money, when selecting the most appropriate method of data collection. Issues to consider include:

- ***Population and Sampling issues*** – can the population be easily identified? Are there any geographical restraints? Will the population cooperate? Are there any language or literacy barriers? What data will be available? Will response rates be an issue?
- ***Question and content issues*** – Will respondents know about the issues? Will respondents need to refer to records or view visual aids? What type of questions can be asked? Will question sequencing need to be controlled? Will screening questions be asked? Will scales be used to record responses? Will validated measures be used?
- ***Bias issues*** – Can social desirability be avoided? Could false respondents be problematic? Could interviewer persuasion and leading be an issue?

The relative advantages and disadvantages of face-to-face, mail, internet and telephone surveys are presented in table 4, informed by Czaja & Blair (1996). Some research questions are more amenable to one method over another. Mail and internet surveys involve respondents completing questionnaires themselves, whilst face-to-face and telephone administration usually involves the administration of a questionnaire by a researcher/interviewer. Different methods of data collection will now be considered in relation to the costs incurred, available content and response rates.

Costs involved in different methods of data collection

With regards to costs, both financial and time, internet surveys are very low cost. They do not involve having to pay interviewers as face-to-face research does or cover the costs of producing questionnaire material and postage of questionnaires as mail surveys do. In addition internet surveys generate large amounts of data in a short space of time, typically 10 to 20 days, from a worldwide geographical spread, assuming all potential respondents have access to the internet and are IT literate (Czaja & Blair, 1996). Telephone surveys can also provide data in a short space of time, however if sample sizes are large (exceeding five hundred) then postal surveys and internet surveys will be more economical. The cost of the telephone calls can now be moderated, using computer based voice-over Internet protocol (VoIP) to allow phone calls to be made using a broadband Internet connection instead of a standard phone line (Shi, 2011). In the majority of instances interviewers are

required to administer questionnaires. This is not the case however if using Computer-Assisted Self Interviewing (CASI) which makes use of visual and audio capabilities of portable computers to present questions on computer monitors or over headphones to respondents who then enter responses on a keyboard (Aday & Cornelius, 2006). Face-to-face surveys can involve high costs. Researchers must plan time for travel, conducting the interview, wasted time due to missed/cancelled interview appointments, and transcribing data when interviews are conducted. The use of face-to-face methods takes on average 2.6 times longer than telephone approaches (Groves et al., 2011) and is more appropriate with smaller sample sizes. In addition, use of face-to-face methods of data collection, particularly when conducted in respondents' homes are also associated with significant safety issues for researchers that must be addressed in study protocols.

Table 4:Modes of survey administration: advantages and disadvantages

	Characteristics	Advantages	Disadvantages
Mail	Cover letter, questionnaire sent to specific address. Respondents self-complete the questionnaires. Must be clear, concise and easy to follow.	Costs can be low - postage and composition and production of questionnaires/material. Cheap to translate into different languages or for visually impaired. Can reach large geographical spread Flexibility in responding for participant Explore sensitive topics due to anonymity.	Not able to explore complex topics with detailed, open-ended items- Interviewer unable to probe. Questionnaires must be brief and self-explanatory. Lengthy data collection period - It takes approximately eight to ten weeks to conduct a survey if all respondents are mailed at the same time – regardless of the sample size and geographical distribution (Czaja & Blair, 1996). No control of environment or item order. Low response rate relative to face-to-face methods High potential for response bias
Internet	Contact potential respondent by email, telephone or regular mail initially and provide instructions for accessing the survey. Unique personal	Low cost Cheap to translate into different languages or for visually impaired. Short duration of data collection Large amount of data generated and can be	Must be easy to understand Difficult to explore complex topics Sampling bias No control of environment

	Characteristics	Advantages	Disadvantages
	identification numbers (PIN) are usually required to gain access to the online questionnaire (Czaja & Blair, 1996). Online surveys guide the respondent through the survey, allowing skip patterns, pop-up and visuals aids to be used.	automatically coded and analysed. The possibilities presented by evolving technology allows for interactions closer to human-human interactions (Tourangeau et al., 2001). Able to use visual aids and control item order.	Limited information on non-responders Cannot access all members of society Limited by internet connections
Face-to-face	Involves a researcher interviewing respondents	Control of environment to a degree Coverage of in-depth topics and explore/probe/prompt if necessary. Higher response rate	Can be expensive - time and money. Lengthy to conduct Difficult if non-English speakers and no translator Difficult to cover sensitive topics Social desirability bias
Telephone	As with face-to-face but over telephone. Mailed information/cover letters	Relatively fast to conduct with smaller samples Good response rates Cover large geographical area at relatively low cost	May be problematic for hearing impaired or non-English speaker if no translator used. Some social desirability bias

	Characteristics	Advantages	Disadvantages
	with details of the research/ organisation/ researcher will increase participation.	Coverage of more complex/in-depth topics Reduces responder burden Cover more sensitive topics than face-to-face	Less able to cover sensitive topics than mail/internet Higher cost than internet but lower than face-to-face and with smaller samples, mail. No control of environment

Survey content

Face-to-face and telephone interviewer administered surveys allow for more complex topics to be explored, whilst mail and internet surveys must be clear, concise and usually brief in order for participants to complete them. Face-to-face and telephone surveys are thought to provide more detailed data. The use of an interviewer in telephone and face-to-face surveys reduces the burden on respondents and allows for control over item order and the inclusion of complex skip patterns and probing of respondents for more complete, quality data. However, it may be hypothesized that respondents completing surveys at home in their own time have a lot of time to consider their responses and so one may expect longer, detailed responses to open-ended items (Groves et al., 2011). De Leeuw (1992) found no difference in responses using interviewer delivered versus self-administer questionnaire open-ended items. With internet surveys complex layouts, prompts and reminders of missing responses can be accommodated. However, Dillman (2007) cautions against forcing respondents to respond to items before proceeding and controlling the order of response as this often leads to decreased response rates and increased exits from surveys. Online surveys are developing quickly and can incorporate talking heads, virtual interviewers and audio material to increase the sense of rapport for respondents. Furthermore, data entry can be synchronised with respondent's answers, saving time and potential errors from separate data entry (Dillman, 2007; Shi, 2011).

With face-to-face survey's respondents are less likely to report personal or socially undesirable behaviours and attitudes or may make their responses to items more socially desirable when a researcher is present. Although this may apply to telephone surveys also, to a lesser degree (Czaja & Blair, 1996). The extent to which the researcher impacts on respondents' personal disclosure will in part depend on the skills of the researcher in making the respondent feel comfortable and at ease and in part depend on the character of the respondent. Dressing appropriately for the population and topic under investigation can impact on the data generated. The lack of visual information when using the telephone for research purposes has been found to enable people to be more honest and open over the telephone, discussing a range of sensitive topics with relative anonymity (Applefeld, 1986). In general however the more anonymous the method of data collection the higher the rate of reported behaviour. Mail and internet surveys generally allow for more sensitive topics to be investigated. That said, although the internet allows for anonymity to be preserved, research has found this advantage is outweighed by individuals concerns

relating to the security of the Web (Couper et al., 2011; Dillman, 2000). Methods can be used to increase the credibility of the research and respondents sense of security, such as including organisations logos on all documentation sent to respondents and including a photograph and/or paragraph of background information on the organisation/interviewers for potential respondents (Easton, Gask, Lidbetter & Lovell, 2008).

Response

Response rates (the number of eligible sample members who complete a questionnaire divided by the total number of eligible sample members) are an important indication of survey quality. Response rates below 40% are unacceptably low in survey methods (Czaja & Blair, 1996). In mail and internet surveys response rates are more of an issue than in face-to-face or telephone surveys. Response rates for telephone surveys range between 40% to 80% depending on the number of call-backs used (Czaja and Blair, 2005). Rates of 70%> have been reported as acceptable when using the telephone to administer surveys (Shi, 2011). The use of repeated call backs, on different days and varying times of the day can increase response rates, particularly when the trained interviewer is able to allay any doubts regarding the relevance and authenticity of the research.

For mailed surveys a response rate of 50% or more is considered acceptable (Shi, 2011). Follow-up cover letters, copies of questionnaires and phone reminders all encourage higher response rates (Dillman, 2000). Response rates for internet surveys are lower than those for postal surveys, usually 40-50% online (Couper et al., 2011; Cobanoglu et al., 2011). Online survey responses are limited by respondent's level/quality of technology and Ethernet connection. If surveys take too long to download or cause respondents computers to 'crash' then response rates will be affected. Usually the higher the response rate, the better the quality of the study, assuming the sampling frame was unbiased. Response rates can be increased by reducing the cost to respondents, with regards to time, money, inconvenience and embarrassment and increasing the rewards, through financial incentive, increased salience to respondents and by highlighting the importance of the research (Shi, 2011; Dillman, 2000; Yammarino et al., 1991). Monetary incentives, such as cash, lottery tickets and vouchers, all increase response rates, by up to 19% (Church, 1993). However, the impact is only observed when the incentive is included in the initial correspondence, not when the incentive is conditional on return of the questionnaire. Ethically, incentives

must not be of such value as to persuade the respondent to complete something that they would otherwise not agree to.

Responder bias refers to the potential for particular groups in society to be represented or underrepresented in research. A drawback of mail surveys is that the potential for response bias is high, with particular populations less likely to respond including those from low educational backgrounds, those with poor literacy or those who do not have an interest in the topic. A mail questionnaire is easier to ignore than a persistent but polite interviewer. Where possible it is important to gather socio-demographic and clinical data for non-responders to identify if the final sample differs in any significant way from the intended sampling frame.

Bias in sampling can occur in internet surveys as not everyone has access to the internet or is proficient with using a computer. In 2010 30.1 million adults (60%) accessed the internet almost on a daily basis (Office of National Statistics, 2011a). Although this does represent a large portion of the UK population, it also means that it may difficult to sample many groups of society including the homeless (although it is also not possible to sample this section of society using postal or telephone surveys), individuals over 65 years and populations who live in areas with no internet facilities; although it is acknowledge that internet services can be accessed though shared computer clusters such as libraries or internet cafes (Office of National Statistics, 2011a). The accessibility to populations and indeed sampling frames from which to contact potential respondents does limit the application of this approach to surveying.

The four outlined approaches are currently among the most common forms of survey methods. Each has their own advantages and disadvantages. There is no requirement however to adopt a singular approach in isolation. A large variety of combinations of methods to surveying can be used and are only limited by the imagination of the researcher and resources available to them (Dillman, 2007).

Ethical considerations in health services research

All research conducted with participants is reviewed by ethical committees to ensure that the interests of the participants are paramount. Participants should not be placed in

psychological or physical harm, should take part voluntarily, after providing informed consent. Their privacy should be safeguarded either through anonymity or confidentiality. The involvement of patients and members of the public in the research process can help to ensure that participant's rights and welfare are considered.

Patient and public involvement (PPI)

The involvement of patients and the public (service-users) in the research process is increasingly considered advantageous for many primary research endeavours. Service user involvement in research has been defined by INVOLVE (a formal public participation organisation) as "An active partnership between the public and researchers in the research process, rather than the use of people as the 'subjects' of research…" (INVOLVE, 2004)[6]. Service-users can offer different perspectives on issues, can prioritise issues important for those who use a service, increase the opportunities to empower people who use a service and can help recruit their peers and disseminate researcher to a wider audience (INVOLVE, 2003).

Policy and Practice

Service-user involvement in health and social care research or 'user involvement' as it is also known, developed in the area of social care policy and planning in the 1980's and early 1990's (Beresford, 2005). In the areas of disability, minority and feminist research, emancipatory research, with the aim of empowering individuals, has existed for a long time (Barnes & Mercer, 1997). As health and social care research is linked inextricably to policy and practice the input of service users into research should follow as a matter of course. The incorporation of service user 'evidence' into health and social care research has however been slower to develop, compared with the area of service planning for example (Beresford, 2005). The reasons for this are unclear; however disagreements relating to the level of involvement of service users from academic and clinical circles and a lack of understanding of the ways in which service users can be involved in research may in part have hindered the advancement of this participatory process. Other reasons identified for not involving members of the public in research are listed in table 5.

[6] (www.invo.org.uk)

Table 5: Reasons and arguments against not involving the public in research

Reasons provided for not involving service users in research*	Arguments against them
One or two people who use a service can't be representative of all relevant groups	One or two people will not be representative of all people who use a similar service. Similarly, one or two doctors or academics will not be representative of all in their area of expertise. Advisory group member are there to provide their perspective not to be representative. Obtaining a diverse range of perspectives is aim of collaborating with service users.
Many service users collaborating in research are trained patient 'advocates', the same ones attend a range of meetings.	Service users who are willing to participate and put their views across to a range of professionals may not be 'typical' of all users of a service but they can offer valuable insight from a patient/user perspective. Even though they attend research meetings and may be 'research articulate' they still use the services you are asking them to comment about.
Members of the public have unrealistic expectations of research and its implementation.	Briefing people fully before they get involved in research regarding how long the project can run for, what will be involved and the potential for it to be put into practice should eliminate this issue.
It will be too expensive and time consuming.	If you involve members of the public it will cost more in terms of time and money. Payment should be at a level consistent with other members of the research team. If a group is entirely voluntary then payment cannot be reasonably expected. However, asking someone to give up their time for free when others are paid as part of their job creates inequalities within a group (INVOLVE). Not including users to reduce costs could compromise the relevance of the research and reducing the funding opportunities available. Budgets should accommodate the cost of including users in research.
Health and social care professionals can act as advocates for people who use their services.	Research indicates that people who use services have different priorities and views regarding research than those who deliver their care. Even if health professionals are patients they have dual agendas
People won't understand the research	Many service users have been involved in complex randomised controlled trials in areas such as HIV/AID and cancer. Complex ideas can be learned if they are explained without jargon.
People who use services are too emotionally engaged in topics to be objective in the research process	No one can be fully objective. Service users bring relevant knowledge based on past experience to a project. They tend to be focused on the fundamental reasons for undertaking a project and ensure it remains relevant.

*Developed with reference to INVOLVE (2003) Involving the public in NHS, Public Health and Social Care research: Briefing notes for researcher.

The national advisory group, INVOLVE (formerly a DH initiative called *Consumers in NHS Research*) is funded by the National Institute for Health Research (NIHR) to promote and advise researchers with regards to PPI. The impact of these policy developments has been to introduce service user involvement into a range of funding streams. Researchers are encouraged, if not required to demonstrate service user participation in research projects in order to obtain funding (Telford & Faulkner, 2004). Examples of this can be seen in NIHR funding streams including the Research for Patient Benefit (RfPB) programme. Additionally if a research project requires National Research Ethics Service (NRES) approval an application must be completed including an item asking researcher 'In which aspects of the research process have you actively involved, or will you involve, patients, service users, and/or their carers, or members of the public?' options include:

- Design of the research
- Management of the research
- Undertaking the research
- Analysis of results
- Dissemination of findings
- None of the above

Applicants must provide details of involvement, or if none they must justify the absence of involvement. Not all funding bodies require applicants to have active service user involvement in research and ethical approval is unlikely to be refused due to a lack of involvement. However, service user involvement is increasingly becoming a feature of modern health and social care research, justifiably so. A description of the involvement of patients and the public in the design of this survey can be found in Appendix 2.

Summary

- A survey methodology was selected to investigate phase two aims as this allows for a multiple variables to be measured in a relatively large sample of individuals compared with more qualitative, in-depth methods, such as interviews.

- With quantifiable data it is possible to explore patterns and associations more readily.

- A longitudinal design was not selected due to time and resource restrictions.

- In addition the aims were to investigate associations between variables rather than underlying mechanisms and therefore a cross-sectional design was appropriate.

- Based on the philosophical assumptions of this research the concepts that will be investigated can be measured using questionnaires in a larger sample than would be possible using interview methods.

- Participants will be recruited using face-to-face techniques, supplemented with reminder telephone calls to encourage participation. Questionnaires will be completed by respondents at home and posted back to the researcher in order to maximise resources and response rate and reduce patient burden.

- The role of patient's and the public in research has been presented and will be considered further in the survey design. Contributions of the advisory group, including patient representatives can be found in appendix 23.

The following chapter presents the methods, results and discussion of the first phase of research: the systematic review to identify the aggregated prevalence of anxiety disorders and symptoms among people with heart failure and factors associated with potential heterogeneity in reported prevalence of anxiety.

CHAPTER THREE: **SYSTEMATIC REVIEW**

Research investigating the prevalence and impact of anxiety in HF patient populations is increasing. Reported rates of anxiety vary widely in the literature. A systematic review was conducted to synthesise research evidence on the prevalence of anxiety and identify reasons for variations in reported rates.

Part one of chapter three reports the methods for the systematic review.

Part two presents the results from the review.

Part three presents a discussion of the review findings, followed by a consideration of the limitations and strengths of the review. Clinical implications from the findings and the direction of future search are considered in the chapter five summary.

Part One: **Systematic Review Methods**

This systematic review was conducted in line with the methods outlined by the Centre for Reviews and Dissemination (CRD) in their publication Systematic reviews: CRD's guidance for undertaking reviews in healthcare (CRD, 2009). It has been reported with guidance from the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) statement and checklist (Moher et al., 1995), which replaces the QUOROM guidelines for reporting systematic reviews (Clarke, 2000).

The review search was conducted from May 2008, with updates concluded in October 2009. Research published after this date was not included in the review but has been incorporated into the introductory chapter and discussion of the systematic review in order to critically appraise studies published after this time.

Review questions

The review questions address the first phase of research and were as follows:

1. What is the aggregated prevalence of anxiety disorders and anxiety symptoms among people with a diagnosis of heart failure?

2. What factors explain variance in reported rates of anxiety? Specifically, is the way in which anxiety is conceptualised and measured associated with potential heterogeneity in reported prevalence of anxiety?

Inclusion criteria

The inclusion criteria were developed to be as inclusive as possible in order to capture the widest range of studies that sampled patients with a HF diagnosis and a measure of anxiety symptoms/disorder, whilst focusing tightly on the research questions. See appendix 3 for definitions of included and excluded conditions and interventions. Table 6 below presents the inclusion and exclusion criteria for the systematic review.

Table 6: Inclusion and exclusion criteria for the systematic review

Inclusion criteria	
Population	• Acquired left-sided ischaemic and non-ischaemic HF, including [1]DCM, characterised by the inability of the heart to effectively pump blood around the body resulting from structural or functional damage to the heart (Department of Health, 2000) and confirmed by medical records and/or patients' currently receiving treatment for [2]HF • Stable in-patients or community based patients • 18≥ years • HF as the primary diagnosis • HF patients who received an [3]ICD, [4]CRT, [5]CABG or [6]PCI will be included if a measure of anxiety symptoms/disorder is not immediate pre/post intervention (must be at least 3 months duration following intervention)
Outcome	• Measure of the severity of anxiety symptoms, clinical anxiety or anxiety disorders • Anxiety symptoms are defined as physical and psychological symptoms of generalised anxiety disorder ([7]DSM –IV 300.02) • Anxiety disorders are categorised as outlined in DSM – IV (APA, 2004)
Study design	• All primary research studies with a quantitative measure of anxiety. • [8]RCTs, uncontrolled trials and observational research including cohort studies, case control trials, and case series as defined by the Royal College Of Nursing, Evidence-Based Nursing levels of evidence guidelines (http://ebp.lib.uic.edu/nursing/?q=node/12
Exclusion criteria	
Population	• HF due to congenital heart disease or isolated right-sided HF patient (when specified) or where there is a diagnosis of pulmonary hypertension or cor pulmonale. • Patients hospitalised with acute, unstable HF. • Concurrent disabling or life threatening diagnosis being the focus of the study • Heart transplant or artificial heart pump patients

Outcome	• Proxy measures of anxiety that did not assess recognised symptoms of anxiety; general mental health measures, dichotomous measures that asked patients if they were anxious.
Study design	• Case studies, commentaries, reviews, letters and other non-primary research will be excluded. • Dissertations • Non English language papers

1 = Dilated Cardiomyopathy; 2 = heart failure; 3 = Implanted Cardioverter Defibrillator Device; 4 = Cardiac Synchronisation Therapy; 5 = Coronary Artery Bypass Graft; 6 = Percutaneous Coronary Intervention; 7 = Diagnostic Statistical Manual; 8 = Randomised Controlled Trial

Search strategy

The search strategy was developed to identify all published and unpublished research that had included a measure of anxiety symptoms or disorders in a HF patient population.

The search terms and strategies were generated in consultation with a Faculty of Medical and Human Sciences librarian at the John Ryland's University of Manchester library and were reviewed by the supervisory team. The searches were piloted in various forms and required several iterations until returns were relevant and sensitive to the review aims. Efficiency of search terms was determined by assessing the number of hits returned and screening articles for relevance to the research question. If any known key articles were not identified then steps were taken to rectify the search strategy. A cautious approach was adopted as a wide range of terms have been used in the literature to describe anxiety such as emotional distress, worry and psychological symptoms and so an comprehensive search was developed to avoid missing relevant articles. The search for relevant articles was conducted by the author in three phases, an initial search of databases (June 2008), an updated search the following year (October 2009) with a final update of the main electronic databases in January 2013.

The following databases were searched from year of inception to January 2013:

- MEDLINE on the OVID platform (1950- Jan 2013)
- British Nursing Index (BNI) and Archive on the OVID platform (1985 – Oct 2009) and on Proquest (January 2013)

- EMBASE on the OVID platform (1980-Jan 2013)
- PsycINFO using the OVID platform (1806 – Jan 2013)
- CINAHL (Cumulative Index to Nursing and Allied Health Literature) was search initially using the Ovid platform (1982 –June 2008) and for the updated search using its current host EBSCOhost (2008-2013)
- ISI Web of Science with conference proceedings (1990- Jan 2013)
- Cochrane Central Register of Controlled Trials using Wiley Interscience (1980-Oct 2009)
- MetaRegister Current Controlled Trials (mRCT) was searched selecting all registers with the exception of the Leukaemia Research Fund.
- Leading experts in the field were emailed to enquire about any unpublished work or work in progress.

Searches were conducted initially on the electronic database, MEDLINE. Index terms (called MESH terms in MEDLINE); subheading and free-text terms were used. Truncation was used to account for variations in ending of terms, for example, single and plural terms. Boolian operators, AND and OR were used to combine and expand searches accordingly. The search terms were developed from the components of the inclusion criteria as is advised in the CRD handbook (2009). Population included terms such as *heart failure, left sided heart failure, cardiac failure and cardiomyopathies.* Outcome included a wide range of terms for anxiety such as *nervousness, mood disorder, anxiety, psychological stress, emotional factors,* and diagnostic terms such as *generalised anxiety disorder, panic disorder and agoraphobia.* Design terms were limited to *prevalence* to capture any prevalence studies that may be missed using the other search terms. Initially a third aim of the review was proposed; to measure the association between anxiety and HRQoL. As a consequence in addition to the terms listed above, health related quality of life terms *health related quality of life, well being, life satisfaction and life quality* were also included in the in the first two phases of searching. However, as the number of studies included in the review was larger than anticipated this aim was removed from the protocol and therefore the terms were not used in the final updated search.

Where possible the filters ‘English language only’ and ‘humans’ were selected. For the main databases the search strategies contained up to 48 lines. The Cochrane database, the

Current Controlled Trials metaRegister and ISI Web of Science had limited search functions and as a result the terms 'Anxiety AND Heart failure' were with limiters selected to refine the search. Databases were searched separately with the exception of MEDLINE, BNI and CINAL (for the first round of searching), which were searched using the OVID platform. Search strategies can be found in appendix 4.

Since the bulk of the searches for this review have been conducted a HF filter for Medline has been developed. The validated HF filter aids researchers and clinicians in identifying HF literature on the Medline database and would have been useful in the current review (Damarell et al., 2011).

In this review the search was restricted to English language journals only as resources were not available for translating studies. Attempts were made to identify all unpublished reports, conference abstracts and ongoing research. Contacting authors for further data from abstracts or ongoing trials can be time consuming and often lacks the details needed to conduct quality assessments of studies (CRD, 2009). However in this review attempts have been made to contact authors to obtain data where possible. Dissertations were excluded due to resource limitations. All attempts were made to locate papers, abstracts or presentations associated with dissertations.

Key articles reference lists were hand searched in order to minimise the risk of missing relevant articles. Hand searching of specific journals was not conducted however due to time restrictions and as the search undertaken was considered comprehensive.

All results were exported into Reference Manager 12. As the number of references was so large the programme could not remove duplicates electronically and so duplicates were removed manually, cross referencing authors and titles of research.

Study Selection and data extraction process

Studies were obtained, screened and selected by KE using the inclusion and exclusion criteria in three stages: titles, abstracts and full texts. Where KE was unsure about whether a study should be included the review team (KL, CD and PC) were consulted until a

consensus was reached. It was possible to obtain the majority of full text papers electronically from John Rylands University of Manchester Library (JRULM). For papers from journals not subscribed to by the University, papers that pre-dated subscription to electronic sources, or not held at The University Library, inter-library loans were sought. Data from ongoing trials, abstracts, conference presentations and unpublished work were obtained by contacting the authors by email.

Procedural rules

Screening

- Where it was unclear as to whether the sample consisted of HF patients the supervisory team was consulted to reach a consensus decision over inclusion.

Obtaining data

- Where studies had included a HF sample and a valid measure of anxiety but did not report anxiety data in corresponding papers authors were emailed. If the author could not provide data, did not respond or could not be contacted the study was excluded.
- Where anxiety symptom scores or the prevalence of clinical anxiety and/or disorders were not reported separately for HF patients in mixed samples authors were contacted. In the event that the authors could not provide data, did not respond or could not be contacted the study was excluded.
- Where demographic and clinical data were reported for a different number of participants to that of anxiety scores authors were contacted for clarification. If clarification could not be obtained the study was excluded.

Extraction

- Where studies reported variance of anxiety data at baseline prior to intervention and subsequent follow up, only baseline data was extracted.
- Post intervention data was not extracted.
- Where studies reported demographic, clinical and outcome data for separate groups of HF patients mean values and standard deviation were combined using weighted aggregate means and standard deviation pooled estimates See appendix 5 for the formula used to calculate mean and SD estimates.

- Where studies appeared to replicate samples the authors were contacted for clarification. When papers were based on the same sample the paper with the largest number of participants was selected for inclusion. Where sample sizes were equal the study with the most complete data set was selected for synthesis.

Data extraction was conducted independently by four reviewers. KE screened and extracted data from all studies whilst the other three reviewers (KL, CD and PC) each extracted data from a third of the studies. Screening by two independent reviewers ensured that any extraction errors were identified and resolved by consensus. Any discrepancies in data extraction were discussed over several meetings with the supervisory team until consensus was reached. The data extraction form was created electronically by modifying an existing extraction sheet used in previous systematic reviews devised by Dr Peter Bower (Gellatly et al., 2007). The extraction form was piloted by each reviewer on two papers that met inclusion criteria (Moser et al., 2005; Jiang et al., 2004). Following piloting, the form was further refined (see appendix 6 for a copy of the extraction form). Information on sample size; average age; proportion of males; NYHA functional class; LVEF %; ethnicity; study design, sampling method; response rate/attrition; geographical location; setting; definition of anxiety; measurement tool; number of people with anxiety; average scores on anxiety measurement and prevalence rate of anxiety were extracted from every study. Additional data relating to HRQoL in the samples were extracted from studies but this element of the review was discontinued due to the large returns relating to primary aims of the review. All completed extraction forms were sent to KE who then used an Excel spreadsheet to enter and collate data relating to the population characteristics, study aim and design, outcomes measurement and results, limitations and study quality.

Quality assessment

The quality of included studies in the review should be assessed in order to determine the degree to which findings from the studies have been influenced by study design or conduct for example (pp. 33, CRD, 2009). The quality of studies was assessed in three stages during this review. Firstly, a minimum quality threshold for inclusion in the review was established. Only studies with a validated measure of anxiety symptoms were included in the review. Secondly, the design of studies was extracted and used as a variable in meta-

regression analysis in order to consider the impact of design on outcome data. Finally, a component approach was used to assess included studies on a range of factors considered important for internal validity.

The choice of quality components selected in this review was guided by an assessment of epidemiology systematic review literature, the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (von Elm et al., 2007), with reference to Boyle (1998) and in consultation with the review team (KL, CD, PC). The internal and external validity of studies was assessed by descriptively evaluating the following components:

Sampling

- Are probability or non-probability sampling techniques used? (yes, no, unclear from information reported)
- Are sample characteristics adequately reported? (yes, no)
- Does the study report a response rate? (yes acceptable: 80% >, or 70% if characteristics of non-responders are reported and match the sample characteristics (Boyle, 1998) (yes unacceptable, no)

Assessing the quality of studies sampling techniques and reporting of sample characteristics provides important information regarding the external validity of the included studies. If the samples from included studies are not representative of HF patients and particular settings or do not contain sufficient detail to accurately describe the sample then results must be extrapolated with caution.

Measurement

- Has anxiety been adequately defined in the study? (yes, no)
- Is data collection standardised, with respect to timing and method of administration? (yes, no, unclear from information reported)
- Does the measurement tool omit somatic symptoms of anxiety to account for overlap in physical symptoms of cardiac conditions and anxiety? (yes, No, Unclear).

- Does the measurement tool distinguish between anxiety and depression? (yes, No, unclear). Refer to table 7 to show whether tools omit somatic items and ability to distinguish between anxiety and depression.
- Have confidence intervals been presented for prevalence rates?

Assessing whether included studies have defined anxiety will tell us more about the standard of reporting in this area and how anxiety is being conceptualised in research to date. Identifying if data collection is standardised will help determine the internal validity of studies and report whether rates of anxiety are a true reflection of levels of anxiety in the sample or may be biased due to errors in research designs. Assessing how anxiety is measured, the validity of measurement tools and their ability to measure what they purport, is also important when determining the internal validity of included studies.

Table 7: Table to show whether anxiety measures distinguish between anxiety and depression and omit somatic items in the assessment of anxiety

Measurement tool	Omit somatic items*	Distinguish between anxiety and depression*
SCID	Unclear	Yes
ICD-9 codes	Unclear	Unclear
GAD-7	Yes	Yes
PHQ	No	Yes
HADS	Yes	Yes
STAI	Yes	Unclear
HARS	No	Unclear
GAI	No	Unclear
BSI-A	Yes	Yes
MACCL	No	Unclear
POMS	Unclear	Unclear

*Determined by analysis of measures conceptual development, content and from empirical research of tools psychometric properties.

No definitive checklist or guidance for assessing the quality of a range of research designs in a review that seeks to estimate the prevalence of a condition exists (Whiting et al., 2005). The majority, if not all guidelines relating to quality appraisal of studies for systematic review refer to effectiveness research. Debate over the quality appraisal of studies to inform reviews of incidence and prevalence is in its infancy. Boyle (1998) has published guidelines for assessing the quality of prevalence studies which have been applied in a number of reviews to date, albeit modified to meet the review aims (Cooper, 2007; Latthe et al., 2006; Prins, 2002). A component approach was selected in this review. The use of measurement scales and checklists for assessing the quality of studies in systematic reviews is not recommended (CRD, 2009; Moher et al., 1995; Greenhalgh, 1997). The majority of checklists of study quality and measurement scales that assign numerical values to study quality have not been rigorously developed and tested (Moher et al., 1995). This can lead to high levels of variability when assessing study quality.

The quality components of sample composition, setting, conceptualisation of anxiety and measurement tool were entered into sensitivity analysis of the meta-regression in order to determine whether levels of anxiety varied as a result of these components. The outcomes of the quality appraisal were synthesised with results from the review to interpret findings and inform recommendations for future research and clinical practice (CRD, 2009).

Descriptive synthesis

Data were synthesised in tabular form. Study characteristics, population and outcomes were descriptively synthesised and frequencies and percentages, aggregate means and 95% confidence intervals are reported where appropriate.When studies provided demographic, clinical data or psychological data for separate groups of HF patients mean values and standard deviation were combined (appendix 4 presents the formulae used to calculate weighted aggregate means and standard deviation pooled estimates).

In order to synthesise the anxiety outcome data studies were clustered into groups that measured similar concepts of anxiety. Studies that identified clinical anxiety disorders were clustered together (termed ‘anxiety disorder’). Studies that used measures to screen for levels of probable anxiety above a given threshold were clustered together (termed

'probable clinical anxiety'). Studies that used questionnaires to measure anxiety symptoms that reached levels above the norm for the general population were clustered together (termed 'elevated symptoms of anxiety'). The remaining studies that used measures to assess symptoms of anxiety with no reference to thresholds with which to identify anxious cases were clustered together. Mean scores and proportions from these studies were considered separately from other studies anxiety outcome data. Initially attempts were made to transform mean and standard deviation (SD) values into proportions; however, using only mean (SD) data it is impossible to determine the distribution of raw scores with any confidence, and therefore it would have been questionable to transform data. Therefore studies with only mean (sd) anxiety data were retained in the review but excluded from meta-analysis.

With regards to NYHA functional class data included study samples were categorised as either mild (> 70% sample NYHA I and/or II), moderate to severe (> 70% NYHA III and/or IV), or mixed (distribution of NYHA class spread).

Quantitative synthesis

Quantitative synthesis of data has been conducted with caution and with consideration of the differences in studies methodology, sample composition and outcome measurement, to assess variations in reported prevalence and measurement of anxiety in HF samples.

The level of statistical heterogeneity in included study outcomes (prevalence of anxiety) was assessed. Variation in prevalence rates of anxiety resulting from factors other than sampling error requires consideration before any formal synthesis of data is attempted. If included study outcomes are found to be heterogeneous then attempts should be made to identify the source of variation in study outcomes (Chpt 8, Sutton et al, 1998).

Heterogeneity among study outcomes was explored using Cochran's Q (reported as x^2 and p – value) and I^2 statistic. Cochran's Q identifies whether all studies to be combined are measuring the same underlying population parameter (Sutton et al, 1998). Based on guidance from the HTA 'Systematic reviews of Trials and other Studies' (Sutton et al, 1998) a significance level of $p < 0.10$ was set for the Q statistic due to inherent low statistical power in this test (Sutton et al, 1998). As the strength of formal tests of

heterogeneity (or more accurately homogeneity) are low an additional informal test was conducted to determine the degree of heterogeneity in the study outcomes.

I^2 describes variance across studies, as a percentage, due to heterogeneity as opposed to chance (Higgins et al., 2003). Unlike Q it is not affected by the number of included studies. I^2 values of 25%, 50% and 75% are indicative of low, moderate, and high levels of heterogeneity (variance between studies) respectively. When heterogeneity was high, >75%, random effects models were used for summary statistics, using the command METAN in order to identify pooled estimates of the prevalence of anxiety in HF samples (Higgins et al., 2003). Random effects models assume variance in the outcome (effect) and calculate the individual study weight as the sum of the weight used in a fixed effects model and the between-study variability; to produce study weights that reflect between-study variation, providing close to equal weighting.

Meta-analysis has been found to be useful for explaining variance in outcomes (prevalence rates in this instance but effect sizes in reviews of effectiveness) as it is for improving the estimates of an outcome. This type of meta-analysis (meta-regression) has been referred to as 'exploratory' where the characteristics of the studies or participants become the focus of analysis (Anello and Fleiss, 1995).

The association between levels of anxiety and the manner in which anxiety had been conceptualised and measured was investigated in pre-planned sensitivity analysis. Pre-planned post-hoc meta-regression analysis was performed using the command METAREG. Meta-regression is a form of sub-group analysis, used to explore any relationships and differences within overall pooled prevalence estimates (Thompson & Higgins, 2002). Univariate meta-regression analysis was conducted on the following factors; type of anxiety (anxiety disorders, probable clinical anxiety and elevated symptoms of anxiety), age (both as a continuous variable of mean age in years and a categorical variable of < 59yrs, 60-69 yrs, 70+), gender (% males in the sample), setting (inpatient, outpatient or mixed), LVEF (mean %), NYHA class (mild (> 70% of the sample in classes I & II), moderate/severe (> 70% of the sample in classes III & IV), mixed), design (RCT versus uncontrolled trials, cohort, case controlled, case series), country (USA versus, UK & Europe, Asia, Australasia and mixed samples). In addition post-hoc analysis was

conducted to explore whether rates of anxiety varied as a result of anxiety measurement method.

Not all studies included in the review reported a prevalence rate of anxiety. A meta-analysis of anxiety symptom severity (mean, sd, median, IQR) by anxiety measurement tool was conducted to determine how levels of anxiety reported as central tendencies varied as a result of measurement methods. Meta-regression was attempted on anxiety severity data where sufficient observations allowed determining reasons for variations in anxiety symptom severity.

All analysis was done in STATA statistical software package, version 11 (Statacorp, 2009) using commands METAN (for meta-analysis) and METAREG (for meta-regression).

Part Two: **Systematic Review Results**

Identification and selection of studies

In total 14,367 study references were identified from the databases searched (see table 8 for a breakdown of database hits). After duplicates had been manually removed from the database 9983 references remained following the original search. These were screened for relevance to the inclusion criteria based on information provided in the title and abstract.

Table 8: Electronic search details

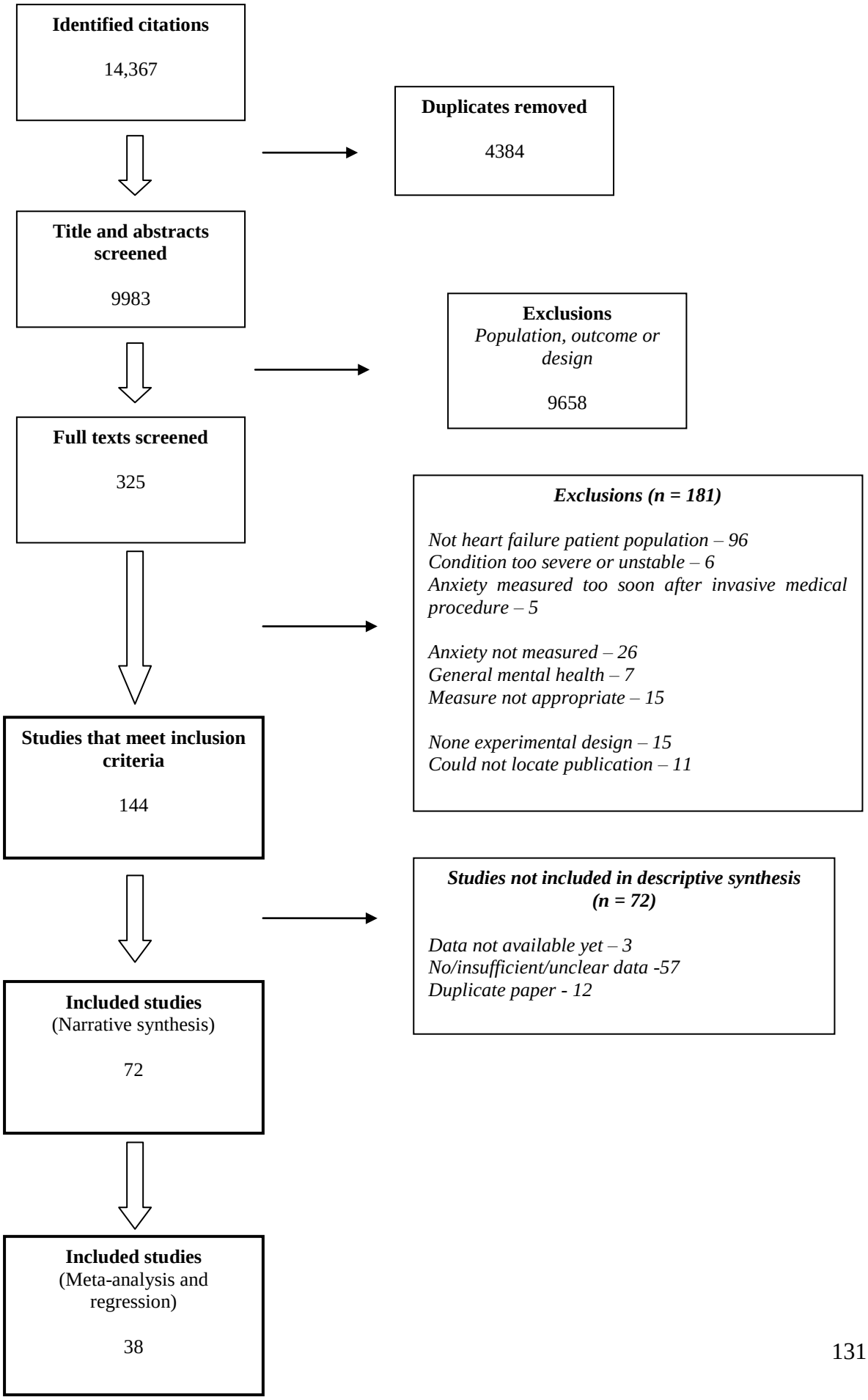
Source	Platform	Dates covered	Hits
MEDLINE	OVID	1950- Oct 2009	6734
BNI and Archive	OVID	1985 – Oct 2009	
CINAL	OVID	1982 –June 2008	
MEDLINE updates	OVID	Oct 2009 – Jan 2013	374
BNI updates	ProQuest	Oct 2009 – Jan 2013	8
EMBASE	OVID	1980- Jan 2013	5980
CINAL updates	EBSCO*host*	2008- Jan 2013	63
PsychINFO	OVID	1806 – Jan 2013	865
ISI Web of Science with conference proceedings	Thomson Rueturs	1990- Jan 2013	183
Cochrane	Wiley Interscience	1800-Oct 2009	47
*m*RCT	-	-	113
			14, 367
			Minus duplicates **9983**

A hierarchy was established for screening abstracts with the population (heart failure) placed highest, followed by outcome (anxiety) and finally design (primary research design). Figure 11 presented below shows the flow of papers through the screening process. 9658 references were excluded as it was clear from reading abstracts that the papers did not contain the target population, outcome or design.

Of these 9658 studies, 24 were PhD references that were excluded due to resource restrictions. 325 full-texts were screened. Of these 96 did not report research in a heart failure population, six papers contained samples too unstable or with HF too severe to be representative, five measured anxiety too soon after an invasive procedure. With respect to outcome 26 studies were excluded as they did not use a measure to identify anxiety symptoms or disorders. An additional seven studies assessed only general mental health and 15 assessed anxiety using a dichotomous item to ask respondents 'are you anxious'? Yes/no. Fifteen studies did not use a primary research design. In addition to these exclusions a number of studies were excluded as the publication could not be located from the reference (n = 11) See appendix 7 for a list of excluded studies with reasons.

One-hundred and fourty-four separate references met inclusion for the review. However of these 72 were excluded from further synthesis. Three studies were ongoing trials with no available data, the papers lacked data, or insufficient or unclear data which could not be clarified through contact with the author (n = 57), the papers reported duplicate samples/data found in other included papers (n = 12). See appendix 8 for a list of studies which met inclusion criteria but were not included in subsequent descriptive, quantitative or narrative analysis).

Figure 11: Flow diagram to show numbers and reasons for exclusions



Narrative Synthesis

Characteristics of included studies

The final sample consisted of 72 studies published between 1994 and 2013, of these studies 38 contained sufficient data relating to the prevalence of anxiety to be entered into subsequent meta-analysis and regression. The characteristics of included studies, specifically their design, setting, population and outcome will now be presented. The characteristics of included studies can be viewed in table 9.

Design

The aim of 34 of the studies was to measure the prevalence, incidence or severity of anxiety (47%), the majority of which were published between the latter parts of 2009 to early 2013. In thirty-eight studies (53%) anxiety was not the primary outcome. Thirteen of the included studies used an RCT design (18%), one used a non-randomised controlled design (Sullivan et al., 2009), whilst five used uncontrolled trial designs (Laederach-Hofmann et al., 2007; Witham et al., 2008; Karapolat et al, 2009; Jackson et al, 2011; Houchen, 2012). Twentey-two (31%) used a cohort design, five used a case-control design, whilst 25 of the studies used a case series design (35%). One study used what appears to be a mixed cohort/case controlled design (Steptoe et al, 2000).

Only eleven (15%) of the included studies reported a comparison sample/s. Patients who had recently experienced a myocardial infarction were used on four occasions (Moser et al., 2010; Moser et al., 2009b; Yu et al., 2009; de Jong et al., 2004) and four studies used healthy elders as a comparison sample (Almeida et al, 2012; de Jong et al., 2004; Steinke et al., 2008; Moser et al., 2010; Steptoe et al., 2000). Coronary heart disease (Strauber et al, 2012; Almeida et al, 2012; Moser et al., 2009a), CABG (Moser et al., 2010), hypertrophic cardiomyopathy (Steptoe et al., 2000), patient's with hypertension (Serafini et al, 2010), angina (Yu et al., 2009), peripheral artery disease (Strauber et al, 2012) and individuals with cardiovascular risk factors (Herrmann-Lingen et al., 2003) were used as comparisons in single studies. One study compared patients' levels of anxiety and quality of life to that of their spouses (Chung et al., 2009) and unusually one study had a group of pneumonia patients for comparison purposes (Abrams et al., 2008).

Setting

Fourty-nine studies recruited participants from outpatient samples (68%). Twenty-six of the outpatient samples came from secondary care cardiology clinics or medical centres (Lee et al, 2013; Brouwers et al, 2012; Eisenberg et al, 2012; Huang et al, 2012; Strauber et al, 2012; Damen et al, 2011; de Jong et al, 2011; Khalil et al, 2011; Shen et al, 2011; Hallas et al, 2010; Ansa et al, 2009; Chung et al., 2009; von Kanel et al, 2009; Doering et al., 2004; Dracup et al., 2003; Dracup et al., 2007; Evangelista et al., 2009; Haworth et al., 2007; Jolly et al., 2009; Koukouvou et al., 2004; Moser et al., 2010; Muller-Tasch et al., 2008; Schiffer et al., 2008; Steinke et al., 2008; Steptoe et al., 2000; Witham et al., 2008), six recruited from samples of patients recently discharged from hospital into the community (Dar, 2009; de Jong, 2005; Heo, 2008; Moser, 2005; Yu, 2007b; Zwisler, 2008), three studies recruited outpatients from primary care settings (Peters-Klimm, 2007; Luyster, 2009; Scherer, 2008), three from previous multi-site trials (Dekker et al, 2012; de Jong et al, 2004; Freidmann, 2006), three from veteran hospital services (Cully et al, 2010; Covera-Tindel, 2009; Paukert, 2009) and three studies did not provide further detail of their outpatient sample setting (Jackson et al, 2010; Moser, 2009; Tsuchihashi-Makaya, 2009).

Five studies recruited heart failure patients from inpatient settings (Houchen et al, 2012; Falk, 2009; Lee, 2005; Jiang, 2004; Song, 2008), whilst eight studies sampled a mixture of inpatient, outpatient participants and/or community based patients (Almeida et al, 2012; Dekker et al, 2012; Mulligan et al, 2012; Freyssin et al, 2009; Abrams, 2008; Sullivan, 2008; Herman-Lingen, 2003; Schweitzer, 2007). Three additional studies stated their sample came from previous clinical trials but did not report the setting (Lader, 2003; Thomas, 1997; Clarke, 2000) and for eleven studies the recruitment setting was either unreported or unclear (Mitchell et al, 2012; Freyssin et al, 2012; Huang et al, 2011; Serafini et al, 2010; Karapolat et al, 2009; Barrow, 2008; Kostis, 1994; Kulcu, 2007; Laederach-Hofmann, 2007; Yu, 2009; Junger, 2005).

The majority of the studies were conducted in the USA (n = 32, 44%), with four studies recruiting patients from multiple countries including the USA (Huang et al, 2012; Khalil et al, 2011; Freidmann et al, 2006; Thomas et al, 1997). Nine studies originated in the UK (Mulligan et al, 2012; Houchen et al, 2012; Hallas et al, 2010; Dar et al, 2009; Jolly et al, 2009; Witham et al, 2008; Barrow et al , 2007; Haworth et al, 2007; Steptoe et al, 2000), five from Germany (Scherer et al, 2008; Muller-Tasch et al, 2008; Peters-Klimm et al, 2007; Junger et al, 2005; Hermann-Lingen et al, 2003), three studies from Switzerland (Volz et al, 2012; Von Kanel et

al, 2009; Laederach-Hoffman, 2007), two studies from China (Yu et al, 2009a; Yu et al, 2007b), Australia (Almeida et al, 2012; Schweitzer et al, 2007), Denmark (Brouwers et al, 2012; Zwisler et al, 2008), Holland (Damen et al, 2011; Schiffer et al, 2008), and two studies from Turkey (Karapolat et al, 2009; Kulcu et al, 2007). Finally one study each was conducted in Hong, Kong (Lee et al, 2005), Tiawan (Chen et al, 2010), Greece (Koukouvou et al, 2004), Nigeria (Ansa et al, 2009), Korea (Song et al, 2008), Sweden (Falk et al, 2009); France (Freyssin et al, 2012), Italy (Serafini et al, 2010) and Japan (Tuschihashi-Makaya et al, 2009).

Table 9: Characteristics of included studies in the systematic review

First author, yr	Aim of study	Design	HF patient population (N, Source of patients, age, sex, ethnicity, NYHA class, LVEF)	Comparison
Barrow, 2007[7]	To test the effect of Tai Chi on exercise tolerance in patients with moderate heart failure	RCT	65 Outpatients UK 68.1 yrs (8.7) 53 male (82%) Ethnicity not reported Clinical characteristics not reported	---
Dar, 2009	Examine the impact of home telemonitoring on all-cause re-hospitalisation in typical heart failure patients recently discharged from hospital	RCT	182 Outpatients UK 71.7 yrs (11.62) 121 male (66%) South Asian (20%) Clinical characteristics not reported	---
Dracup, 2007	Determine the effects of a home-based exercise program on clinical outcomes in patients with heart failure	RCT	173 Outpatients USA 54 yrs (12.5) 123 male (71.1%) White (60%) NYHA II (27%); III (63%); IV (10%)	---

[7] Additional data sent by author

First author, yr	Aim of study	Design	HF patient population (N, Source of patients, age, sex, ethnicity, NYHA class, LVEF)	Comparison
			LVEF 26.4% (6.8)	
Freyssin, 2012	To compare the effects of an 8-week, high-intensity interval training protocol versus continuous training for chronic heart failure patients.	RCT	26 Setting not reported France 54.5 yrs (10.50) 13 Male (50%) Ethnicity not report NYHA class not reported LVEF 29.10%	---
Huang, 2011	To examine whether biofeedback relaxation techniques can improve heart failure patient's anxiety, depression and HRQoL.	RCT	39 Outpatients USA 60.80 yrs (11.70) 25 males (64%) Ethnicity not reported NYHA I (8%); II (46%); III (38%); IV (8%) LVEF not reported	---
Jolly, 2009	Assess the effectiveness of a home-based exercise programme in addition to specialist heart failure nurse care in heart failure outpatients	RCT	169 Outpatients UK 68 (12.6) 126 male (75%) White (77%) NYHA I (6%); II (74%); III (20%) LVEF not reported.	---

First author, yr	Aim of study	Design	HF patient population (N, Source of patients, age, sex, ethnicity, NYHA class, LVEF)	Comparison
Kostis, 1994	Compare the effects of a multimodal nonpharmacologic intervention to digoxin and to placebo in patients with congestive heart failure receiving background therapy with angiotensin-converting enzyme inhibitors	RCT	20 Setting not reported USA 65.7(6.1) 14 (70%) Ethnicity not reported NYHA II (95%); III (5%) LVEF 33.8% (7)	---
Koukouvou, 2004	Assess the physiological and psychosocial effects of exercise training in chronic heart failure patients	RCT	26 Outpatients Greece 52.5 (9.7) 26 male (100%) Ethnicity not reported NYHA II (58%); III (42%) LVEF not reported	---
Kulcu, 2007	Investigate the effects of aerobic exercise on quality of life, depression, and anxiety levels in a Turkish patient population	RCT	44 Setting not reported Turkey 59.3 (10.7) 32 male (72%) Ethnicity not reported NYHA II/III 44 (100%) LVEF 34.6% (13.3)	---
Lader, 2003	Evaluate the effects of digoxin therapy on health related	RCT	589 Setting not reported USA 64.6 (11.7)	---

First author, yr	Aim of study	Design	HF patient population (N, Source of patients, age, sex, ethnicity, NYHA class, LVEF)	Comparison
	quality of life in patients with heart failure		433 male (73.5%) None white (14%) NYHA (14%); II (54%); III (30%); IV (2%) LVEF 34.7% (13.2)	
Peters-Klimm et al, 2007[8]	To evaluate a primary-care based complex intervention to improve the quality of life of heart failure patients	RCT	199 Outpatients Germany 69.6 yrs (9.8) 146 male (73%) Ethnicity not reported NYHA I (3%); II (64%); III (32%); IV (1%) LVEF 37% (7.3)	---
Yu, 2007b[9]	Examine the effects of exercise training on psychological outcomes and disease-specific quality of life in older heart failure patients	RCT	153 Outpatients China 75.1 yrs (7.9) 77 male (50.3%) Ethnicity not reported NYHA II (60%); III (40%) LVEF not reported	---
Zwisler, 2008[10]	Evaluate the effects of	RCT	91 Outpatients Denmark	

[8] Additional unpublished data from trial sent by Muller-Tasch
[9] Same sample as Yu 2007a

First author, yr	Aim of study	Design	HF patient population (N, Source of patients, age, sex, ethnicity, NYHA class, LVEF)	Comparison
	hospital-based comprehensive cardiac rehabilitation compared with usual care among a broad group of cardiac patients		71.4 yrs (11.4) 57 male (63%) Ethnicity not reported Clinical characteristics not reported	---
Sullivan, 2009	Examine the effects of a psycho educational intervention on depression, anxiety, quality of life, symptoms and medical outcomes inpatient's with heart failure	Non-randomised controlled trial	208 Outpatients USA 61.3 (13.6) 146 male (70%) White (63%) NYHA I (9 %); II (46%); III (37%); IV (8%) LVEF 25% (20.3)	---
Houchen, 2012	To evaluate the effectiveness of an 'early rehabilitation after hospital admission' service on future readmissions and anxiety and depression for heart failure patients	Uncontrolled trial	17 Inpatients UK 67.3 yrs (10.4) 13 Males (77%) Ethnicity not reported Clinical characteristics not reported	---

[10] Additional data sent by author

First author, yr	Aim of study	Design	HF patient population (N, Source of patients, age, sex, ethnicity, NYHA class, LVEF)	Comparison
Jackson, 2011	To evaluate the relationship of coping style with quality of life among women with heart failure, and the role of illness knowledge in this relationship.	Uncontrolled trial[11]	35 Outpatients USA 55.7 yrs (14.5) All female White (60%), African American (40%) NYHA class not report LVEF 42% (15.8)	---
Karopolat, 2009	To compare the effects of home-based and hospital-based exercise programs on exercise capacity, quality of life, psychological symptoms, and hemodynamic parameters in heart failure patients	Uncontrolled trial	69 Outpatients Turkey 44.6 yrs (12.5) 43 Males (62%) Ethnicity not reported NYHA II (62%); III (38%) LVEF not reported	---
Laederach- Hofman, 2007	To evaluate the effects of a comprehensive out-patient rehabilitation program in chronic heart failure on quality	Uncontrolled trial	25 Outpatients Switzerland Age not reported 20 male (80%) Ethnicity not reported	---

[11] Secondary analysis of baseline data

First author, yr	Aim of study	Design	HF patient population (N, Source of patients, age, sex, ethnicity, NYHA class, LVEF)	Comparison
	of life in relation to emotional status and clinical severity of disease		NYHA I (44%); II (40%); III (16%) LVEF 28.7% (7..2)	
Witham, 2008	To test the acceptability and tolerability of an outpatient exercise programme in older heart failure patients with comorbid disease	Uncontrolled trial	17 Outpatients UK 81.6 yrs (5.5) 12 male (70.6%) Ethnicity not reported NYHA class II (47%); III (53%) LVEF not reported	---
Almeida, 2012	To compare the cognitive decline of heart failure patient's compared with adults with and without coronary artery disease over a 2 year period.	Cohort study	77 Outpatients and community volunteers Australia 64.4 yrs (10.2) 64 Males (83%) Ethnicity not reported NYHA class not reported LVEF 29.3% (7.8)	73 CAD patient's 81 Older adult controls
Cully, 2010	To determine the relative contribution of heart failure disease severity, depression, and comorbid anxiety to	Cohort study	96 Veteran Outpatients USA 71.89 yrs (7.83) 95 Males (99%) White (74%)	---

First author, yr	Aim of study	Design	HF patient population (N, Source of patients, age, sex, ethnicity, NYHA class, LVEF)	Comparison
	quality of life.		NYHA II (11.5%); III (41.7%); IV (46.9%) LVEF not reported	
Damen, 2011	To determine whether symptoms of anxiety are associated with 12-month cardiac hospitalizations in heart failure patients.	Cohort study	237 Outpatients Netherlands 66.9 yrs (8.7) 51 Males (21.5%) Ethnicity not reported NYHA I/II (91%) LVEF 33.6% (6.7)	---
De Jong, 2011	To examine the relationship between anxiety and event-free survival for patients with heart failure, and examine whether behavioural and physiologic mechanisms mediate any association between anxiety and outcomes.	Cohort study	147 Outpatients USA 61 yrs (11) 44 males (30%) *White (88%), Black (11%)* NYHA I (6%), II (32%), III (44%), IV (15%) LVEF 35% (14)	---
Dracup, 2003	Determine if perceived control reduces emotional distress in patients with heart failure and	Cohort study	222 Outpatients USA 57 yrs (12.5) 181 male (82%)	---

First author, yr	Aim of study	Design	HF patient population (N, Source of patients, age, sex, ethnicity, NYHA class, LVEF)	Comparison
	explore the demographic, clinical and psychological characteristics of patients with high and low perceived control.		Ethnicity not reported NYHA I (14%); II (27%); III (46%); IV (13%) LVEF 25.8% (7.6)	
Evangelista, 2009[12]	Examine and compare the incidence of anxiety and depression in ethnic minorities with chronic heart failure	Cohort study	241 outpatients USA 56.7 yrs (13) 168 male (70%) White (70%), Hispanic (23%), Black (7%) NYHA II (35%); III (54%); IV (11%) LVEF 26.5% (7)	-
Geobel, 2009	To identify correlates of pain sensitivity in a population of heart failure patients.	Cohort study[13]	96 Veteran Outpatients USA 67.2 yrs (11) 92 Males (96%) African American (27%), White (58%), Other (15%) NYHA class not reported	-

[12] Additional data provided by author
[13] Secondary analysis

First author, yr	Aim of study	Design	HF patient population (N, Source of patients, age, sex, ethnicity, NYHA class, LVEF)	Comparison
			LVEF 39.1% (16.7)	
Hallas, 2010	To identify psychological and clinical variables predicting mood and QoL for people diagnosed with heart failure	Cohort Study	146 Outpatients UK 48.6 yrs (9.5) 120 Males (82%) White (88%) NYHA class not reported LVEF 38.2% (15.1)	-
Junger, 2005	To investigate the influence of depression on mortality in patients with chronic heart failure	Cohort study	209 Setting not reported Germany 54 (10) 180 male (86%) Ethnicity not reported NYHA I (12%); II (44%); III (44%) LVEF 22% (10)	-
Khalil, 2011	To test the psychometric properties of the Brief Symptom Inventory depression and	Cohort study[14]	590 Outpatients USA & Australia 63 yrs (13) 378 Males (64%) White (74%)	-

[14] Secondary analysis of data

First author, yr	Aim of study	Design	HF patient population (N, Source of patients, age, sex, ethnicity, NYHA class, LVEF)	Comparison
	anxiety subscales in patients with heart failure, with or without renal dysfunction		NYHA I/II (64%); III/IV (53%) LVEF 35% (15)	
Lee, 2013[15]	To identify and link common profiles of physical and psychological symptoms to 1-year event-free survival in adults with moderate to advanced HF	Cohort study	202 Outpatients USA 56.9 yrs (13.3) 101 Males (50%) White (86%) NYHA II (40%); III (56%); IV (4%) LVEF 28.6% (12.4)	-
Mitchell, 2012	To investigate the accuracy of three short screening instruments in detecting depression, anxiety and distress in patients with cardiac diseases.	Cohort study	129 Setting unclear USA 61.2 yrs 84 Male (65%) White (54%) Clinical characteristics not reported	-
Muller-Tasch, 2008	Assess the prevalence of panic	Cohort study	258 Outpatients Germany	

[15] Referred by author

First author, yr	Aim of study	Design	HF patient population (N, Source of patients, age, sex, ethnicity, NYHA class, LVEF)	Comparison
	disorder, its influence on quality of life, and the presence of further anxiety and depressive comorbid disorders in outpatients with chronic heart failure		62.1 (11.8) 199 male (77%) All white NYHA I (4%); II (47%); (38%); IV (1%), missing (10%) LVEF with 31.5 (11.2), without 30.7 (11.2)	-
Paukert, 2009[16]	Determine the factors associated with depressive symptoms in older veterans with heart failure	Cohort study	104 Veteran Outpatients USA 71.7 yrs (7.7) 103 male (99%) White (70%), African American (23%), Hispanic (7%) NYHA II (11%); III (39%); IV (50%) LVEF not reported	-
Scherer, 2008[17]	Identify the psychosocial determinants for frequent primary health care utilisation in patients with heart failure	Cohort study	310 Outpatients Germany 72.9 yrs (9) 145 male (46.7%) Ethnicity not reported NYHA I (52%); II (35%); III	

[16] Same sample as Cully, 2008
[17] Same sample as Scherer, 2007

First author, yr	Aim of study	Design	HF patient population (N, Source of patients, age, sex, ethnicity, NYHA class, LVEF)	Comparison
			(8%); IV (2%); missing data - 9 (3%) LVEF not reported	
Schiffer, 2008	Determine whether type-D personality and depressive symptoms would predict clinically significant anxiety at 1-year follow-up	Cohort study	149 Outpatients Holland 66 yrs (8.6) 118 male (79%) Ethnicity not reported NYHA III/IV – 72 (48%) LVEF 30% (7)	-
Serafini, 2010	The impact of anxiety, depression, and suicidality on quality of life and functional status of patients with heart failure and hypertension	Cohort study	120 Unclear setting Italy 59.7 yrs (12) 79 Males (66%) Ethnicity not reported NYHA I (15%); II (30%); III (30%); IV (25%) LVEF not reported	120 Hypertension patients
Song, 2008[18]	Determine whether depressive symptoms mediate the link between anxiety and event-free	Cohort Unclear reporting	260 Inpatients Korea 63 yrs (9)	-

[18] Abstract, additional data sent by author

First author, yr	Aim of study	Design	HF patient population (N, Source of patients, age, sex, ethnicity, NYHA class, LVEF)	Comparison
	survival		145 males (56%) Ethnicity not reported NYHA III/IV - 125 (48%) LVEF not reported	
Strauber, 2012	To compare psychosocial risk factors for cardiovascular disease across the affective spectrum (depression, anxiety, vital exhaustion, positive affect), personality characteristics (hostility, type D personality), and social support between 3 groups of cardiovascular patients.	Cohort study	105 Outpatients USA 59.7 yrs (10.7) 89 Males (85%) Ethnicity not reported NYHA class not reported LVEF 27.3% (6.9)	548 Coronary Artery Disease patients 79 Peripheral Artery Disease patients
Thomas, 1997[19]	Examine the independent contributions of psychosocial and physiological status to survival in patients who had experienced a myocardial infarction	Cohort study	66 Outpatients USA & Canada 64.7 yrs (1.1) 45 Males (38%) White (58%), Black (23%), Hispanic (9%), American Indian Inuit (5%), Asian (2%)	-

[19] Additional data sent by author

First author, yr	Aim of study	Design	HF patient population (N, Source of patients, age, sex, ethnicity, NYHA class, LVEF)	Comparison
			NYHA I (29%); II (58%); III (13%) LVEF not reported	
Tuschihashi - Makaya, 2009	Determine if depression and anxiety are associated with adverse outcomes in patients with heart failure and identify the independent determinants of these psychological states.	Cohort study	139 Outpatients Japan 67.6 yrs (12.9) 91 Males (66%) Ethnicity not reported NYHA I (32%); II (52%); III (16%) LVEF 48.2% (18)	-
Volz, 2012	To investigate the prognostic impact of depression, anxiety, vital exhaustion, social support and Type D personality on prognosis of patients with heart failure.	Cohort study	111 Outpatients Switzerland 57 yrs (14) 91 Males (82%) Ethnicity not reported NYHA I (23.4%/); II (59.5%); III 16.2%); IV (0.9%) LVEF 32.6% (13.6)	-
Steptoe, 2000	Assess the health related quality of life and psychological well-being of dilated cardiomyopathy	Mixed case-control/cohort	60 Outpatients UK 47.6 yrs (14.4) 40 male (67%) Ethnicity not reported	-

First author, yr	Aim of study	Design	HF patient population (N, Source of patients, age, sex, ethnicity, NYHA class, LVEF)	Comparison
	patients, and relate these to clinical variables and psychological adjustment		NYHA I (60%); II (33%); III/IV (7%) LVEF not reported	
Chung, 2009	Examine whether heart failure patients' and spousal caregivers' depressive symptoms and anxiety predicted their own quality of life as well as their spouse's.	Case control	58 Outpatients USA 61 yrs (12) 43 male (74%) White (93%), African American (7%) NYHA III/IV- 24 (43%) LVEF 34.2% (13)	58 primary carers of HF patients.
De Jong, 2004[20]	Determine whether heart rate and blood pressure were related to level of anxiety in acutely ill cardiac patients	Case control	32 Outpatients USA 53.5 yrs (13.3) 22 male (69%) White (85%), Black (12%), American Indian (3%) Clinical characteristics not reported	54 AMI 31 healthy individuals
Freidmann, 2006[21,22]	Examine the independent	Case control	149 Outpatients, USA, Canada &	

[20] Additional data provided by author

First author, yr	Aim of study	Design	HF patient population (N, Source of patients, age, sex, ethnicity, NYHA class, LVEF)	Comparison
	contributions of psychosocial factors and disease severity to mortality in heart failure outpatients		NZ 60.8 yrs (10.9) 186 male (64%) White (87%) White 130 (87%) NYHA II (75%), III (25) LVEF 25.3% (6.9)	---
Hermann-Lingen, 2003	Determine whether plasma levels of pro – ANP were associated with anxiety in chronic heart failure patients	Case control	46 Mixed Germany 62.4 (14.2) 40 male (87%) Ethnicity not reported NYHA I (15%); II (41%); III - (24%); IV - (20%) LVEF 28% (9)	73 participants at least one cardiovascular risk factor but no known HD and no clinical signs of HF
Steinke, 2008	To explore the relationships and predictors between sexual activity and psychosexual, demographic variables in	Case control	85 Outpatients USA 60.6 yrs (10.6) 52 male (61%) White (88%), African American	59 healthy elders recruited from senior centres

[21] Duplicate sample Thomas, 2006
[22] Duplicate sample Thomas, 2009

First author, yr	Aim of study	Design	HF patient population (N, Source of patients, age, sex, ethnicity, NYHA class, LVEF)	Comparison
	healthy elders and patients with heart failure		(12%) NYHA I (7%); II (28%); III (45%); IV (20%) LVEF 33% (13)	
Abrams, 2008	Determine whether associations between psychiatric co- morbidity and hospital mortality vary depending on the method used to identify psychiatric co-morbidity in patients with acute medical conditions	Case series	15, 146 Mixed USA 70.7yrs (11.5) 14, 843 male (98 %) White (58%), Black (20%), Hispani (1%), Missing (21%) Clinical characteristics not reported	16, 927 Pneumonia
Ansa, 2009	To determine prevalence of psychological distress in Nigerian patients with heart failure as well as identifying the possible predictive factors in the environment.	Case series	111 Outpatients Nigeria Not reported 61 male (55%) African Black (100%) NYHA II (2%); III (4%); IV (94%) LVEF not reported	-
Brouwers, 2012	To examine the link between NTproBNP	Case series	94 Outpatients Denmark 62 yrs (9)	----

First author, yr	Aim of study	Design	HF patient population (N, Source of patients, age, sex, ethnicity, NYHA class, LVEF)	Comparison
	and a range of psychological risk markers (i.e., depressive symptoms, anxiety, and Type Dpersonality)		75 male (80%) Ethnicity not reported NYHA I (3%); II (65%); III (32%) LVEF 26.1% (6.8)	
Chen, 2010	To examine predictors of fatigue in patients with heart failure, including demographic and disease characteristics, physical factors (symptomatic distress and physical functioning), psychological factors (anxiety and depression) and situational factors (social support).	Case series	105 Outpatients Taiwan 65.2 yrs (15.1) 68 male (65%) Ethnicity not reported NYHA I (3%); II (42%); III (51%); IV (4%) LVEF not reported	----
Clarke, 2000	Explore the predictive ability of psychological and social variables on functional status in patients with left ventricular dysfunction, with and without heart failure.	Case series	2993 Unclear setting USA 60.1yrs (10.0) 2558 male (86%) White (84%), Black (12%), Hispanic (2%), Other (2%) NYHA I (44%); II (43%); III/IV (13%) LVEF 26.7% (6.4)	----

First author, yr	Aim of study	Design	HF patient population (N, Source of patients, age, sex, ethnicity, NYHA class, LVEF)	Comparison
Covera-Tindel, 2009[23]	Examine the relative contribution of physical and emotional functioning to overall quality of life in men with heart failure	Case series	76 Outpatients USA 62.9 yrs (10.6) 76 male (100%) White (49%) NYHA II (80%); III/IV (20%) LVEF 27.3% (8.8)	----
De Jong, 2005	Determine the relative importance of sociodemographic, clinical, health perception and emotional variables in predicting health status in heart failure patients	Case series	87 Outpatients USA 72 yrs (11) 45 male (52%) White (89%), Black (11%) NYHA II (47%); III (47%); IV (6%) LVEF 38% (15)	----
Dekker, 2012[24]	To establish whether depressive symptoms	Case series	635 Mixed Setting USA 62 yrs (12)	----

[23] Additional design data from Covera-Tindel et al (2004)

[24] Conference abstract

First author, yr	Aim of study	Design	HF patient population (N, Source of patients, age, sex, ethnicity, NYHA class, LVEF)	Comparison
	independently predict anxiety symptoms in a sample of heart failure patients		406 male (64%) Ethnicity not reported NYHA III/IV (56%) LVEF not reported	
Doering, 2004	Identify relationships between coping styles and emotional states in patients with advanced heart failure	Case series	87 Outpatients USA 54 yrs (11) 59 male (70%) White (70%), Hispanic (10%), African American (8%), Asian Pacific Islander (4%), American Indian (1%) NYHA I (3%); II (21%); III (49%); IV (27%) LVEF 25% (8)	----
Eisenberg, 2012	To examine whether coping strategies moderated the association between anxiety and self-rated physical functioning.	Case series	273 Outpatients USA 53.5 yrs (11.6) 186 male (68%) White (29%), African American (24%), Hispanic (41%), Other (6%) NYHA I (24%); II (45%); III (27%); IV (4%)	----

First author, yr	Aim of study	Design	HF patient population (N, Source of patients, age, sex, ethnicity, NYHA class, LVEF)	Comparison
			LVEF 27% (13)	
Falk, 2009	Examine the association between fatigue and anxiety, depression and symptom distress in patients with heart failure	Case series	112 Inpatients 77 yrs (10) 67 male (60%) Ethnicity not reported NYHA II (18%); III (73%); IV (6%) LVEF <40% - 55 (49%)	----
Haworth, 2007[25]	Examine the criterion validity of the Hospital Anxiety and Depression Scale (HADS) and Geriatric Depression Scale 15-item (GDS-15) in heart failure outpatients	Case series	88 Outpatients UK 69.9 yrs (7.6) 73 male (83%) Ethnicity not reported NYHA I (7%); II (62%); III (22%); IV (1%), missing data – 7 (8%) LVEF 35% (8)	---
Heo, 2008[26, 27]	Examine the variables that predict physical symptom	Case series	84 outpatients USA 65 yrs (17)	---

[25] Same sample as Haworth 2005
[26] Additional data sent by author

First author, yr	Aim of study	Design	HF patient population (N, Source of patients, age, sex, ethnicity, NYHA class, LVEF)	Comparison
	status and health related quality of life in heart failure patients		51 male (61%) White non-Hispanic (86%), African American (13%), Other (1%) NYHA II (44%); III (33%); IV (6%) LVEF 36% (16)	
Huang, 2012[28]	To determine the age interaction effect between psychosocial factors and HRQOL in patients with heart failure	Case series	489 Outpatients USA & Taiwan 61.7 yrs (13) 344 male (70.3%) Taiwanese (45.8%) NYHA I (11%); II (47%); III (31%); IV (11%) LVEF not reported	---
Jiang, 2004[29]	Examine the prognostic value of anxiety and its interaction with depression in patients with chronic heart failure	Case series	291 Inpatients USA 63 yrs (13) 186 male (64%) White (72%), Black (18%), Other	---

[27] Same sample as Heo 2007a, 2007b
[28] Abstract. Same sample as Yu, 2012; Reigel, 2011
[29] Additional data from Jiang et al (2001)

First author, yr	Aim of study	Design	HF patient population (N, Source of patients, age, sex, ethnicity, NYHA class, LVEF)	Comparison
			(4%) NYHA II (53%); III (39%); IV (8%) LVEF 30.2% (13.2)	
Lee, 2005[30]	To identify significant demographic, clinical and psychosocial factors associated with health related quality of life in patients with chronic heart failure	Case series	227 Inpatients Hong Kong 77.1 (7.9) 108 male (47.6%) Ethnicity not reported NYHA I (12%); II (50%); III (34%) IV (4%) LVEF not reported	---
Luyster, 2009	Examine the impact of psychosocial factors on adherence to dietary recommendations in heart failure patients treated with an Implanted Cardiac Device	Case series	88 Outpatients USA 70 yrs (10.7) 68 male (77%) White (82%), African American (15%), American Indian or Alaska native (2%), Asian (1%) NYHA I (46%); II (52); III (2%) LVEF not reported	---

[30] Same sample as Yu 2004

First author, yr	Aim of study	Design	HF patient population (N, Source of patients, age, sex, ethnicity, NYHA class, LVEF)	Comparison
Moser, 2005[31]	Describe the prevalence of multiple risk factors for rehospitalisation in patients recently discharged from hospital following decompensated heart failure	Case series	202 Outpatients USA 70 yrs (12) 99 male (49%) White (88%), African American (12%) NYHA I (1%); II (30%); III (40%); IV (26%) LVEF not reported	---
Moser, 2009[32]	To test the psychometric properties of the Control Attitudes Scale-Revised (CAS-R) in a group of cardiac patients	Case series	146 Outpatients USA 68 yrs (13) 80 male (84.8%) White (59%) NYHA I (2%); II (40%); III (47%); IV (8%) LVEF 36 (15)	3,396 CHD 513 AMI
Moser et al, 2010[33]	Determine the impact of cardiac disease on psychological adjustment	Case series	478 Outpatients USA 65.6 yrs (9.2) 355 male (74%) White (65%). African American	298 Post MI 131 post CABG 260

[31] Duplicate sample Reigel, 2011
[32] Same sample as DeJong 2008
[33] Unpublished manuscript sent by author

First author, yr	Aim of study	Design	HF patient population (N, Source of patients, age, sex, ethnicity, NYHA class, LVEF)	Comparison
			(9.4%), Hispanic (7.5%), Other (8.8%) NYHA class not reported LVEF 29.5 (12.2)	healthy elders.
Mulligan, 2012[34]	To examine how heart failure patients' mood and quality of life change during the early high-risk period after a diagnosis and to identify factors that may influence change.	Case series	166 Mixed setting UK 73 yrs (median) (IQR 25-91) 111 male (67%) Ethnicity not reported NYHA I (27%); II (58%); III (14%); IV (1%) LVEF not reported	---
Shen, 2011	To examine whether depression, anxiety, social support, and their changes predicted the decline of physical functioning in heart failure patients over 6 months	Case series	238 Outpatients USA 54.1 yrs (11) 163 male (68%) White (26%), African American (24%), Hispanic (44%), Other (5%) NYHA I (14%); II (42%); III (37%); IV (6%) LVEF not reported	

[34] 6 month anxiety data

First author, yr	Aim of study	Design	HF patient population (N, Source of patients, age, sex, ethnicity, NYHA class, LVEF)	Comparison
Schweitzer, 2007	To test whether depression, anxiety, and self-efficacy are independent predictors of adherence to self-care maintenance recommendations	Case series	115 Mixed Australia 63.6 yrs (14.2) 72 male (70 %) Ethnicity not reported NYHA I (6 %); II (27 %); III (57 %); IV (10%). LVEF 32.9 % (0.7)	---
Von Kanel, 2009	To determine whether anxiety, depression and quality of life are assocaited with decreased heart rate recovery in heart failure patients	Case Series	56 Outpatients Switzerland 58 yrs (12) 47 male (84%) Ethnicity not reported NYHA not reported LVEF 36.5% (7.2)	---
Yu, 2009	To test the psychometric properties of the Myocardial Infarction Dimensional Assessment Scale (MIDAS) in Chinese cardiac patients	Case series	95 Setting unclear China 64.2 yrs (12) 64 male (67.4) Ethnicity not reported NYHA class not reported LVEF <40% - 59 (62%)	162 angina and 124 MI

N = number; Yrs= years; sd = standard deviation; freq = frequency; % = percentage; NYHA = New York Heart Association; UK= United kingdom; LVEF = Left Ventricular Ejection Fraction; RCT = Randomised Controlled Trial; MI = myocardial infarction

Population

The sample sizes in the studies varied greatly with a range from 17 to 15,146 (Abrams et al, 2008; Witham, 2008). A large proportion of the studies (42%) sampled less than 100 patients in their sample. These sample sizes are considered small as the majority of included studies were observational in design. What is determined as acceptable in terms of sample size is actually calculated based on the number of factors under investigation. However, as a general rule the larger the sample the lower the chance of error in measurement of variables.

The total sample size from the included studies was 26, 366 participants with a diagnosis of HF. Two studies included all male samples (Koukouvou, 2004; Covera-Tindel, 2009), one an all female sample (Jackson et al, 2011). The remaining studies reported on mixed samples, all of which had a higher proportion of males to females, with the exception of de Jong et al, 2011, Lee, 2005, Scherer, 2008, Moser et al, 2005 and Thomas, 1997. The weighted proportion of males was 94% (n = 24, 691). The weighted average age from included studies was 67.5 years (sd 11.4), with a range of 44.6 yrs to 81.6 yrs (Karapolat et al, 2009; Witham, 2008).

Sixteen studies did not report any NYHA functional class and thirty-three studies did not report LVEF data to describe the clinical characteristics of the sample, of these studies eight reported failed to report either NYHA or LVEF clinical characteristics of the sample (Houchen et al, 2012; Mitchell et al, 2012; Dar et al, 2009; Yu et al, 2009; Abrams et al, 2008; Zwisler et al, 2008; Barrow et al, 2007; de Jong et al, 2004) Of the studies that did measure clinical variables of HF severity 56 papers reported NYHA functional class data for their sample. Reporting of these data varied, with some papers collapsing classes II/III and classes III/IV and one paper measuring classes as 2, 2.5 and 3 (Kulcu, 2007). Fourteen studies' samples were categorised as mild (19%), six were moderate to severe (8%) and 36 (2%) were mixed.

Thirty-nine studies measured the LVEF of participants, presenting either a mean percentage (SD) or in the case of two studies the percentage of patients with an EF below 40% (Falk, 2009; Yu, 2009). The weighted average LVEF was 31.1% (from 39 studies). The mean LVEF ranged from 22% to 48.20% (Junger, 2005; Tuschihashi-Makaya, 2009).

Ethnicity data was reported in under half of the studies (n =35), with the vast majority of these originating in the USA. Few studies from Europe or Asia measured ethnicity, and only three studies from the UK assessed patient's ethnic background (Hallas et al, 2010; Jolly et al., 2009; Dar et al., 2009).

Outcome data

Anxiety Disorders

Of the 72 included studies six used clinical interviews, clinical questionnaires or diagnostic criteria to identify the presence of specific clinical anxiety disorders in samples of patients with a HF diagnosis (Mitchell et al, 2012; Goeobel et al, 2009; Abrams, 2008; Muller-Tasch, 2008; Haworth, 2007; Peters-Klimm, 2007). All of these studies provided proportional data (percentages) for patients meeting diagnostic criteria for anxiety disorders. One UK study used the Structured Clinical Interview (SCID-I) (First et al, 2002) to measure the prevalence of Generalised Anxiety Disorder in their sample (Haworth, 2007). Two studies used the GAD-7 (Mitchell et al, 2012; Peters-Klimm et al, 2007) and one study used the GAD-2 (Geobel et al, 2009) to identify Generalised Anxiety Disorder (Spitzer et al, 2006). None of these studies were from the UK. The Patient Health Questionnaire (PHQ) (Spitzer et al, 1999) was used to identify Panic Disorder in a German Study (Muller –Tasch, 2008). Finally in one US study medical notes from outpatient mental health appointments were studied and anxiety disorders identified using ICD-9-CM codes (Abrams, 2008). Table 10 in the text presents anxiety outcome data from included studies.

Probable clinical anxiety

Fourty-five studies used questionnaire measures or interviews that assess anxiety symptoms and allow for the interpretation of scores as 'normal', mild/moderate or possible/probable/severe clinical anxiety'. Of these studies 27 reported prevalence rates using a range of recommended thresholds to identify caseness.

Of the 45 studies that screened for probable clinical anxiety using questionnaires and interviews 28 used the **Hospital Anxiety and Depression Scale (HADs)** (Zigmond AS, 1983), three of which were Chinese translation (Lee, 2005; Yu, 2007b; Yu, 2009) and two of which were the German translation (von Kanel et al, 2009; Junger, 2005). Twenty of the

28 studies that used the HADS (71%) originated in the UK or Europe. Seven studies used a cut-off of 11 to identify the prevalence of moderate cases of anxiety (Volz et al, 2012; Almeida et al, 2012; Chen et al, 2010; Hallas et al, 2010; Mulligan et al, 2012; Falk, 2009; Steptoe, 2000), of these studies five provided additional prevalence rates using a range of cut-off thresholds (Volz et al, 2012; Chen et al, 2010; Hallas et al, 2010; Mulligan et al, 2012). Two studies used a cut-off of 10> to identify anxiety (Eisenberg et al, 2012; Shen et al, 2011) and in addition provided prevalence data using a cut-off of 8-10.

Two studies used a cut-off of 10 (Junger, 2005, Laederach-Hofman, 2007), five studies identified anxiety using a threshold of 8> (Ansa et al, 2009; Brouwers et al, 2012; Damen et al, 2011; Dar et al, 2009; von Kanel et al, 2009) and one study used a cut-off of seven (Haworth, 2007).

Eleven studies used the **State Trait Anxiety Inventory (STAI)** to assess anxiety. Four studies used the State scale in isolation (Jackson et al, 2011; Freidmann, 2006; Lader, 2003; Tuschihashi - Makaya, 2009), three studies used the trait scale in isolation (Luyster, 2009; Schweitzer, 2007; Song, 2008) and four reported both state and trait scores (Karaploat et al, 2009; Jiang, 2004; Kulcu, 2007; Thomas, 1997). Many of the studies using the STAI were from the US or Canada (six studies); the STAI was not used in any papers from the UK. All studies that reported prevalence rates of anxiety using this scale used a cut-off of 40 to identify caseness of anxiety.

Three studies used the **Hamilton Anxiety Rating Scale (HARS)** also known as the HAM-A clinical interview, one study originated in USA (Kostis et al, 1994), one from Holland (Schiffer et al, 2008), one from Italy (Serafini et al, 2010). Only one of the studies using the HARS reported prevalence data, using a cut-off of 17 to identify anxious individuals (Schiffer, 2008). Two American studies (Cully et al, 2010; Paukert et al, 2009) used the **Geriatric Anxiety Inventory (GAI)** (Pachana et al, 2007) to measure anxiety symptoms, using a score of eight as a cut-off to identify anxious individuals.

Elevated symptoms of anxiety

Nineteen studies measured symptoms of anxiety using tools that can identify elevated levels of anxiety compared with published norms from a range of groups including the general population. Of these studies eight reported average scores and variance, reporting

the prevalence of anxiety as a proportion of the sample with scores above published norms. The **Brief Symptom Inventory – Anxiety (BSI-A)** (Derogatis 1994) was used in thirteen studies (Lee et al, 2013; Huang et al, 2011, 2012; Dekker, 2012; Khalil et al, 2009; Evangelista, 2009; Moser, 2009; Chung, 2009; Heo, 2008; Stienke, 2008; de Jong, 2004, 2005, 2011), all of which came from the USA or USA mixed samples. Of the thirteen studies to use this measure five reported the prevalence of anxious participants in their sample using a cut-off of 0.35 (general population norm) (Dekker, 2012, Chung, 2009; de Jong, 2004; 2005; Heo, 2008), one study used a cut-off of 0.98 (Evangelista, 2009); a mean score found in previous research using HF samples. The **Symptom Checklist revised anxiety subscale (SCL-90-R)** (Derogatis, 1994), an extended version of the BSI-A, was used in one UK study (Barrow, 2007).

The **Multiple Adjective Affect Checklist (MAACL)** (Zuckerman & Lubin, 1965) was used in five studies to measure anxiety symptoms (Covera-Tindel, 2009; Dracup, 2003, 2007; Moser, 2005; 2010), all of which came from the USA. Only one of these studies reported prevalence rates of anxious participants using a cut-off of seven (Moser, 2005).

Anxiety symptoms

Finally three studies used a measure to assess symptoms of anxiety with no reference to normative values or thresholds to identify caseness of anxiety (Clarke, 2000; Doering, 2004; Sullivan, 2009). The **Profile of Mood States (POMS)** anxiety and tension subscale (McNair et al, 1981) was used in the three studies, all from the USA (Clarke, 2000; Doering, 2004; Sullivan, 2009).

Table 10: Included studies participant characteristics and anxiety outcomes

First author, yr.	Participant characteristics	Anxiety		
	Age (yrs, sd) **Gender freq (%)** **Ethnicity freq (%)** **NYHA class Freq (%)** **LVEF Mean % (SD)**	**Anxiety Measure**	**Symptom Score mean (SD)**	**Prevalence sample above cut-off for anxiety %**
Anxiety Disorders				
Haworth, 2007[35,36]	88 Outpatients UK 69.9 yrs (7.6) 73 male (83%) Ethnicity not reported NYHA I (7%); II (62%); III (22%); IV (1%), missing data – 7 (8%) LVEF 35% (8)	SCID – I (GAD)	-	11.4%
Peters-Klimm et al, 2007[37]	199 Outpatients Germany 69.6 yrs (9.8) 146 male (73%) Ethnicity not reported NYHA I (3%); II (64%); III (32%); IV (1%) LVEF 37% (7.3)	GAD – 7 >10	3.6 (3.5)	6.3%
Mitchell, 2012	129 Setting unclear USA 61.2 yrs 84 Male (65%) White (54%) Clinical characteristics not reported	GAD -7 > 10	5.05 (5.7)	23%
Geobel, 2009	96 Veteran Outpatients USA 67.2 yrs (11) 92 Males (96%) African American (27%), White (58%), Other (15%) NYHA class not reported	GAD 2	1.62 (1.97)	26%

[35] Same sample as Haworth 2005
* Proportion calculated using PQRS software
[36] Reference repeated using HADs data for narrative but not statistical synthesis
[37] Additional unpublished data from trial sent by Muller-Tasch

First author, yr.	Participant characteristics	Anxiety		
	Age (yrs, sd) **Gender freq (%)** **Ethnicity freq (%)** **NYHA class Freq (%)** **LVEF Mean % (SD)**	**Anxiety Measure**	**Symptom Score mean (SD)**	**Prevalence sample above cut-off for anxiety %**
	LVEF 39.1% (16.7)			
Muller-Tasch, 2008	258 Outpatients Germany 62.1 (11.8) 199 male (77%) All white NYHA I (4%); II (47%); (38%); IV (1%), missing (10%) LVEF 30.8% ()	PHQ – Panic disorders and other anxiety disorders	-	9.3% panic disorder 6.6% had other unspecified anxiety disorders
Abrams, 2008	15, 146 Mixed USA 70.7yrs (11.5) 14, 843 male (98 %) White (58%), Black (20%), Hispanic (1%), Missing (21%) Clinical characteristics not reported	ICD-9-CM Anxiety disorders codes diagnosed using medical notes	-	Inpatients: 1.4% Outpatients: 11.7%
<u>Clinical levels of anxiety symptoms</u>				
Volz, 2012	111 Outpatients Switzerland 57 yrs (14) 91 Males (82%) Ethnicity not reported NYHA I (23.4%/); II (59.5%); III 16.2%); IV (0.9%) LVEF 32.6% (13.6)	Self reported HADS 15-21 11-14 8-10 8>	-	 3.6% 5.4% 19% 28.8%
Almeida, 2012	77 Outpatients and community volunteers Australia 64.4 yrs (10.2) 64 Males (83%)	Self reported HADS 11>	1(0, 3)[38]	6.2%

[38] Median and Inter-Quartile Range

First author, yr.	Participant characteristics	Anxiety		
	Age (yrs, sd) **Gender freq (%)** **Ethnicity freq (%)** **NYHA class Freq (%)** **LVEF Mean % (SD)**	**Anxiety Measure**	**Symptom Score mean (SD)**	**Prevalence sample above cut-off for anxiety %**
	Ethnicity not reported NYHA class not reported LVEF 29.3% (7.8)			
Chen, 2010	105 Outpatients Taiwan 65.2 yrs (15.1) 68 male (65%) Ethnicity not reported NYHA I (3%); II (42%); III (51%); IV (4%) LVEF not reported	Self reported HADS 11> 8-10	-	 7% 15.2%
Falk, 2009	112 Inpatients Sweden 77 yrs (10) 67 male (60%) Ethnicity not reported NYHA II (18%); III (73%); IV (6%) LVEF <40% - 55 (49%)	Self reported HADS 11 >	4.9 (3.9)	10%
Hallas, 2010	146 Outpatients UK 48.6 yrs (9.5) 120 Males (82%) White (88%) NYHA class not reported LVEF 38.2% (15.1)	Self reported HADS 11> 8>	8.43 (4.8)	30% 56%
Mulligan, 2012[39]	166 Mixed setting UK 73 yrs (median) (IQR 25-91) 111 male (67%) Ethnicity not reported NYHA I (27%); II (58%); III (14%); IV (1%) LVEF not reported	Self reported HADS 11> 8>		 10.4% 11.4%
Steptoe,	60 Outpatients UK	Self		

[39] Six month anxiety data

First author, yr.	Participant characteristics	Anxiety		
	Age (yrs, sd) **Gender freq (%)** **Ethnicity freq (%)** **NYHA class Freq (%)** **LVEF Mean % (SD)**	**Anxiety Measure**	**Symptom Score mean (SD)**	**Prevalence sample above cut-off for anxiety %**
2000	47.6 yrs (14.4) 40 male (67%) Ethnicity not reported NYHA I (60 %); II (33%); III/IV (7%) LVEF not reported	reported HADS 11>	8.10 (3.9)	52%
Eisenberg, 2012	273 Outpatients USA 53.5 yrs (11.6) 186 male (68%) White (29%), African American (24%), Hispanic (41%), Other (6%) NYHA I (24%); II (45%); III (27%); IV (4%) LVEF 27% (13)	Self reported HADS 10> 8-10	-	 21% 24%
Junger, 2005	209 setting not reported Germany 54 (10) 180 male (86%) Ethnicity not reported NYHA I (12%); II (44%); III (44%) LVEF 22% (10)	Self reported HADS –D German version 10 >	7.0 (4.0)	22%
Laederach-Hofman, 2007	25 Outpatients Switzerland Age not reported 20 male (80%) Ethnicity not reported NYHA I (44%); II (40%); III (16%) LVEF 28.7% (7..2)	Self reported HADS 10>	5.5 (4.1)	14%
Shen, 2011	238 Outpatients USA 54.1 yrs (11) 163 male (68%) White (26%), African American (24%), Hispanic	Self reported HADS 10> 8-10		 21% 24%

First author, yr.	Participant characteristics	Anxiety		
	Age (yrs, sd) **Gender freq (%)** **Ethnicity freq (%)** **NYHA class Freq (%)** **LVEF Mean % (SD)**	**Anxiety Measure**	**Symptom Score mean (SD)**	**Prevalence sample above cut-off for anxiety %**
	(44%), Other (5%) NYHA I (14%); II (42%); III (37%); IV (6%) LVEF not reported			
Ansa, 2009	111 Outpatients Nigeria Not reported 61 male (55%) African Black (100%) NYHA II (2%); III (4%); IV (94%) LVEF not reported	Self reported HADS 8>	-	16%
Brouwers, 2012	94 Outpatients Denmark 62 yrs (9) 75 male (80%) Ethnicity not reported NYHA I (3%); II (65%); III (32%) LVEF 26.1% (6.8)	Self reported HADS 8>	5 (4.5)	23.4%
Damen, 2011	237 Outpatients Netherlands 66.9 yrs (8.7) 51 Males (21.5%) Ethnicity not reported NYHA I/II (91%) LVEF 33.6% (6.7)	Self reported HADS 8>	-	25%
Dar, 2009[40]	182 outpatients UK 71.7 yrs (11.62) 121 male (66%) South Asian (20%) Clinical characteristics not reported	Self reported HADS 8 >	5.74 (4.65)	28%

[40] Additional data sent by author

First author, yr.	Participant characteristics	Anxiety		
	Age (yrs, sd) **Gender freq (%)** **Ethnicity freq (%)** **NYHA class Freq (%)** **LVEF Mean % (SD)**	**Anxiety Measure**	**Symptom Score mean (SD)**	**Prevalence sample above cut-off for anxiety %**
Von Kanel, 2009	56 Outpatients Switzerland 58 yrs (12) 47 male (84%) Ethnicity not reported NYHA not reported LVEF 36.5% (7.2)	Self reported HADS –G German version 8>	4.5 (3.4)	21%
Haworth, 2007[41,42]	88 Outpatients UK 69.9 yrs (7.6) 73 male (83%) Ethnicity not reported NYHA I (7%); II (62%); III (22%); IV (1%), missing data – 7 (8%) LVEF 35% (8)	Admin HADS 7 >	-	17%
Freyssin, 2009	26 Setting not reported France 54.5 yrs (10.50) 13 Male (50%) Ethnicity not report NYHA class not reported LVEF 29.10%	Self reported HADS	7.09 (2.10)	-
Houchen, 2012	17 Inpatients UK 67.3 yrs (10.4) 13 Males (77%) Ethnicity not reported Clinical characteristics not reported	Self reported HADS	5 (4.40)	-
Hermann-Lingen, 2003	46 Mixed Germany 62.4 (14.2) 40 male (87%) Ethnicity not reported NYHA I (15%); II (41%); III	Self reported HADS	6.4 (4.0)	-

[41] Same sample as Haworth 2005

* Proportion calculated using PQRS software

[42] Reference repeated - additional anxiety data from paper

First author, yr.	Participant characteristics	Anxiety		
	Age (yrs, sd) **Gender freq (%)** **Ethnicity freq (%)** **NYHA class Freq (%)** **LVEF Mean % (SD)**	**Anxiety Measure**	**Symptom Score mean (SD)**	**Prevalence sample above cut-off for anxiety %**
	- (24%); IV - (20%) LVEF 28% (9)			
Jolly, 2009	169 Outpatients UK 68 (12.6) 126 male (75%) White (77%) NYHA I (6%); II (74%); III (20%) LVEF not reported	Self reported HADS	5.76 (4.2)	-
Koukouvou, 2004	26 Outpatients Greece 52.5 (9.7) 26 male (100%) Ethnicity not reported NYHA II (58%); III (42%) LVEF not reported	Self reported HADS	12.4 (1.60)	-
Lee, 2005[43]	227 Inpatients Hong Kong 77.1 (7.9) 108 male (47.6%) Ethnicity not reported NYHA I (12%); II (50%); III (34%) IV (4%) LVEF not reported	Self report HADS –C Chinese version	5.15 (3.90)	-
Scherer, 2008[44]	310 Outpatients Germany 72.9 yrs (9) 145 male (46.7%) Ethnicity not reported NYHA I (52%); II (35%); III (8%); IV (2%); missing data - 9 (3%) LVEF not reported	Self reported HADS	5.9 (3.7)	-

[43] Same sample as Yu 2004
[44] Same sample as Scherer, 2007

First author, yr.	Participant characteristics	Anxiety		
	Age (yrs, sd) **Gender freq (%)** **Ethnicity freq (%)** **NYHA class Freq (%)** **LVEF Mean % (SD)**	**Anxiety Measure**	**Symptom Score mean (SD)**	**Prevalence sample above cut-off for anxiety %**
Strauber, 2012	105 Outpatients USA 59.7 yrs (10.7) 89 Males (85%) Ethnicity not reported NYHA class not reported LVEF 27.3% (6.9)	Self reported HADS	5.4 (3.9)	-
Witham, 2008	17 Outpatients UK 81.6 yrs (5.5) 12 male (70.6%) Ethnicity not reported NYHA class II (47%); III (53%) LVEF not reported	Self reported HADS	2.1 (2.2)	-
Yu, 2007b[45]	153 Outpatients China 75.1 yrs (7.9) 77 male (50.3%) Ethnicity not reported NYHA II (60%); III (40%) LVEF not reported	Self reported HADS –C Chinese version	4.3 (3.9)	-
Yu, 2009	95 Setting unclear China 64.2 yrs (12) 64 male (67.4) Ethnicity not reported NYHA class not reported LVEF <40% - 59 (62%)	Self reported HADS – C Chinese version	5.85 (3.67)	-
Zwisler, 2008[46]	91 Outpatients Denmark 71.4 yrs (11.4) 57 male (63%) Ethnicity not reported Clinical characteristics not reported	Self reported HADS	9.5 (1.9)	-

[45] Same sample as Yu 2007a
[46] Additional data sent by author

First author, yr.	Participant characteristics	Anxiety		
	Age (yrs, sd) **Gender freq (%)** **Ethnicity freq (%)** **NYHA class Freq (%)** **LVEF Mean % (SD)**	**Anxiety Measure**	**Symptom Score mean (SD)**	**Prevalence sample above cut-off for anxiety %**
Freidmann, 2006	149 Outpatients, USA, Canada & NZ 60.8 yrs (10.9) 186 male (64%) White (87%) White 130 (87%) NYHA II (75%), III (25) LVEF 25.3% (6.9)	Self report STAI –S 40 >	36.7 (11.6)	45%
Jackson, 2011	35 Outpatients USA 55.7 yrs (14.5) All female White (60%), African American (40%) NYHA class not report LVEF 42% (15.8)	Self report STAI - S	41.3 (10.9)	-
Jiang, 2004[47]	291 Inpatients USA 63 yrs (13) 186 male (64%) White (72%), Black (18%), Other (4%) NYHA II (53%); III (39%); IV (8%) LVEF 30.2% (13.2)	Self report STAI 40 >	State 33.5 (12.8) Trait 33.5(11.7).	State 29% Trait 28%
Karapolat, 2009	69 Outpatients Turkey 44.6 yrs (12.5) 43 Males (62%) Ethnicity not reported NYHA II (62%); III (38%) LVEF not reported	Self report STAI	State 44.8 (9.04) Trait 44.5 (11.2)	-

[47] Additional data from Jiang et al (2001)

First author, yr.	Participant characteristics	Anxiety		
	Age (yrs, sd) **Gender freq (%)** **Ethnicity freq (%)** **NYHA class Freq (%)** **LVEF Mean % (SD)**	**Anxiety Measure**	**Symptom Score mean (SD)**	**Prevalence sample above cut-off for anxiety %**
Kulcu, 2007	44 setting not reported Turkey 59.3 (10.7) 32 male (72%) Ethnicity not reported NYHA II/III 44 (100%) LVEF 34.6% (13.3)	Self reported STAI	State 42.8 (14.7) Trait 61.6 (10.1)	- -
Lader, 2003	589 Setting not reported USA 64.6 (11.7) 433 male (73.5%) None white (14%) NYHA (14%); II (54%); III (30%); IV (2%) LVEF 34.7% (13.2)	Self reported STAI – S	16.40 (7.2)	-
Luyster, 2009	88 Outpatients USA 70 yrs (10.7) 68 male (77%) White (82%), African American (15%), American Indian or Alaska native (2%), Asian (1%) NYHA I (46%); II (52); III (2%) LVEF not reported	Self reported STAI – T 40>	35.6 (10)	36%
Schweitzer, 2007	115 Mixed Australia 63.6 yrs (14.2) 72 male (70%) Ethnicity not reported NYHA I (6%); II (27%); III (57%); IV (10%). LVEF 32.9% (0.7)	Self reported STAI – T 40 >	35.47 (10.35)	31%
Song, 2008[48]	260 Inpatients Korea	Self reported	50.8 (8.5)	-

[48] Abstract, additional data sent by author

First author, yr.	Participant characteristics	Anxiety		
	Age (yrs, sd) **Gender freq (%)** **Ethnicity freq (%)** **NYHA class Freq (%)** **LVEF Mean % (SD)**	**Anxiety Measure**	**Symptom Score mean (SD)**	**Prevalence sample above cut-off for anxiety %**
	63 yrs (9) 145 male (56%) Ethnicity not reported NYHA III/IV - 125 (48%) LVEF not reported	STAI-T 40>		
Thomas, 1997[49]	66 Outpatients USA & Canada 64.7 yrs (1.1) 45 male (38%) White (58%), Black (23%), Hispanic (9%), American Indian Inuit (5%), Asian (2%) NYHA I (29%); II (58%); III (13%) LVEF not reported	Self reported STAI	State 41.58 (1.620) Trait 40.58 (20-67)	State cut off >40 47.1% anxious Trait cut off >40 54.5% anxious
Tuschihashi - Makaya, 2009	139 outpatients Japan 67.6 yrs (12.9) 91 male (66%) Ethnicity not reported NYHA I (32%); II (52%); III (16%) LVEF 48.2% (18)	Self reported STAI -S	36.6 (9.1)	37%
Schiffer, 2008	149 Outpatients Holland 66 yrs (8.6) 118 male (79%) Ethnicity not reported NYHA III/IV – 72 (48%) LVEF 30% (7)	Interview HARS >17	-	11%
Serafini, 2010	120 Unclear setting Italy 59.7 yrs (12) 79 Males (66%) Ethnicity not reported NYHA I (15%); II (30%); III	Interview HARS	14.1 (2.6)	-

[49] Additional data sent by author

First author, yr.	Participant characteristics	Anxiety		
	Age (yrs, sd) Gender freq (%) Ethnicity freq (%) NYHA class Freq (%) LVEF Mean % (SD)	**Anxiety Measure**	**Symptom Score mean (SD)**	**Prevalence sample above cut-off for anxiety %**
	(30%); IV (25%) LVEF not reported			
Kostis, 1994	20 setting not reported USA 65.7(6.1) 14 (70%) Ethnicity not reported NYHA II (95%); III (5%) LVEF 33.8% (7)	Interview HARS	13.1 (8.7)	-
Cully, 2010	96 Veteran Outpatients USA 71.89 yrs (7.83) 95 Males (99%) White (74%) NYHA II (11.5%); III (41.7%); IV (46.9%) LVEF not reported	Self report GAI	4.99 (5.48)	-
Paukert, 2009[50]	104 Veteran Outpatients USA 71.7 yrs (7.7) 103 male (99%) White (70%), African American (23%), Hispanic (7%) NYHA II (11%); III (39%); IV (50%) LVEF not reported	Self reported GAI >8	5.04 (5.47)	24%
Elevated anxiety symptom scores				
Chung, 2009	58 Outpatients USA 61 yrs (12) 43 male (74%) White (93%), African American (7%) NYHA III/IV- 24 (43%)	Self reported BSI – A 0.35	0.64 (0.76)	43.1%

[50] Same sample as Cully, 2008

First author, yr.	Participant characteristics	Anxiety		
	Age (yrs, sd) Gender freq (%) Ethnicity freq (%) NYHA class Freq (%) LVEF Mean % (SD)	**Anxiety Measure**	**Symptom Score mean (SD)**	**Prevalence sample above cut-off for anxiety %**
	LVEF 34.2% (13)			
de Jong, 2004[51]	32 Outpatients USA 53.5 yrs (13.3) 22 male (69%) White (85%), Black (12%), American Indian (3%) Clinical characteristics not reported[52]	Self reported BSI –A 0.35	0.98 (0.89)	62.5%
de Jong, 2005	87 Outpatients USA 72 yrs (11) 45 male (52%) White (89%), Black (11%) NYHA II (47%); III (47%); IV (6%) LVEF 38% (15)	Self reported BSI -A 0.35	0.90 (0.70)	72.3%
de Jong, 2011	147 Outpatients USA 61 yrs (11) 44 males (30%) White (88%), Black (11%) NYHA I (6%), II (32%), III (44%), IV (15%) LVEF 35% (14)	Seld reported BSI-A 0.35	0.71 (0.7)	54.1%
Evangelista, 2009[53]	241 outpatients USA 56.7 yrs (13) 168 male (70%) White (70%), Hispanic (23%), Black (7%) NYHA II (35%); III (54%); IV (11%) LVEF 26.5% (7)	Self reported BSI – A > 0.98	0.96 (1. 7)	40%

[51] Additional data provided by author
[52] Paper cites reference for clinical characteristics that can not be located
[53] Additional data provided by author

First author, yr.	Participant characteristics	Anxiety		
	Age (yrs, sd) **Gender freq (%)** **Ethnicity freq (%)** **NYHA class Freq (%)** **LVEF Mean % (SD)**	**Anxiety Measure**	**Symptom Score mean (SD)**	**Prevalence sample above cut-off for anxiety %**
Dekker, 2012	635 Mixed Setting USA 62 yrs (12) 406 male (64%) Ethnicity not reported NYHA III/IV (56%) LVEF not reported	Self reported BSI –A > 0.35	0.72 (0.5)	55%
Heo, 2008[54,55]	84 outpatients USA 65 yrs (17) 51 male (61%) White non-Hispanic (86%), African American (13%), Other (1%) NYHA II (44%); III (33%); IV (6%) LVEF 36% (16)	Self reported BSI –A > 0.35	0.86 (0.71),	70%
Huang, 2011	39 Outpatients USA 60.80 yrs (11.70) 25 males (64%) Ethnicity not reported NYHA I (8%); II (46%); III (38%); IV (8%) LVEF not reported	Self reported BSI-A	0.53 (0.7)	-
Huang, 2012	489 Outpatients USA & Taiwan 61.7 yrs (13) 344 male (70.3%) Taiwanese (45.8%) NYHA I (11%); II (47%); III (31%); IV (11%) LVEF not reported	Self reported BSI-A	0.58 (0.7)	-

[54] Additional data sent by author
[55] Same sample as Heo 2007a, 2007b

First author, yr.	Participant characteristics	Anxiety		
	Age (yrs, sd) **Gender freq (%)** **Ethnicity freq (%)** **NYHA class Freq (%)** **LVEF Mean % (SD)**	**Anxiety Measure**	**Symptom Score mean (SD)**	**Prevalence sample above cut-off for anxiety %**
Khalil, 2011	590 Outpatients USA & Australia 63 yrs (13) 378 Males (64%) White (74%) NYHA I/II (64%); III/IV (53%) LVEF 35% (15)	Self reported BSI-A 0.35	0.68 (0.7)	-
Lee, 2013	202 Outpatients USA 56.9 yrs (13.3) 101 Males (50%) White (86%) NYHA II (40%); III (56%); IV (4%) LVEF 28.6% (12.4)	Self reported BSI-A	0.52 (0.6)	-
Moser, 2009[56]	146 Outpatients USA 68 yrs (13) 80 male (84.8%) White (59%) NYHA I (2%); II (40%); III (47%); IV (8%) LVEF 36 (15)	Self reported BSI -A	0.86 (0.8)	-
Steinke, 2008	85 Outpatients USA 60.6 yrs (10.6) 52 male (61%) White (88%), African American (12%) NYHA I (7%); II (28%); III (45%); IV (20%) LVEF 33% (13)	Self reported BSI -A	0.83 (0.8)	-
Barrow, 2007	65 Outpatients UK 68.1 yrs (8.7) 53 male (82%) Ethnicity not reported	SCL – R anxiety sub-scale	56.2 (12.5)	-

[56] Same sample as Dejong 2008

First author, yr.	Participant characteristics	Anxiety		
	Age (yrs, sd) **Gender freq (%)** **Ethnicity freq (%)** **NYHA class Freq (%)** **LVEF Mean % (SD)**	**Anxiety Measure**	**Symptom Score mean (SD)**	**Prevalence sample above cut-off for anxiety %**
	Clinical characteristics not reported			
Covera-Tindel, 2009[57]	76 Outpatients USA 62.9 yrs (10.6) 76 male (100%) White (49%) NYHA II (80%); III/IV (20%) LVEF 27.3% (8.8)	Self reported MAACL	5.1 (3.6)	-
Dracup, 2003	222 Outpatients USA 57 yrs (12.5) 181 male (82%) Ethnicity not reported NYHA I (14%); II (27%); III (46%); IV (13%) LVEF 25.8% (7.6)	Self reported MAACL	7.5 (5.1)	-
Dracup, 2007	173 Outpatients USA 54 yrs (12.5) 123 male (71.1%) White (60%) NYHA II (27%); III (63%); IV (10%) LVEF 26.4 % (6.8)	Self reported MAACL	7.4 (4.6)	-
Moser, 2005	202 Outpatients USA 70 yrs (12) 99 male (49%) White (88%), African American (12%) NYHA I (1 %); II (30%); III (40%); IV (26%) LVEF not reported	Self reported MAACL 7 >	7.8 (4.6)	50%

[57] **Additional design data from Covera-Tindel et al (2004)**

First author, yr.	Participant characteristics	Anxiety		
	Age (yrs, sd) **Gender freq (%)** **Ethnicity freq (%)** **NYHA class Freq (%)** **LVEF Mean % (SD)**	**Anxiety Measure**	**Symptom Score mean (SD)**	**Prevalence sample above cut-off for anxiety %**
Moser et al, 2010[58]	478 Outpatients USA 65.6 yrs (9.2) 355 male (74%) White (65%). African American (9.4%), Hispanic (7.5%), Other (8.8%) NYHA class not reported LVEF 29.5 (12.2)	Self reported MAACL	6.9 (4.7)	-
Clarke, 2000	2993 Unclear setting USA 60.1yrs (10.0) 2558 male (86%) White (84%), Black (12%), Hispanic (2%), Other (2%) NYHA I (44%); II (43%); III/IV (13%) LVEF 26.7% (6.4)	Self reported POMS – Anxiety and Tension subscale	8.5 (6.6)	-
Doering, 2004	87 Outpatients USA 54 yrs (11) 59 male (70%) White (70%), Hispanic (10%), African American (8%), Asian Pacific Islander (4%), American Indian (1%) NYHA I (3 %); II (21%); III (49%); IV (27%) LVEF 25% (8)	Self reported POMS – Anxiety and Tension subscale	15.2 (6.2)	-
Sullivan, 2009	208 Outpatients USA 61.3 (13.6) 146 male (70%) White (63%) NYHA I (9 %); II (46%); III (37%); IV (8%) LVEF 25 % (20.3)	Self reported POMS – Anxiety and Tension subscale	9.6 (6.5)	-

[58] Unpublished manuscript sent by author

Yrs= years; sd = standard deviation; freq = frequency; % = percentage; NYHA = New York Heart Association; UK= United kingdom; LVEF = Left ventricular Ejection Fraction; GAD = Generalised Anxiety Disorder 7 item; SCID = Structured Clinical Interview –I; PHQ = Patient Health Questionnaire; HADS = hospital Anxiety and Depression Scale; HADS G = HADS german; HADS – C = HADS Chinese; STAI – s = State Trait Anxiety Inventory state scale; STAT – t = State Trait Anxiety Inventory trait scale; HARS = Hamilton Anxiety Rating Scale; GAI = Geriatric Anxiety Inventory; BSI-A = Brief Symptom Inventory – anxiety; SCL =r = Symptom Checklist –revised; MAACL = Multiple Affect Adjective Checklist; POMS = Profile of Mood States.

Quality Appraisal

All included papers were assessed for quality using the following seven items;

- Evidence of probability sampling
- Adequate reporting of sampling characteristics
- Adequate response rates
- Conceptualisation of anxiety
- Standardised data collection
- Appropriateness of anxiety measure tool; specifically the omission of somatic items and ability to distinguish between anxiety and depression.

The outcomes of the quality appraisal can be found in table 11.

Of the 72 studies, seven used *probability sampling* techniques to obtain a sample of HF patients (Peters-Klimm, 2007; Steptoe, 2000; Jolly, 2009; Koukouvou, 2004; Zwisler, 2008; Thomas 1997; Clarke, 2000). Fifty studies, the majority in the review, did not use probability sampling techniques; instead using consecutive sampling or opportunity sampling. For fifteen studies it was not possible to identify the sampling procedure used (Lee, 2013; Dekker, 2012; Huang, 2011, 2012; Shen, 2011; Jackson, 2011; Karapolat, 2009; Moser, 2009; Freyssin, 2009; Song, 2008; de Jong, 2004, 2005, 2011; Lader, 2003; Kostis, 1994). Four of these studies were presented as an abstract only, limiting the data available for extraction (Dekker, 2012; Huang et al, 2011, 2012; Song, 2008). Three studies took samples from larger trials and failed to report previous sampling techniques

(de Jong, 2004, 2005, 2011; Moser, 2009). The remaining studies contained insufficient data to determine sampling techniques

With regards to the reporting of demographics and clinical data, the majority of the included studies reported sufficient data (76%). Eight studies reported sufficient data and additional data was also provided by authors for the review (Mitchell, 2012; Evangelista, 2009; Dar, 2009; Jiang, 2004; Zwisler, 2004; de Jong, 2004; Heo, 2008; Covera-Tindel, 2009). Five studies were considered to have reported insufficient demographics and clinical data (Houchen, 2012; Dekker, 2012; Huang, 2011; Peters-Klimm, 2007; Laederach-Hofmann, 2007, Thomas, 1997; Song, 2008). From these studies four study authors supplied additional data for the review (Peters-Klimm, 2007; Thomas, 197; Song, 2008). One of these studies was an on-going trial (Peters-Klimm, 2007) and another was published as an abstract only (Song, 2008).

Concerning reporting of response rates, 53 studies (74%) failed to report response rates. From these 53 studies one was an on-going trial (Peters-Klimm, 2007), four were reported as an abstract only (Dekker, 2012; Huang et al, 2011; 2012; Song, 2008) and one used secondary data from medical records making the reporting of a response rate none applicable (Abrams, 2008). Of the 19 studies that did report a response rate only five provided information about characteristics of non-responders (Mulligan, 2012; Damen, 2011; Geobel, 2009; Zwisler, 2008; Steptoe, 2000). One study reported matching characteristics (Damen, 2011; Geobel, 2009; Steptoe, 2000), and the other study stated that non-responders did not match responders with regards to demographic and clinical characteristics (Mulligan, 2012; Zwisler, 2008). From the nineteen studies that reported response rates or data that allowed the calculation of response rates, values ranged from 8% to 93.8% (Paukert.2008; Mitchell, 2012).

Of the 72 included studies in the review, nine defined or operationalised the construct of anxiety in the reporting of the study (Eisenberg, 2012; Haworth, 2007; Peters-Klimm, 2007; Muller-Tasch, 2008; Abrams, 2008; Kulcu, 2007; Schweitzer, 2007; Jiang, 2004; de Jong, 2004). Four of these studies investigated specific anxiety disorders (Haworth, 2007; Peters-Klimm, 2007; Muller-Tasch, 2008; Abrams, 2008). Kulcu (2007), and to a lesser extent Moser (2010) provided detailed information regarding their chosen anxiety measurement tool that may indicate how anxiety was defined for the purposes of the study.

Half of studies in the review (55%) reported using standardised data collection techniques to obtain anxiety outcome data. Twenty-one studies did not provide sufficient information in their reporting to establish whether data collection was standardised. A further ten studies did not use standardised data collection procedures, with patients completing questionnaire data both as self report at home or assisted in clinic settings (Lee, 2013; Houchen, 2012; Hallas, 2012; Strauber, 2012; Jackson, 2011; Luyster, 2009; Chung, 2009; Ansa, 2009; Evangelista, 2009; Dracup, 2007).

The choice of tool to measure anxiety was a key quality component for the current review. Nine studies used tools that were considered to contain somatic items; i.e. items that assessed physical symptoms of anxiety (Serafini, 2010; Muller-Tasch, 2008; Schiffer, 2008; Kostis, 1994; Paukert, 2009; Covera-Tindel, 2009; Dracup, 2003, 2007; Moser, 2005, 2010). For one study the identification of anxiety was subjectively determined by a trained interviewer, and as such could not be said to be free from somatic assessment (Haworth, 2007). One study relied on secondary diagnosis data extracted from medical notes; therefore it is unclear whether a diagnosis of anxiety was based on somatic items (Abrams, 2008), Finally, three studies used a measure that made it difficult to say for certain whether physical symptoms of anxiety were omitted from assessment of anxiety (Clarke, 2000; Doering, 2004; Sullivan, 2009). Twenty-five studies used tools to evaluate levels of anxiety or identify cases of anxiety that could not be said to effectively distinguish between anxiety and depression. In the current review only the HADs, BSI-A, GAD-7 and the PHQ were evaluated as demonstrating sound psychometric evidence for their ability to distinguish between anxiety and depression.

Table 11: Quality **appraisal components**

First author, yr	Sampling			Measurement			
	Probability sampling conducted?	**Adequate reporting of Sampling characteristics**	**Response rate reported**	**Anxiety defined**	**Data collection standardised**	**Tool omit somatic symptoms**	**Tool distinguish between anxiety and depression**
Haworth, 2007	No	Yes	Yes 44% No data on non-reponders	Yes	Yes	Yes – HADs Unclear - SCID	Yes – HADs Unclear - SCID
Peters-Klimm et al, 2007	Yes	No Current trial Additional data from author	No	Yes	Unclear from design paper	Yes	Yes
Mitchell, 2012	No	Yes	Yes 93.8% No data on non-responders	No	Yes	Yes	Yes
Geobel, 2009	No	Yes Additional data sent by author	Yes 69.2% Non-responders matched	No	Unclear	Yes	Yes
Muller-Tasch, 2008	No	Yes	Yes 77% No data for non-responders	Yes	Yes	No	Yes

First author, yr	Sampling			Measurement			
	Probability sampling conducted?	Adequate reporting of Sampling characteristics	Response rate reported	Anxiety defined	Data collection standardised	Tool omit somatic symptoms	Tool distinguish between anxiety and depression
Abrams, 2008	No	Yes	No	Yes	Unclear	Unclear	Unclear
Volz, 2012	No	Yes	No	No	Unclear	Yes	Yes
Almeida, 2012	No	Yes	No	No	Yes	Yes	Yes
Chen, 2010	No	Yes	No	No	Unclear	Yes	Yes
Falk, 2009	No	Yes	No	No	Yes	Yes	Yes
Hallas, 2010	No	Yes	Yes 51% No data on non-responder	No	No	Yes	Yes
Mulligan, 2012	No	Yes	Yes 53% Non-responders older, more females, better LVEF	No	Unclear	Yes	Yes

First author, yr	Sampling				Measurement		
	Probability sampling conducted?	Adequate reporting of Sampling characteristics	Response rate reported	Anxiety defined	Data collection standardised	Tool omit somatic symptoms	Tool distinguish between anxiety and depression
Steptoe, 2000	Yes	Yes	Yes 61% Non reponders matched	No	Yes	Yes	Yes
Eisenberg, 2012	No	Yes	No	Yes	Unclear	Yes	Yes
Junger, 2005	No	Yes	No	No	Unclear	Yes	Yes
Laederach-Hofman, 2007	No	No	No	No	Yes	Yes	Yes
Shen, 2011	Unclear	Yes	No	No	Yes	Yes	Yes
Ansa, 2009	No	Yes	No	No	No	Yes	Yes
Brouwers, 2012	No	Yes	Yes 65.8% No data on non-responders	No	Unclear	Yes	Yes

First author, yr	Sampling			Measurement			
	Probability sampling conducted?	Adequate reporting of Sampling characteristics	Response rate reported	Anxiety defined	Data collection standardised	Tool omit somatic symptoms	Tool distinguish between anxiety and depression
Damen, 2011	No	Yes	Yes 62% Non-reposnders matched	No	Unclear	Yes	Yes
Dar, 2009	No	Yes Additional data sent by author	Yes 40% No data on non-responders	No	Yes	Yes	Yes
Von Kanel, 2009	No	Yes	No	No	Unclear	Yes	Yes
Freyssin, 2009	Unclear	Yes	No	No	Yes	Yes	Yes
Houchen, 2012	No	No	No	No	No	Yes	Yes
Hermann-Lingen, 2003	No	Yes	No	No	Yes	Yes	Yes
Jolly, 2009	Yes	Yes	No	No	Yes	Yes	Yes

First author, yr	Sampling			Measurement			
	Probability sampling conducted?	Adequate reporting of Sampling characteristics	Response rate reported	Anxiety defined	Data collection standardised	Tool omit somatic symptoms	Tool distinguish between anxiety and depression
Koukouvou, 2004	Yes	Yes	No	No	Yes	Yes	Yes
Lee, 2005	No	Yes	No	No	Unclear	Yes	Yes
Scherer, 2008	No	Yes	Yes 39% No data on non-responders	No	Yes	Yes	Yes
Strauber, 2012	No	Yes	No	No	No	Yes	Yes
Witham, 2008	No	Yes	Yes 65% No data on non-responders	No	Yes	Yes	Yes
Yu, 2007b	No	Yes	No	No	Unclear	Yes	Yes
Yu, 2009	No	Yes	No	No	Yes	Yes	Yes

First author, yr	Sampling			Measurement			
	Probability sampling conducted?	Adequate reporting of Sampling characteristics	Response rate reported	Anxiety defined	Data collection standardised	Tool omit somatic symptoms	Tool distinguish between anxiety and depression
Zwisler, 2008	Yes	Yes Additional data sent by author	Yes 47% Non-responders did not match responders	No	Yes	Yes	Yes
Freidmann, 2006	No	Yes	No	No	Unclear	Yes	Unclear
Jackson, 2011	Unclear	Yes	No	No	No	Yes	Unclear
Jiang, 2004	No	Yes Additional data sent by author	No	Yes	Yes	Yes	Unclear
Karapolat, 2009	Unclear	Yes	Yes 53% No data on non-responders	No	Unclear	Yes	Unclear
Kulcu, 2007	No	Yes	No	Yes	Yes	Yes	Unclear

First author, yr	Sampling			Measurement			
	Probability sampling conducted?	Adequate reporting of Sampling characteristics	Response rate reported	Anxiety defined	Data collection standardised	Tool omit somatic symptoms	Tool distinguish between anxiety and depression
Lader, 2003	Unclear	Yes	No	No	Yes	Yes	Unclear
Luyster, 2009	No	Yes	No	No	No	Yes	Unclear
Schweitzer, 2007	No	Yes	No	Yes	Yes	Yes	Unclear
Song, 2008	Unclear	No- abstract additional data sent by author	No	No	Unclear	Yes	Unclear
Thomas, 1997	Yes	No Additional data sent by author	No	No	Unclear	Yes	unclear
Tuschihashi - Makaya, 2009	No	Yes	No	No	Yes	Yes	Unclear
Schiffer, 2008	No	Yes	Yes 82% No data on non-responders	No	Yes	No	Unclear

First author, yr	Sampling			Measurement			
	Probability sampling conducted?	Adequate reporting of Sampling characteristics	Response rate reported	Anxiety defined	Data collection standardised	Tool omit somatic symptoms	Tool distinguish between anxiety and depression
Serafini, 2010	No	Yes	No	No	Yes	No	Unclear
Kostis, 1994	Unclear	Yes	No	No	Yes	No	Unclear
Cully, 2010	Yes	Yes	Yes 76%[59] No data on non-responders	No	Yes	No	Unclear
Paukert, 2009	No	Yes	Yes 8% No data on non-responders	No	Yes	No	Unclear
Chung 2009	No	Yes	No	No	No	Yes	Yes
de Jong, 2004	Unclear	Yes Additional data from author	No	Yes	Yes	Yes	Yes

[59] Response rate generated from participants who had been initially screened and consented to take part in study.

First author, yr	Sampling			Measurement			
	Probability sampling conducted?	Adequate reporting of Sampling characteristics	Response rate reported	Anxiety defined	Data collection standardised	Tool omit somatic symptoms	Tool distinguish between anxiety and depression
de Jong, 2005	Unclear	Yes	No	No	Yes	Yes	Yes
de Jong, 2011	Unclear	Yes	No	No	Yes	Yes	Yes
Heo, 2008	No	Yes Additional data sent by author	No	No	Yes	Yes	Yes
Dekker, 2012[60]	Unclear	No	No	No	Unclear	Yes	Yes
Huang, 2011[61]	Unclear	No	No	No	Unclear	Yes	Yes
Huang, 2012[62]	Unclear	Yes	No	No	Unclear	Yes	Yes

[60] Abstract
[61] Absract
[62] Abstract

First author, yr	Sampling			Measurement			
	Probability sampling conducted?	Adequate reporting of Sampling characteristics	Response rate reported	Anxiety defined	Data collection standardised	Tool omit somatic symptoms	Tool distinguish between anxiety and depression
Khalil, 2011	No	Yes	No	No	Unclear	Yes	Yes
Lee, 2013	Unclear	Yes	No	No	No	Yes	Yes
Moser, 2009	Unclear	Yes	No	No	Unclear	Yes	Yes
Steinke, 2008	No	Yes	No	No	Yes	Yes	Yes
Evangelista, 2009	No	Yes	No	No	No	Yes	Yes
Barrow, 2007	No	No Additional data sent from author	Yes 24% No data on none repsonders	No	Yes	Yes	Yes
Covera-Tindel, 2009	No	Yes Additional data from author	No	No	Yes	No	Unclear
Dracup,	No	Yes	No	No	Yes	No	Unclear

First author, yr	Sampling			Measurement			
	Probability sampling conducted?	Adequate reporting of Sampling characteristics	Response rate reported	Anxiety defined	Data collection standardised	Tool omit somatic symptoms	Tool distinguish between anxiety and depression
2003							
Dracup, 2007	No	Yes	No	No	No	No	Unclear
Moser, 2005	No	Yes	No		Yes	No	Unclear
Moser et al, 2010	No	Yes	No	Partially	Yes	No	Unclear
Clarke, 2000	Yes	Yes	Yes 73% No data on non-responders	No	Yes	Unclear	Unclear
Doering, 2004	No	Yes	No	No	Yes	Unclear	Unclear
Sullivan, 2009	No	Yes	No	No	Yes	Unclear	Unclear

Meta-Analysis

Meta-analysis was conducted on prevalence and symptom severity (mean) data in order to establish a combined prevalence of anxiety across included studies. Of the 72 included studies, 38 provided anxiety prevalence estimates and sufficient data to be entered into a meta-analysis. Once meta-analysis was complete meta-regression was conducted to determine sources of variations (causes of heterogeneity) in reported prevalence rates.

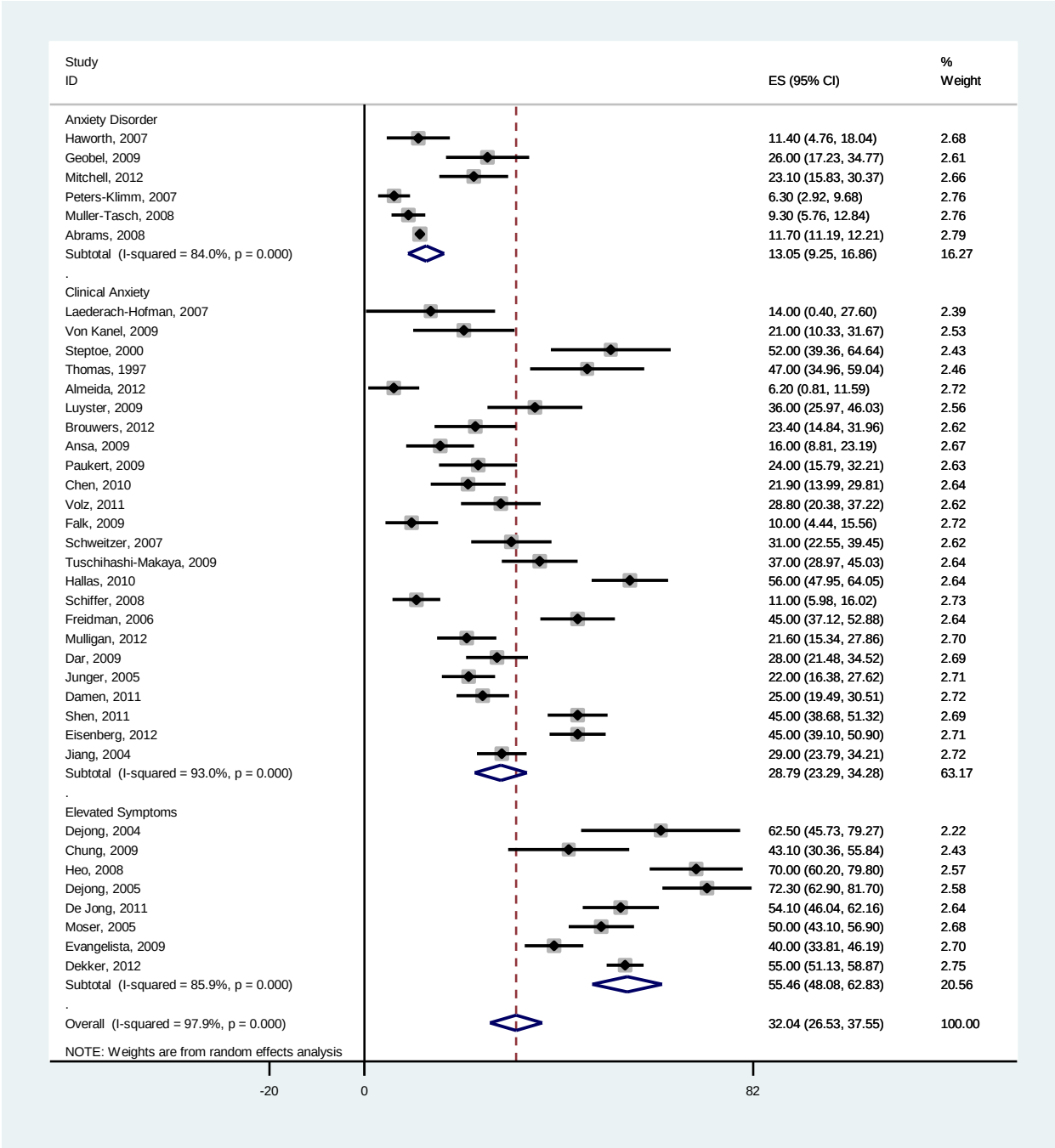
A similar analysis was conducted on mean (SD) data from each of the included measurement tools. Meta-analysis was conducted for each of the measurement tools and meta-regression was carrid out to identify sources of heterogeneity in anxiety symptoms severity scores.

Prevalence of anxiety

The prevalence of reported anxiety varied in the 38 included studies from 6.3% to 72.3% (Peters-Klimm, 207; de Jong, 2005), with an overall random effects pooled prevalence of 32.04% (95% CI 26.53% - 37.56%). Substantial heterogeneity in the rates of anxiety reported was found among included studies (x^2 = 1745.1, d.f = 37, p = 0.000, I^2 = 97.9%). Figure 12 presents a forest plot from the analysis, with studies grouped by type of anxiety. The graph shows that, overall the prevalence of anxiety increases as the way in which anxiety is conceptualised or defined becomes less stringent.

The way in which anxiety has been measured, or more accurately the manner in which anxiety was conceptualised and measured in studies was hypothesised as a source of heterogeneity in rates of anxiety among included studies. In pre-planned post-hoc sensitivity analysis meta-analysis was conducted on anxiety grouped by type/conceptualisation (specific anxiety disorders, probabale clinical anxiety and elevated symptoms of anxiety) and measurement tool.

Figure 12: Prevalence of anxiety disorders, probable clinical anxiety and elevated symptoms of anxiety in HF patient samples grouped by type of anxiety



0 = Specific anxiety disorders group
1 = Probable clinical anxiety group
2 = Elevated symptoms of anxiety above general population norms group
ES = Effect size
CI = Confidence Interval

Differences in reported prevalence of anxiety as a result of conceptualisation of anxiety and measurement tools used

Table 12 presents a breakdown of included studies prevalence and symptom severity estimates by type of anxiety and measurement tool. The prevalence of *specific anxiety disorders* were reported in six studies with a random effects pooled prevalence of 13.1% (95% CI 9.25% - 16.86%). Estimates ranged from 6.3% to 26%, with a moderate level of heterogeneity found among estimates (x^2 = 31.17, d.f = 5, p = 0.000, I^2 = 84.0%). The prevalence of *probable clinically significant anxiety* was measured in 24 studies, with a random effects pooled prevalence of 28.79% (95% CI 23.30% - 34.29%). Estimates ranged from 6.2% to 52% and a high level of heterogeneity was found among estimates (x^2 = 327.39, d.f = 23, p = 0.000, I^2 = 93.0%). The prevalence of *elevated symptoms of anxiety above general population norm* was identified in eight studies, with a random effects pooled prevalence of 55.5% (95% CI 48.08% - 62.83%). Estimates ranged from 40% to 72%, with high levels of heterogeneity among estimates (x^2 = 49.77, d.f = 7, p = 0.000, I^2 = 85.9%). Figure 12 displays the forest plot of the random effects models for each of the conceptualisations of anxiety.

Lower rates of anxiety were found in studies that measured specific anxiety disorders in HF patients. Rates of anxiety rose in studies that used screening tools to measure valid symptoms of anxiety and provide thresholds with which to identify probable caseness of clinical anxiety. Rates of anxiety increased further still in those that measured valid symptoms of anxiety and present a threshold by which to identify anxious cases as those with scores above general population norms.

Table 12 shows the pooled prevalence of anxiety for each of the measurement tools identified in included studies. With regards to the tools used to measure anxiety pooled prevalence rates of anxiety were highest when measured by the BSI-A (56.8%, 95% CI 44.68%- 68.9%) and lowest when measured using a tool to identify specific anxiety disorder, the GAD-7 (14.38%, 95% CI -2.07-30.8). High levels of heterogeneity were identified in all meta-analysis models (I^2> 0.80). Forest plots of meta-analysis by anxiety measurement tool can be found in appendix 9 showing corresponding outcomes from tests of heterogeneity.

Table 12: Prevalence estimates and anxiety symptom severity estimates from meta-

Conceptualisation of anxiety	Number of studies	Weighted means 95% CI	Number of studies	Pooled prevalence % 95% CI
Anxiety disorders	6	-	6	13.05 (9.25 - 16.86)
GAD-7	2	4.26 (2.84-5.68)	2	14.38 (-2.07 – 30.8)
Probable clinical anxiety	45	-	24	28.79 (23.3 - 34.3)
HADS	22	6.16 (5.3 - 7.1)	17	26.54 (19.8 - 33.32)
STAI - state	8	36.68 (26.60 – 46.76)	4	38.8 (29.9 - 47.6)
STAI – trait	7	43.14 (35.61- 50.66)	4	36.4 (26.5 - 46.3)
HARS	2	14.07 (13.6 – 14.53)	1	11
GAI	2	5.016 (4.26 – 578)	1	24
Elevated symptoms	19	-	8	32.04 (26.53 - 37.56)
BSI-A	13	0.74 (0.68 – 0.81)	6	56.8 (44.68 - 68.9)
SCL-R	1	56.2 *(12.5)	-	-
MAACL	5	7.0 (6.2 - 7.7)	1	50
Symptoms of anxiety	2	-	-	-
POMS	3	11.1 (7.7 - 14.5)	-	-

analysis group by type of anxiety

* Standard deviation; CI = Confidence Interval; GAD – 7 = Generalised Anxiety Disorder 7-item (GAD-7); HADS = Hospital Anxiety and Depression Scale; STAI = State-Trait Anxiety Index; HARS = Hamilton Anxiey Rating Scale; GAI = Geriatric

Anxiety Inventory; BSI-A = Brief Symptom Inventory – anxiety; SCL-r = Symptom Checklist 90-revised; MAACL = Multiple Affect Adjectvie Checklist; POMS = Profile of Mood States.

Reported levels of anxiety symptom severity

Average scores with variance from measurement tools were also extracted from included studies. Table 12 shows the pooled average values from each measurement tool identified in the review. Forest plots of the severity of anxiety by measurement tool meta-analysis can be found in appendix 10. The random effects estimate from the 22 studies using the **HADs** was 6.16 (95% CI 5.23% - 7.10%). The estimates ranged from 2.1 to 12.4, and there was substantial heterogeneity among these estimates (X^2 = 888.19, d.d = 21, p = 0.000, I^2 = 97.6%). The estimate from the eight studies that used the **STAI – state scale** was 36.68 (95% CI 26.6% - 46.76%) using a random effects model. Estimates ranged from 16.4 to 44.8, with substantial heterogeneity among estimates (X^2 = 5745.52, d.f = 7, p = 0.000, I^2 = 99.9%). From the seven studies that measured anxiety using the **STAI – trait** scale an estimate of 43.14 (95% CI 35.61% - 50.66%) was calculated using a random effects model. Estimates ranged from 33.5 to 61.6, with a substantial level of heterogeneity observed among estimates (X^2 = 670.99, d.f = 6, p = 0.000, I^2 = 99.1%). Random effects mean estimates for the **GAD-7**, the **HARS** and the **GAI** can also be found in table 12.

The random effects mean estimates calculated from the 13 studies that used the **BSI-A** to measure anxiety was 0.74 (95% CI 0.68% - 0.81%); the level of heterogeneity among mean estimates was high (X^2 = 86.1, d.f = 12, p = 0.000, I^2 = 86.1%). Reported scores on the BSI-A ranged from 0.52 – 0.98. Five studies measured anxiety using the **MAACL**, with estimates ranging from 5.1 to 7.8. The random effect mean estimate was 7.0 (95% CI 6.2% - 7.7%) (X^2 = 30.9, p = 0.000, I^2 = 87%). Finally, from the three studies to measure anxiety using the **POMS** a random effects mean estimate of 11.1 (95% CI 9.7% - 14.5%) was calculated. The estimates ranged from 8.5 to 15.2, with substantial heterogeneity (X^2 = 77.1, p = 0.000, I^2 = 97.4%).

Meta-regression

Sources of variation in prevalence rates of anxiety

As all random effects meta-analysis models identified high levels of heterogeneity in prevalence rates, which were not reduced dramatically by assessing prevalence by sub-group of anxiety in sensitivity analysis, attempts were made to identify factors which may account for the significant heterogeneity in prevalence rates. Table 13 presents outcomes from the meta-regression models. In univariate meta-regression analyses, exploring variations in *overall prevalence* of anxiety, concept anxiety that is the way in which anxiety had been conceptualised and measured accounted for significant variance in anxiety prevalence rates. Studies that had conceptualised anxiety as specific anxiety disorders identified lower rates of anxiety compared with studies that measured clinical levels of anxiety symptoms (β = -14.40 standard error [se(β)] = 5.63, p = 0.015 and studies that measured symptoms of anxiety, identifying anxious individuals as those who scored higher than a general population norm (β = -41.24, standard error [se(β)] = 6.77, p = 0.000.

In addition, studies with a younger mean age (yrs) reported higher prevalence rates of anxiety (compared to studied with an older mean age) (β = -1.01, standard error [se(β)] = 0.41, p = 0.020), studies with samples that had a higher proportion of females to male (as opposed to a higher proportion of males) had higher prevalence of anxiety (β = -0.62, standard error [se(β)] = 0.21, p = 0.006). Studies conducted in the USA reported a higher prevalence of anxiety when compared with studies conducted in the UK and mainland Europe (β = -19.98, se[β] = 5.78, p = 0.002). No other factors were found to explain the heterogeneity in overall prevalence rates to a significant level.

Post-hoc sensitivity analysis

As the variable ‘concept of anxiety’ unsurprisingly accounted for a large and significant amount of variance in prevalence rates, it was considered of interest to examine the variance in prevalence rates accounted for by additional variables whilst controlling for the concept of anxiety. A two factor meta-regression analysis on prevalence rates was conducted whilst controlling for the conceptualisation of anxiety (specific anxiety disorders, probable clinical anxiety or elevated symptoms of anxiety), see appendix 11. Covariates included in anaysis were demographic covariates of gender and age (coded as both mean age and categorical age), clinical covariates of LVEF mean %; NYHA class

(coded as mild, moderate/severe or mixed) and setting (coded as inpatient, outpatient or mixed), and methodological factors of country of origin and design (coded as RCT, uncontrolled trial, cohort, case controlled and case series) was also conducted. When controlling for the variance in rates accounted for by the conceptualisation and measurement of anxiety only age (mean yrs), NYHA functional class and country of origin explained variations in anxiety prevalence to a significant degree. Studies with samples of a lower mean age ($\beta = -0.79$, se[β] = 0.29, $p = 0.009$), higher proportion of individuals with milder NYHA functional class ($\beta = -15.06$, se[β] = 6.98, $p = 0.041$) origniating from the USA ($\beta = -11.20$, se[β] = 5.48, $p = 0.050$) reported increased prevalence rates of anxiety (see appendix 11). Exploration of variance in prevalence rates within type of anxiety as a result of measurement tool, for example the HADs or STAI was not possible as the observation values for each were the same as the prevalence rates, and as such could not meaningfully be explored.

Unplanned post-hoc sensitivity analysis within anxiety sub-groups

The manner in which anxiety had been conceptualised was found to account for significant variance in study outcomes; however significant heterogeneity also existed within the combine estimates of anxiety prevalence within the concepts of anxiety (specific anxiety disorders, Probable clinical anxiety, elevated symptoms of anxiety). Meta-regression analysis was attempted within each of the categories of type of anxiety; specific anxiety disorders, probable clinical anxiety and elevated symptoms of anxiety (table 13). It was not possible to examine the influence of all variables on prevalence rates as the number of observations within some cells was low (4 to 6 observations). In addition some cells contained no variations in data (collinearities), for example, elevated symptoms of anxiety were only measured in studies from the USA.

Within the category of **specific anxiety disorders**, no variables entered in the meta-regression where found to account for variance in reported prevalence rates. Within the category of **probable clinical anxiety** two variables were associated with variance in prevalence rates; mean age and NYHA functional class. Studies with a younger sample and a higher proportion of individuals with mild NYHA class versus moderate/severe were significantly associated with higher rates of anxiety estimates ($\beta = -1.12$, se[β] 0.31, $p = 0.002$ and $\beta = -17.31$, se[β] = 7.69 $p = 0.038$ respectively). No variables were found to be associated with the variance in **elevated levels of anxiety symptoms**

Table 13: Univariate meta-regression for overall anxiety, anxiety disorder, clinical anxiety and elevated symptoms of anxiety: values of β, se[β], and the significance of β for each study characteristic.

Characteristic of study	Overall Anxiety (22-38 obs) β, (se[β]), p	Anxiety disorders (4-6 obs) β, (se[β]), p	Clinical Anxiety (13-24 obs) β, (se[β]), p	Elev symp anx (5-8 obs) β, (se[β]), p
Age:				
Yrs mean	-1.01(0.41) p=0.020*	-0.70 (0.84) p=0.45	-1.12(0.31)p=0.002*2	0.89 (0.71) p=0.259
Age:				
< 59 yrs versus 60-69	-12.33 (7.14) p=0.94	Co linearity	-11.8(6.3) p=0.07	6.5 (11.4) p=0.59
< 59 yrs versus 70 +	-4.48		-14.2(8.11) p=0.09	11.50 (13.0) p= 0.14
Gender:				
% males in sample	-0.62 (0.21) p=0.006*	0.07 (0.30) p=0.84	-0.29 (0.23) p=0.22	-0.51 (0.44) p=0.29
Setting:				
Outpatient versus Inpatient	13.54 (13.69) p=0.33	Co linearity	10.61 (10.6) p=0.33	Co linearity
Outpatient versus Mixed	2.97 (11.0) p=0.80		-3.93 (10.7) p=0.7	0.68 (12.9) p =0.96
LVEF: % means	0.79 (0.7) p=0.27	1.30 (1.4) p=0.45	054 (0.64) p=0.42	0.73 (1.5) p=0.63
NYHA:				
Mild versus mod/severe	-8.06 (11.0) p=0.47	Insuff obs	-17.3 (7.7) p=0.038*	Co linearity
Mild versus Mixed	0.25 (7.6) p=0.97		-5.27 (5.6) p=0.36	0.88 (14.4) p=0.95
Design:				
RCT versus uncontrolled	-3.01 (22.3) p=0.89	Insuff obs	-14 (20.3) p=0.50	Insuff obs
RCT versus cohort	13.42 (13.1) p=0.32		2.21 (14.4) p=0.89	-5.1 (12.5) p=0.71
RCT versus case controlled	32.7 (16.3) p=0.05*		17 (19.5) p=0.39	

RCT versus case series	14.12 (13.1) p=0.29		-2.56 (14.3) p=0.86	11.8 (11.7) p=0.37
Country: ·				
USA versus UK[$]	-20.0 (5.8) p=0.002**	Insuff obs	-11.3 (7.5) p=0.15	Co linearity
USA versus Asia	-13.7 (12.2) p=0.27		-8.4 (11.9) p=0.49	
USA versus Australasia	-12.2 (16.9) p=0.78		-6.88 (15.6) p=0.67	
USA versus mixed	-17.9 (12.1) p=0.15		-12.7 (15.5) p=0.18	
USA versus Africa	-27.2 (16.7) p=0.11		-21.9 (15.5) p=0.18	
Concept of anxiety:				
Anx Dis[2] versus Clin Anx	14.40 (5.6) p=0.015*			
Anx Dis versus Elev Symp	41.24 (6.8) p = 0.000**			

[$] UK and Europe
* Significant at the 0.05 level
** Significant at the 0.01 level
Obs (observations); LVEF (Left Ventricular Ejection Fraction; NYHA (New York Heart Association); RCT (Randomised Controlled Trial); Insuff obs (Insufficient observations); Anx Dis (anxiety disorders); Clin Anx (clinical anxiety); Elev Symp anx(elevated symptoms of anxiety)

Variations in anxiety symptoms scores

The average anxiety symptom severity scores (means and SD) from specific measurement tools were also evaluated in meta-regression analysis. A table in appendix 12 shows the output from meta-regressions models conducted to identify reasons for variance in anxiety measurement tool average estimates (appendix 12). Two variables were associated with heterogeneity in HADs estimates. Studies with samples of a lower mean age were progressively associated with higher estimates (mean SD) using the HADS, indicative of higher levels of anxiety (β = -0.13, se[β] = 0.04, p = 0.006). This association was also found when the variable of age was transformed into a categorical variable; with samples < 59 years having significantly higher scores on the HADs compared with samples over the age of 70 yrs (β = - 42.78, se[β] = 1.05, p = 0.016).

No variables were associated with variance in STAT-S, STAI-T, BSI-A, MACCL, or POMS symptom severity mean scores.

Part Three: **Systematic review discussion**

This is the first systematic review, meta-analysis and regression and the most extensive review to date to consolidate the evidence base for the prevalence of anxiety in HF samples. One-hundred and fourty-four studies were identified that met inclusion criteria and seventy-two studies were included in the review and synthesis, sampling 26, 366 individuals.

Main findings

There are three main findings from the systematic review:

- First, random effects pooled prevalence estimate of anxiety was of 32.o4% (95% CI 26.53% - 37.56%). The pooled prevalence estimate of anxiety disorders are not considered unique to HF samples and have been observed in older adult community samples and clinical samples alike (Bryant et al, 2007). The pooled prevalence estimate of symptoms of anxiety is similar to, and the range exceeds, levels found in research conducted with other LTC samples. The random effects pooled prevalence estimate for anxiety disorders was 13.1% (95% CI 9.25% - 16.86%), with a random effects pooled prevalence of, for probable clinically significant anxiety was 28.79% (95% CI 23.30% - 34.29%) and the random effects pooled prevalence estimate for elevated symptoms of anxiety was 55.5% (95% CI 48.08% - 62.83%).
- Second, there was substantial heterogeneity among study prevalence estimates, indicating that pooled prevalence estimates should be interpreted with caution. Prevalence estimates ranged from 6.3% to 72.3%. In meta-regression analysis the way in which anxiety had been conceptualised and measured in studies was most strongly associated with heterogeneity. Inflated rates of anxiety are most likely an artefact of measurement method.
- Third, many different measurement tools were used to study identify anxiety in the included studies, some of which are more appropriate for screening for anxiety in individuals with a diagnosis of HF than others.

Levels of anxiety

In a critical review of the literature published in 2010 Yohannes et al identified only eight studies that explored anxiety co- morbid to HF, with prevalence estimates ranging from 11% (Yu et al, 2009) to 45% (Friedmann et al, 2006). The current review identified many more studies that included a measure of anxiety in samples of individuals with a diagnosis of HF. The current review shows that prevalence estimates of anxiety range dramatically from 6.3% to 72.3%, with lower prevalence estimates found in studies measuring specific anxiety disorders as opposed to elevated levels of anxiety symptoms.

Anxiety disorders

The findings from this comprehensive systematic review, meta-analysis and regression indicate that levels of anxiety are moderate in patients with a diagnosis of HF. However, rates of anxiety disorder in particular are comparable to those found in other clinical samples, and in healthy older adults living in the community. This finding is supported by MacMahon (2002). Previous research has indicated that 3% to 15% of older community dwelling adults experience diagnosable anxiety disorders (Bryant et al, 2007; Singleton et al, 2000; Beekman et al, 1998). The range of prevalence estimates identified in this review and the pooled estimates suggest that individuals with HF experience similar levels of anxiety disorders to older adults living in the community. Although the extent to which these 'healthy' older adult samples are free from all LTCs and other medical and psychiatric conditions is unclear.

Rates of anxiety disorders in clinical samples are comparable to those found in this review of HF samples. Bryant et al (1997) found that anxiety disorders where prevalent in 1% to 28% of older adults in clinical settings including hospitals and rates of 18% have been found in older adults with pulmonary disease (Yohannes et al, 2000). When compared with the pooled prevalence estimates of anxiety disorders of 13.1% found in the current systematic review we see that the levels of anxiety disorders are notable in a range of elderly samples, not exclusively HF samples. This is in contrast to previous research that reported major anxiety is present in as many as 40% of patients with a diagnosis of heart failure (Konstam et al, 2005; Moser et al, 2010).

Symptoms of anxiety

It has been reported previously that individuals with HF experience symptoms of anxiety as high, if not higher than those found in samples of patients with other LTCs, for example cancer, lung disease and other cardiac conditions (de Jong et al, 2004; Riedinger et al, 2002). In the current review pooled prevalence estimate of probable clinically significant anxiety symptoms (28.8%) and elevated symptoms of anxiety (55.6%) were slightly higher than rates found in older adult community samples (15% to 52.3%) (Bryant et al, 2007); in clinical samples (15% to 56%) (Bryant et al, 2007); samples of CAD patients (20-25%) (Januzzi et al, 2000); following acute cardiac events (20-25%) (Moser & Dracup, 1996); following ICD intervention (24% to 87%) (Sear et al, 1999); and in diabetic populations (40%) (Grigsby et al, 2002).

The upper range of prevalence estimates found in this review could indicate that levels of anxiety symptoms, as measured by some instruments, may be higher than in many other cardiovascular conditions, with the exception of samples immediately post invasive procedures. However the instruments used to measure anxiety symptoms and thresholds used to identify caseness of anxiety have played a crucial role in determining the levels if anxiety identified. Variations in prevalence estimates may not always reflect true differences in anxiety between different patient populations, but may be an artefact of measurement.

Outcome

Conceptualisation of anxiety

With respect to the conceptualisation of anxiety, studies were synthesised into four categories:

- Those that used measures to identify specific anxiety disorders
- Those that used questionnaires to measure anxiety symptoms and identify
    - Probable clinically significant anxiety
    - Elevated symptoms of anxiety

      Or
    - Report the severity of anxiety symptoms with no reference to normative or comparison data.

Heterogeneity in the conceptualisation and measurement of anxiety was significantly associated with variance in prevalence estimates. Quality appraisal indicated that anxiety was very rarely defined in studies. The primary aim of many studies was not to measure

levels of anxiety in HF samples and so it is understandable that many did not define the concept of anxiety. However, if research in this area is to evolve and increase in sophistication then a level of clarity with respect to the defining of anxiety is required. The way in which specific anxiety disorders and varying levels of symptom severity are managed and treated differs in clinical practice and so it is vital that researchers and clinicians working in this area are clear about what they are referring to when they speak of 'anxiety', particularly within the context of LTC care.

Measurement of anxiety

Anxiety was measured using 11 different questionnaires or interviews methods in the included studies. Scores on questionnaire measures were interpreted using a variety of different threshold to define anxiety, making synthesis of outcome data difficult, across and within measurement tools. The quality of measurement tools included in the review varied. Only some have been evaluated as appropriate for use in cardiac, elderly samples and able to distinguish between anxiety and depression.

Only one study used a gold standard diagnostic tool (SCID-I) (Spitzer et al, 1990) to diagnose specific anxiety disorders (Haworth et al., 2007), corresponding to NICE guidelines for the assessment of generalised anxiety disorder in primary, secondary and community care (NICE, 2011). Although this method of assessing patients is considered robust, it can take over an hour to assess patients and involves subjective interpretation of self reported symptoms by a skilled interviewer. Therefore the ability of the tool to distinguish between anxiety and depression and to disentangle symptoms of anxiety from those of a cardiac condition is reliant on its correct administration and interpretation by the interviewer. This tool would not be appropriate for routine use to screen HF patients for mental health complaints in clinical practice, nor for use in research to identify patients with anxiety and depression due to the time taken to complete the assessment and the training required to conduct the interview.

The GAD-7 offers a solution to the problem of assessing anxiety using DSM-IV criteria in a very short space of time. The tool was only used in two studies identified in the review (Mitchell et al, 2012; Peters-Klimm et al., 2007) and the GAD-2, a brief version of the tool was used in pne additional study (Goebel et al, 2009). The GAD-7 (Spitzer et al., 2006) is one of the minimum data set requirements used by the Increasing Access to Psychological Treatment (IAPT) programme in the UK to screen for and identify caseness of anxiety (mild/moderate)

(IAPT, Outcomes tool kit 2008/2009, 2008). Surprising then it was interesting to note that no studies conducted in the UK used the tool. This is likely to be due to the fact that the IAPT programme is a relatively new national initiative, running in primary care services. Many of the studies included in the review will have been conducted prior to its initiation and the majority of research to date has sampled outpatients, primarily from secondary services. The tool is free to use and very brief (7 items). It contains no questions relating to somatic complaints and can distinguish between anxiety and depression, making its use in cardiac populations appropriate (Spitzer et al., 2006). Scores over 10 have been found to correspond to caseness of moderate to severe anxiety (Spitzer et al, 2006) that can impact individual's ability to perform everyday activities, cause marked distress but responds well to psychological interventions (NICE, 2011; IAPT Toolkit, 2008). The use of the tool in the UK in particular should be encouraged as large amounts of data are being routinely collected using this tool. Comparisons with a variety of samples using the same measurement tool would vastly improve our understanding of the levels of anxiety in this patient group relative to other LTCs.

The HADs was the most frequently used measurement tool in the studies included in the review, followed by the STAI and the BSI-A. The HADs is a popular and brief (14-item) screening tool that assesses symptoms for anxiety. Thresholds of 8 to10, 11 to 15 and 16 and above have been found to correlate with mild, moderate and severe cases of anxiety respectively (Crawford, 2001). The tool was developed to exclude somatic items, although the measure does however have an item asking whether people 'feel slowed down', which may overlap with physical symptoms experienced by many with chronic physical conditions. The tool has received extensive psychometric testing which has demonstrated a predominantly two factor loading of items, distinguishing between anxiety and depression (Bjelland et al., 2002); although this has been questioned more recently and will be highlighted in the survey limitations chapter four (Cosco et al, 2012; Coyne & Sonderen, 2012). The HADs was used mainly in studies from the UK and Europe, with studies applying a range of thresholds to identify caseness of anxiety. The majority of studies used a threshold of 8 to identify mild anxiety, which has been supported through psychometric testing of specificity and sensitivity (Bjelland et al., 2002). The tool is routinely used in both primary and secondary care in the UK, which makes the choice of this measure appropriate in the UK context however, issues with the language used in the measure has reduced its' application in the USA (Coyne & Sondersen, 2012). The review has highlighted that the HADS is increasing in use in research over time, compared with other tools. The majority of studies conducted since the start of 2010 used the HADS to screen for mild, moderate and severe levels of anxiety symptoms. Indeed many of the

studies chose to present the prevalence of anxiety for more than one level of anxiety severity, which mirrors the use of the HADS in clinical practice and the ability of the tool to match patient's to 'stepped care' treatment options.

The STAI was used in 11 studies in total. Four reported the state score in isolation, three the trait score and four reported both state and trait scores. State scores correspond to transitory emotions, whereas trait scores measure characteristics of a more enduring, disposition. Scores over 40 on both scales have been found to discriminate between anxious and non-anxious individuals (Jiang et al., 2004). As with the HADs, the measure omits somatic symptoms, however, the evidence surrounding the tools ability to discriminate between anxiety and depression is less persuasive (McDowell, 2006). Research has indicated the children's version of the tool may be more appropriate for use in geriatric samples (Patterson et al., 1980), where cognitive ability may be impaired. None of the studies using the STAI used the children's version of the tool. The use of state and/or trait scales across research is not standardised and it is unclear from the included studies how clinicians and researchers may feel the two concepts affect cardiac populations.

Both the BSI-A and the MAACL were used to measure symptoms of anxiety and identify anxious cases with reference to data from general population samples. All of the studies using these measures originated from the USA. Twelve studies used the BSI-A, in addition one study used the SCL-R, which was the original measure from which the BSI was developed (Barrow, 2007). The tool is psychometrically sound, excludes somatic items and has been shown to adequately distinguish between anxiety and depression (Ruz et al, 2010; Derogatis & Melisarato, 1983). However at 36 items it may be considered too lengthy for busy clinical practice. The MAACL is a 132 item tool measuring anxiety, depression, hostility, positive affect and sensation seeking (Zukerman et al, 1986). The tool is a validated measure; however, the evidence to support its ability to identify depression and distinguish between anxiety and depression is lacking and in addition the measure uses somatic symptom items to identify anxiety and depression (McDowell, 1996). The use of summary scores in isolation is not advised (Hunsley, 1990).

The BSI-A and the MAACL are not widely used in the UK, where the HADs and GAD-7 currently meet the needs of assessing anxiety in an elderly cardiac population. The use of the BSI-A and MAACL and the interpretation of scores derived from them based on comparison with general population norms, produced the highest levels of anxiety observed in the review.

The tools were designed to measure symptoms of anxiety. As far as can be established, no normative data exists for comparison purposes for either scale. Therefore scores are interpreted by comparison with other groups, in particular healthy adults with no known cardiac disease (personal communications Moser 10/06/2009). Individuals are considered to have elevated anxiety if they score higher than seven on the MAACL and higher than 0.35 on the BSI-A, although one study used a comparison threshold of 0.98 taken from a sample of participants with known psychiatric complaints (Evangelista et al., 2009). Increases in the level of anxiety on the BSI-A and MAACL are hard to interpret clinically as no thresholds have been identified to indicate mild/moderate or severe levels of anxiety. As these tools identify individuals with elevated symptoms of anxiety using low thresholds it is not surprising that they identify extremely high prevalence estimates of anxiety. However, the clinical relevance of identifying such a wide range in the levels of anxiety is unknown, as is the ability to target patient's at the right treatment using either the BSI-A or the MAACL.

The POMS was used in three studies (Clarke, 2000; Doering, 2004; Sullivan, 2009) to assess anxiety. The 65 item measure assesses anxiety/tension, fatigue/inertia, depression/dejection, anger/hostility, vigor/activity and confusion/bewilderment and does not exclude somatic items from the assessment of anxiety and depression (McNair, Lorr & Droppelman, 1984). The measure has been tested in elderly populations however the tool has been found to overestimate anxiety in a chronically ill population (Higginson et al, 2001).The studies in the review did not report prevalence rates of anxiety relative to any normative comparisons making the data from the POMS difficult to interpret; although normative data from geriatric populations do exist (Nyenhuis et al, 1999).

Variations in prevalence estimates

It is important and of value to estimate approximate levels of anxiety to encourage the assessment and identification of anxiety by clinicians and promote additional research into the impact of psychological factors in LTCs. It is also crucial to explore sources of heterogeneity in prevalence estimates, as a result of the research process and due to actual variations in reported levels of anxiety. The findings from meta-regression indicate that significantly higher rates of anxiety are found in studies that identified anxiety as probable clinical anxiety and more so elevated symptoms of anxiety which exceed levels found in the general population when compared with specific anxiety disorders. In addition higher estimates of overall anxiety

prevalence were associated with a higher proportion of females in the sample and the location of studies in the USA versus the UK & Europe.

Within the category of anxiety disorders, gender was associated with variance in prevalence estimates. In contrast to findings from meta-regression of overall prevalence estimates, samples with a higher proportion of males reported higher levels of anxiety than those with a higher proportion of females. Within the concept of probable clinical anxiety only NYHA functional class was associated with prevalence estimate variance. Samples classified as mild NYHA functional class were associated with higher prevalence estimates of probable clinical anxiety compared with samples classified as moderate/severe and mixed.

Variations in anxiety based on population, methodology and setting

The finding that overall anxiety increases as the proportion of females in a sample increases is consistently supported by research that indicates females experience higher levels of anxiety compared with males and report more symptoms of anxiety. Evidence from the gerneal population suggests that females are at higher risk of experiencing Generalised Anxiety Disorder (GAD) than males, with a 2:1 ratio often found in prevalence studies (Brown, O'Leary, and Barlow, 2001). Research examining anxiety in HF samples and following acute cardiac events identifies female patients as significantly more anxious than males (Moser et al, 2010; Paukert et al, 2009; Moser, 2007; Schweitzer et al, 2007). Females may experience levels of anxiety 25% higher than those of males (Heo et al, 2007; Moser et al, 2003). Whether this difference in prevalence rates reflects a behavioural, social, or physiological propensity towards anxiety in females is still unclear. Alternatively, or in addition, higher rates of anxiety identified in females may reflect a higher frequency in reporting in females comparative to males.

Meta-regression analysis of heterogeneity in overall prevalence of anxiety and within the different conceptualisations and measurement of anxiety showed that the variable age accounted for significant variance in prevalence rates. This finding does not support the evidence from general population samples which has found that anxiety increases with age, with up to 17 % of elderly men and 21.5 % of elderly women experiencing severe anxiety, although the term elderly is not defined, but does support research conducted with HF samples (Heo et al, 2007b). It is unknown at present whether the difference in prevalence rates reflects a ‘real’ variation in the prevalence of anxiety in younger and older aged adults, or whether anxiety is underdiagnosed in elderly HF patients. It could be

hypothesised that younger adults with HF may have more financial, work-related stress and a more marked reduction in social functioning as a consequence of their HF condition, relative to elderly, retired patients. It may be that elderly individuals. Alternatively, it has been suggested that the mental health of elderly patients in general is over-looked by clinicians, possibly as they feel that worries about deteriorating health in old age is a normal part of aging (Lenze et al, 2001).

In the current review NYHA functional class was found to be associated with heterogeneity in anxiety defined as probable clinical anxiety. Samples with a higher proportion of patients with mild NYHA functional class (Classes I/II) were associated with higher prevalence estimates than moderate/severe NYHA functional class. However, this analysis used up to 24 observations, so should still be considered with caution. It has previously been reported that as NYHA functional class (a subjective measure of HF functioning based on signs and symptoms of heart failure) increases, levels of anxiety increase (Heo et al, 2007a; Haworth et al, 2005; Doering et al, 2004). NYHA functional class data was difficult to synthesise for data analysis purposes. Most studies reported frequencies or proportional data for individual classes, some combined classes and one included a class 2.5 in their reporting (Kulcu et al, 2007). NYHA functional class data needed to be transformed into categorical data for the purposes of analysis, which may have affected the integrity of the data and may explain the contradictory findings in the review compared with previous literature. Hypothesising, it may be suggested that patients with less severe NYHA functional class may be newly diagnosed with HF, and subsequently may not have adjusted to living with a LTC, thus reporting higher rates of anxiety compared with patients with moderate to severe NYHA functional class. Further research is required to explore further how disease severity influences HF patient's emotional states.

The setting from which samples were recruited from was not significantly associated with variations in anxiety prevalence estimates. The majority of included studies assessed anxiety in outpatient samples. Relatively few studies have examined anxiety in primary care or in hospitalised patients. Which may have hindered current analysis due to a lack of variance in settings across studies. Research conducted in primary care settings on patients with a diagnosis of COPD has indicated that the psychological health of patients is often neglected in favour of physical care (Coventry et al, 2011). It would be interesting to examine in more detail whether the levels of psychological distress in samples of HF patients do vary as a result of the care they are given.

It was found that higher prevalence estimates were associated with studies that originated from the USA compared with the UK and Europe. This may represent underlying differences in the levels of anxiety found in the USA compared with the UK, and may potentially reflect differential health service provisions, or highlight disparity in the levels of anxiety among diverse cultural groups. Ethnicity and cultural variations within and between study samples was not explored in the current review due to variations in reporting and insufficient data, subsequently it is difficult to state whether ethnicity influenced the reporting of anxiety levels in the current review. A likely explanation for the variation in reported prevalence between studies originating from the USA and UK & Europe is the choice of measurement tools and conceptualisation of anxiety. With the exception of one study (Barrow et al., 2007) all of the studies included in the review that identified individuals as anxious based on elevated symptom scores above general population norms, using the BSI-A and MAACL, originated from the USA.

Quality appraisal

The conceptualisation of anxiety in studies was lacking and the choice of measurement tool was at times inappropriate for the sample. This makes the validity of prevalence estimates uncertain. Response rate reporting in the included studies was poor. The majority of studies did not report response rates. Of the 19 studies supplying response rates, only five provided information on non-responders. These findings make it difficult to ascertain whether prevalence estimates have been obtained from biased samples. That said the reporting of sample demographics and clinical characteristics was adequate in many included studies, which means it is possible to consider the context in which prevalence estimates have been generated. Future research would benefit from transparency in sampling procedures to ensure prevalence estimates are reliable and valid.

Limitations

This systematic review of the prevalence and variance of anxiety in HF samples is novel, extensive and comprehensive. That said the review has several limitations. Attempts have been made to identify all existing evidence that captures a measure of anxiety in samples of individuals with a diagnosis of HF; however non-English language articles and dissertations

were excluded from the review due to resource restrictions. A strength of the review is the extent to which all known English language publications and on-going studies were searched for and identified. A number of databases were searched and additional information from studies was sought from authors to ensure that the maximum number of studies could be eligible for the review. In addition hand searching of reference lists of articles from research leaders in the area were cross-reference to ensure no studies were missed through databases searches.

Study screening was conducted by only one reviewer which may increase the chance of missing potentially relevant studies. This risk was minimised through consultation with the review team to ensure inclusion and exclusion criteria were appropriate.

Study quality, although assessed, was was not an exclusion criterion therefore the review may contain studies of low quality which may have impacted on the robustness of reported prevalence rates. The manner in which anxiety was conceptualised was included in meta-regression however. It is clear from multi-regression that studies identifying specific anxiety disorders using gold standard tools and DSM-IV criteria reported lower rates of anxiety; the pooled estimates from these studies had less heterogeneity than other studies. Study design was also included as a variable in meta-regression and could be considered an important quality appraisal item, particularly as the review did not exclude any studies based on quality/design criteria. Design was not however, found to be associated with variance in prevalence estimates.

For synthesis and appraisal purposes the manner in which studies have conceptualised and measured anxiety has been categorised in this review into anxiety disorders, probable clinical anxiety and elevated symptoms of anxiety above normative thresholds. On reflection, more stringent inclusion criteria and a more focused question may avoid the need for such subjective synthesis in future reviews and may decrease the amount of heterogeneity found between studies. The validity or appropriateness of measurement tools to identify anxiety in clinical populations and distinguish between anxiety and depression has been subjectively evaluated based on available empirical evidence and in consultation with the review team. It is hoped that transparency with regards to the appraisal process of measures should allow decisions to be scrutinised.

The combined overall prevalence estimate of anxiety, which in this review is 32.04%, has been influenced by the relatively larger number of studies that measured symptoms of anxiety

compared with the handful that identified anxiety disorders. The higher prevalence rates generated from studies that measured severity of anxiety symptoms may have skewed the pooled prevalence estimates somewhat. It is hoped however, that the subgroup analysis of types/conceptualisations of anxiety (anxiety disorders, probable clinical anxiety and elevated symptoms above normative thresholds) and reported heterogeneity will allow the reader to interpret overall prevalence estimates with caution.

Findings should be interpreted with caution due to the high levels of heterogeneity between studies and small numbers of observations involved in meta-regression analyses. However, for example when using the I_2 test, substantial variability exists in the literature with regards to acceptable in upper limits (Ioannidis, Patsopoulos & Rothstein, 2008) making it difficult to determine just how much heterogeneity is acceptable between studies. Further exploration of sources of heterogeneity in anxiety prevalence estimates and subgroup analysis within concepts of anxiety was often not possible, due to the small number of observations and collinearity of data. No clear consensus exists regarding the lower limit to the number of studies that a meta-regression should be performed on. Simulations to test the stability of parameter estimates indicate that fewer than ten studies produce unstable estimates, a problem exacerbated further when sample sizes are small (Morton, Adams et al, 2004). In the current review no lower limit for number of observations was set. In some sub-group analyses the number of observations was low (below eight), and therefore the reader is advised to interpret findings from meta-regression with caution.

The use of meta-analysis with studies that contain significant amounts of heterogeneity with respect to outcomes, sample characteristics and study design is controversial. However, the use of meta-analysis in this review has been applied with caution in order for overall and sub-group pooled prevalence estimates to be considered and for heterogeneity in outcomes to be explored using meta-regression and as such is considered justifiable, if not essential for exploration of stratified prevalence estimates (Ioannidid, Patsopoulos & Rothstein, 2008). That said, the heterogeneity in conceptualisation of anxiety, measurement, sample characteristics and study design does make the pooled prevalence estimates unstable. Overall prevalence estimates should be interpreted with caution and readers are advised to explore study level data on sample characteristics and prevalence rates further for a better understanding of the prevalence, levels and variance of anxiety in HF patient samples.

Finally, the last search for papers was conducted in January 2013. The speed and frequency at which research is publish often makes findings from systematic reviews outdated quickly. This may be more of an issue for reviews of effectiveness than for epidemiology reviews; however, for a review to provide the best available evidence it must be up-to-date. The Cochrane Handbook (2008) recommends that reviews are updated every two years, or earlier if the area experiences significant changes that would impact on the outcomes of the review (Chapter 3, Higgins et al, 2008). The current review is comprehensive and included a large number of studies which is a strength, however over time measurement tools change and so an update of the review will be necessary in the next year in order to accurately identify levels of anxiety in this patient population.

Conclusions

The review has shed some light on the reasons for such diverse reported prevalences rates of anxiety in HF patient populations; which was primarily the way in which anxiety has been conceptualised and measured.

The review has highlighted that many researchers are using measurement tools that could be considered inappropriate for disentangling symptoms of anxiety within the context of a patient population experiencing a physical disease. Taking the medical model as a basis for the conceptualisation of anxiety and depression, using signs and symptoms of a condition to identify and diagnoses, it becomes particularly crucial to correctly identify the specific and unique symptoms of a particular mental health condition. All of the included studies, through the use of measures and tools that use symptoms to identify anxiety, have conceptualised anxiety using a medical model as a foundation. Therefore, it is essential that researchers consider the validity and appropriateness of anxiety measures in their work. In addition, the clinical utility of some measurement tools that are in use has been questioned. To identify all individuals who score over a norm for the general population for example, does not allow for appropriate health care provisions to be targeted at the highest need.

Interestingly, the use of the HADS in HF research has been shown as increasing in recent years, although the GAD – 7, a commonly used tool in the UK primary care settings, has not. No new measurement tools have emerged in the past few years to assess anxiety in HF patient populations, at least not that have been identified in research literature. There remains the

question, are we currently assessing, screening and monitoring HF patients using the most appropriate tools available? And can these tools be improved?

Summary

- This systematic review of the prevalence of anxiety in HF patient samples and exploration of variance in prevalence estimates is the most comprehensive review to date and only meta-analysis and regression to synthesise anxiety measurement in a HF patient population.

- Anxiety was rarely the main outcome in research and was often poorly defined.

- Levels of anxiety variety widely and considerable heterogeneity was found between studies.

- A wide range of measures were used to identify anxiety, using a range of cut-offs. Not all studies used measurement tools that have been shown to be appropriate for use in clinical, elderly patient populations and have the ability to discriminate between anxiety and depression.

- The clinical utility of some measures is of concern, particularly in an economic climate that requires health provisions to be effectively directed as the highest need.

- The way in which anxiety had been conceptualised and measured had a significant impact on the level of anxiety identified.

- Rates of anxiety disorders, clinically significant anxiety and elevated symptoms of anxiety above general population norms were not noticeably greater than those found in general population and chronic condition samples.

- The review has a number of strength including comprehensiveness and transparency that contribute to confidence in the findings.

CHAPTER FOUR: **SURVEY**

Chapter four presents the working methods from the second phase of research; the cross-sectional survey.

Part one of this chapter contains the working methods including the study design, sampling strategy, survey measurement tool selection and data collection.

Part two of the chapter presents descriptive data from the survey and statistical analysis of results from the study.

Part three presents the discussion of research findings and considers the strengths and limitations of the research.

Part Two: Survey methods

Aims and objectives

The aims of the second phase of research were to explore variance in reported anxiety symptoms in a HF patient sample using an appropriate tool for use in older, clinical populations and determine whether anxiety symptoms contribute signifcaintly to determining variance in HRQoL.

The research questions were as follows:

1. What is the prevalence and variance of anxiety symptoms in a sample of individuals with a diagnosis of HF attending specialist out-patient HF clinics?

2. What amount of variance in HF patients' self reported HRQoL is accounted for by anxiety symptoms after controlling for physical symptoms, perceived social support, depression and known demographic, environmental and medical covariates?

Design

A cross-sectional, self-administered, mail returned questionnaire survey, supported by face-to-face initial contact and supplemented with a telephone reminder was used. The method was selected to best meet the aims of this phase of research. The combination of approaches was selected to maximise participant recruitment and minimise both participant burden and expense with regards to time and money.

Sample

Sites

Patients with a diagnosis of HF were recruited from HF clinics in two large University teaching hospitals in Greater Manchester. Both sites were chosen for the number of attending patients with a HF diagnosis and for practical reasons including established contacts and proximity to the University of Manchester.

University Hospital of South Manchester (UHSM) NHS Foundation Trust

UHSM is a major acute teaching hospital trust providing services for adults and children at Wythenshawe Hospital and Withington Community Hospital. The HF clinic is located within the Northwest (NW) Heart Centre at Wythenshawe Hospital which provides specialist cardiac and thoracic surgical services to a regional population of 3.2 million people. The HF clinic is staffed by two specialist HF nurses, a number of cardiologists, dieticians, psychologists and cardiac rehabilitation physiotherapists. Clinics run four days a week, with approximately eight to ten patients seen per clinic. Patients must have a diagnosis of left ventricular systolic dysfunction in order to be managed by the specialist team.

Central Manchester University Teaching Hospitals NHS Foundation Trust

Central Manchester University Hospitals NHS Foundation Trust cares for more than one million patients a year and consists of the following hospitals: Royal Manchester Children's Hospital, Manchester Royal Infirmary, Manchester Royal Eye Hospital, St Mary's Hospital, University Dental Hospital of Manchester and Community Services[63]. The Heart Failure clinic is located within the Manchester Royal Infirmary (MRI). The centre provides review and follow up to patients with either a confirmed or a suspected diagnosis of heart failure, of any type. The clinic provides four doctor and two nurse-led clinics a week, in addition there is a group education session every four to six weeks that patients and their relatives can attend. Data from 2010 audit shows that 194 new patients were referred to the service within a one-year period. The clinic managed 722 doctor's appointments and 446 nurse-led appointments. The separate nurse-led group education session sees around 90-100 patients annually.

The Greater Manchester Area

Although not all patients attending the HF clinics reside in the Greater Manchester area, the majority come from Manchester and the surrounding areas. Greater Manchester is a geographically spread region comprising of Manchester Central, Bolton, Bury, Oldham, Rochdale, Salford, Stockport, Tameside, Trafford and Wigan. As of mid 2010 the total population stood at just over two and half million residents, 20 per cent of whom are 60 years and over (Office of National Statistics, 2011a). The average life expectancy of males

[63] http://www.cmft.nhs.uk/home.aspx

as of 2007 to 2009 was 74 yrs and for females was 79 yrs, compared with 78yrs for males and 82yrs for females in England overall (Office of National Statistics, 2011b). The percentage of households in the Manchester area with one or more persons with a limiting long-term condition is around 39.5%, compared with a national prevalence of 33.5% (Office of National Statistics, 2011a). Around ten per cent of the Manchester population is on incapacity benefit compared with an average seven per cent in England as a whole. The rates of Coronary Heart Disease (CHD) have increased in Manchester, with a 30% increase in diagnosis based on hospital admission from April 2003 to March 2008 (6,752 to 9,589). This compares with a 26.5% increase in CHD rates in England as a whole for the same time period (735,244 to 1,000,332) (Office of National Statistics, 2011a).

Sample size calculation

Considering the number of patients seen at one of the sites for a given year and the duration of time permitted for recruitment and data collection it was estimated that approximately 400 potential patients could be approached to take part in the study. Extrapolating from previous research (Kaprana, 2009) recruiting 400 patients with a conservative estimate of a 50% response rate (returned completed questionnaires) should generate a feasible and sufficient sample size.

Assuming a medium sized relationship between the explanatory variables and the outcome variables at the 5% (2-sided) level of significance and 80% power, the number of participants required to power statistical calculations can be determined using a general rule of calculation for multiple regression found in Tabachnick & Fidell (Tabachnick, 2007). If 'm' is the number of explanatory variables, then the required sample size, 'N', is $N \geq 50 + (8m)$, to test the whole model and $N \geq 104+m$ to test individual variables. Using the formula $N \geq 50 + (8m)$ obtaining a modest sample size of 186 participants allows for up to seventeen explanatory variables to predict anxiety symptom scores and HRQoL.

Inclusion criteria

1. 18> years or over
2. A medical diagnosis of HF of at least 3 months duration taken from medial notes.

Exclusion criteria

1. Medically unstable (requiring acute hospitalisation)
2. Immediately prior to or 3 months post recipients of:
    - Implantable cardiac device (cardioverter defibrillator or coronary resynchronisation therapy)
    - Coronary artery bypass graft
    - Percutaneous coronary intervention See appendix 13 for definitions of medical procedures.
3. Heart transplant or artificial heart pump patients
4. Patients with an end stage co- morbid medical condition.
5. Individuals who are unable to provide informed consent (due to diminished capacity as in dementia or learning disabilities or due to the patient currently experiencing a psychotic episode)
6. Patients unable to communicate verbally or in written English, as the cost of translators or the translation of measures was not feasible in this student research project.

Specialist HF nurses within the clinics responsible for patients' care had access to patient medical records and identified patients who met inclusion criteria during their clinic appointments.

Recruitment procedure

No comprehensive database of HF patients exists for both sites; therefore no sampling frame existed from which patients could be systematically identified and posted research packs. In addition the practice of identifying patients from medical databases and approaching them before they have provided consent for their personal details to be viewed is questionable and so was avoided in this research. Patients meeting the inclusion criteria for the study were identified on a daily basis by HF nurses with reference to medical records prior to their clinic appointments.

HF nurses informed patients about the research at the end of their routine clinic appointment. Interested patients were then introduced to the researcher by the specialist nurses. The research aims were briefly discussed with patients, placing the research in context and highlighting the need to improve services particularly for vulnerable groups.

Potential participants were shown a research pack containing a cover letter, an information sheet, two consent forms, a questionnaire booklet and a returns envelope. See appendix 14 for cover letter, information sheet, consent form and questionnaire booklets. Patients had the opportunity to ask questions about research and were encouraged to do so. If patients stated they would like to participate in the research they were given the research pack to take away and complete in their own time. Patients were asked to provide consent for a reminder telephone call from the researcher during initial contact at clinic, if after a period of two weeks the questionnaire booklets had not been returned. If patients consented to a reminder telephone call their names, identification numbers and telephone numbers were recorded. This reminder was included to address any questions potential participants may have, to remind those who had forgotten about the research to complete their questionnaires and to identify potential respondents who required an additional questionnaire posting to them.

On occasions when the researcher could not attend clinics the specialist HF nurses, distributed the research packs and recorded patient details for reminder telephone calls of interested patients.

Strategies to increase the response rate

Potential participants were recruited face-to- face to encourage participation. Patients had the opportunity to ask questions and have concerns relating to their participation allayed. In order to increase the response rate a number of strategies were used:

1. Following face-to-face contact all patients received a one-off follow-up reminder telephone call after two weeks if they had not returned their questionnaire booklets and consent forms.
2. All documents sent to potential respondents had official University of Manchester logos on them and telephone and email contacts for the researcher, supervisors and a University contact for official complaints.
3. The research was supported by the host NHS organisation and patients were introduced to the researcher by specialist nurses associated with their care.
4. All return envelopes were included in research packs already pre-paid using business reply permits to ensure only returned questionnaires were paid for.

The number of research packs distributed and returned was monitored on a monthly basis to ensure targets were met. If recruitment was slow the reasons for this could be determined with the intention of rectifying problems in reaching the required sample size.

Data collection

Selection of variables to be entered into regression analysis

The selection of variables for inclusion in regression analysis to determine predictors of both anxiety symtoms and HRQoL in the sample of individuals with a diagnosis of HF was informed by the weight of evidence in the empirical literature and from the model of HRQoL presented in part five of chapter one (Ferrans et al, 2005). The number of variables included in the regression was limited by the realistic sample size achievable in a given period from both included clinical study sites. As previously stated, sample size calculations indicated that up to 17 variables could be entered into regression models to predict anxiety symptoms and HRQoL.

Table 14 presents' potential variables selected, their values and the number of explanatory variables they constitute in multiple regression analysis to address the research questions in phase two of the study.

Table 14: Variables for entry in multiple regression analysis

Variable	Value	No. of explanatory variables for analysis
Dependent variables		
HRQoL (Overall KCCQ)	Score	1
OR		
Anxiety symptoms	Score	1
Covariates		
Age	Years	1
Gender	Male / Female	1
Ethnicity	White British/None	1
Social deprivation	Score	1
Functional status	NYHA (I/II/III/IV)	3
LVEF	Mild/moderate/severe	2
Physical symptoms	Symptom scale score	1
Duration of HF	Years	1
Medical co-morbidity	Score	1
Previous hospital admission	Frequency (self report)	1

Previous ICD implantation	Yes/No	1
Perceived social support	Score	1
Depression	Score	1
	Total	17

HRQoL (health-related quality of life); KCCQ (Kansas City Cardiomyopathy Questionnaire); NYHA (New York heart Association); LVEF (left ventricular ejection fraction); HF (heart failure); ICD (implantable cardioverter defibrillator)

The variables presented in table 14 were conceptualised and available measurement tools were reviewed. Table 15 presents a summary of included variables in the survey and those included in the regression, in addition to choosen measurement tools and the primary reasons for their selection. Data were collected using self-completion questionnaires and from patient medical notes. A limitation of previous research in this area is the poor conceptualisation of variables and the selection of inappropriate measures for the given sample. The conceptualisation of variables and their measurement is discussed in detail below.

Table 15: Variables and measurement methods for the survey

Variable	Measurement tool	Data collection	Reason for selection in regression analyses
Age, gender, ethnicity	Structured questionnaire	Self completion questionnaire	Potential demographic covariates of anxiety and HRQoL identified in the empirical literature.
Social deprivation	Index of Multiple Deprivation (DCLG, 2011)	Medical notes	Potential characteristic of the environment thought to influence HRQoL in Ferrans model. Empirical evidence suggests better indicator of socio-econmic status than educational level or occupation. The IMD considers a comprehensive range of social and economic indicators of deprivation.
Type of HF	Echocardiogram	Medical notes	N/A
Cause of HF	Consultation with cardiologist	Medical notes	N/A
Duration of HF	Previous medical correspondence	Medical notes	Under research covariate that may be indicative of the amount of time a patient has been able to process their diagnosis or have had to manage a complex treatment regimen.
HF Functional class	Consultation with cardiologist or HF nurse	Medical notes	Indicative of disease severity and functional status in Ferrans HRQoL model and empirical evidence is contradictory in linking disease severity with both anxiety and HRQoL. NYHA functional class more accurate predictor of function in patients than HRQoL proxy measures.

History of ICD	Document ICD implantation	Medical notes	Empirical evidence suggests that the presence of an ICD increases anxiety in HF patients – research in its infancy.
Left Ventricular Ejection Fraction	Echocardiogram	Medical notes	Additional indicator of HF disease severity that is considered key variable in Ferrans HRQoL model. Empirical evidence for the influence of LVEF and NYHA functional class on HRQoL is contradictory. Inclusion of both an objective and subjective measure of disease severity is of value in the regression analysis.
Co-morbid conditions	Charlson co- morbidity index(Charlson et al, 1987)	Medical notes	The added burden of multiple diseases and their subsequent treatment regimens is a timely variable of interest that may influence both emotional health and HRQoL of HF patients. Using an index of co- morbid conditions allows for the addative effects of diseases to be considered and gives weight to diseases known to have more severe implications for person's health outcomes.
Perceived symptoms	Physical Symptom Incidence and Distress Scales (rPSIDS) (Glazer et al,2002)	Self completion questionnaire	Symptoms are a variable thought to influence HRQoL (Ferrans, 2005) and can also be indicative of the physical functioning of a patient. Empirical evidence shows that physical symptoms are significant predictors of HRQoL in HF samples. Few studies assess a comprehensive range of physical symptoms and by doing so the impact of a range of LTCs and physical co -morbid conditions can be considered.

Hospitalisation	Item on structured questionnaire	Self completion questionnaire	The frequency of hospitalisations and execerbations of HF is a potential influential variable on patient's levels of anxiety and perceptions of their health and subsequent HRQoL. The variable is under-researched in this area.
	Discharge letters	Medical notes	
Anxiety	Hospital Anxiety and Depression Scale (HADS)(Zigmond &Snaith, 1983)	Self completion questionnaire	The evidence for the influence of anxiety on HRQoL in HF patient samples is limited and contradictory. Anxiety symptoms will be measured using a tool that has been found to distinguish between symptoms of anxiety and depression and omits somiatic items that may also be indicative of physical diseases. The tool provides established cut-offs to indicate varying severity of anxiety, with levels akin to clinical anxiety as measured using the SCID-IV clinical interview. The tool is brief and can be self-administered.
Depression	HADS	Self completion questionnaire	Depression is a characteristic of the individual thought to influence the impact of disease severity, physical symptoms and functional status on HRQoL. Empirical evidence shows a strong link between depression and HRQoL in HF samples. The variable will be measured using a tool that is appropriate for use in this patient population and has clinical utility.
HRQoL	Generic SF 12v2(Ware JE, 1996)	Self completion questionnaire	N/A
	Disease specific Kansas	Self completion questionnaire	The KCCQ was selected for use in the survey as it is

	City Cardiomyopathy Questionnaire (KCCQ) (Green et al, 2000)		a valid and reliable tool and evidence suggests it is sensitive in the clinical population and contains items thought to be favourable for the target population. The use of the overall summary score from the KCCQ was selected as research suggests the measure is senstitive to change. The use of the overall summary was favourable in the current review to the use of a physical functioning sub-scale of the SF12 as one aim of the study was to identify predictors of HRQoL rather than singular components of the concept.
Perceived social support	ENRICHD social support inventory(Mitchell et al., 2003)	Self completion questionnaire	Social support is a variable that could represent the influence of characteristics of the environment on HF patient's HRQoL. Research suggests that assessing the frequency, nature and satisfaction with personal contacts is a more valid measure of social support than either the number of people in a person's social network or marital status. The ESSI was selected as the tool is valid and reliable in the choosen population and is brief (7-items) so places fewer burdens on respondents relative to other appropriate tools (MOS Social Support Survey).

HF (Heart Failure); ICD (Implantable Cardiac Device); HRQoL (health-related quality of life); DCLG (Department for Communities and Local Governement)

Data from medical notes

As table 15 shows, a number of clinical variables were included in the survey. The type and location of a person's HF, the cause of their HF, the duration of their condition, NYHA functional class, LVEF, co- morbid medical conditions, number of hospital admissions for HF exacerbations and postcode data to obtain a score of social deprivation were obtained from medical notes.

1. *The type (*LVSD or HFPEF) *and location of individuals' HF* (left sided, right sided or biventricular) was determined by echocardiogram, interpreted by cardiologists and taken from medical notes.

2. The *aetiology or cause of individuals' HF* was defined as ischemic (conditions that lead to a restriction of the blood supply), or non ischemic (not a result of ischemic causes).

3. The *duration of an individuals' HF* was defined as the number of years from diagnosis until 2010 taken from HF diagnosis in clinic letters.

4. *New York Heart Association (NYHA) functional class* was used to define individuals' level of functioning. **NYHA functional class** is recorded as NYHA class I (asymptomatic), NYHA class II (mild symptoms and slight limitation on ordinary activity), NYHA class III (marked limitation in less-than-ordinary activity as a result of symptoms, only comfortable at rest) and finally NYHA class IV (Severe limitations as a result of symptoms, even at rest). NYHA functional class was determined by cardiologists or HF nurses based on consultations with patients and recorded from medical notes at the date closest to when patients' returned their questionnaires.

5. *Left ventricular ejection fraction* was defined as mild (41–49%), moderate (35–40%) or severe (<35%) (Mahadevan et al., 2008) dysfunction and was recorded as an additional measure of patients' cardiovascular functioning. LVEF was determined from echocardiograms and recorded from the most recent test performed in patients' notes.

6. *Co- morbid medical conditions* can be measured using index scales or by measuring the frequency of particular conditions, such as hypertension, diabetes and respiratory disease (Franzen, 2007; Lesman – Leegte, 2007; Jaarsma et al, 1999). However, as little research exists to suggest which conditions may play a role in predicting HRQoL in this patient group it was decided that an index of co-morbidity may be more appropriate. The **Charlson Co- morbidity Index** (Charlson et al., 1987) was selected for this study. Medical conditions listed in the index are assigned weights and totalled to generate a co- morbidity score for each patient. Scores represent both frequency and severity of conditions based on the impact medical conditions have on the risk of mortality at one year. The scores are as follows:

   Score of 1 = Myocardial infarction; Peripheral vascular disease; Cerebrovascular disease; Dementia; Chronic pulmonary disease; Connective tissue disease; Diabetes.

   Score of 2 = Hemiplegia; Moderate or severe renal disease; Diabetes with end stage organ damage; any tumour; leukaemia; Lymphoma.

   Score of 3 = Moderate or severe liver disease.

   Score of 6 = Metastatic solid tumour; AIDS

The Charleson Comorbidity Index has shown good construct, concurrent and predictive validity. Test-retest reliability is good and inter-rater reliability is moderate (de Groot et al, 2003).

Medical notes were consulted to identify the presence of the above conditions. HF nurses were consulted for clarification of medical terminology to assist identification of conditions.

7. *Hospital admissions* were defined as the number of admissions to hospital in the past 12 months prior to questionnaire completion for exacerbations of HF. The number of admissions was measured in two ways: first, from the frequency of discharge letters with a recorded HF exacerbation cited as the reason for hospital admission in medical notes and secondly, from patient self-report in questionnaires included in the research packs provided to participants. With regards to self-reported hospitalisations, patients were asked using a single item in a socio-demographic tool ‘How many times in the past year have you been admitted to hospital as a result of your heart failure?’

8. *Social deprivation* was calculated from patient postcode data recorded from medical notes and interpreted using the English Indices of Deprivation 2010 (EID) to calculate an **Index of Multiple Deprivation (IMD)** (Communities and Local Governent, 2011). The EID uses 38 separate indicators (many measured in 2008), organised into seven distinct domains: income, employment, health and disability, education skill and training, barriers to housing and other services, crime and finally living environment, which can be combined to calculate an overall IMD. The IMD measures relative levels of deprivation in small areas of England called Lower layer Super Output Areas (LSOAs). Areas are allocated a ranked value. Rankings closer to one show high levels of social deprivation. The bottom 10% of the rankings are considered socially deprived. With 32,482 LSOAs in England the bottom 3248 ranks would be considered socially deprived.

Self-report data from questionnaires

A questionnaire was developed by the researcher to record socio-demographic data; items include age, gender, and ethnicity. Ethnicity was included as a multiple choice single item, with responses categories taken from the Office of National Statistics 'Ethnic group statistics: a guide for the collection and classification of ethnicity data' (Office of National Statistics, 2003). See appendix 13 for questionnaire booklet containing self-report measures. Existing validated tools were included in the self-completion questionnaire to assess self-reported physical symptom frequency and severity, perceived social support, anxiety and depression, and HRQoL.

Physical symptom scales

The way physical symptoms have been conceptualised and measured in HF literature varies across studies (Landrum, 2008). Symptoms can be conceptualised based on severity, burden, the pattern of symptoms, or distress caused and can be measured as isolated symptoms, health status, functional status, and HRQoL among others. Symptom subscales from HRQoL tools such as the MLHFQ and the KCCQ subscales have been used in previous research (Myers et al, 2006; Rector et al, 1996). The use of a symptom subscale from a HRQoL tool as a proxy for symptom assessment has not been selected in this survey. As an aim of phase two of the research is to examine factors that account for variance

in reported HRQoL it would not make substantive sense to use an additional HRQoL as part of the set of independent variables to predict HRQoL.

No comprehensive, validated measure exists to investigate physical symptoms in HF patient populations. The *Memorial Symptom Assessment Scale* (Chriss et al, 2004) is a 24 item measure that assesses a wide range of symptoms, both physical and emotional, that are not specifically relevant to HF or cardiac patients. In addition the measure emphasises psychosomatic symptoms. For these reason the measure was not selected to measure physical symptoms in the survey. *The Cardiac Symptom Survey* (Neiveen et al, 2008) was also considered as a measure of physical symptoms for this survey. The tool is brief and assesses the frequency, severity and interferences of ten symptoms, both emotional and physical. A final item asking patients to comment on any additional symptoms they experience is also included. The tool was however developed to assess symptoms in patients following cardiac surgery and contains an item relating to recent surgery, along with emotional items. It was felt that this measure may not be the most appropriate tool for a HF sample and in addition emotional symptoms will be measured separately in this study.

The Dyspnoea - Fatigue Index (de Jong, Moser & Chung, 2005; Feinstein et al, 1989) is a HF-specific symptom tool that has been extensively used in cardiac populations (Heo et al, 2008, 2007a/b, 2005; de Jong et al, 2005; Moser et al, 2005). The tool focuses specifically on symptoms of breathlessness and fatigue and assesses the magnitude of tasks that produce the symptoms, the pace of the task that produces symptoms and the level of functional impairment; generating a composite index ranging from severely limited to no limitations. In reading around the measure it is unclear exactly how the tool should be administered. The tool seems to assess functional impairment more than identify the presence of physical symptoms and their burden for patients. Focusing as narrowly as it does on two, albeit common symptoms of HF the measure is fairly limited by its narrow focus and was therefore not selected for the survey.

Symptom measures can also be developed for specific studies. In her 2007 thesis Ivonne Lesman – Leegte assessed HF symptoms in the COACH study by totalling the sum score of oedema, sleep disturbance, fatigue, dyspnoea, coughing and loss of appetite. In email communication with the author (august 2009) Lesman-Leegte reported that patients were asked 11 items on symptom occurrence and burden, ranging from 1 to 10. As the tool was

not validated the items were discussed with the advisory group for this PhD research in detail. See advisory group contributions in appendix 23. Ultimately the aim of this PhD was not to develop a validated tool to measure HF symptoms and the tool was excluded from the survey.

Physical symptoms were ultimately defined as patients self-reported perceived level of symptom frequency and severity using the 21 item ***revised Physical Symptom Incidence and Distress Scale (PSIDS)*** (Glazer et al, 2002). The only measure identified from a review of the literature which assesses a broad range of physical symptoms in cardiac patient populations using a relatively modest number of items. The original 20 item scale assesses the frequency and severity of physical symptoms on a scale of zero (not experienced) to three (very bothersome). The scale was revised in a recent thesis (Kaprana, 2009) with the addition of an item on ankle swelling, a common symptom of HF and a further item was re-worded (item 6) as feeling faint or tired' as it was deemed too similar to item 16 'legs feeling weak'. Kaprana (2009) stated that all modifications were included with the expressed permission of the measure's author (Professor C Emery). Total scores are summed and range from zero to sixty-three, with higher scores denoting a higher frequency and severity of perceived physical symptoms by patients. The scale has been reported as valid and reliable (Cronbach's α – 0.89, Glazer et al, 2002), however it has not been extensively tested and is rarely used in the literature. The tool was selected for the survey as it was developed for use in cardiac populations, covers a wide breadth of symptoms, has a relatively low number of items compared with some available measures, has demonstrated validity and reliability, although not extensively and has been used previously in research conducted with comparable samples (Kaprana, 2009). The Cronbach α for the rPSIDS in the current study was 0.89, indicating the measure was reliable in this sample and in accordance with the author's findings of 0.89 (Glazer et al, 2002). If the additional item (21 – swelling of ankles) was removed the calculated coefficient remained exactly the same, indicating its addition has not reduced the reliability of the measure.

Perceived social support measures

Social support has previously been conceptualised as marital status, represented by network size, or the presence of a confidant. However in the current study social support is seen as multi-dimensional, covering instrumental, emotional and practical support.

The *Social Support Questionnaire (SSQ)* Sarason et al (1983), assesses appraisal, emotional support, structural support and a person's degree of satisfaction with the support available. The SSQ is a twenty-seven-item social support measure, with each item assessing both the number of available 'others' the individual feels he or she can turn to in times of need (number score) and the individual's degree of satisfaction with the perceived support for a given situation (satisfaction score). Satisfaction scores are marked on a 6-point likert scale from 'very dissatisfied' to 'very satisfied'. The measure has a brief six-item validated version (Sarason et al, 1987) which reduces the burden on respondents. The SSQ is a valid and reliable scale, although it has not been tested extensively with chronically ill populations. However the scale has little coverage of instrumental or practical support, which although the author states are less important, means the breadth of coverage of this measure is reduced. The SSQ asks people to count the number of people available for help and perceived satisfaction with support, yet it has been shown that network size is not linearly linked to perceived satisfaction with support (Mclaughlin et al, 2012).

The *Medical Outcome Study (MOS) Social Support Survey* is an 18-item measure, developed for use in LTCpatient population to assess emotional, informational, affectionate, tangible support and positive social interactions (Sherbourne & Stewart, 1991). The measure has been tested extensively and shows good validity and reliability. However, as a number of other variables are being investigated in the current study all included tools needed to be a brief as possible.

Therefore perceived social support was measured in this study using the ***ENRICHD Social Support Inventory (ESSI)*** (Mitchell et al., 2003). The seven-item scale measures structural (partner), instrumental (tangible help), and emotional (caring) support previously found to be predictive of mortality individually in cardiovascular patients (Mitchell et al., 2003). Scores range from eight to thirty-four, with higher scores indicating better levels of perceived social support. Scores <18 were used to identify low social support according to authors recommendations (Mitchell et al, 2003). The measure has been well tested particularly in cardiac samples and has shown good reliability (Chronbach's $\alpha = 0.88$) (Vaglio et al, 2004). In the current study the ESSI social support measure had a Cronbach's α coefficient of 0.84, again indicating this measure had a high level of internal consistency. The scale has only seven items, however as the correlation was high there was no need to report the inter-item correlation for this scale.

Assessing anxiety and depression

Assessing anxiety and depression in populations with LTCs, particularly cardiac samples, is challenging, as reported in chapter one, as many physical symptoms resulting from a HF condition overlap with somatic symptoms of anxiety and depression, including fatigue, weight gain, palpitation, dizziness and shortness of breath. The assessment of common mental health conditions in HF patient populations must therefore be conducted with these challenges in mind.

To assess the presence of specific anxiety disorders and major depression a clinical interview is required. Signs and symptoms of particular disorders can be explored and assessed based on their presence, duration and impact. A diagnosis is either present or absent; anxiety and depression are not assessed on a continuum with a clinical interview. However, clinical interviews could not be used to screen for the presence of possible or probable anxiety or depression in a clinical HF patient population as the interviews are time intensive and require a trained interviewer. In addition, it would take a skilled interviewer, familiar with both physical and mental health to disentangle the somatic symptom overlap between physical and mental health conditions. Neither are they practical to screen for common mental health conditions in busy clinical settings and so the clinical relevance of their use in this study is limited.

The value of measuring anxiety with objective physiological measures has been thrown into question, as parameters such as heart rate and blood pressure do not correlate with levels of anxiety in patients with cardiac conditions (de Jong et al, 2004). What is required in order to study anxiety effectively is a standardised approach that can be replicated across studies and aid direct comparisons of findings (Carroll & Reiger, 2008).

In the current survey anxiety and depression have been conceptualised using a medical model, which proposes that the presence of conditions can be identified using signs and symptoms. Anxiety and depression are view here as varying on a continuum from normal through to severe; as opposed to specific anxiety disorders. The most commonly used self report questionnaire measures to identify the levels of anxiety and depressive symptoms are listed in table 16 along with a description of the measures, the range of scores considered to indicate levels of probable clinical anxiety and any advantages and limitations associated with the measures.

From the measures featured in table 16 the ***Hospital Anxiety and Depression Scale (HADS)*** (Zigmond AS, 1983) was selected for use in the current survey. The tool is brief, reliable and valid (Cronbach's $\alpha = 0.83$ for anxiety and Cronbach's $\alpha = 0.82$ for depression; Bjelland et al, 2002) and can be used to measure both anxiety and depression at the same time, reducing respondent burden. As the tool was developed for use in hospitalised populations somatic items are omitted, therefore the measure should in theory distinguish between medical symptoms and those of mental health complaints. The HADS is widely used in HF literature as the systematic review identified, making comparisons with other study data possible. The tool assesses respondent's mood over the past week with 14 statements, seven items measuring anxiety and seven measuring depression. Four response options are provided for each item, with scores ranging from zero to three. Scores range from zero - 21 for each scale, with higher scores representing more distress. Scores under eight on either scale have been regarded as being in the normal range, a score of eight or above indicating possible caseness of both clinical anxiety and depression (Bjelland et al, 2002). The ability of the HADS to provide a clinically meaningful threshold for anxiety makes it valuable in a clinical setting.

In the current study Cronbach α for the anxiety subscale was 0.89, indicating a high level of internal consistency even with a small number of items in the scale. The Cronbach's α for the depression subscale was 0.83. The Cronbach's α for the HADs as a whole was 0.91, indicating both a high level of internal validity for the tool as a whole and for each individual subscale.

Table 16: Table to describe and evaluate tools that assess symptoms of anxiety and depression

Measure	Description	Advantages	Limitations
Beck Anxiety Inventory (BAI) (Beck, 1988)	21-item questionnaire (14 somatic symptoms, 7 subjective aspects of anxiety and panic). Reponses on 4 point intensity scale. Takes 5 minutes to complete. Differentiates between anxiety and depression (avoid confounding). Sum scores: 0-7: minimal level of anxiety; 8-15: mild anxiety; 16-25: moderate anxiety; 26-63: severe anxiety	- Fast and easy to administer and score. - Highly reliable and commonly used tool. - Good at identifying panic disorders as many physiological items. - Tested with older adults (Kabacoff et al, 1997).	- Assesses somatic symptoms of anxiety - Does not cover avoidant behaviour and under investigates cognitive and behavioural aspects of anxiety (OCD, social phobias). - Not tested specifically on hospitalised/chronically ill populations
State-Trait Anxiety Inventory (STAI) (Spielberger, 1977)	40-item (two 20-item questionnaires). Used to screen for anxiety and anxiety disorders. Intensity of feelings of anxiety, distinguishes between state (temporary, situational anxiety) and Trait (long standing tendency to perceive situations as threatening). Takes 10 minutes to complete. State scales measure intensity of feelings on 0-4 point scale (not at all – very much so. Trait scales measure frequency of feeling 0-4 (almost never-almost always). Total scores for state and trait are calculated, ranging from 20 to 80. Cut-off score >40	- Most widely used and best established anxiety measure. - Both scales have good internal consistency (Cronbach's α of 0.92 and 0.90 for state and trait respectively) (Lane et al, 2001).	- Although unclear as to extent depression is measured alongside anxiety. Form Y attempts to distinguish between anxiety and depression (Jiang et al, 2004)

Measure	Description	Advantages	Limitations
	indicates anxious individual.		
The Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983)	14-item scale to quantify clinically significant anxiety (7-items) and depression (7-items) in hospitalised patients. 3 items in the anxiety scale cover panic/fear, 4 cover GAD. Takes 2-5 minutes to complete. Distinguishes between anxiety and depression. Identifies mild degrees of anxiety and depression, assessed based on mood over past week. Scores range from 0-21 for each scale; higher scores represent more distress. Thresholds of 8 to10, 11 to 15 and 16 and above have been found to correlate with mild, moderate and severe cases of anxiety respectively (Crawford, 2001). Bjelland et al (2002) found a balance between specificity and sensitivity was achieved when caseness was defined as scores over 8 on both scales	- Developed for use with medically ill populations - Excludes somatic items that might reflect physical illness - Separates anxiety and depression - Easy to use and brief. - Widely used and empirically tested. Cronbach's $\alpha = 0.83$ anxiety, 0.82 depression (Bjelland et al, 2002).	- Not a general screening tool to identify clinical anxiety and depression in general practice as too many screen-positives found.
Generalised Anxiety Disorder (GAD-7) (Spitzer et al,	A 7 item scale to screen for Generalised Anxiety Disorder and determine the severity of the condition. Scores of 5, 10, and 15 are taken as the cut off points for mild, moderate, and severe anxiety,	- Omits somatic items - Part of the IAPTS Toolkit - Brief	- Although this tool is probably the most appropriate for the survey it is fairly new and not widely used yet in HF research and so comparisons with other literature would be difficult.

Measure	Description	Advantages	Limitations
2006)	respectively. When used as a screening tool, further evaluation is recommended when the score is 10 or greater.	- Can also identify Panic Disorder, Social Anxiety Disorder and PTSD (Kroenke et al, 2007) -Scores relate to impairments in distress that can be modifiable	
Geriatric Anxiety Inventory (GAI) (Pachana, Byrne & Siddle et al, 2007)	20-item, yes/no response measure, asking respondents how they have felt over the past week. Positive responses are summed, with higher scores indicating higher anxiety.	- Tested in older populations - Good validity and reliability in older populations (Rozzini et al (2009)	- Not tested in younger or very old populations (McDowell, 2006) - Somatic items are limited but not omitted| - Not used often in HF literature
Brief Symptom Inventory (Anxiety Scale) (Derogatis & Melisaratos, 1983)	Provides an overview of symptoms and severity. Consists of 9 primary symptom dimensions, including anxiety (6 items), obsessive compulsive, phobic anxiety, and 3 global indices of severity. Takes 8-10 minutes to complete. Each item has 0-4 response from 0 = no symptoms to 4 = always symptoms. Score is calculated by summing the ratings and diving by the sum of the number of items in the scale. Scores can therefore be between 0 (no anxiety) to 4 (extremely anxious). Normative mean score for non-psychiatric patients is 0.35.	- Acceptable validity and reliability. - Easy to administer and does not rely on somatic symptoms to indicate anxiety (physiological symptoms).	- Not as widely used in medical patients/hospitalised samples as HADS or State-Trait Anxiety Inventory. - No cut off points that correlate with clinical levels of anxiety, only elevated levels above general population norms.

Measure	Description	Advantages	Limitations
Multiple Affect Adjective Checklist-revised (MAACL-R) (Zuckerman & Lubin, 1985)	132 alphabetically arranged adjectives, respondents tick all adjectives that describe how they feel. State and Trait forms available. Takes 5 minutes to complete. Scale assessed Anxiety, Depression, Hostility, Positive Affect, Sensation Seeking. Scores for anxiety range from 0-21 Normative score is 7, any higher indicates the presence of anxiety. Higher scores reflect higher levels of anxiety.	- Valid and reliable for range of populations including HF patients. - Can measure a number of concepts including anxiety and depression	- Less common than HADS, STAI, BSI in HF research - Lengthy and many sub-scales redundant in current study - Unethical to overburden respondents and not use data - No cut-off to determine clinical levels of anxiety or varying degrees of severity other than normative data.
Profile Of Mood States (POMS) (McNair et al, 1971)	The POMS is a 65 item (although a 37 item scale does exist) measure assessing 6 domains: fatigue, vigor, anxiety/tension, depression/dejection, anger/hostility and confusion/bewilderment.	- Measures both anxiety and depression - Good levels of reliability	- Lengthy - Measures redundant concepts Includes somatic items
SCL-90-R (Miricle et al, 1991)	90 item measure assessing 9 symptom domains including: Somatization, Obsessive-Compulsive, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic Anxiety, Paranoid Ideation, Psychoticism.	- Measures both anxiety and depression - Extensively tested in a range of samples	- Lengthy, generating redundant information in the current study.

Measure	Description	Advantages	Limitations
Beck Depression Inventory (BDI, BDI II) Beck et al (1961, 1996)	21-items assessing symptoms of depression such as hopelessness and irritability, cognitions such as guilt or feelings of being punished, as well as somatic symptoms such as fatigue, weight loss, and lack of interest in sex. The cutoffs for the BDI II differ from the original: 0–13: minimal depression; 14–19: mild depression; 20–28: moderate depression; and 29–63: severe depression. Higher total scores indicate more severe depressive symptoms. Originally developed quantify the intensity of depression.	- The test has high internal consistency (Cronbach $\alpha = 0.91$) (Beck et al 1996b). - Good to monitor change over time.	- Includes somatic items - Not tested with HF patients - Not sensitive to daily changes in mood, test-retest reliability over one-week Pearson $r = 0.93$ (Beck, et al, 1996a)
The Geriatric Depression Scale (GDS) (Yesavage et al, 1983)	30 items (short form of 15 items) developed as screening tool for depression in older samples. Takes 8 – 10 minutes. Respondents select yes/no answers to statements, scoring a point for each positive response. Higher scores reflect higher levels depression. Sum score: 0-10 normal, 11-20 moderate depression, 20> severe depression (McDowell, 2006).	- Validated and reliable in older samples. Cronbach's α from 0.81 to 0.89 (Wise et al, 2006). - Widely used to screen for depression in older adults. - Omits somatic items	- May not be sensitive in younger HF patient samples
Centre for Epidemiological Studies	20 item scale developed to screen for risk of depression in the general population.	- Extensively tested	- Does not omit somatic items - Complex scoring and no

Measure	Description	Advantages	Limitations
Depression Scale (CED-D) Radloff, 1972)	Each item used a 0-3 point scale, exception of 4 positive items. Higher scores indicate greater depression. Summed scores range from 0 to 60.		standardised cut-off points ranging from 16 to 28 (McDowell, 2006) – elderly samples have higher cut-off points (Himmelfarb et al, 1983). - Cannot distinguish anxiety from depression (0.68 correlation with BAI, McQuiad et al, 2000)

Health-related quality of life measurement

As conceptualisations of HRQoL can be many and varied so too can the measurement methods used to assess the concept in HF literature. Translating the many components of health into a quantitative value that represents HRQoL is a complex task (Lessman – Leegte, 2007). Health-related quality of life can be measured using a single global item, for example with Cantril's Ladder of Life (Testa & Simonson, 1996), however as HRQoL has been conceptualised here as a multi-dimensional concept, multi-item scales are more appropriate (Fayers & Machin, 2000) and as such single item measures have not been selected in this survey. HRQoL can be assessed using objective measures of functional status or health, for example some studies have used NYHA functional class, physical activity or the HF Functional Status Inventory as a proxy for HRQoL (Freidman, 2003; Jaarsma et al, 1999). However research indicates that individuals with the same objectively assessed health status can vary with regards to subjectively rated HRQoL. Therefore it is likely that HRQoL is dependent on a person's subjectively perceived symptoms, expectations of health and their coping abilities, and should subsequently be measured subjectively (Franzen, 2007).

Generic measures allow for comparisons of data across diseases and can present a broader picture of threats to HRQoL. The data generated from generic HRQol tools may be useful when patients are experiencing a number of co-morbid LTCs, in order to capture the influence of a range of medical problems on a person health (Spertus et al 2008). However, generic measures may be unresponsive to impact of disease-specific conditions (Fayers and Machin, 2000) and may not be as sensitive to changes in HRQoL as disease-specific tools (Spertus et al, 2008). This makes the use of generic measures use in clinical practice limited as it is difficult to identify specific areas of improvement or deterioration in HRQoL as a result of disease specific interventions. Disease specific instruments are designed to be responsive to specific disease related burden and symptoms (Johansson et al, 2004). As a result they have better content validity, sensitivity and responsiveness than generic instruments (Fayers and Machin, 2000). However, if patients are experiencing co-morbid conditions that are impacting on their health, particularly in similar ways to HF, it is uncertain whether HF disease specific measures will accurately identify the impact of HF on patient's health status and HRQoL (Spertus et al, 2008).

A large number of tools exist to measure HRQOL. A recent ten year review found over 47 different generic, health-related, condition specific and utility measures used in HF research , with the majority of studies opting for a condition specific HRQoL to measure the concept (Morgan, McGee & Shelley, 2007). Few condition specific tools have been developed, yet this has increased the ability of researchers to compare data across studies. Only five commonly used tools for assessing HRQoL in HF patient populations were identified in a recent systematic review and meta-analysis (Garin et al, 2009).

Guyatt (1993) recommends that in order to measure HRQoL comprehensively in LTCs both a generic and disease specific measure of HRQoL should be administered. Using two measures in combination increases the application of findings from research (Bowling, 2005).

Generic

Table 17 presents an evaluation of a number of generic HRQoL outcome measures. *The Short Form 36* (SF36) (Ware and Sherbourne, 1992) is the most commonly used health measure globally, particularly in older aged samples (McDowell, 2006). The tool assesses HRQoL using eight dimensions, subsequently used to calculate two summary scores: physical and mental. The tool has been extensively tested in a wide range of samples and has shown excellent reliability and validity (McDowell, 2006).

The tool has been revised and redeveloped into the ***Short Form 12 - SF12$_{v2}$,*** which is less burdensome for respondents, with only 12 items, but retains the same domains and psychometric properties of the SF36, accounting for at least 90% of the variance in SF36 (Ware, 2002). The SF12$_{v2}$ has no ceiling or floor effect in HF samples (Bennett al al, 2002) and has been tested in UK populations with samples of over 60,000. The tool does lack assessment of cognition and memory and so could be considered to have limited use in elderly samples where such issues are common. However, the measure is widely used and has reported reliability coefficients for summary scales of 0.89 (PCS) and 0.86 (MCS) (Ware et al, 2002). The measure is very brief, taking only two minutes to complete. The SF12$_{v2}$ was selected as a generic HRQOL tool for use in this survey. All subscales of the SF 12 showed high internal consistency in the current study. The reliability of the SF12$_{v2}$ was not calculated as each subscale contributes different weights towards the two domains and SPSS cannot calculate an internal consistency for the scale. The measure has however

been extensively tested on a wide range of populations and has demonstrated a high level of internal consistency.

The data from the SF12 generic HRQoL measure will be used to place the HRQoL of the study sample in context with previous research.

Disease specific

Disease specific HRQoL outcome tools are evaluated in table 18 below. The most common disease-specific HRQoL measure in HF is currently the *Minnesota Living with HF Questionnaire* (MLHFQ) (Rector et al 1987) which has been extensively tested in the patient population and used in a large number of studies (Johansson et al, 2004; Gorin et al, 2009). The measure has sounds psychometric properties. A recent meta-analysis found good reliability Cronbach's $\alpha = 0.92$ for the physical summary score and Cronbach's $\alpha = 0.87$ for the emotional summary score, making overall reliability high, Cronbach's $\alpha = 0.94$ (95% CI: 0.91 – 0.95 (Gorin et al, 2009). However it has been suggested that more validation is required in elderly samples where research is lacking (Franzen, 2007). Franzen (2007) notes that the psychometric properties of the measure in older samples may differ as a result of age as some items have poor face validity for elderly populations. Many respondents refuse to answer items relating to medication costs, work and sexual activity; although the UK version of the measure removes the item on medication costs (Owen & Crocuher, 2000).

The Kansas City Cardiomyopathy Questionnaire **(KCCQ)** (Green et al, 2001)[10] is a 23-item validated HRQoL HF disease-specific measure which assesses physical limitations, physical symptoms (frequency, burden and stability), self-efficacy, social function and quality of life. Combining the physical limitation subscale with symptom domains (excluding symptom stability) forms a health status summary (Clinical HRQoL). An overall HRQoL score can be calculated by combining the health status summary with the QoL and social limitation domains. The tool is the only HF HRQoL to take patient and expert opinion into account in the development of the content and retaining items (Garin et al, 2009). The KCCQ has excellent psychometric properties, although it has not been tested extensively as it is a newly developed tool relative to other disease-specific measures (Masterson Creber et al, 2012; Gorin et al, 2009; Spertus et al, 2008; Pettersene t al, 2005;

Green et al, 2000). Reliability of the domains ranges between Cronabach's α = 0.78 to 0.91, although the self-efficacy domain has slightly lower internal consistency (Garin et la, 2009). The KCCQ has an item relating to patients' sexual relationships but is worded more subtly than the MLHFQ; asking patients about their intimate relationships with loved ones rather than sexual activities. The tool assesses a broad range of HF symptoms and its use in this study will add to the body of knowledge regarding the tools application in HF patient samples. The measure is more sensitive to change in HF patients than the MLHFQ (Green et al, 2000) and is therefore considered to be more appropriate for use in clinical settings.

The KCCQ was selected to measure disease-specific HRQoL in the current study as it is felt it covers a broader range of areas thought to influence HRQoL than the MLHFQ. Overall HRQoL (composite of health status summary, QoL, and social limitations) will be used in the study to identify the amount of variance anxiety can predict in HRQoL.

The SF12 summary scales were used in the survey in order to characterise the sample and to make comparisons with other LTC cohorts possible. The SF12 summary scales were not selected for use in the regression models as a single summary score capturing both the impact of physical limitations, social limitations and emotional limitations was thought to be more holistic and appropriate for use in clinical practice. If the objective were to understand the influence of anxiety on physical functioning then the physical summary score of the SF12 may have been appropriate, or indeed NYHA functional class.

The KCCQ is also more sensitive to change in clinical practice than the MLHFQ and the SF36/SF12, therefore it is of increased value for use in health service research, in clinical practice and for patient's self-monitoring.

The reliability of KCCQ items was calculated for subscale only, as summary scales were calculated in a similar manner to the SF12v2, with items and subscales contributing different weights towards each summary scale. As subscales were calculated using only a few items the inter-item correlations are reported where Cronbach's α is low. The reliability of the following subscales were as follows:

Physical limitation: Cronbach's α = 0.90
Symptom stability: *not possible to calculate as only one item*.

Symptom frequency: Cronbach's α = 0.77 (inter-item correlation 0.46, range 0.36 – 0.69)

Symptom burden: Cronbach's α = 0.74 (inter-item correlation 0.49, range 0.36 – 0.66)

Self efficacy: Cronbach's α = 0.636 (inter-item correlation 0.50, range 0.503 -0.503)

Quality of life: Cronbach's α = 0.83

Social limitation: Cronbach's α = 0.87

Total symptom score: *not possible to calculate.*

Overall summary score: *not possible to calculate.*

Clinical summary score: *not possible to calculate.*

Table 17: Generic HRQoL measures, descriptions and evaluation

Generic	Description of the measure	Strengths	Limitations
Sickness Impact Profile (Bergner et al, 1976)	136 items in 12 categories, measures perceived health status with sickness measured in relation to the impact it has on behaviour.	- Well validated in a range of groups including elderly, and reliable. - Gold standard in scales. - Cronbach's α between 0.87 and 0.97.	- Too long. It takes 20-30 minutes to complete. - Significant emphasis on psycho-social aspects - Has a ceiling effect compared with SF 36 - Scoring difficult as only responses of yes are scored and so a blank may mean no or missed data.
Nottingham Health Profile (Hunt et al, 1981)	Developed in lay language, how people feel when they have ill-health. Not developed as a HRQoL measure. Consists of two parts, 38 items in part 1 and 7 items in part 2 (sleep, pain, emotional reactions, social isolation, mobility and energy levels). Asks about how people feel and emotional states as opposed to behavioural change.	- Short and easy to use - Asks about effect of sleep/lack of, a symptom relevant to HF patients	- Too short to assess the impact of a condition on HRQoL - Too shallow a profile on domains such as symptoms, function, social functioning etc need additional scales. - SF 36 superseded, use is in decline - Cronbach's α between 0.44 and 0.85, variations in reliability.
The Quality of Life Index	Five themes, each with 3 items– activity, daily living, health, support, outlook.	- Simple and basic scale taking 2 minutes to complete.	- Designed for use with palliative care patients

Generic	Description of the measure	Strengths	Limitations
(Spitzer, 1980)	Designed for use with terminally ill cancer patients or palliative care LTCpatients.	- All items are weighted equally so easy to score -Cronbach's α around 0.77 (McDowell, 2006)	- To be administered by health professional - Themes and items are simplistic
OARS Multi-dimensional Functional Assessment Questionnaire (Duke University, 1975, 1988)	Designed to assess functional status social and economic resources, mental and physical health, activities of daily living) and health service use of elderly persons. 120 items.	- Widely used in USA veterans health research. - Activities of daily living items have been compared favourably with other purpose-built measures (McDowell, 2006).	- Long measure, time-consuming and burdensome for elderly. - Must be administered by a trained interviewer - Lack of data n reliability and validity -More appropriate for cost analysis evaluations.
Euqo-QoL (EQ-D5) Euro-Qol Group, 1990, 1993)	Basic tool, 5 items assessing physical (pain, mobility, self-care), mental (depression and anxiety) and social functioning (usual activities) and a visual analogue scale of imaginable health state. Developed with requirement of disease-specific to supplement. Designed for policy research and drug trials.	- Brief and simple. - Cronbach's α 0.69 to 0.94 for original and 0.89 for revised (McDowell, 2006).	- Revised version asks respondents if they are anxious or depressed, rather than assessing symptoms of the conditions. - Correlations between health dimension items are high, suggesting they are not independent.

Generic	Description of the measure	Strengths	Limitations
Short form 36 (Ware and Sherbourne, 1992)	36 item health status measure. Eight dimensions: physical functioning, role limitation due to emotional and physical problems, social functioning, mental health, energy, pain, general health perceptions. Two summary subscales – physical and emotional.	- Most frequently used health measure across the world, particularly in older age - UK version available and extensively tested, with reliable results (cronbach's α 0.78 to 0.93) and raised ceiling.	- Lengthy - Expensive to purchase license - Scoring complicated, require software, to be purchased from publishers. - Does not assess sleep quality
Short form 12$_{v2}$ (Ware 1996)	Brief version of the SF36 that retains similar levels of validity but significantly reduces the burden on respondents. Developed to account for at least 90% variance in the SF-36. 12 items generating two subscale scores: physical and mental components scores, along with the additional domain scores.	- One page and takes 2 minutes to complete. - Extensive list of reference norms, greater than any other measures. UK norms from sample of over 60,000 . - 0.94 correlation between SF36 and SF12. - Cronbach's α 0.89 for the physical subscale and 0.86 for the mental sub-scale (Ware et al, 2002). - No ceiling or floor effect in HF samples (Bennet et al, 2002)	- Has no items on cognition and memory so limited in the elderly. - Expensive to purchase license and complicated scoring performed on software making outputs feel hard to interpret.

Generic	Description of the measure	Strengths	Limitations
		- Online scoring system allows for missing values	

Table 18:Disease specific HRQoL measures, descriptions and evaluation

Disease Specific	Description of the measure	Strengths	Limitations
Chronic Heart Failure Questionnaire **(***Guyatt et al)*	16 items assessing dyspnoea, fatigue, emotional function and mastery. Scores range from 16-112, with higher scores indicating better HRQoL.	- Valid and reliable (Cronbach's α 0.86 – 0.95) - Brief -Commonly used tool in HF research	- Symptom assessment focuses on fatigue only - Issues relating to construct validity (Gorin, et al, 2009) - Complex to administer requires an interviewer
MacNew HD Questionnaire/ Quality of life after MI 2 (*Valenti et al, 1996)*	Developed to assess HRQoL following acute MI. 27 items cover emotional, physical and social domains.	- Item on sexual activity modified to include a no response/not applicable option - Excellent reliability (Cronbach's α = 0.93 – 0.95) for domains (Valenti et al, 1996)	- Large portion of measure assesses emotional symptoms to the detrement of physical functioning - Not tested in HF patient population.
Quality of Life in severe HF (QLQ –HF) Wiklind, 1987	26 items exploring symptom impact, physical functioning and life satisfaction. Scores range from zero to 130, with higher scores indicating poorer HRQoL.	- Good repeatability and content validity (Deaton et al , 2001)	- Narrow focus
Minnesota Living With Heart Failure	21 items on physical, emotional and social, measured	- Widely used tool in heart failure, used in over 80 papers (Garin et al,	- Tested in younger samples

Disease Specific	Description of the measure	Strengths	Limitations
questionnaire –	on a 6 point likert scale scores from 0-105, higher scores indicate poorer HFQoL. Generates two summary scores: physical and emotional.	2009) - Highly reliable and validated - Responsive to major symptom changes in HF patients but not sensitive enough for subtle changes (Reigel et al, 2002).	- No assessment of life satisfaction - Generates a physical and mental health composite – no total HRQoL summary
Kansas city cardiomyopathy questionnaire # *(Green et al, 2000)*	Self-administered 23 items Five to seven point likert scales. Scores 0-100 with higher scores indicating better HRQOL. Assesses physical limitations, symptoms, self-efficacy, social limitation and quality of life and provides a functional status score and an overall summary score.	- Range of symptoms explored - Chronbach's alpha reliability was 0.93 for functional status and 0.95 for clinical in development tests - Self efficacy and social limitations explored - Flexible and responsive scaling on likert scales - Wording more acceptable for elderly – ask about intimate relationships with loved ones as opposed to sexual activities. - Developed using patient and expert panels to guide items.	- Majority of validation in a young population

Disease Specific	Description of the measure	Strengths	Limitations
		- Physical domain correlates highly with NYHA functional class. - Sensitive to change (more so than MLWHF) and so clinically useful.	

Summary of data collection and included measures

A combination of data collection from medical records and self report data from both existing and specifically created tools was used to gather data for the cross-sectional study. With regards to medical records, the type and location of a person's HF, the cause of their HF, the duration of their diagnosis, NYHA functional class, LVEF, co-morbid medical conditions, number of hospital readmissions for HF exacerbations and postcode data to obtain a score of social deprivation were obtained.

The questionnaire pack (see appendix 13) that patients received to provide self report data contained previously validated tools, a revised version of a previously used measure and a tool designed specifically for the study, which were presented to patients in the following order:

- Socio-demographic tool (age, gender, ethnicity, and self-report hospital readmission in the previous 12 months for exacerbations of HF
- rPSIDS (Physical symptoms)
- HADS (Anxiety and depression)
- KCCQ (Disease specific HRQoL)
- ESSI (ENRICHD Perceived social support)
- $SF12_{v2}$ (Generic HRQoL)

Ethics approval

A Local Research Ethics Committee (LREC) application was submitted in November 2009 to North West 11 Research Ethics Committee; following amendments a favourable ethical opinion was obtained in December 2009 (REC reference number 09/H1016/125). Research and Development approval for both NHS sites was granted in January 2010.

As part of the consent process patients were informed that if their scores on either scale of the HADs were high (11 and over for either anxiety or depression) their GP would be informed. In total 35 letters were sent to patients' GPs. In addition a distress protocol was in place to identify any participants who may be experiencing distress at the time the research was conducted. See appendix 15 for the distress protocol.

Data analysis

The analysis of data from the survey was conducted to address the research questions:

1. Identify the prevalence and variance of anxiety symptoms in a sample of individuals with a diagnosis of HF attending specialist out-patient HF clinics.

2. Determine whether anxiety symptoms contribute significantly to determining HRQoL in HF patients whilst controlling for demographic, environmental, clinical and psycho-social factors.

All data were assigned a unique and anonymised patient identifier and entered onto a database on a statistical software package (SPSS v.19.0). Data were cleaned and checked for validity following a number of stages:

1. Participants self reported age was checked against medical records to ensure patients were correctly identified.
2. Data entered were checked to identify any errors in data inputting. Descriptive analysis was conducted in order to identify any out-of-range scores. Out-of-range values were identified and cross checked with original questionnaire and clinical data in order to correct mistakes.
3. Histogram and box plot data were checked to identify outliers, which were then checked to ensure no errors had occurred when entering data. Errors were amended by referring back to participants' original responses.

Missing data

All questionnaires were screened for missing data. It is important to identify any errors in data entry and also to identify any patterns in missing data which may indicate issues with the choice of measurement tool in a particular sample. Missing data can significantly impact the results of statistical tests if not handled appropriately.

Where a page or a measure was missing from a booklet the participant was contacted to determine whether this was an error or if they had intentionally left the items blank. All other missing items were analysed to look for patterns in missing items. Where more than one measure was missing from a questionnaire the case (participant) was excluded from

analysis. Attempts were made to locate any responses to missing socio-demographic and clinical data from participant's medical notes. If missing data could not be located it was reported as missing and recorded as such on the SPSS data file (coded 999), thus ensuring SPSS treats data as missing in any statistical tests rather than a score of zero on a measure for example.

Questionnaire manuals and academic development papers were consulted to ensure the scoring of measures was not affected by missing data. No manuals exist for the rPSID symptom measure or the ENRICHD perceived social support measure (ESSI). In personal communication with the ESSI authors, they stated that the scale is valid if items four and seven are dropped and so if these items are missing the scale can be used as a five item measure. The authors do not recommend substituting any other item scores for mean values however, as the scale is short and has not been validated in this way (Mitchell, personal communication September 27th 2011). With respect to the rPSIDS no recommendations are made. If more than 20% of the items were missing the case was excluded from analysis. Where only a few items were missing the item was scored as zero (bothered by symptom in the past week - not at all) (Kaprana, 2009).

The *SF12v2* permits a few missing items per summary score. (Ware et al, 2002) The publishers recommend using the scoring software, which automatically adjusts scores to account for any missing items using the advanced scoring programme. As the manual does not explain how many missing items are permitted for a summary score to be generated it is difficult to determine which responses, if any should be excluded due to excessive missing items. All data were entered into the SF12v2 scoring software and where summary scores could not be generated for the Physical and mental component the case was excluded from analysis. This decision was taken rather than replacing missing values with mean scores of reported items for two reasons, firstly the measure is brief with limited items and therefore correcting missing items may affect outcomes dramatically, and secondly it is unclear how summaries are generated and so correcting missing items without instructions from a manual may distort results.

The original HADS manual (Snaith and Zigmond, 1994) does not contain any information on how to handle missing items. On the publisher's website, GL Assessment, the advice states that 'a score for a single missing item from a subscale is inferred by using the mean

of the remaining six items. If more than one item is missing, then the subscale should be judged as invalid'[64].

The handling of missing items was adjusted for in KCCQ scoring[65]. The scoring of the KCCQ was quite complex and was based on mathematical syntax to be entered by hand into the SPSS software. The scoring of the tool allowed for a number of missing items per subscale. Examples of syntax included:

'If at least three of Questions 1a-f are not missing, then compute
Physical Limitation Score = 100[(mean of Questions 1a-f actually answered) – 1]/4'* to calculate the physical limitations score.

'If at least two of Questions 3, 5, 7 and 9 are not missing, then compute:
S3 = [(Question 3) – 1]/4
S5 = [(Question 5) – 1]/6
S7 = [(Question 7) – 1]/6
S9 = [(Question 9) – 1]/4

Symptom Frequency Score = 100(mean of S3, S5, S7 and S9)'* to calculate the symptom frequency score.

If more than the permitted number of missing items were present in a participant's data the case was excluded from analysis.

Planned data analysis

Testing assumptions

In order to assess correlations and differences between variables univariate and multivariate statistical tests were used. The selection of variables in univariate and multivariate analysis was guided by empirical research and with reference to conceptual models presented in part four of chapter one.

Parametric tests of the data are powerful, however they do require the data to be normally distributed with the majority of scores in the middle of a bell-curve and smaller numbers of scores at either extreme (Pallent, 2001). The distributions of data for all variables were

[64] http://www.gl-assessment.co.uk/health_and_psychology/resources/hospital_anxiety_scale/faqs.asp?css=1

[65] KCCQ scoring instructions. Included in documents purchased with licensing agreement from CV Outcomes Inc http://cvoutcomes.org/topics/3038

examined using histograms, skewness and kurtosis values and the Kolmogorov – Smirnov statistical test of normality. A histogram provides the actual shape of the distribution of data which can be inspected to gauge how 'normal' the data are. Skewness values show the symmetry of the distribution, whilst kurtosis provides information on the vurve of the distribution. Zero shows a normal distribution, whilst positive and negative skewness show the direction of clustering of data, positive kurtosis indicate a peaked distribution and negative kurtosis shows that many scores lie at extremes of a scale (Pallent, 2001). With the Kolmogorov-Smirnov statistic a non-significant result (above 0.05) indicates a normal spread of data.

If data are non-normally distributed then the results from parametric test would be seriously compromised. Transformation of skewed data was attempted, however corressponding transformations for the pattern of distribution including square root and logarithm were not sucessful to the point where data appeared normally distributed. Therefore the decision was taken to use non-parametric tests where data were non-normally distributed (Pallent, 2001). These tests are less powerful than parametric tests and so may not identify relashionships where they exist, however this was considered an acceptable solution to the controversial transformation of data (Pallent, 2001).

In addition outliers in the data were investigated using descriptive statistics to show the range of scores, box-plots to identify any outliers in data and the 5% Trimmed Mean to show how strong an influence any outliers have over the calculations of central tendency. Outliers in the data set can seriously affect the strength of any correlations between variables. Therefore where outliers are identified they have been investigated in order to establish if they are a data entry error. If outliers were an error they have been corrected. If extreme values had been found to be genuine and found to influence the mean through comparison with the 5% Trimmed Mean they would have been removed; however this did not occur in the current data set (Tabachnick and Fidell, 2007).

Standard multiple regression analysis was used to determine which factors, from a set of predetermined variables, accounts for the most variance in participants' anxiety scores and overall disease-specific HRQoL (KCCQ). Multiple regression analysis requires a certain number of cases per independent variable for a model to be reliable. Initial power calculations estimated that in order to enter seventeen independent variables into the multiple regression models a sample size of 186 would need to be achieved, using the

formula ($N \geq 50 + (8m)$) where n = sample size and m is the number of independent variables (Tabachnick & Fidell (2007).

The achieved sample size for this study was n = 158. Attempts were made to recruit to target. However recruitment at one site in particular was much slower than anticipated and attempts to rectify this, such as increasing the researcher's presence at the clinic and reminding HF nurses about the research project did not seem to improve recruitment rates. Due to the reduced sample size the maximum number of variables for entry into the multiple regression model was reduced to thirteen (refer to table 19). Table 16 shows the variables selected for entry in models of anxiety symptoms and overall disease-specific HRQoL (KCCQ). Ethnicity was excluded from regression analysis due to a lack of variation in data. Initially, NYHA functional class was coded as NYHA classes I, II, III, IV, however as the required sample size was not achieved to power the multivariate models with 17 explanatory variables and as some categories had few observations NYHA class was collapsed into classes I/II and III/IV. In addition LVEF categories were collapsed into mild/moderate and severe in order to reduce the number of explanatory variables in the models; thus achieving a total of 13 variables for inclusion in the regression analysis and enough data to power statistical calculations.

Table 19: Table to show variables entered into analysis to predict anxiety symptom scores and the level of data.

Variable	Level of measurement	No. of explanatory variables in mode
Age (yrs)	Ratio	1
Gender (male/female)	Nominal	1
Social deprivation (score)	Interval	1
NYHA functional class (I/II, III/IV)	Ordinal	1
LVEF (mild/moderate, severe)	Nominal	1
Duration of HF diagnosis (yrs)	Interval	1
History of an ICD (yes, no)	Nominal	1
Physical Symptom (score)	Interval	1
Co-morbid medical conditions (score)	Interval	1
Self-reported hospital admissions (freq)	Interval	1
*Anxiety (score)	Interval	1
Depression (score)	interval	1
Social Support (score	Interval	1

* Anxiety is only entered into HRQoL model as a predictor.
NYHA = New York Heart Association; LVEF = Left Ventricular Ejection Fraction; HF = Heart Failure; ICD = Implantable Cardiac Device; SR (self-reported).

Descriptive data

Data were initially explored and reported descriptively, reporting central tendencies for continuous data, with median values and IQRs presented for non-normally distributed data, and proportional values for nominal data. The characteristics of the sample are described including the age, gender, ethnic background and level of social deprivation compared with normative data for England. The clinical characteristics of the sample are presented including the level of functional status of the sample, the reported physical symptom burden and documented clinical events including number of reported hospital admissions in the previous year. Patients' perceived social support is reported using a cut-off of 18 to indicate low levels of social support in the sample and finally HRQoL is explored, reporting sub-scale and summary scores for both the SF12 and the KCCQ. Graphical representations of the data are presented where appropriate.

Research question one

To identify the prevalence and variance of anxiety symptoms in a sample of individuals with a diagnosis of HF attending specialist out-patient HF clinics, the levels of anxiety, depression and anxiety/depression are reported using a cut-off of eight to identify caseness of possible clinical anxiety and depression in the sample (Bjelland et al, 2002). The relative levels of anxiety and depression for males and females are reported using Mann-Whitney U test.

In order to identify factors which contribute to variance in anxiety symptom scores the correlations between continuous variables and anxiety, and the differences in nominal variables and anxiety symptom scores were explored (see table 19 for a list of variables used in univariate and multivariate analysis). Scatter graphs were generated for continuous variables to consider the strength and direction of correlations with anxiety symptom scores. Scatter graphs were examined to identify the distribution of the data which indicates a strong or weak correlation, the shape of the data which will show if the relationship is linear or not and the direction of the relationship which may be positive or negative. Subsequent to this statistical tests were conducted in order to understand more about the relationships between a number of socio-demographic, clinical and psycho-social variables and anxiety symptom scores.

Continuous data that were normally distributed or near-normal were to be assessed for correlations with anxiety symptom scores using Pearson's Correlation Coefficients; however all data in the study, with the exception of the Physical Component summary from the SF12 were non-normally distributed. Where continuous data were significantly non-normally distributed then the non parametric test of correlation, Spearman's Rho was used. Correlations of -/+ .10 to -/+ .29 will be considered small, -/+ .30 to -/+ .49 medium and -/+ .50 to -/+ 1.0 large (Pallant, 2001).

In order to identify any differences in anxiety symptom scores by nominal variables, Mann-Whitney U Test for non-normally distributed data was used.

Data were entered in the multiple regression model using the 'simultaneous' enter method as the sample size was conservative (Brace, Kemp and Snelgar, 2003). The output of the analysis will be interpreted as follows:

1. The Adjusted R Square of value of the model will be reported in order to demonstrate the amount of variance the model can explain in anxiety symptom scores in the sample.
2. The relative contribution of each variable entered in to the model will be considered by reporting the standardised Beta coefficient and the statistical significance of each variable's contribution to determining anxiety symptom scores (p-value).
3. Correlations between the independent variables and anxiety will be checked to ensure a correlation (above .3).
4. Independent variables must not be too highly correlated or multicollinearity will occur, making conclusions regarding the relative contribution of variables to the model difficult. Tabachnick and Fidell (2007) recommend omitting variables with a univariate correlation of above .7 from multiple regression analysis (Tabachnick and Fidell, 2007, p. 86). Where independent variables show high correlation with each other the tolerance coefficient will be examined. Values close to zero indicate two variables may be measuring a similar construct and which will impact on the accuracy of estimates of variance.
5. Normality of data will be checked by examining the Normal Probability Plot of the regression standardised residuals. Points should lie in a straight line, diagonally

from bottom left of the graph to indicate no major deviations from normality that would invalidate the results of the model.

6. A residuals scatter plot will also be examined to identify whether assumptions for multiple regression analysis have been violated. Residual points should not form any clear pattern but should be concentrated about the zero centre point.

What amount of variance in HF patients' self reported HRQoL is accounted for by anxiety symptoms after controlling for physical symptoms, perceived social support, depression and known demographic, environmental and medical covariates?

Research question two

In order to determine the amount of variance in HF patients' self reported HRQoL accounted for by anxiety symptoms, after controlling for physical symptoms, perceived social support, depression and known demographic, environmental and medical covariates a second model was tested using multiple regression techniques. Variables used in univarate and multivariate analysis can be found in table 19. The following steps were taken:

1. Scatter plots of continuous variables and HRQoL were generated to look at correlations between variables.
2. Univariate statistical correlations and tests of difference were performed with variables and HRQoL overall and clinical summary scores from the KCCQ.
3. Multiple regression analysis using the simultaneous enter method will be performed to test variables presented in table 16.
4. Interpretation of multiple regression output will be as aim two, model one.
5. In the event that depression and anxiety scores are highly correlated a further model will be tested excluding depression scores in order to estimate the amount of unique variance anxiety symptoms scores account for in overall disease-specific HRQoL scores.

Summary

- Part one of chapter four has presented the survey aims, design, setting, sample calculations and inclusion criteria, along with the recruitment procedure.

- The data collection strategy has been presented along with an evaluation of measures for selection in the survey. The following tools will be used measure the following concepts in the order presented below:

    - Socio-demographic tool (age, gender, ethnicity, and self-report hospital readmission in the previous 12 months for exacerbations of HF
    - rPSIDS (Psychical symptoms)
    - HADS (Anxiety and depression)
    - KCCQ (Disease specific HRQoL)
    - ESSI (ENRICHD Perceived social support)
    - $SF12_{v2}$ (Generic HRQoL)

- The methods of data cleaning and data analysis have been discussed.

- Two regression models will be tested in order to identify factors associated with variance in anxiety symptoms in HF patients and to determine the relative contribution anxiety symptoms make to HF patients perceived overall disease-specific HRQol.

The results from the survey are now presented in part two of this chapter.

Part Two**: Survey results**

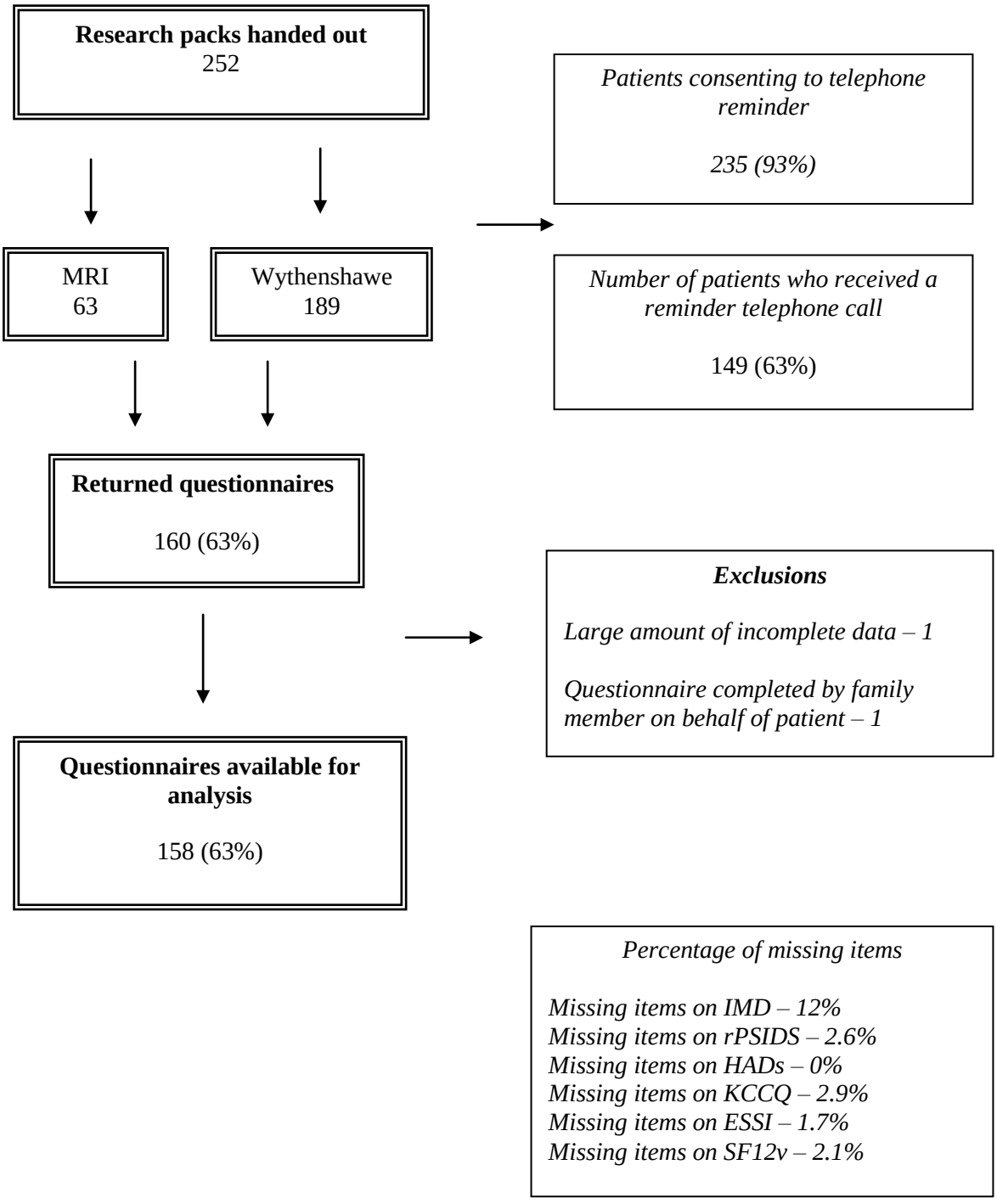
Part two of chapter four presents the results from the survey. The response rate of the sample is reported. Missing data from participants and measures are presented. The sample characteristics are reported. Questiona one and two from the survey are addressed using descriptive, univariate and multivariate statistics.

Response rate

Recruitment began in March 2010 and concluded in November 2010. Two hundred and fifty-two research packs were handed out to patients across both sites; 63 at the MRI and 189 at Wythenshawe hospital (see figure 13 for flow of participants through the study). Of the 252 patients who agreed to take home a research pack, 93% consented to a reminder telephone call after a two week period and provided their telephone numbers. Of the 235 patients who provided informed consent to be contacted if their questionnaires were not returned after a two week period, only 63% required a telephone call. In total 160 patients returned their questionnaires and consent forms (63% response rate). Of these cases 158 were available for analysis (63%). The target response rate was not achieved.

No data are available to indicate reasons for non response or to compare the demographic or clinical characteristics of non responders with patients who did return completed questionnaires, as ethical approval stipulated that patient data would not be obtained or accessed prior to receiving informed consent from patients.

Figure 13: Consort diagram to show flow of study participants



IMD (Index of Multiple Deprivation); rPSIDS (revised-Physical Symptom Incidence and Distress Scale); HADS (Hospital Anxiety and Depression Scale); KCCQ (Kansas City Cardiomyopthy Questionnaire); ESSI (ENRICHD Social Support Inventory); SF12 (Short Form 12).

Missing data analysis

Screening of questionnaire data identified two cases with missing rPSIDS data. These participants were contacted via telephone and indicated that the missing data was an oversight .They were happy to complete the measure over the telephone with KE.

Missing data analysis of items within measures indicated that the proportion of missing data for each measure analysed was low (figure 13). With regards to patterns of missing items one item on the KCCQ (15d), '*Please indicate how your heart failure may have limited your participation in the following activities over the past 2 weeks, Intimate or sexual relationships'* was unanswered in fifty-six cases (35%). No corrections were made for this as the KCCQ scoring syntax allows for a small number of missing items per case. No additional patterns of missing data were identified either by item or case-wise and no corrections needed to be made in order to score measures in accordance with individual scoring instructions.

Testing assumptions

The distributions of continuous data were examined. The distributions of the two dependent variables, anxiety symptom scores and disease-specific overall HRQoL are presented below in figures. Corresponding histograms for variables can be found in appendix 16. A table to show the skewness and kurtosis values, the Kolmogorov – Smirnov statistical test of normality and the mean and 5% trimmed mean can be found below (table 20). All variables data were significantly non-normally distributed with the exception of scores for the physical component of HRQoL as measured by the SF12. Figures 14 and 15 below illustrate non-normal distributions of the two dependent variables, anxiety symptom scores and overall HRQoL. Additional histograms are presented in appendix 15. Box-plots of the data were generated (see appendix 16). Outliers were identified in the data however 5% trimmed means indicated none had a strong influence on the mean estimates.

Figure 14: Histogram to show the distribution of anxiety symptom score data

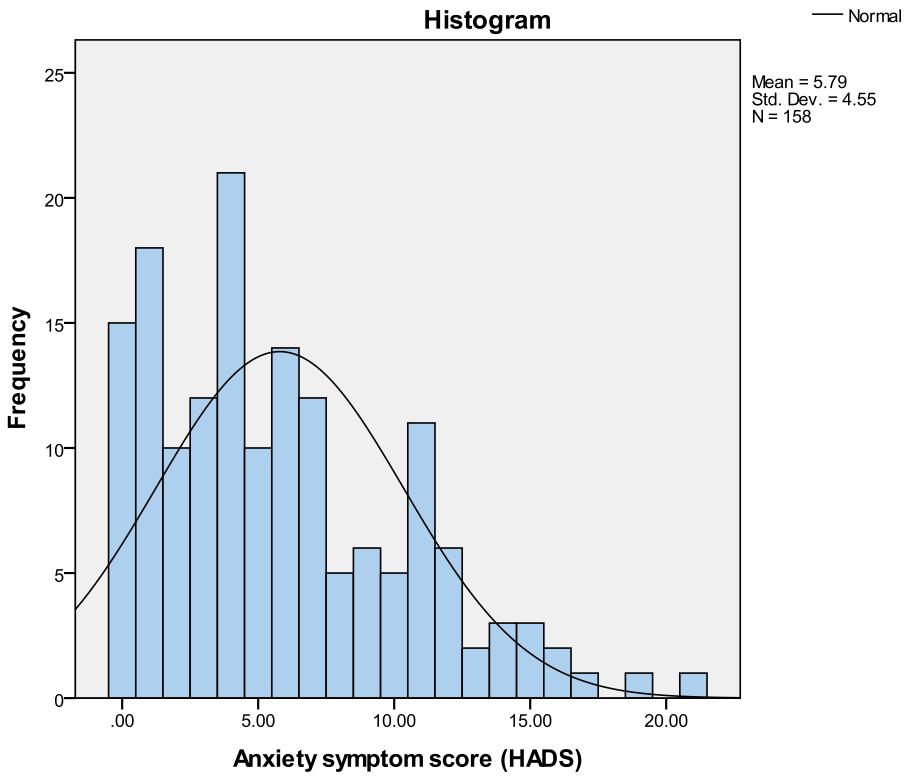


Figure 15: Histogram to shw the distribution of Overall Disease-Specific HRQoL data

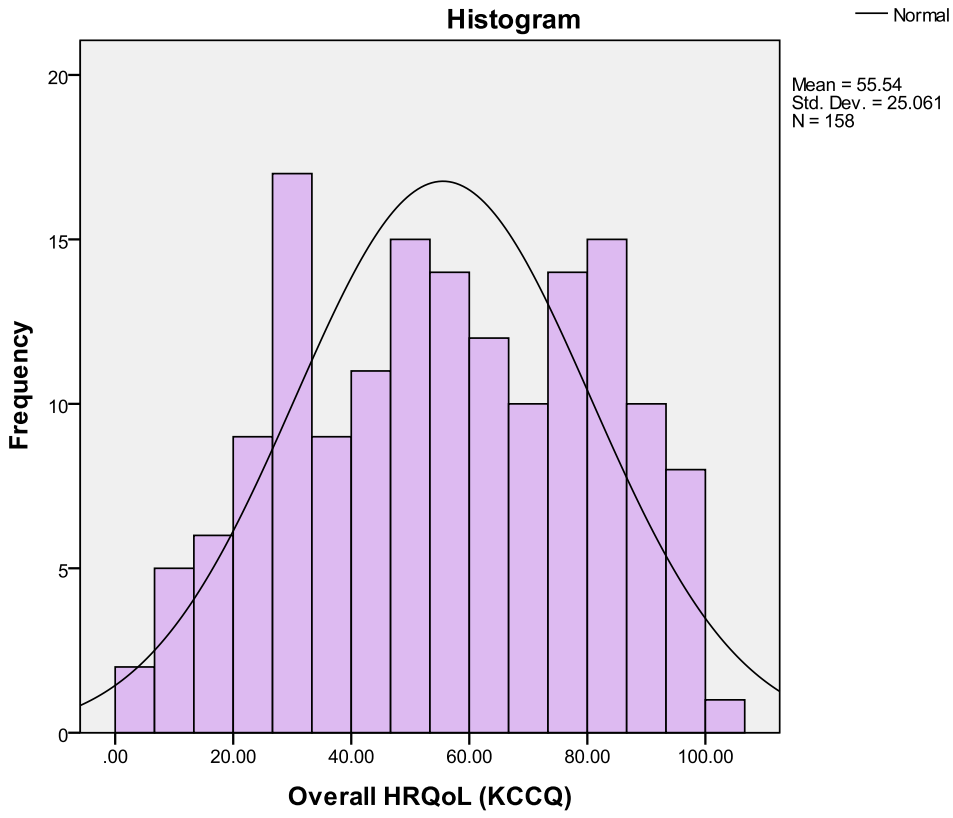


Table 20: Table to show output describing the distribution of continuous data and influence of outliers on estimates of central tendency

Variable	Skewness	Kurtosis	Kolmogorov-Smirnov statistical significance	Mean	5% Trimmed Mean
Age (yrs)	-0.636	0.564	0.071, p = 0.050	70.73	71.21
Social deprivation	1.181	0.393	0.203, p = 0.000	20.82	19.54
Duration of HF (yrs)	2.512	7.443	0.249, p = 0.000	2.76	2.32
Co-morbidity	1.063	0.943	0.235, p = 0.000	2.46	2.35
Physical Symptoms	1.092	0.576	0.151, p = 0.000	14.34	13.51
[1]Hospital admission	1.558	2.358	0.303, p = 0.000	0.87	0.73
Anxiety	0.817	0.197	0.134, p = 0.000	5.79	5.50
Depression	0.804	0.101	0.125, p = 0.000	6.15	5.88
Social Support	-1.069	0.214	0.088, p = 0.000	27.90	28.33
KCCQ Overall	-.053	-1.044	0.074, p = 0.041	55.54	55.73
KCCQ Clinical Summary	-0.167	-1.067	0.084, p = 0.008	59.38	59.84
SF12 Physical	0.071	-.394	0.060, p = 0.200	31.51	31.43
SF12 Emotional	-0.386	-0.561	0.174, p = 0.000	48.34	48.62

[1] Self-reported hospital admissions for exacerbations of heart failure in the previous 12 months; HF (Heart Failure); KCCQ (Kansas City Cardiomyopathy Questionnaire)

Socio – Demographic data

Socio-demogrpahic data are presented in table 21 below. Of the 158 patients included in the study 108 (68%) were male. The median age of the sample was 72 years, with an inter-quartile range (IQR) from 64 yrs to 78 yrs. Data were negatively skewed indicated a larger proportion of the sample were in younger age range. The median age of the female participants was 70 yrs (IQR 63yrs to 78.3 yrs) and for the male participants was 72 yrs (IQR 66yrs to 78 yrs). The majority of the sample were White British (n = 150, 94.9%). The distribution of ethnicity data was not tested as variance in data was so low the variable was not entered into univariate or multivariate analysis.

The median social deprivation scores based on Lower Super Output Areas (LSOAs) was 15.39 (IQR 8.5 to 28.5), indicating that the sample on average were not considered socially deprived. The median average ranking of the sample was 17892 (IQR 8770 to 25939). Of the current sample 13.7% of participants were considered socially deprived using a threshold of <10% of the total rankings . Data were positively skewed again indicating a small proportion of the sample were socially deprived.

Table 21: Socio - Demographic characteristics of the sample

Characteristics		N	%	Mean (sd)	Median (IQR)	95% CI	Range
Gender		158	-	-	-	-	-
	Male	108	68%	-	-	-	-
	Female	50	32%	-	-	-	-
Age yrs		158	-	70.7 (10.5)	72 (64-78)	69.07-72.39	10-94
	Male	108	-	70.9 (10.7)	72 (66–78)	68.88 – 72.94	41-94
	Female	50	-	70.3 (10.5)	70 (63–78)	67.37-73.31	40-89
Ethnicity n (%)							
	White British	150	94.9%	-	-	-	-
	Asian or Asian British Pakistani	3	1.9%	-	-	-	-
	Black or Black British Caribbean	1	0.6%	-	-	-	-
	Other Asian backgrund	1	0.6%	-	-	-	-
	White Irish	1	0.6%	-	-	-	-
	Not specified	1	0.6%	-	-	-	-
IMD score (deprivation)		139	-	20.82 (16.7)	15.39 (9–29)	-	1.46 – 68.04
Social deprivation ranks and % deprived		139	13.7	17290.90 (16.7)	17892 (8770 – 25939)	-	312 – 32415

N (frequency); SD (standard deviation); IQR (Inter Quatile Range); CI (Confidence Interval); IMD (Index of Multiple Deprivation)

Clinical characteristics

Clinical data are presented in table 22. The majority of the sample had ischemic aetiology of HF (53%). As would be expected due to referral criteria for treatment at the main recruitment site, 124 participants had left ventricular systolic dysfunction (LVSD) (79%).

The median average duration since HF diagnosis was two years (IQR 1-4 yrs). Duration of HF data were positively skewed, the majority of participants had not had a diagnosis of HF for a long period of time.

With regards to co-morbid medical conditions the median average score was two (IQR 1-3). Many participants had experienced previous MIs or had co-existing pulmonary and/or renal dysfunction. Most participants had a small number of co-morbid conditions classified as less severe on the Charleson Co-morbidty Index.

Table 22: Clinical characteristics of the sample

Clinical Characteristics	N (%)	Median (IQR)
Aetiology (n %)		
Ischaemic	83 (52.5%)	-
Non ischaemic	75 (47.5%)	-
HF diagnosis (n %)		
LVSD	141 (89%)	-
HFPEF	17 (11%)	-
Duration of HF diagnosis (median, IQR)	-	2 (1 - 4)
Charlson comorbidity Index (score)	-	2 (1 - 3)

N (Frequency); % (percentage); IQR (Inter-Quartile Ramge); HF (heart failure); LVSD (Left Ventricular Systolic Dysfunction);.

Functional status

Table 23 presents functional status data for the sample. Only four respondents were classified as functional class IV 'unable to walk more than a few steps and experiencing symptoms of breathless and fatigue even at rest'. Ninty-seven partipants (61%) were in functional class II, forty (25%) were in funcitonal class III and seventeen participants (11%) were assigned a functional class of I, indicating they had' no demonstrable symptoms of HF.. In contrast to the NYHA functional class distribution the majority of participants had severely impaired ejection fractions (60%).

Participants reported a wide range of symptom frequency and severity, as demonstrated in the large variation in symptom scores (0-52). The median symptom score was 10.5 (IQR 6 -19.25). Analysis of individual items within the PSIDS shows that participants in this sample most often felt burdened by 'feeling faint or tired', 'weak legs', 'difficulty breathing', 'dry mouth', 'pain or discomfort other than in their chest', and 'swelling in their ankles'(see appendix 18 to show the item analysis of the rPSIDS).

Table 23: Functional status of the sample

Characteristics		N	%	Mean (sd)	Median (IQR)	95% CI	Range
NYHA class							
	I	17	10.8	-	-		
	II	97	61.4	-	-		
	III	40	25.3	-	-		
	IV	4	2.5	-	-		
LVEF							
	Mild	29	18.4	-	-		
	Medium	34	21.5	-	-		
	Severe	95	60.1	-	-		
Physical symptom score		158	-	14.3 (11.2)	10.5 (6-19.25)	12.6 – 16.1	0-52

N (frequency); % (percentage); sd (standard deviation); IQR (Inter-quartile Range); CI (Confidence Interval); NYHA (New York Heart Assocoation); LVEF (Left Ventricular Ejection Fraction).

Clinical events

Table 24 presents the clinical events recorded from the sample. Of the 158 participants in the sample, thirty-seven (23%) were fitted with an ICD. Around half the sample (54%) reported no admissions to hospital in the past 12 months preceeding their involvement in the research for HF related exacerbations. Hospital discharge letters from the sites located in patient's medical notes indicate that 75% of participants had no admissions for the same period[66]. Data gathered from hospital discharge letters indicated that participants in the sample were admitted on no more than three occasions for HF related exacerbations at the sites included in the study.

Table 24: Table to present clinical events

Characteristics		N	%	Mean (sd)	Median (IQR)	95% CI	Range
ICD							
	Present	37	23.4	-	-	-	-
	Not present	121	76.6	-	-	-	-
Hospital admissions*				0.87 (1.2)	0	0.68–1.06	0-6
	0	85	53.8	-	-	-	-
	1	36	22.8	-	-	-	-
	2	19	12.0	-	-	-	-
	3	12	7.6	-	-	-	-
	4	4	2.5	-	-	-	-
	5	1	0.6	-	-	-	-
	6	1	0.6	-	-	-	-
Documented hospital admission				0.59 (1.2)	0	0.40– 0.79	0-3
	0	118 (74.7%)					
	1	15 (9.5%)					
	2	10 (6.3%)					
	3	1 (0.6%)					
	Unknown	14 (8.9%)					

***** Self-reported rates of hospital admission for heart failure exacerbations in the past 12 months.

[66] Discrepancy may be due to admissions at other hospitals

Psycho-social characteristics

Table 25 displays the psycho-social data recorded in this survey. A cut-off of below eight was used to identify no anxiety/depression symptoms on the HADS, eight to ten for mild levels, eleven to fifteen for moderate levels and sixteen plus for severe anxiety/depression symptoms.

Question one of phase two research is partially addressed using anxiety data presented in table 22. The majority of the sample was classified as 'normal' based on their anxiety scores (71%). However, the prevalence of anxiety symptoms in a sample of individuals with a diagnosis of HF attending specialist out-patient HF clinics was 29% (N = 46) (HADS anxiety score >8). A proportion of the sample, 19%, scored over eleven on the anxiety subscale, indicating moderate levels of anxiety akin to clinical anxiety. Females in the sample reported higher levels of anxiety compared with males, with 34% of females reporting symptoms of anxiety over the threshold of normal compared with 27% of males. Females in particular experienced anxiety at moderate levels to a higher degree than males (figure 16). The difference in the levels of anxiety between males and females was significant ($Z = 3.171$, $N_1 = 50$, $N_2 = 108$, $p = 0.002$, two-tailed). Median values and IQRs are presented in table 24. Analysis of individual items within the anxiety subscale suggest that 23% of the sample experienced worrying thoughts a lot of the time, 27% felt restless a lot of the time and 12% often experienced sudden feelings of panic.

Using a threshold above eight 34% of the sample were depressed. The median depression score in this sample was five (IQR 3-9). Around 15% of the sample reported symptoms of depression at a moderate/severe level. Again females reported higher levels of depression than males in the current sample (figure 17) although the difference in scores across gender was not significant. Analysis of individual items on the HADs depression subscale indicates a high proportion of the sample reported feeling slowed down (60%).

Interestingly, 22% of the total sample were both anxious and depressed, which equates to a rate of co-morbid anxiety and depression in 76% of cases of participants with either anxiety and/or depression.

The average social support scores were high indicating the majority of the sample had high levels of perceived social support as measured by the ESSI. The median social support score was 30 (IQR 26- 32). Using a cut-off of 18 to indicate low social support 8.2% of the

sample could be considered as having low social support. Half of the sample (51%) indicated they were currently married or living with someone.

Table 25: Table to show the psycho-social characteristics of the sample

Characteristics	N	%	Mean (sd)	Median (IQR)	95% CI	Range
Anxiety score (HADs)	158	-	5.79 (4.5)	5 (2-9)	5.08 -6.51	0 - 21
Normal (<8)	112	70.9	-	-	-	-
Mild (8-10)	16	10.1	-	-	-	-
Moderate (11-15)	25	15.8	-	-	-	-
Severe (16>)	5	3.2				
Females	50	-	7.22(4.3)	7 (4-11)	6.0-8.44	0-17
Normal anxiety (<8)	33	66	-	-	-	-
Males	108	-	5.13(4.5)	4 (1-8)	4.27-5.99	0-21
Normal anxiety (<8)	79	73.1	-	-	-	-
Depression score (HADs)	158		6.15 (4.3)	5 (3-9)	5.48- 6.83	0 - 18
Normal (<8)	105	66.5	-	-	-	-
Mild (8–10)	29	18.4	-	-	-	-
Moderate (11–15)	17	10.8	-	-	-	-
Severe (16>)	7	4.4	-	-	-	-
Female	50	-	6.26(4.4)	6 (2-10)	5.0 - 7.52	0-17
Normal (<8)	32	64	-	-	-	-
Males	108	-	6.10(4.2)	5 (3-9)	5.29-6.91	0-18
Normal (<8)	73	67.6	-	-	-	-
Perceived Social Support (EESI)	158		27.90 (5.7)	30 (26 – 32)	27.00 – 28.80	11 - 35
Low social support (<18)	13	8.2				
Female	5	10				
Male	8	7.4				
Married or living with someone	78	49				
Female	24	48				
Male	54	50				

SD (Standard deviation); IQR (Inter Quartile Range) CI (Confidence interval); HADS (Hospital Anxiety and Depression Scale); ESSI (ENRICHD Social Support Inventory)

Figure 16: Bar chart to show the comparison in prevalence of anxiety symptoms by gender.

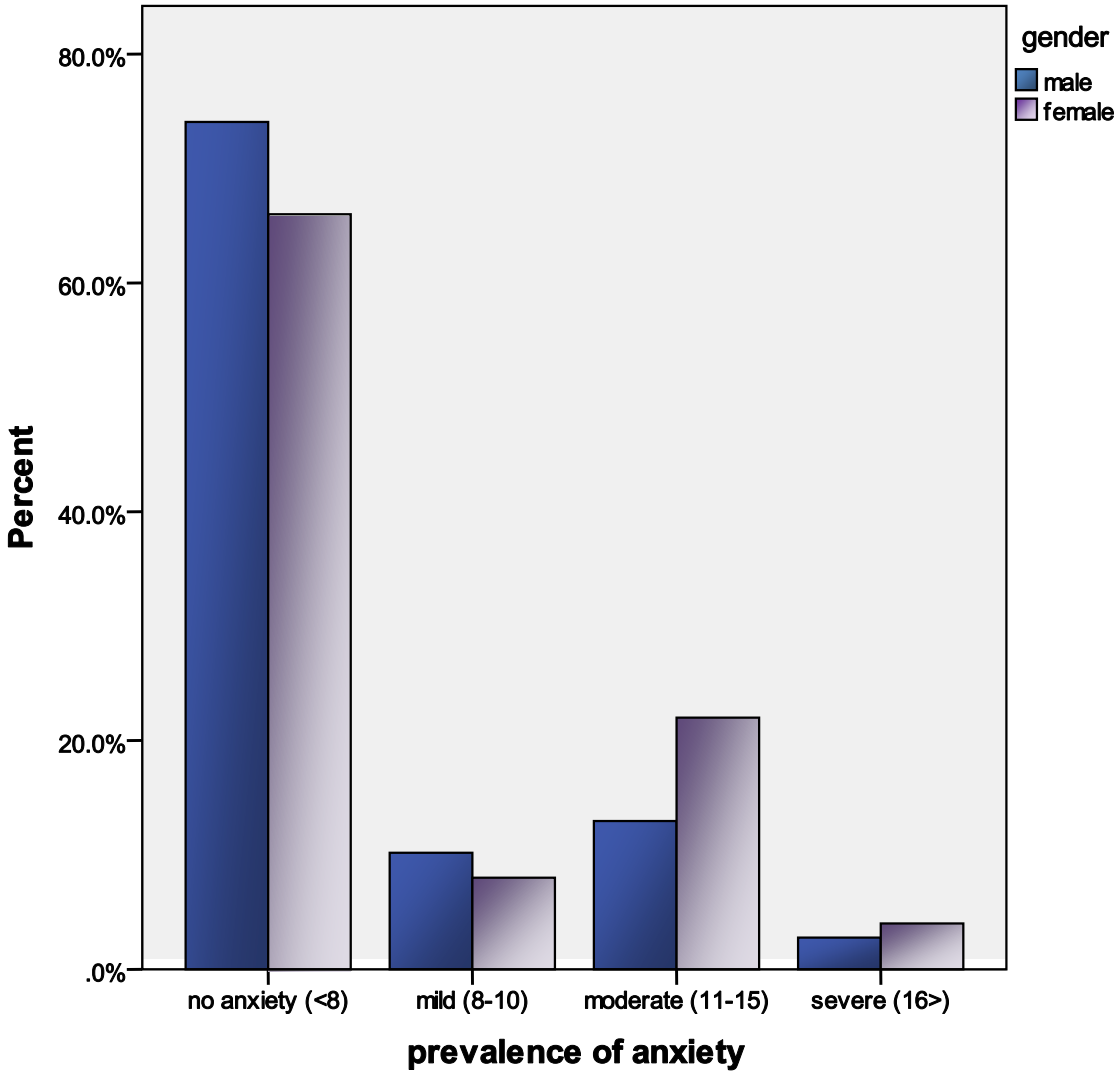
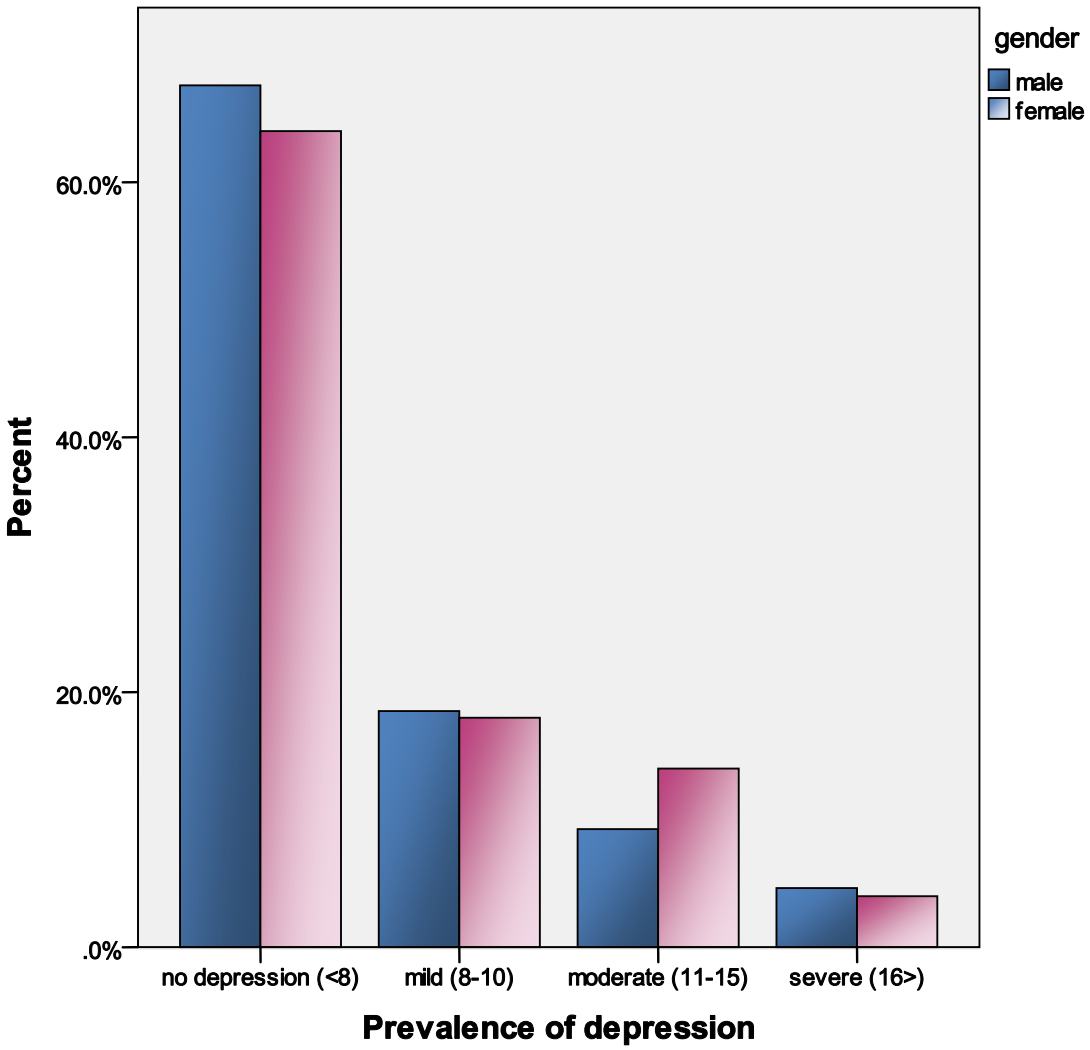


Figure 17: Bar chart to show the comparison in prevalence of depression symptoms by gender.



Health-related quality of life outcomes

Using a generic HRQoL tool, the Short Form 12 version 2 (SF12 $_{v2}$), the sample reported better mental HRQoL than physical HRQoL. Physical HRQoL data were normally distributed, whereas mental HRQoL was non-normally distributed. The mean Physical Component Score (PCS) was 31.51 (11.0) and the median Mental Health Component Score (MCS) was 49.64 (IQR 39.47 - 57.57). Physical functioning scores in the sample were low, however bodily pain in comparison was not reported to be as affected by participants' health. The sample reported low levels of vitality and general health, however, social and emotional functioning were not percieved to be as impaired in the sample when measured using the SF12 (table 26). In a sub-analysis by gender, females reported poorer MCSs and PCSs than males. The difference in generic HRQoL summary scores across gender was non-significant, although the difference in MCS scores did show a trend towards significance ($Z = -1.931$, $N_1 = 50$, $N_2 = 108$, $p = 0.053$, two-tailed) (see table 22 for medians and IQRs).

The Kansas City Cardiomyopathy Questionnaire (KCCQ) was used to measure disease-specific HRQoL, with higher scores indicating better HF related HRQoL. The median overall KCCQ summary score (encompassing clinical summary, social limitations and overall QoL) was 55.08 (IQR 33.33- 78.06). The median clinical summary score (symptoms and functional limitations) was similar at 59.90 (IQR 36.98 - 81.51) (table 23). With regards to sub-scales, the sample reported high levels of self-efficacy and relatively moderate levels of symptom burden and symptom stability compared with overall perceptions of their quality of life. Heart failure patients in the study varied greatly with respect to their self-rated QoL, as can be seen in the confidence intervals in table 27. Participants reported that their HF impacted significantly on their social lives, which is in contrast to the SF12 data, which indicated that although participants' physical health was rated as poor their social functioning was less affected (table 26). Females reported poorer overall disease-specific HRQoL and clinical HRQoL compared with males, however the difference in scores for both summary scales was not significant.

Table 26: A table to show SF12v2 scores for the sample

Characteristics	Mean (sd)	Median (IQR)	95% CI	Range
Physical functioning	25.16 (30.2)	25.00	20.41 – 29.90	0 - 100
Role functioning (physical)	39.26 (28.9)	37.50	34.72 – 43.81	0 - 100
Bodily pain	62.97 (35.0)	75.00	57.48 – 68.47	0 -100
Vitality	31.65 (27.9)	25.00	27.27 – 36.02	0 - 100
General Health	31.74 (26.2)	25.00	27.62 – 35.86	0 - 100
Mental health	66.46 (21.6)	68.75	63.06 – 69.85	0 - 100
Role functioning (emotional)	66.78 (33.0)	75.00	61.61 – 71.96	0 - 100
Social functioning	67.72 (32.7)	75.00	62.58 – 72.86	0 - 100
Physical Composite score (PCS)	31.51 (11.0)	31.98 (22.57– 38.61)	29.78 – 33.23	0 – 56.15
Males	32.34 (25.9)	32.74 (24.36- 32.74)	30.32 - 34.37	7.79 - 56.15
Females	29.70 (11.6)	28.16 (21.48- 37.48)	26.41 – 33.0	0 – 54.80
Mental Health Composite Score (MCS)	48.34 (11.5)	49.64 (39.47- 57.57)	46.52 – 50.15	15.05 – 70.62
Males	49.44 (11.6)	50.51 (40.77- 59.33)	47.23 – 51.65	23.69 – 70.51
Females	45.95 (11.2)	46.20 (37.54-54.0)	42.78 – 49.13	15.05 – 70.62

SD (Standard deviation); IQR (Inter quartile range); CI (Confidence Interval).

Table 27: Table to show KCCQ HRQoL outcomes

Characteristics	Mean (sd)	Median (IQR)	95% CI	Range
Symptom burden	66.51 (26.5)	66.67 (50.0–91.67)	62.35-70.67	0 -100
Symptom stability	63.18 (28.4)	70.83 (41.67–88.54)	58.72-67.63	0 - 100
Total Symptom score	64.84 (26.4)	69.79 (45.10–87.50)	60.70-68.99	3.13-100
Self efficacy	80.30 (23.0)	87.5 (62.5–100.0)	76.69-83.91	0-100
QoL	55.46 (26.9)	50.0 (40.63 – 70.0)	51.23-89.70	0-100
Social limitation	47.94 (31.5)	46.88 (18.75 – 85.0)	43.0-52-90	0-100
Overall HRQoL score	55.54 (25.1)	55.08 (33.33–78.06)	51.60-59.48	2.08-100
Males	60.75 (26.4)	62.81 (33.14-79.69)	51.12-61.0	2.08-98.96
Females	54.41 (23.3)	52.86 (35.29 – 74.75)	47.79-61.05	10.10-100
Clinical summary score	59.38 (25.6)	59.90 (36.98 – 81.51)	55.36-63.41	4.17-100
Males	60.75 (26.40)	62.81 (35.94 - 84.69)	55.71-65.78	4.17-100
Females	56.44 (23.8)	56.77 (38.75 – 77.34)	49.67-63.20	10.94 – 100

SD (Standard deviation); IQR (Inter Quartile Range); CI (Confidence Interval)

Question One analysis: Prevalence and Variations in reported anxiety

In order to identify factors which contribute to variance in anxiety symptom scores the correlations between continuous variables and anxiety and the differences in nominal variables' anxiety symptom scores were explored. Refer to table.19 in part one of chapter four, pp 265, for the list of variables used in univariate and multivariate analysis.

Descriptive data

Where appropriate scatter plots of continuous variables and anxiety symptom scores were generated. All scatter plots can be found in appendix 19. Only physical symptom scores and depression symptom scores appear to correlate positively with anxiety symptoms in a linear fashion, with both the frequency and distress of physical symptoms and depressive symptoms increasing with higher levels of anxiety symptoms.

Univariate Analysis

As all independent variable data were non-normally distributed and many did not show a linear correlation with anxiety symptom scores Spearman Rank Order Correlations were performed for continuous data. All nominal data were analysed using Mann-Whitney Test, the non-parametric alternative to Independent-Samples T-Tests. Correlations can be found in table 28, whilst tests of difference are in table 29.

Large correlations were found between anxiety symptom scores and depression and physical symptom scores. A significant positive correlation was found between anxiety symptoms and depression symptoms ($rho = 0.640$, $n = 158$, $p < 0.000$, two-tailed), which shows that participants reporting high levels of anxiety also reported high levels of depression. A significant positive correlation was found between anxiety symptoms and physical symptom scores ($rho = 0.495$, $n = 158$, $p < 0.000$, two-tailed), indicating that higher levels of anxiety symptoms are correlated with a higher frequency and distress level of self report physical symptoms.

A medium sized negative significant correlation was found between anxiety symptoms and perceived social support ($rho = - 0.368$, $n = 158$, $p < 0.000$, two-tailed), which indicates

that high levels of anxiety were found in participants with low or poor levels of perceived social support.

Smaller, although significant correlations were found between anxiety symptoms and age in years (rho = - 0.244, n = 158, $p < 0.005$, two-tailed), which shows that as participants age increased their levels of anxiety decreased and the number of self reported hospital admissions for exacerbations of HF symptoms in the past 12 months (rho = 0.213, n = 158, $p < 0.007$, two-tailed), which indicates that as the levels of anxiety symptoms increase in participants their self reported rates of hospital admission were also found to increase.

When nominal data were explored the distribution of anxiety scores was found to vary significantly by gender ($Z = 3.171$, $N_1 = 50$, $N_2 = 108$, $p = 0.002$) indicating that anxiety scores were significantly higher for females compared with males (table 29).

No other variables were found to correlate significantly with anxiety symptoms scores. No other nominal data showed significant variations in distribution of anxiety symptom scores.

Table 28: A table to show the correlations between independent variables and anxiety symptom scores

Independent variable	Spearman's Rho	P value	Mean (sd)	Median (IQR)
Anxiety	-	-	5.79 (4.5)	5 (2-9)
Age (yrs)	-.224**	0.005	70.72 (10.6)	72 (64-78)
Social Deprivation	.109	0.200	20.82 (16.7)	15.39 (9-29)
Duration of HF diagnosis (yrs)	.063	0.453	2.76 (3.1)	2 (1-4)
Physical Symptoms	.495**	0.000	14.34 (11.2)	10.5 (6-19.25)
Co-morbid medical conditions	-.070	0.383	2.46 (1.4)	2 (1-3)
[1]Hospital admissions	.213**	0.007	0.87 (1.2)	0
Depression	.640**	0.000	6.15 (4.3)	5 (3-9)
Social Support	-.368**	0.000	27.90 (5.7)	30 (26-32)

**. Correlation is significant at the 0.01 level (2-tailed).
*. Correlation is significant at the 0.05 level (2-tailed).
1 = Self-reported hospital admissions for exacerbations of heart failure in the past 12 months.
LVEF (Left Ventricular Ejection Fraction); NYHA (New York Heart Association); ICD (Implantable Cardiverter Defibrillator); P value (probability value).

Table 29: A table to show tests of difference, Mann-Whitney U Tests, between anxiety symptom scores for nominal/ordinal independent variables

Independent variable	N	Median anxiety score (range)	Mann-Whitney U Z score	P value
Gender				
Male	108	4 (0-21)		
Female	50	5 (0-17)	3.171**	0.002
NYHA Functional Class				
NYHA I/II	114	4.5 (0-19)		
NYHA III/IV	44	6 (0-21)	.450	0.653
LVEF				
Mild/Mod	63	4 (0-19)		
Severe	95	5 (0-21)	1.827	0.068
History of an ICD				
Yes	37	6 (0-17)		
No	121	5 (0-21)	-.268	.789

LVEF (Left Ventricular Ejection Fraction); NYHA (New York Heart Association); ICD (Implantable Cardiverter Defibrillator); P value (probability value); Mod (Moderate).

Multi-variate analysis

All variables were entered into a standard multiple regression model using the simultaneous enter method to predict anxiety symptom scores.

A significant model emerged. The Adjusted R Square value for the model was 0.533, which means the model explains 53% of the variance in anxiety symptom scores ($F_{12, 126}$, = 14.140, $p < 0.0005$).

Coefficient statistics and p values from the model can be found in table 30. Depression symptom scores make the largest unique significant contribution to explaining the variance in anxiety symptom scores, with higher depression predicting higher levels of anxiety. Perceived social support, physical symptom burden, gender and the presence of an ICD also explained a significant proportion of the variance in anxiety symptom scores; being a female with an ICD, having a higher frequency and burden of physical symptoms and low perceived social support predicts higher anxiety levels in this sample of HF patients. Other variables entered into the model did not make a significant unique contribution to explaining anxiety symptom scores. Although age (yrs) and self-reported hospital admissions correlated significantly with anxiety symptom scores in univariate analysis they no longer contribute significantly to the variance in anxiety symptom scores once other variables are controlled.

Depression scores were highly correlated with physical symptom scores at Pearson's Product Moment Correlation = 0.632. However, the tolerance coefficient for this variable with anxiety symptom scores was 0.480, which is higher than the zero value that indicates two variables may be measuring a similar construct (Tabachnick & Fiddel, 2007). None of the variables included in the model showed univariate correlations as high as 0.70 with other independent variables, suggesting that multicollinearity does not exist (Tabachnick & Fidell, 2007, pp. 86). All tolerance values were also high indicating assumptions required for multiple regression analysis have not been violated.

Finally the Normal Probability P of the regression standardised residuals shows that the standardised residuals lie in a reasonably straight diagonal line from the bottom left corner to the top right. This would suggest the model has no major deviations from normality (figure 15). The residuals scatter plot also shows a clustering of points around the zero

point with no clear pattern to the residuals, which suggests assumptions for multiple regression analysis have not been violated (Pallant, 2001) (figure 16).

Table 30: Table to show the Beta value for each variable in the anxiety symptom regression model and the significance value of their unique contribution to the model, ordered by largest contribution.

Variable	Beta (β) Standardised Coefficients	95% CI of β	T - test	P value
Depression	.449**	0.311-0.671	5.394	< 0.0005
Social Support	- .193**	-0.253- -0.046	-2.865	0.005
Physical Symptoms	.183*	0.011-0.138	2.315	0.022
Gender	.165**	0.428-2.723	2.718	0.007
History of an ICD	.148*	0.311-2.921	2.451	0.016
Duration of Diagnosis	.104	-0.023-0.310	1.701	0.091
Co-morbid conditions	- .088	-0.677-0.121	-1.376	0.171
NYHA (I/II, III/IV)	- .082	-2.045-0.399	-1.332	0.185
LVEF (mild/moderate, Severe)	.095	-0.255-2.0	1.531	0.128
[1]Hospital admissions	.059	-0.227-0.657	.962	0.338
Age (yrs)	- .048	-0.077-.035	-0.745	0.0457
Social deprivation	.044	-0.020- 0.043	.737	0.462

Standard Multiple Regression Analysis
**. Correlation is significant at the 0.01 level (2-tailed).
*. Correlation is significant at the 0.05 level (2-tailed).
1 = Self-reported hospital admissions for exacerbations oh heart failure in the past 12 months.
ICD (Implantable Cardiac Device); HF (Heart Failure); NYHA (New York Heart Association); LVEF (Left Ventricular Ejection Fraction); CI (Confidence Interval); P value (probability value).

Figure 18: Normal Probability Plot of standardised residuals from the anxiety symptom score model

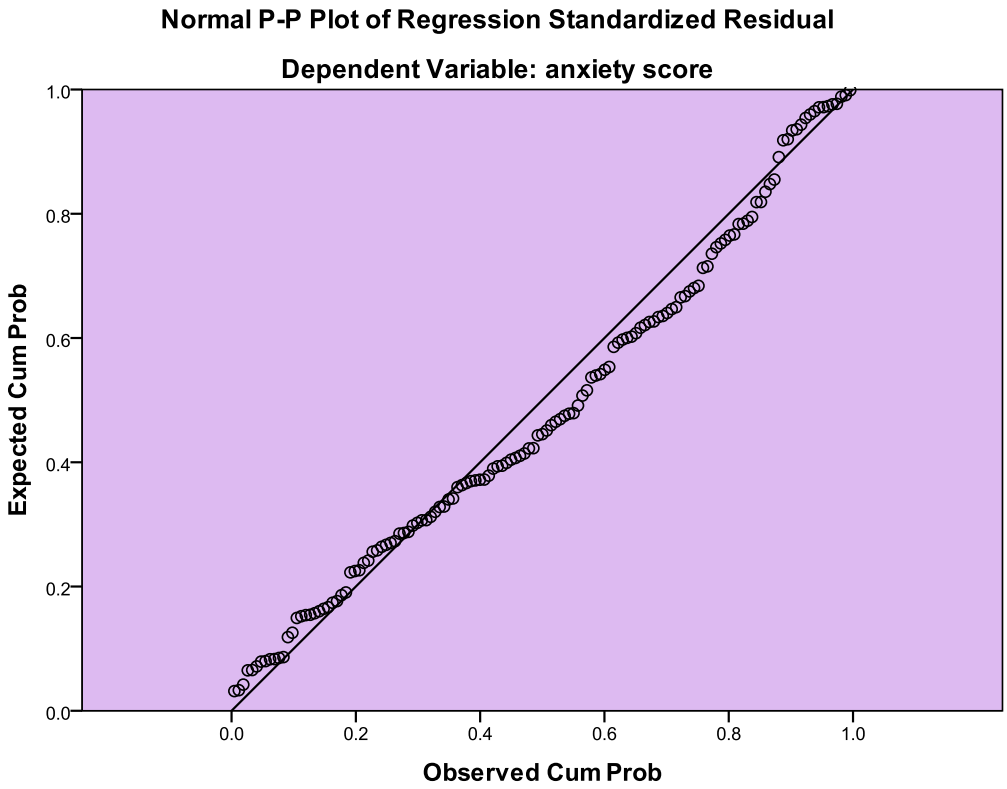
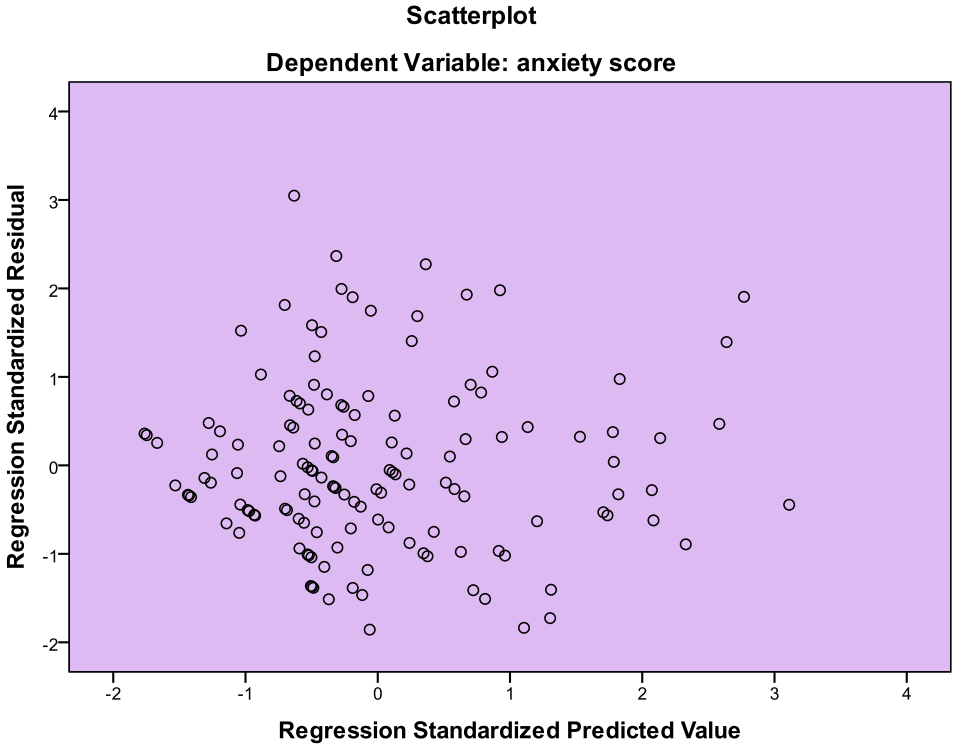


Figure 19: Scatter plot of standardised residuals from the anxiety symptom score model



Question Two analysis: Variance in HRQoL

In order to establish whether anxiety symptoms account for a significant amount of variance in overall disease-specific HRQoL scores in HF patients the correlations between continuous variables and HRQoL scores and the difference in clinical HRQoL scores between nominal variables were initially explored in univariate analysis. Table 19 in part one of chapter four, pp 265, presents the variables selected for univariate and multivariate analysis.

Descriptive statistics

Scatter plots of continuous variables and KCCQ overall HRQoL scores were generated where appropriate and are presented in appendix 20. Physical symptom scores appear to correlate negatively with HRQoL in a linear fashion, with patients who reported lower physical symptom frequency and severity also reporting less impaired HRQoL. Similarly depression and anxiety scores are also negatively correlated with HRQoL, with HRQoL reducing as depression and anxiety increase in severity; although these correlations appear to be weaker than the physical symptom correlation. No other patterns emerged from scatter plots.

Univariate analysis

The associations between independent variables and HRQoL were subsequently analysed using univariate statistics. Spearman's Rank Order Correlations were performed for continuous data (table 31). Comparisons of HRQoL scores between nominal variables were analysed using the Mann-Whitney U test (table 32).

In univariate analysis physical symptom severity and burden showed a large negative correlation with HRQoL scores (rho = - 0.740, n = 158, $p < 0.001$). Following this depression (rho = -.0.720, n = 158, $p < 0.001$) and anxiety (rho = - 0.463, n = 158, $p < 0.001$) were strongly negatively correlated with HRQoL; with more severe symptoms correlating with lower levels of reported HRQoL. Co-morbid physical conditions (rho = - 0.264, n = 158, p = 0.001) and self-reported rates of hospital admissions (rho = - 0.233, n

= 158, p = 0.003) were also significantly negatively correlated with HRQoL. Perceived social support scores showed a small but significant positive correlation with HRQoL; with higher levels of support associated with better perceptions of HRQoL in participants (rho = 0.184, n = 158, p = 0.021). No other significant correlations were identified.

In tests of difference NYHA functional class categories showed significantly different distributions of HRQoL scores (Z = - 3.251, n = 158, p = 0.001). Participants classified in lower NYHA functional class categories of I/II reported significantly higher levels of HRQoL compared with those in NYHA classes III/IV. No significant differences were found for other nominal data (table 32).

Table 31: A table to show Spearman's Rank Order Correlations between continuous independent variables and overall HRQoL

Independent variable	Spearman's Rho	P value	Mean (sd)	Median (IQR)
Overall HRQoL	-	-	55.54 (25.1)	55.08 (33.33–78.06)
Age (yrs)	.043	0.590	70.72 (10.6)	72 (64-78)
Social Deprivation	-.080	0.350	20.82 (16.7)	15.39 (9-29)
Duration of HF diagnosis (yrs)	-.159*	0.046	2.76 (3.1)	2 (1-4)
Physical Symptoms	.740**	0.000	14.34 (11.2)	10.5 (6-19.25)
Co-morbid medical conditions	-.264**	0.001	2.46 (1.4)	2 (1-3)
[1]Hospital admissions	.233**	0.003	0.87 (1.2)	0
Anxiety	-.464	0.000	5.79 (4.5)	5 (2-9)
Depression	.720**	0.000	6.15 (4.3)	5 (3-9)
Social Support	-.184*	0.021	27.90 (5.7)	30 (26-32)

**. Correlation is significant at the 0.01 level (2-tailed).
*. Correlation is significant at the 0.05 level (2-tailed).
HRQoL (Health-Realted Quality of Life)

Table 32: A table to show the Mann-Whitney U Tests of difference between nominal variables and overall HRQoL.

Independent variable	N	Median Overlal HRQoL score (range)	Mann-Whitney U Z score	P value
Gender				
Male	108	56.25 (2.08-98.96)		
Female	50	52.86 (10.10-100)	-.391	0.696
NYHA Functional Class				
NYHA I/II	114	60.94 (2.08-100)		
NYHA III/IV	44	41.71 (10.10-98.96)	.450**	0.001
LVEF				
Mild/Mod	63	60.42 (2.08-97.40)		
Severe	95	49.48 (4.43-100)	-1.15	0.250
History of an ICD				
Yes	37	44.06 (4.43-98.44)		
No	121	57.81 (2.08-100)	1.474	.140

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

LVEF (Left Ventricular Ejection Fraction); NYHA (New York Heart Association); ICD (Implantable Cardiac Device).

Multivariate analysis

Variables as reported in table 19 were entered into a standard multiple regression model to predict overall HRQoL using the simultaneous enter method.

A significant model emerged. The Adjusted R Square value for the model was 0.687, which means the model explains 69% of the variance in overall HRQoL scores. The model explained a significant proportion of the variance in HRQoL scores ($F_{13, 125}$, = 24.344, $p <$ 0.0005). Table 33 below presents the standardised coefficients and p values for each independent variable; with the variables accounting for the most variance in overall HRQoL presented first.

Table 33: Table to show the Beta value for each variable in the overall HRQoL regression model and the significance value of their unique contribution to the model, ordered by largest contribution.

Variable	Beta (β) Standardised Coefficients	95% CI of β	T - test	P value
Physical Symptoms	-.533**	-1.492- -0.897	-7.953	<0.0005
Depression	- .442**	-3.500- -1.669	-5.586	<0.0005
Age (yrs)	.167**	-.638- -.155	-3.244	0.002
Co-morbid conditions	.146**	-4.438- -.747	-2.780	0.006
Anxiety symptoms	.105	-.254 – 1.410	1.375	0.172
Social deprivation	.082	-.002-2.69	1.678	0.096
NYHA class (I/II, III/IV)	- 0.066	-9.278-1.921	-1.300	0.196
Social support	-.043	-.296-.670	.766	0.445
[1]Hospital admissions	-.030	-2.831-1.362	-.693	0.489
History of an ICD	-.030	-7.815- 4.302	-.574	0.567
Duration of diagnosis (yrs)	- .020	-.985-.660	-0.391	0.696
Gender	-.015	-6.219-4.590	-.298	.766
LVEF (Mild/moderate, Severe)	-.013	-5.809-4.490	-.254	0.800

Standard Multiple Regression Analysis
**. Correlation is significant at the 0.01 level (2-tailed).
*. Correlation is significant at the 0.05 level (2-tailed).
ICD = Implantable Cardiac Device; HF = Heart Failure; NYHA = New York Heart Association;

Anxiety symptoms did not account for a significant amount of unique variance in overall HRQoL scores. The model showed that physical symptom burden and severity makes the largest unique contribution to explaining the variance in overall HRQoL scores, with higher self reported frequency and burden of physical symptoms predicting poorer HRQoL. Participants' level of depression was the second largest predictor of HRQoL in the model, with more severe levels of depression predicting poorer HRQoL. Co-morbid

physical conditions and age in years also made significant unique contributions to the variance in HRQoL scores.

Multicollinearity was not identified in the model. Anxiety and depression were highly correlated (Rho = 0.700) as were depression and physical symptoms (Rho = 0.639). Tolerance values were checked. All values were above 0.350 which although close to zero suggests that assumptions for the model have not been violated (O'Brien, 2007). Refer to appendix 21 for a copy of the model coefficient table with reported tolerance values.

Finally the normal probability plot shows that the standardised regression residuals lie in a reasonably straight diagonal line from the bottom left corner to the top right (figure 20). This would suggest the original HRQoL model has no major deviations from normality. The scatter plot of residuals (figure 21) indicates no violations of assumptions in the model.

Unplanned Post-Hoc Analysis

As anxiety symptom scores and depression symptom scores were highly correlated in univariate analysis an unplanned post-hoc sensitivity analysis was performed in order to consider the variables' relationships with overall HRQoL in more detail. Depression scores were omitted from the HRQoL model in order to identify whether the variables' presence in the model was masking any influence of anxiety symptom scores. The resulting model was significant ($F_{12,126} = 19.176$, $p < 0.0005$) and explained 61% of the variance in HRQoL scores; however anxiety was still not a unique significant predictor of HRQoL scores. Physical symptoms appear to account for a larger proportion in the variance of HRQoL with the omission of depression. A copy of the coefficient table from this post-hoc analysis can be found in appendix 22.

In addition an unplanned post-hoc model using total HADS distress scores to assess the combined contribution of both anxiety and depression led to a significant model explaining 65% of the variance in HRQoL ($F_{12, 126} = 22.085$, $p < 0.0005$). The variable 'total HADS score' explained a significant unique proportion of the variance in HRQoL scores ($\beta = -0.294$, $p < 0.0005$), although this was less than the variance explained by physical symptoms. Refer to appendix 23 for a table of the unplanned post-hoc regression model featuring Total HADS scores.

Figure 20: A plot to show the regression standardised residual distribution from the overall HRQoL model featuring anxiety and depression symptom scores

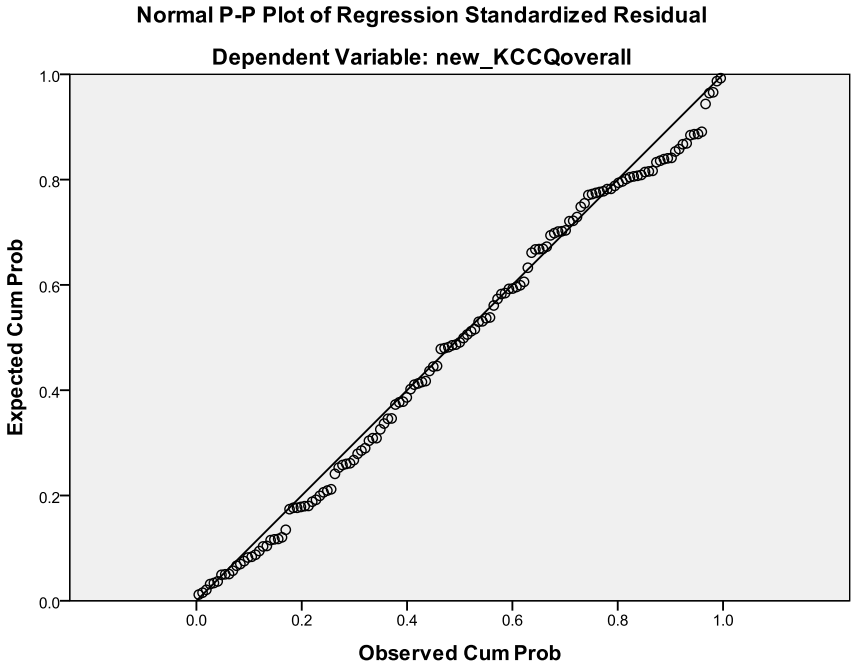
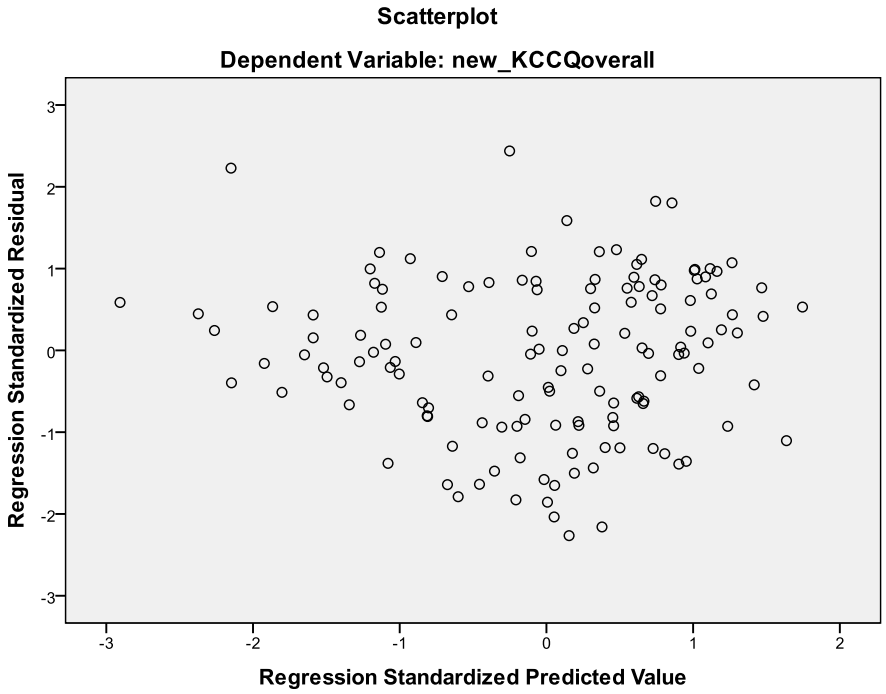


Figure 21: A scatter plot to show the standardised residuals from the overall HRQoL model featuring anxiety and depression symptoms



Part Three**: Survey Discussion**

Part three of chapter four will present an interpretation and discussion of the survey results. Each aim of the survey will be addressed in turn followed by a discussion of the surveys strengths and limitations. A synthesis of the systematic review findings from chapter three and the findings from the survey will be considered in chapter five. Considerations for future research and implications for clinical practice can also be found in the summary presented in chapter five.

The survey was primarily conducted as a review of the literature indicated that variations in reported HRQoL in HF patients were not fully accounted for by clinical factors alone, such as physical symptom severity and functional status. The role of mental health conditions in determining reported HRQoL has been proposed, however the manner in which depression and anxiety have been conceptualised and measured has been inconsistent. The role of anxiety in determining HRQoL in HF patients required clarification.

The research questions were as follows:

1. What is the prevalence and variance of anxiety symptoms in a sample of individuals with a diagnosis of HF attending specialist out-patient HF clinics?

2. What amount of variance in HF patients' self reported HRQoL is accounted for by anxiety symptoms after controlling for physical symptoms, perceived social support, depression and known demographic, environmental and medical covariates?

Findings from the survey

The results from this study include a number of important findings.

- The levels of probable clinical anxiety in this sample of HF patients (11>) were slightly higher than levels found in the general population when measured using a validated tool for clinical populations.
- Levels of depression far exceed those found in general population sample.
- Anxiety was often co- morbid to depression.

- Patients' levels of depression, perceived social support, perceived physical symptom burden, gender and history of an ICD were found to be significant predictors of a large amount of variance in anxiety symptom scores.
- The model of HRQoL identified in this survey explained a large amount of variance in overall HRQoL. Physical symptom burden, depression, age and co-morbid medical conditions were significant predictors of overall HRQoL scores. Anxiety symptoms as measured with the HADS were not direct predictors of overall HRQoL.

Characteristics of the sample

The sample consisted of 158 HF patients who attended specialist nurse-led HF outpatient clinics in the North-West of England. The sample were predomintly elderly, white males. The socio-demographics of the sample indicate that they are representative of the UK HF population with respect to age, gender and ethnicity when compared to a recent UK National HF audit (NHS Information Centre, 2011). Most of the sample had mild HF as defined by NYHA functional class, few medical co-morbidities, a low physical symptom burden, and a small number of reported hospital admissions in the year prior to participation in the survey. When NYHA functional class, physical co-morbidity and symptom data are considered as a whole it suggests that this sample of patients may have better functioning and be less compromised than some previous studies that have investigated predictors of HRQoL in HF samples (Shen et al, 2011; Cully et al, 2010; Heo et al 2007a,b; 2005).

Prevalence of anxiety

In this sample of 158 HF patients the HADS was used to measure anxiety symptoms. Using a cut-off of eleven to indicate moderate levels of anxiety symptoms that correlate with probable clinical anxiety 19% of the current sample are anxious. Rates of anxiety that may benefit from intervention were even higher at 29% (score 8>), indicating that nearly a third of the sample in the current study are experiencing symptoms of anxiety above a 'normal' level. Rates of severe anxiety, akin to specific anxiety disorders were reported in 3.2% of the sample.

Rates of severe anxiety, akin to specific anxiety disorders were comparable to those found in the general population, with rates of GAD identified in 4.4% of the general population (ONS, 2007). The rates of probable clinical anxiety identified in the survey exceed those from normative data using the HADS in non-clinical sample of 1792 members of the general population (19% versus 12.6% respectively) however, overall rates of anxiety above a score of eight were slightly lower than those found in the general population (29% and 33% respectively) (Crawford et al, 2001). Research has indicated that many members of the general population experience mild symptoms of anxiety with a recent review indicating that 20 % to 26 % of healthy older adults in the community and clinical settings felt fearful, tense and nervous 'a little' or 'quite a bit' (Bryant, Jackson & Ames, 2007; Mehta et al, 2003; Flint, 1994). Therefore it seems that HF patients in the current sample experience low levels of anxiety at a similar rate to the general population, but that rates of severe anxiety more akin to clinical anxiety are higher in this patient population than the general population. In contrast rates of depression in the current sample far exceeded those found in general population samples (33.6% compared with 11.4% respectively using a cut-off of 8>) (Crawford et al, 2001).

The systematic review presented in chapter three found that prevalence estimates of anxiety ranged from 6.3% to 72.3%. In meta-regression analysis the way in which anxiety had been conceptualised and measured in studies was most strongly associated with heterogeneity. The pooled prevalence of anxiety in HF literature using a range of measuement tools was 32.04% (95% CI 26.5% - 37.6%). The current rates of anxiety identified in the survey are lower than this pooled prevalence however the rates are comparable to the pooled prevalence of 26.5% (95% CI 19.8% - 33.3%) using the HADS and a range of cut-off values.

As noted the levels of anxiety identified in the sample of outpatients attending specialist clinics are lower than the highest rates of anxiety reported in the HF literature (77%); however studies identifying extremely high rates of anxiety have been found to use questionnaire measures to classify anxiety based on normative scores derived from members of the general population (Evangelista et al, 2009; Heo et al, 2007; de Jong et al, 2004). These high rates do not seem to reflect actual increased rates of anxiety in HF samples as much as they do differential measurement of the construct or more accurately the use of a liberal cut-off to identify 'anxiety'.

The criteria by which HF patients are labelled ‘anxious’ will be discussed further in the summary chapter five as currently researchers in this area do not appear to consider the clinical implications when selecting tools to measure anxiety in HF patient samples.

Variations in levels of anxiety

The variance of anxiety symptoms in HF patient samples has rarely been explored in research, and when it has investigators have examined the relationship between anxiety and only a few variables in isolation. Determining factors that are associated with higher levels of anxiety in HF patients may alert clinicans to possible risk factors for potential anxiety and guide interventions to reduce anxiety in this clinical popualtion. In multivariate analysis higher levels of anxiety symptoms were predicted predominantly by higher rates of depression, lower levels of social support, a higher incidence and burden of physical symptoms, the covariate of female gender and a previous history of an ICD; which explained 53% of the variance in anxiety symptom scores.

Depression

Depression (HADS depression score 8>) was identified in 33% of the sample and was found to be a predominant predictor of anxiety in this survey. In support of previous research rates of co-morbid anxiety and depression were high; 76 % of patients reporting anxiety scores 8> also reported depressive symptoms with a score 8>. The occurrence of symptoms of anxiety, particularly panic and excessive worry can lead to increased social isolation and decreased social functioning, which in turn contributes to symptoms of depression. Moreover, persistent worry regarding one’s health and mortality can over time lead to feels of hopelessness and despair. The finding that depression accounts for the highest amount of variance in anxiety scores is not surprising. Depression is often highly correlated with anxiety and is found to be comorbid to anxiety in both clinical and non-clinical samples (NICE, 2011; Kessler et al, 2008; Bjelland et al, 2002; Sartorious et al, 1996). Some authors have reported that co-morbid depression and anxiety is the rule rather than the exception in up to 60% of patients with a clinical diagnosis of major depression (Aina & Susman, 2006; Kessler et al, 2003). From the current findings it is impossible to say whether anxiety proceeds depression or visa versa in the current sample, as the research design was neither prospective nor longitudinal. In hindsight it may have been

possible to extrapolate data to address this research question from a reported history of mental health conditions and treatment. Clearly, a different research design would be needed to accurately identify the trajectory of anxiety and depression in this patient population and as this was not the primary aim of the current research a prospective design was neither appropriate nor feasible.

Perceived social support

Perceived social support was also found to predict levels of anxiety in the current study with patients reporting high levels of anxiety if they reported low levels of perceived social support. Overall the current sample reported high levels of percieved social support; interestingly only half of the sample reporting being married or currently living with a partner, which indicates that the presence of a spouse need not necessary equate to the availability of social support. In the current study social support was conceptualised as multi-dimensional including structural (partner), instrumental (tangible help), and emotional (caring) support. It may be that previous research has failed to consistently find an association between social support and anxiety as the majority of research in HF samples has conceptualised support as the availability of a partner or marital status (Evangelista et al, 2007; Yu et al, 2004, Westlake et al, 2002). Social support has been shown to be a buffer against negative life events in general (Sarason et al, 1998) and has been found to assist HF patients in counteracting avoidance coping and improve concordance to treatment regimen (Krumholz et al (1998). The findings here that increased anxiety is associated with a decrease in social support justify the proposal for provision of support groups for HF patients and the inclusion of social support components in HF interventions to improve HF patients' psychological well-being. This is in concordance with aims of the UK NHS and Social Care LTC model as presented in figure 3, chapter one.

Physical symptom frequency and severity

In the current study higher levels of anxiety were predicted by higher frequency and burden of physical symptoms as reported by patients on the rPSIDS (Glazer et al, 2002). This finding contradicts previous research which found correlations between anxiety and physical symptoms (measured using the Dyspnoea and Fatigue Index) in univariate analysis, however the relationship disappeared once other factors were adjusted for in multivariate analysis (Heo et al, 2007). In an earlier study anxiety as measured with the

HADS and POMS, and physical symptoms, conceptualised as sleep quality, fatigue and dyspnoea were measured in a small sample of 61 HF patients, with a mean age of 58.7 yrs (12.8). The authors found that only sleep disturbances and fatigue contributed toward explaining variance in anxiety levels; however, dyspnoea did not (Redeker, 2006).

In the current study physical symptoms have been conceptualised in a different way to previous HF research. Instead of considering HF symptoms in isolation, such as dyspnoea, fatigue or sleep disturbances a range of physical symptoms that may span a variety of conditions have been measured. Analysis of reported physical symptoms indicates that a large proportion of HF patients in the current sample are experiencing fatigue and difficulty in breathing. However, many patients also reported a high frequency and burden of symptoms such as 'legs feeling weak', 'dry mouth', 'pain and discomfort other than in their chest' and 'swelling in their ankles', supporting previous research (Zambroski et al, 2005; Ekmann et al, 2005). The significant association between physical symptoms and anxiety in this study may be a consequence of assessing a range of physical symptoms in this patient population. As HF rarely occurs in isolation from other medical conditions it may be important to take a more holistic approach to symptom management in HF patients as the current research indicates that patients' levels of anxiety are affected by a number of physical symptoms that transcend standard HF treatment management.

History of an ICD

The documented history of an implanted cardiac device in patient's medical notes was also found to be a significant predictor of increased anxiety in the current sample. As far as can be established this is the first time the variable has been associated with variance in anxiety scores in multivariate analysis whilst controlling for socio-demographic and clinical variables in a sample of HF patients. An increased rate of anxiety in ICD recipients is documented (Sears and Conti, 2002) resulting from fear and related catastrophic cognitions associated with potential ICD discharges (Pauli et al, 1999). Additionally the presence of an ICD alerts patients to their own mortality, focusing patients' attention on bodily symptoms that can be misinterpreted as predictions of sudden death. As the use of ICD is standard treatment for HF patients with an EF $\leq$ 35% to reduce the chances of sudden cardiac death, the appropriate psychological support for patients should be an essential part of post-implantation management. Research has, and is currently being conducted to determine the most appropriate interventions to improve HF patient's psychological well-

being and coping following ICD implantation. (Berg et al, 2011; Pedersen et al, 2007; Smuelder et al, 2007).

The regression model tested in this thesis, to predict anxiety symptom scores, was significant and accounted for a large proportion of variance. However, a small amount of variance in anxiety scores was unaccounted for. A number of additonal factors have been investigated in recent literature which may account for further variance in the levels of anxiety in HF patient samples including, percieved control, self efficacy, type D personaility, previous/current treatment for anxiety and medication.

Health-Related Quality of Life

Levels of HRQoL

Generic

In the current study HRQoL overall physical (PCS) HRQoL as measured using the SF12 was moderately poor. Norms from a general population sample of 7069 older (65-74 years) US citizens show that the current sample of HF patients reported poorer physical HRQoL than the general population (mean PCS 31.5 compared with 43.9 respectively), but that emotional HRQoL (MCS) was comparable to levels in the general US population (mean MCS 49.4 and 51.6 respectively) (Ware et la, 2002).

The physical HRQoL of the current sample is also poorer than that of a sample of 644 older patients with a diagnosis of heart disease (mean PCS 38.7), 1689 patients with hypertension (mean PCS 43.7); 320 patients with lung disease (mean PCS 38.3). The emotional HRQoL of the sample is comparable with the reported samples norms previously mentioned and much better than that of a sample of 928 individuals with a diagnosis of depression (mean MCS 37.4) (Ware et al, 2002).

Females reported lower physical and mental HRQoL compared with males; although the differences in scores were not significant. Physical functioning scores in the sample were low, however bodily pain in general was not reported to be poor. The sample reported low levels of vitality and general health, however, social and emotional functioning was not percieved to be poor when measured using the SF12.

Disease-specific

The Kansas City Cardiomyopathy Questionnaire (KCCQ) was used to measure disease-specific HRQoL. The tool is relatively new and has only been used in a handful of studies aimed at investigating psychological influences on HRQoL (Cully et al, 2010; Peters-Klimm et al, 2010). Levels of overall HRQoL, comprised of the health status summary, QoL and social functioning, were moderately poor in the sample (mean 55.6) as were levels of clinical HRQoL comprised of symptom burden and physical limitations (mean 59.4). Both the Overall and Clinical HRQoL of the sample, as measured using the KCCQ, was poorer than that of two larger samples of HF patients with poorer heart functioning than the current sample reported as NYHA and LVEF (Reigel et al, 2012; Gottlieb et al, 2009) and comparable to a sample of HF patients with a diagnosis of depression (Gottlieb et al, 2009).

With regards to sub-scales, the sample reported high levels of self-efficacy and significantly impaired social functioning, contrasting with the SF12 data, which indicated that although participants' physical health was rated as poor their social functioning was relatively less affected. Interestingly correlations between the SF12 and overall KCCQ were significant, which does suggest the tools may be tapping in tosimilar constructs. Other factors, unknown in the curent research may have been influencing patient's reporting on socialing functioning on the two measures. What this finding does highlight is that the use of different HRQoL tools in research can impact on how a sample is reported in the literature.

The emotional health of the current sample is not rated as poor when measured using the HRQoL tool, SF12. However, data from the HADS indicated that up to a third of the sample were experincing anxiety and/or depression. This may suggest that the SF12 is not capturing symptoms of psyhcological distress in a manner congruent with the HADS. As the KCCQ does not have a summary or subscale exclusively to identify emotional symptoms it is difficult to establish whether the KCCQ assessed common mental health conditions in a similar manner to the HADS.

Although the current sample did not demonstrate severe impairments in physical functioning defined as NYHA class and physical symptom burden, their physical/clinical HRQoL and overall HRQoL measured with both generic and disease specific measures

was impaired. Therefore it may be that other variables are influencing patients perceptions of their HRQoL.

Predictors of HRQoL

In standard multiple regression analysis entering socio-demographic variables (age, gender, social deprivation), clinical variables (phyical symptom frequncy and burden, NYHA functional class, LVEF, duration of HF diagnosis, number of hospital admissions in the past 12 months, co-morbid physical conditions, history of an ICD) and psycho-social factors (anxiety, depression, perceived social support) a significant model of predictors emerged, explaining 69% of the variance in HRQoL. Anxiety symptoms did not independently predict HRQoL in this sample of HF patients. A higher frequency and burden of physical symptoms, higher levels of depression, an increase in physical co-morbid conditions and younger age were significant predictors of varince in HRQoL.

As reported throughout this thesis, comparing results of the current research with previous research is problematic as studies vary with regards to the measurement of anxiety and depression, in the measurement of HRQoL and with regards to the variables entered into multivariate analysis.

The finding that anxiety is not a direct predictor of HRQoL in HF patients in the current study contradict findings from a number of recent studies that have found anxiety independently explains variance in HRQoL in HF patients (Volz et al, 2011; Shen et al, 2011; Heo et al, 2008, 2007b; de Jong et al, 2005) and support findings from Cully et al (2010), and Heo et al (2007a; 2005).

Anxiety

In the current study anxiety was not an independent predictor of overall HRQoL, even when depression symptoms were removed from the regression model.

In the earliest study identified to assess the relative contribution of anxiety to determining HRQoL de Jong et al (2005) measured the the influence of age, gender, living arrangements, NYHA functional class. LVEF, cardiac co-morbidities, health perceptions (single item self-report), anxiety, depression and hostility (BSI) on HRQoL (MLHFQ) in a

small (n = 87) sample of older (72 yrs, sd 11) HF patients recently discharged from hospital. The authors found that NYHA class, anxiety and depression were significant independent predictors of HRQoL, explaining 37% of the variance in HRQoL scores. The authors did not assess the impact of physical symptom burden on HRQoL in the study as this was used as a dependent variable in further multivariate analysis. In the study anxiety and depression were measured using the BSI and added to the multivariate model as dichtonomous variables of high and low anxiety and depression based on normative cut-offs from the general population. The corresponding rates of anxiety and depression identified by de Jong et al (2005) are unsurprisingly high at 72% and 73% respectively. It is possible that the liberal rates of anxiety and depression identified and entered into multivariate analysis as nominal data may have biased the associations found between anxiety and HRQoL in the study. In addition the small sample size and relatively high number of explanatory variables in the multivariate analysis mean that findings from de Jong et al (2005) should be interpreted with caution.

More recently two papers have been published identifying anxiety as a predictor of HRQoL in HF patient samples (Shen et al, 2011; Volz et al, 2011). Both studies have used the HADS to measure anxiety and the MLHFQ to assess levels of HRQoL. Both studies found that anxiety independently predicted HRQoL, with one study showing that anxiety was the only prospective psychological predictor of HRQoL at six months (Shen et al, 2011); however both studies have methodological weaknesses decribed below which mean their findings should be interpreted with caution.

Volz et al (2011) assessed the relative contribution of depression, anxiety, vital exhaustion, Type-D personality, social support (using the ESSI), sex, body mass index, exercise capacity, peak oxygen consumption and NYHA functional class to physical HRQoL and emotional HRQoL. The authors found that body mass index, NYHA class, vital exhaustion and anxiety were signifincant predictors of physical HRQoL and anxiety best predicted emotional HRQoL in a small (n = 111) sample of young (57 yrs, sd 14) HF patients, the majority of whom were male (82%). Interestingly anxiety but not depression predicted both physical and emotional HRQoL in the sample. However, although the variables identified in the model were significant predictors of HRQoL they actually explained only a small amount of variance in HRQoL scores once Beta coefficients were examined.

The results from this study may be explained by a number of methodological concerns. The authors do not present any data on multicollinearity however it may be that depression and anxiety were highly correlated in the model which could have led to the omission of depression as a significant predictor in the final model. The authors used stepwise analysis in their multiple regression and so the order in which the variables were entered would have determined whether depression or anxiety was retained in the model if the variables explained a large amount of common variance. Furthermore, vital exhaustion, is a concept that appears to overlap considerably with the somatic symptomology of depression. It too could be proposed that vital exhaustion as a concept/variable accounted for variance that would have been accounted for by depression had vital exhaustion not been entered into the regression. If this is the case it does highlight some potentially interesting considerations regarding the concept of depression. In particular, is it somatic symptomology, such as being slowed down and fatigued that is accounting for variance in HRQoL scores as opposed to more cognitive and emotional aspects of depression? This is a potential area for futher research. The authors (Volz et al) did not measure physical symptoms in the study and so the relative contribution of a potentially important predictor variable in HRQoL can not be determined. It would have been interesting to see the results of the model had the variable been included. However the significance of NYHA functional class in the model may have captured some aspects of physical symptom burden on patients as the variable is based on patients symptom severity. The findings from the current survey that social support (measured using the ESSI) is not a significant predictor of HRQoL is however reflected in results from Volz et al (2011).

Shen et al (2011) assessed the relative contribution of anxiety (measured using the HADS), depression and social support (measured using the MOS social support survey) to physical functioning (measured using the physical component of the MLHFQ) in a six month prospective study of 238, young (54yrs, sd 11) HF outpatients controlling for age, gender, marital status, education, NYHA class, treatment for depression and anxiety and the use of angiotensin-converting enzyme inhibitors. A significant model to predict HRQoL was found with anxiety, depression and NYHA class, but not social support accounting for significant variance in baseline physical HRQoL and only anxiety and baseline HRQoL accounting for variance in six month physical HRQoL; although it is unclear from reporting in the paper how much total variance is accounted for in the models. The findings from this research should be interpreted in light of some considerations.

The authors selected only the physical component of the MLHFQ as a measure of physical functioning in the study. With respect to the aims of the study the authors were testing to identify variance in physical functioning amongst HF patients and so the choice of measurement tool is conceptually appropriate for their aims. The tool is however a HRQoL measure and so the study has been included here for comparison purposes. The use of the physical component of the MLHFQ in isolation does mean that the influence of anxiety on HRQoL in HF patients should be interpreted with caution. Again, the authors have not included a measure of physical symptom status in the model and so it is unclear whether anxiety would account for as much variance in HRQoL if this variable had been included. However, as with Volz et al (2011) NYHA class seems to be accounting for some variance in HRQoL scores that may capture a small mount of symptom burden. Interestingly the authors used the CES-D to measure depression rather than the HADS subscale. The reasons for this are unclear however the authors do allude to an issue in measurement of anxiety and depression stating that some measures fail to distinguish between the two conditions which may have led to the selection of different measures for the concepts. The selection of a variety of measurements for anxiety, depression and HRQoL makes comparisons with the current research difficult and does highlight a common issue with variable measurement in this area of research. Aditionally, Shen et al (2011) found rates of anxiety far greater than in the current study. The difference in reported rates of anxiety may reflect the younger sample in the Shen paper, as anxiety is known to decrease with age. The higher rates of anxiety may have influenced the correlations found with HRQoL to a certain degree.

With regards the choice of HRQoL tools and scales, in the current study a singluar HRQoL summary score was selected as opposed to assessing the relative contribution of anxiety on reported physical and emotional HRQoL. The reasons for this have been outlined previously in the methods section of the survey, however to summerise, a singular summary of overall HRQoL was selected as it's use in clinical setting is advantageous to monitor patient's progress. Furthermore, selecting only a physical HRQoL summary scale for instance would allow for the examination of the influence of anxiety and depression on patient's physical functioning, rather than overall HRQoL, as was the aim in the current research.

In support of the current findings that anxiety is not an independent predictor of KCCQ overall HRQoL Cully et al (2010) assessed the relative contribution that disease severity

(NYHA class), depression and anxiety (Geriatric Depression and Anxiety scales) make to determining overall HRQoL in a small sample (n =96) of predominantly male Veteran outpatients with a diagnosis of HF whilst controlling for age, race, marital status and illness burden (healthcare costs). In standard multiple regression analysis older age, lower NYHA class and lower levels of depression significantly explained a small amount of variance (31%) in HRQoL with NYHA class explaining the most variance in HRQoL. Anxiety was not found to contribute to HRQoL. As with other research which has omitted physical symptom burden from regression models NYHA class was found to be a significant predictor of HRQoL; although the models have not accounted for the same amount of variance as explained in the current study. It may be that NYHA class, the dsyponea/fatigue scale and the rPSIDS are all appropriate measures of physical symptom burden and severity in HF patients but the rPSIDS is a more comprehensive measure of the concept.

The exclusion of anxiety as a significant predictor in a model of HRQoL in Cully et al (2010) mirrors the findings from the current study. This commonality may be a result of the way HRQoL has been measured in the two studies; using the KCCQ. The KCCQ is conceptually constructed using a number of physical symptom components, physical limitations, self-efficacy, social limiations and QoL. It may be that symptoms of depression, such as fatigue, and not those of anxiety are captured more by this HRQoL measure than measures such as the MLHFQ.

In a recently published article researchers identified that different types of anxiety had a differential impact on cardiac outcomes following Acute Coronary Syndrome (Parker et al, 2010). The authors found that agoraphobia, diagnosed using CIDI (ICD-10 clinical interview) predicted poor outcomes, whilst GAD actually predicted superior cardiac outcomes over a 12-month period. The ‘constructive worrying’ that forms part of GAD was hypothesised to support self-management in patients. This may explain why anxiety, measured using the HADS has not been found to predict HRQoL. Clearly, this is an emerging research interest. Further research is required to consider the relative contribution of sub-types of anxiety disorders.

Physical Symptom frequency and burden

Physical symptoms as measured using the rPSIDS explained a significant proportion of unique variance in overall HRQoL in the current study. This finding supports a number of

theoretical model of HRQoL proposed in chapter one, part five, which postulate that physicial symptoms mediate the effects of HF on patient's percieved HRQoL (Rector et al, 2006; Wilson & Cleary, 1996; Ferrans, 2005). As reported not all studies investigating predictors of HRQoL in HF samples have included a measure of physical symptoms in multivariate model, which may account for large variations in identified predictors of HRQoL in this patient group; although it is acknowledged that some studies may use NYHA functional class as a proxy for symptoms as the classificaiton is based on the impact of core HF symptoms on patient's functional ability.

Heo et al (2008) asessed the impact of age, employment status, NYHA functional class, perceived control, anxiety, and depression (using the BSI) and physical symptom status (dysponea and fatigue) on HRQoL (MLHFQ) in stepwise multiple regression. The authors found that physical symptom status, age, employment status and anxiety, explained 45% of the variance in HRQoL in a small sample (n = 84) of young (65yrs, sd 17) HF patients, with 1:1 male to female ratio. The findings from the current study that physical symptom burden is the strongest predictor of HRQoL supports the findings from Heo et al (2008) who also found physical symptoms to be the the strongest predictor of HRQoL, even though they measured only dysponea and fatigue in their sample.

It is not certain why Heo et al (2008) found that anxiety was an independent predictor of HRQoL and the current study did not. A number of factors may be associated with this finding. Firstly, different measures were used to assess anxiety, depression and HRQoL. Heo et al (2008) used the BSI to capture symptoms of anxiety and depression in their sample, as such they will have recorded rates of anxiety and depression far exceeding rates in the current study, which may have impacted on the manner in which anxiety correlated with HRQoL scores. In addition Heo et al (2008) measured HRQoL using the MLHQ questionnaire. This is a valid and reliable tool in HF patient populations however it does not assess patients symptom burden, social limitations and self-efficacy to the same degree as the KCCQ. It is unclear from the reporting in the paper whether the authors used total MLHFQ scores or assessed the variance in physical or emotional components of HRQoL. Therefore differences in identified predictors of HRQoL may result from differences in the the measurement of the dependent variable. Secondly, Heo et al (2008) used stepwise regression in their model, entering only significant variables from univariate correlations into their analysis. This is not advisable in small samples as the order in which variables are entered and therefore retained can be dramatically affected by sampling errors in small

samples (Brace, Kemp and Snelgar, 2003). The resulting model may have been influenced by the statistical techniques used by the authors as much as by actual relationships in the data.

Depression

Depression was found to account for a significant proportion of variance in overall HRQoL in the study after physical symptoms. This finding adds support to a larger body of research which has consistently found that depression accounts for a large amount of variance in HF patient's perceived HRQoL (Dekker et al, 2011; Peters-Klimm et al, 2011; Hallas et al, 2011; Cully et al, 2010; Faller et al, 2010; Muller-Tasch et al, 2007). As reported none of these studies assessed physical symptom severity in HRQoL models. By not including physical symptoms in regression models it could be said that some variance in HRQoL scores explained by depression may actual reflect the impact of somatic symptoms of HF, particularly if mental health measures have not omitted somatic items. However, the fact that both of these variables were include in the current model and remained significant independent predictors of overall HRQoL indicates that the two constructs are independent of one another and both exert an influence over patient's perceived HRQoL.

The finding that depression is a strong and significant predictor of HRQoL in the current study supports findings from a number of studies which have also included anxiety as a covariate (Shen et al, 2011; Cully et al, 2010; Heo et al, 2007a). The prevalence of depression in HF patient's is high and the influence of depression on a range of health outcomes across a variety of LTCs in now well documented. The findings from the current study suggest that the influence of depression on HRQoL in HF is larger than that of anxiety. Conversely anxiety has been found to have a larger influence over HRQoL in COPD patients (Cully et al, 2010) where the authors suggest symptoms of COPD such as anxiety-provoking breathing influence perceptions of HRQoL to a greater degree than depression. Heart failure patients can be extremely limited in their physical functioning, experience fatigue and face lifestyle changes to their diet and exercise regimen as well as managing a complex medication regimen. It may be that the symptoms of depression, which were only slightly more prevalent than anxiety in the current sample, have a greater influence over patients perceptions of HRQoL. Conversely, the impact of depression on overall HRQoL may reflect the content of the KCCQ, which may tap into core symptoms

of depression, such as fatigue and being slowed down, to a higher degree than symptoms of anxiety such as heart palpitations and other cognitive components of anxiety such as worry and fear.

From the research conducted in the current study, and indeed from HF research to date, it is not possible to examine whether pre-morbid depression or post cardiac event/ post HF diagnosis depression is influencing reported HRQoL. As previously highlighted, Dickens and team (2008, 2006, 2005) have found that pre and post cardiac events depression can differ and influence cardiac failure, mortailty and HRQoL in very different ways. As researchers we still have a lot to learn about the trajectory of depression and anxiety in the days, months and years following HF diagnosis. It is important to understand more about the pathways of mental health conditions in HF patients to inform monitoring of such conditions in patient care and better calculate the impact of interventions to treat depression, anxiety and HRQoL in research.

Medical co-morbidities

Physical co-morbidities were also found to significantly predict HRQoL in the current sample, with higher frequency and severity of physical co-morbidities predicting poorer overall HRQoL in the sample. The inclusion of co-morbidities as a contributing factor to HRQoL variance along with physical symptom burden indicates that HRQoL in HF patients is predominantly determined by patient's physical health status, when HRQoL is measured using the summary of the KCCQ. In previous research specific physical conditions of diabetes and respiratory disease but not co-morbid cardiac conditions have been found to correlate significantly with poorer HRQoL in HF samples (Franzen et al; 2007; de Jong et al, 2005). No associations between HRQoL and co-morbid physical conditions have been found in previous research using the Charleson Co-morbidity Index (Pressler et al, 2010). Patients with a diagnosis of HF often experience a number of severe and debilitating physical conditions in addition to HF. The finding that an increase in physical co-morbidity frequency and severity predicts poorer HRQoL supports the need for collaborative care in this patient group. Improvements in patients HRQoL may only be seen once all of their medical conditions are optimally treated and their health is stablised.

Reflections from the regression model of HRQoL

As noted it is difficult to assess the robustness of the findings in the current study relative to previous research as no other study assessing the contribution of anxiety to percieved HRQoL in HF patient samples has assessed anxiety using the HADS and measured HRQoL using the KCCQ.

The relatively moderate levels of anxiety in the current sample, when compared with general population norms and some HF studies may have lead to the non-significant finding in the regression model of HRQoL. The current sample were recruited from secondary care specialist HF clinics, run by specialist HF nurses. Average appointment times ranged from 20 to 40 minutes and patients were able to call the clinics at any time for advice and support. The care setting and care provided may have contributed to the relatively moderate levels of anxiety observed in the current study. Rates of depression on the other hand were high. It may be that health care provisions influence levels of anxiety as they provide a form of social support, found to be a strong perdictor of levels of anxiety in the current study, and help reduce patient's fears and worry associated with their condition As many physical symptoms of anxiety overlap with those of HF support and reassurance from the specialist HF nurses may have hypotheically provided the support needed to reduce the current samples levels of anxiety relating to their HF and increase their perceptions of self-efficacy, which was also reported as high in the current sample.

On the other hand traditional clinic appointments may do little to help alleviate symptoms of depression such as fatigue, lack of motivation, low mood and feelings of hopelessness; which may benefit more from appropriate psychological or pharacological interventions.

Conversely the findings in the current study may have been the result of the choice of measurement tools in the study or as a result of the choice of data analysis strategy. One consideration was that the influence of anxiety on HRQoL in the current study may have been masked by that of depression. The correlation between depression and anxiety scores was high. The two variables are known to correlate highly with one another. Tolerance values for the variables did not indicate that the variables inclusion in the model had violated any assumptions however post-hoc sentivity analysis was conducted in order to identify whether the impact of anxiety on HRQoL was being masked by the influence of depression on HRQoL. This was of particularly concern as the correlation between anxiety and overall HRQoL was slightly positive in multivariate analysis, suggesting that other

variables in the model may be masking or altering the influence of anxiety. Once depression was removed from the model the influence of anxiety did indeed increase and become negative; however the increased variance explained by anxiety was still not uniquely significant in the model.

A further model was tested, this time using a combined HADS score of emotional distress. The rationale for this was based on recent literature which has thrown into question the ability of the HADS to accurately distinguish between anxiety and depression (Costco et al, 2012). An overall emotional distress score would reduce the overlap between the two variables in analysis but still capture the influnce of key symptoms of the two conditions on HRQoL in HF patients. The resulting model was still significant and explained 65% of the variance in HRQoL. The HADS total score was a significant predictor of HRQoL, however the variable explained less variance than depression alone. It therefore seems unlikely that anxiety has been omitted from the model as a result of the inclusion of depression.

Study limitations and strengths

Survey design

A cross-sectional design was used to explore variance in anxiety symptom scores and HRQoL in a sample of outpatients with a diagnosis of HF. The use of a correlational design has allowed for the exploration of associations between variables at a specific point in time. As the aims of the study were not to identify causal factors for the development of anxiety or to explore changes in HRQoL as a result of variable modification a cross-secitonal design was considered appropriate in this instance. With the inclusion of a substantial and comprehensive systematic reivew in the research a longitudinal design would have been unfeasible. However, this does mean that it has not been possible to contribute to the knowledge base on the trajectory of anxiety and depression in HF populations and consider the mechanisms that underlie an association between depression and HRQoL.

Data collection

Some data were collected from medical records. For medical characteristics this method of data collection was essential as the researcher did not have the clinical skills necessary to determine

NYHA classification and LVEF independently at the time of participation in the research. All attempts were made however to ensure that this data was as recent and accurate as possible including discussions with HF specialist nurses directly involved in the care of patients.

Data were also collected using self-report methods. With regards to the variable 'hospital admissions in the previous 12 months for HF exacerbations' attempts were made to cross-reference self-report data with documented admissions in hospital notes. There was a discrepancy between self-reported HF admissions and documented admissions for HF exacerbations. Fifty-four per cent of the sample self-reported no admissions to hospital, whilst documented records indicated that round 25% of the sample had no admissions for HF in the previous year. It may be that hospital records are incomplete or that patients had been admitted to a different hospital in the time period. Conversely it may be patients' recollections of HF admissions are inaccurate or patients may attend A & E with symptoms that they believe indicated HF exacerbation but which later may be recorded as an alternative reason for admission on discharge. The reason for discrepancies in data is not known in this study; however it would be interesting to examine the accuracy in patients' ability to correctly identify exacerbations of their HF in order to inform self-management interventions and education for patients. In this instance it was decided that self-report of admissions would be included in analysis as it is more likely that a patient's perceptions of exacerbations of their condition will influence levels of anxiety and perceived HRQoL.

The accuracy of additional self-report data may have been limited by patients' recollections or their willingness to disclose information. Indeed many patients failed to respond to an item on the KCCQ assessing intimate relationships. Clearly, some level of response bias will have featured in the results; however, cross-sectional designs are commonplace in research and often the only way to measure concepts such as perceived social support, anxiety, depression and HRQoL, to which as researchers we have little insight into from techniques such as observation. In addition it is hoped that the findings from this research may have application in clinical practice. Although the use of interview techniques to assess psychological distress do lead to more accurate identification of clinical anxiety and depression for example they are not appropriate for use by clinicians in busy clinical practice settings. The use of brief, self-report tools was considered more applicable to clinical practice in this instance.

In addition to assessment problems rates of depression and anxiety are also affected by selection and reporting bias in research. Participants in studies are in general likely to be more healthy and less depressed and anxious than those who decline to participate in research which may lead to an underestimation of rates of depression and anxiety (Konstam et al, 2005).

Sample

The response rate for the survey was 63% which is considered adequate for survey methods. The choice of a self-report, mail returned research design may have impacted on the response rate. However, many of the patients attending appointments were experiencing poor health and were elderly. In allowing patients the time to complete the measures at their own pace the burden placed on them is reduced. Additionally during a steering group meeting it was highlighted that patients may be in a hurry to leave following their appointments as parking fees at the hospital sites were high, they may be relying on transport from family or friends and so do not want to inconvenience them or they may have been responsible for the care of a spouse and eager to return home. It was hoped that allowing patients to complete measures at home would increase, rather than decrease participation in the study. Allowing patients the opportunity to complete measures themselves it was hoped that they may feel more comfortable answering potentially sensitive questions or providing responses that they may deems less socially desirable than they would in their regular healthcare setting during an interview process with a researcher.

Analysis of the characteristics of non-responders in the current study was not feasible due to ethical restrictions limiting the amount of patient information available prior to informed consent. Non-responders may have been more severely ill than the sample or may have been experiencing high levels of anxiety and depression which may influence their choice to participate in the research. In addition the ethnic diversity in the sample was low. Unfortunately it was not possible to have measures translated for the study due to financial restraints. Consequently it is unclear whether the sample in the study is fully representative of HF patients in the UK. The aim of the study was to assess anxiety and HRQoL in patients attending outpatient specialist nurse-led clinics with a diagnosis of HF, therefore the applicability of the findings from this study to patients managed in primary care settings may be limited to the UK. However, comparisons of the characteristics of the sample with National HF audit data do suggest that the sample is socio-demographically and clinically similar to the UK HF patient population (NHS Information Centre, 2011).

The patients in the study all received specialist care for their HF from one of two large hospitals in the North-West of England, taking referrals from a geographically dispersed area. It is unclear how these patients compare with primary care patients with regards to the care they receive for their HF; which may influence factors such as anxiety and HRQoL. As noted previously the patients in the current study reported moderate levels of anxiety and were managed well by specialist HF nurses in HF clinics. Patients were seen frequently and appointments ran for as long as necessary, given individual patient's needs. It cannot be said that the care received by the patient's in the current sample will be representative of the care received by all HF in the UK.

In addition the sample in the study was a convenience, self-selecting sample of participants. Selection bias may have excluded highly anxious and depressed patients or those with severely impaired physical functioning. The results from the study must be considered in light of this limitation. However this is a limitation that can be placed on all self-selecting samples, meaning comparisons with other research findings are still valid.

Tools selected

The use of appropriate tools to accurately capture the constructs under investigation is crucial to the validity of the survey findings.

Hospital Anxiety and Depression Scale

In the current study the HADS was selected to measure both symptoms of depression and anxiety. The HADS is not a diagnostic tool for anxiety and depression but can screen for clinically significant anxiety and depression symptoms in medically ill populations Zigmond & Snaith, 1983). The tool was selected as it is brief, easy to obtain and widely used in clincial practice. In addition previous empirical research has been conducted to support the tool's ability to accurately distinguish between anxiety and depression, and identify clinical anxiety with a high degreee of sensitivity and specificity (Bjelland et al, 2002). Additionally the HADS omits somatic items that may over-lap with HF symptoms and lead to inflated estimates of the conditions in the patient poulation. The use of this measure was considered appropriate in the current study.

A recent 10 year systematic review of the use of the tool has revealed that differing latent variable analysis identifies correspondingly different factors structures; with exploratory

factor analysis producing a two-factor structure, confirmatory factor analysis identifying a a primarily three-factor structure and item-response theory finding unidimentional stuctures (Cosco et al, 2012). The authors suggest the tool may not identify separate constructs of anxiety and depression as well as previously thought and that a singular distress scale may be more appropriate. In addition concerns have been raised regarding the wide degree of variation in cut-off used to identify 'caseness' of anxiety and depression across populations and the unsubstantiated exclusion of somatic symptoms such as sleep and appetite disturbance in the construction of the tool; which may lead to inaccurate identification of both anxiety and depression (Coyne & Sonderson, 2012). Furthermore, the HADS does contain items in the depression subscale that verge on somatic in content and have been suggested as indicative of physical symptom burden in HF. An item in the depression subscale asks respondents if they feel 'slowed down'. This item has been found to tap into patient's physical health more than their psychological health and has been shown to load poorly onto psychological factors (Johnston, Pollard and Hennessey, 2000).

These findings taken as a whole do raise some concern over the ability of the tool to accurately identify anxiety in the HF patient sample and may have impacted on the finding that anxiety does not account for a significant proportion of unique variance in overall HRQoL scores. However, Cully et al (2010) also found no correlation between anxiety and overall HRQoL (KCCQ) when using the GAI to measure anxiety, suggesting the findings in the current study are not a result of a measuring bias in the HADS.

In rebuttal to these critiques of the HADS, in recent year it still remains that the HADS is the most frequently used tool for use in clinical, and HF patient populations. Interest in the tool shows no signs of waning, as is evidenced in the current systematic review. Although evidence does exist for additional factor loadings of items, there is still very convincing evidence of a two-factor structure to the measure (Bjelland et al, 2002). The HADS is currently one of the best tools we have to briefly screen for anxious and depressive symptomology in clinical populations. Research evidence exists to correlate scores on the HADS with clinical levels of anxiety, which makes to tool very useful in clinical practice where there is a necessity to refer patients for specific services based on their level of need. To date the HADS has been evaluated in the current study to be one of the most reliable and valid tool we have to screen for clinical levels of depression and anxiety in clinical populations.

Revised Physical Symptom Incidence and |Distress Scale

With regards to the measurement of physical symptom frequency and burden in the current study, the rPSIDS, was selected. The tool is not a well validiated scale but is the only measure to assess a broad range of symptoms in a cardiac population (Kaprana, 2009). This study provided evidence for the reliability of the tool in HF samples and supports the findings from a similar study which used the tool in a sample of patients with Dilated Cardiomyopthy, that physical symptoms account for the largest amount of variance in HRQoL (Kaprana, 2009).

Interestingly, NYHA functional class did not predict anxiety symptoms scores or overall HRQoL in the current study. This finding is in contradiction to previous research which has identified a relationship between NYHA functional class and anxiety (Heo et al, 2007a; Haworth et al, 2005) and NYHA class and HRQoL (Volz et al, 2011; Shen et al, 2011; Peters-Klimm et al, 2010; Pedrosa et al, 2010; Huang et al, 2010; Iqbal et al, 2010; Faller et al, 2010; Heo et al, 2007; Gott et al, 2006; Lee et al, 2005; Zambroski et al, 2005; Yu, Lee & Woo, 2004; Hobbs et al, 2002; Juenger et al, 2002; Reigel et al, 2002; Cline et al, 1999). In addition the systematic review in chapter three of this thesis found that NYHA functional class explained variations in anxiety prevalence to a significant degree; with samples characterised as moderate to severe NYHA functional class associated with lower anxiety than those with mild NYHA functional class. A reason for this may be that physical symptom burden and severity (rPSIDS) and NYHA class may have accounted for shared variance in regression models, as NYHA functional class is an assessment of the impact of core symptoms of HF, dyspneoa and fatigue. The influence of physical symptom burden may have masked that of NYHA class.

On reflection the use of the rPSIDS is considered appropriate to assess a comprehensive range of physical symptoms in HF patient samples. The findings from the current study show that symptoms assessed by the measure account for a significant proportion of variance in both the levels of anxiety and overall HRQoL in the sample. The finding adds weight to need to assess a range of symptoms in patients with LTCs, not just disease-specific symptoms and supports the need for holistic and collaborative care across LTCs, as proposed in the UK NHS and Social Care LTC model.

Charleson Co-morbidity Index

The need to consider the impact of co-morbid medical conditions for patients with HF is supported in the study findings that show an increase in co-morbid conditions predicts poorer HRQoL in HF patients. The Charleson Co-morbidity Index was used in the current study. The index assesses the frequency of 17 weighted diseases selected for their association with mortality (de Groot et al, 2003). One limitation of the tool may be that as the index was developed in the 1980's the associations between weighted diseases and mortality may have altered due to medical advancements and reduced death rates for conditions such as cancer, making the measure less valid. However the measure is psychometrically sound and has been shown to correlate with outcomes such as mortality, disability and hospital readmission (de Groot et al, 2003). The tool is still widely used and has more recently been shown to predict mortality following implantation of an ICD in HF patients and those experiencing an acute MI (Theuns et al, 2009; Nunez et al, 2004).

Selection of variables for regression analysis

As it was not possible to reach the target sample recruitment in the allotted recruitment time it was essential to remove ethnicity as an explanatory variable in the regression analysis. The variable was removed due to a lack of variance data. It would be interesting in future research to consider the influence of ethnicity on reported HRQoL. Ethincity is a characteristic of the individual (as proposed by Ferrans et al, 2005), but could also influence HRQoL as a characteristic of the environment. It has not been possible to examine the influence of many variables on HRQoL. Variables in the current regression anlaysis were selected based on empirical evidence and with reference to a dominant model of HRQoL in HF research, the revised Wilson & Cleary (1996) model (Ferran et al, 2005). However, not all categories included in the model have been entered into regression analysis. Categories such as health perceptions and additional indicators of characteristics of the environment and individual have not been measured. Ultimately, practical limitations on the number of allowable variables in regression analysis existed. Therefore the choice of variables was guided by a review of the empirical evidence. Variables were selected where evidence was contradictory or lacking and where variables had been poorly conceptualised and/or measured innappropriately. In addition, variables such as marital status (perceived social support) and educational level (social deprivation) have been conceptualised differently in the current study to previous research. This may have impacted on the finding of the study. However, given the time available to conduct the research, the number of participants in the study, the interpretation of available evidence

regarding conceptualisation of variables and comparisons with previous research, the regression models in the current study are considered to be comprehensive.

Strengths

Although the study has some limitations and considerations it is a well conducted and considered piece of exploratory research. At time of inception the study was the first to consider the predictive abilities of modifiable variables of anxiety, depression and social support on HRQoL, measured using the KCCQ and is still the only study so far to assess these variables against the KCCQ using the HADS in an older, relatively large HF outpatient population. Also this is the first study to use a comprehensive range of variables to specifically identify variations in level of anxiety, supported with the findings from the systematic review, to facilitate the identification of at risk groups and key components of interventions to improve HF patients levels of anxiety.

The design and procedure of the survey were discussed with the advisory group associated with this study. The advisory group consisted of the supervisory team, a consultant from one included study site, three HF nurses from both included sites, a specialist HF nurse practitioner not associated with the included study sites who had experience in conducting research, a psychiatrist from the University of Manchester with research experience in the area of LTCs and mental health, and two service users with cardiovascular conditions recruited from a local Heart Help group, one of whom had experience as an expert patient advocate. The advisory group were instrumental in helping develop the survey protocol. Many of their contributions were implemented in the survey design and recruitment procedure. The ethical board that reviewed the application for this doctoral research survey commended the level of service-user involvement in the development of the design and data collection procedure. Table 42 in appendix 23 details some of the advisory group's main contributions to the survey.

Evaluation and selection of measurement tools was comprehensive to ensure measures were valid and reliable in both clinical and elderly populations. The appropriate selection of tools means that the findings in the study are valid. The sample is representative of patients attending outpatient HF clinics in the UK but could be considered repreeantative of the wider UK primary care HF patient popualation with respect to demographic and clinical characteristics (NHS Information Centre,2011). With regards to data analysis the data set was meticulously checked, the models were analysed correctly and were

sufficiently powered with an adequate number of participants for the number of variables entered; meaning findings from the study can be interpreted with confidence. A large number of variables were considered in the multivariate analysis of both anxiety symptom and HRQoL with a large amount of variance explained.

Summary

- The survey used a cross-sectional questionnaire design to determine factors that predict anxiety symptoms and HRQoL in individuals with a diagnosis of HF.

- Participants were recruited from two large teaching hospitals in the North-West of England.

- The HADS was used to measure anxiety and the KCCQ was used to assess disease-specific HRQoL.

- The current sample (N = 158) had a higher proportion of females and was older than many samples of HF patients reported in related literature. The sample were moderately functionally impaired as a result of their HF but reported poor Physical and overall HRQoL when compared to general population and LTC population norms. Mental Component summary scores on the SF12 were not impaired.

- Nearly a third of the current sample reported experiencing levels of anxiety symptoms that may benefit from intervention (score >8) and 19% of the sample experienced levels of anxiety that correalate with clinical anxiety disorders (scores>11). These rates of severe, moderate and mild anxiety are interpreted as moderate and comparable with levels in the general population.

- In multiple regression analysis, controlling for known demographic, clinical, and environmental covariates, patient's levels of depression, their levels of percieved social support and physical symptom frequency and burden explained a large and uniquely significant proportion of the variance in anxiety scores.

- The variables entered into multiple regression analysis explained 69% of the variance in overall HRQoL scores. Anxiety symptoms as measured with the HADS were not a significant predictor of overall HRQoL. Physical symptom burden, depression, age and co-morbid medical conditions were significant, unique predictors of overall HRQoL scores.

The main findings from both phases of research will be summarised again chapter five. The main findings from the research are presented and considered. The clinical implications of the findings are considered and recommendations are made for future search.

CHAPTER FIVE**: CONCLUSIONS**

The final chapter of the thesis reiterates the thesis aims, summerises the findings from the two phases of research. Critical reflections on the research are presented. The clinical implications of the research, recommendations for future reseach and policy are presented.

Introduction

The UK government are increasingly acknowledging that mental health conditions are co-morbid to LTCs, and that this pairing has substantial deletrious effects on patient's health, well-being, social functioning and on the wider UK Health and Social Care provisions. Understanding more about the nature, level and impact of common mental health problems in patients with one or more LTCs is necessary and valuable in order to effectively manage this patient popualtion and improve patient outcomes. The mental health of one LTC, heart failure, has been relatively neglected particularly with respect to anxiety.

Research indicated that levels of reported anxiety in HF patient samples varied dramatically; it was unclear what the actual levels of anxiety were in HF patients samples and what factors account for such large discrepanies in reported rates. Indeed Cully et al (2010) note that prevalence estimates of anxiety in HF samples vary widely but that no reivew exists to consolidate the evidence base in this area. As increasing amounts of research are being conducted in this area it was essential to consolidate the knowledge based thus far . Additionally research investigating the impact of anxiety on a primary patient-centred health outcme in HF, HRQoL, was lacking. What evidence existed reported disparate conclusions with regards to the influence of anxiety on HRQoL in this patient population.

This PhD research involved two phases of research addressing related research questions:

Phase One

Questions:

1. What is the aggregated prevalence of anxiety disorders and anxiety symptoms among people with a diagnosis of heart failure?
2. What factors are associated with potential heterogeneity in reported prevalence of anxiety?

Methodology: Systematic review of secondary data

Phase Two

Questions:

1. What is the prevalence and variance of anxiety symptoms in a sample of individuals with a diagnosis of HF attending specialist out-patient HF clinics?

2. What amount of variance do anxiety symptoms account for in HF patients self reported HRQoL whilst controlling for functional status, physical symptom severity, age, gender, and level of social deprivation?

Methodology: Cross-sectional Survey Research

Summary of findings

Systematic review

The systematic review of the prevalence of anxiety in HF patient samples and exploration of variance in prevalence estimates is the most comprehensive review of its kind to date. A large number of studies were included and quantitative analysis of variance in reported rates of anxiety was attempted. Main findings from the review were that:

1. Random effects pooled prevalence estimate of anxiety was 32.04% (95% CI 26.5% - 37.6%). The random effects pooled prevalence estimate for anxiety disorders was 13.01% (95% CI 9.3% - 16.9%), for probable clinically significant anxiety was 28.8% (95% CI 23.3% - 34.3%) and the random effects pooled prevalence estimate for elevated symptoms of anxiety was 55.5% (95% CI 48.1% - 62.8%). These levels of anxiety once considered according to measurement methods are not unusually high compared with general population estimates.
2. There was substantial heterogeneity among study prevalence estimates, indicating that pooled prevalence estimates should be interpreted with caution. Prevalence estimates ranged from 6.3% to 72.3%. In meta-regression analysis the way in which anxiety had been conceptualised and measured in studies was most strongly associated with heterogeneity. Inflated rates of anxiety are most likely an artefact of measurement method.

3. Many different measurement tools were used to study a number of sub-groups of anxiety in the included studies, some of which are more appropriate for identifying anxiety in individuals with a diagnosis of HF than others.
4. The clinical utility of some measures used in studies in the review is questionable.
5. Although a large number of studies were included in the review anxiety was rarely the main outcome in research and was often poorly defined.

Survey

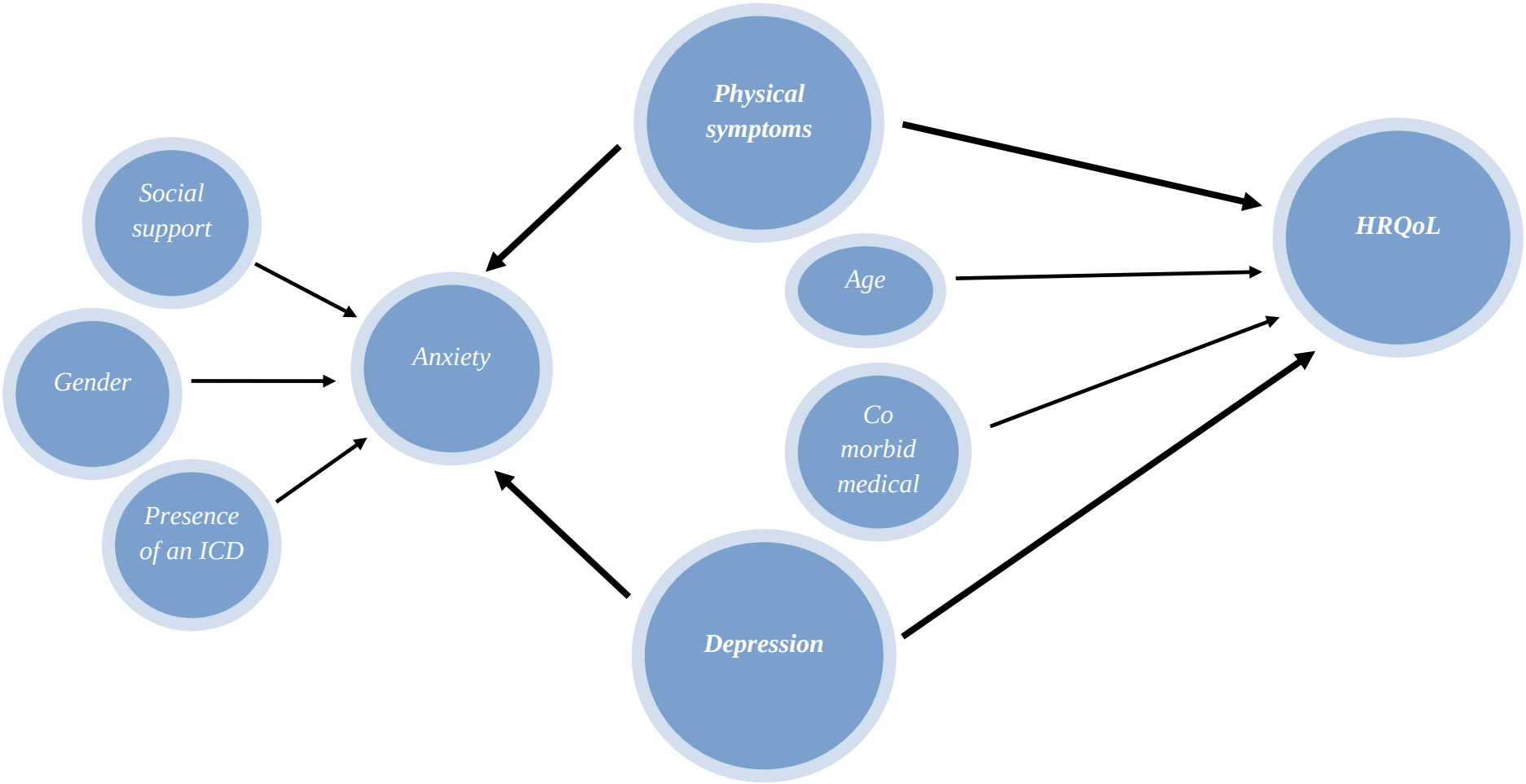
The cross-sectional survey was the first study to identify predictors of variance in anxiety symptoms whilst controlling for a comprehensive set of demographic, clinical and environmental covariates. Identifying variables associated with variance in anxiety symptoms scores will improve interventions aimed at reducing psychological distress in HF patient samples. Importantly, previous research has been inconsistent in determining factors that account for variance in HRQoL in HF patient samples. Psychological variables have rarely been considered as independent variables in regression models to predict HRQoL in HF samples. It is important to determine predictors of HRQoL to guide interventions to improve this important patient-centred outcome. In the study anxiety was measured using a validated tool, appropriate for use in chronically ill, elderly populations. The study found that:

1. Levels of anxiety that would benefit from intervention were present in nearly a third of the sample. Clinical/moderate levels of anxiety were higher than the rates found in the general population. However, mild levels of anxiety were similar to those found in the general population.
2. Anxiety co- morbid to depression was very common.
3. Factors that predicted higher levels of anxiety were increased levels of depression, poor perceived social support, a higher frequency and burden of physical symptoms, female gender and the presence of an ICD.
4. Anxiety symptoms did not predict a significant amount of unique variance in overall HRQoL scores.
5. Physical symptom burden and severity makes the largest unique contribution to explaining the variance in overall HRQoL scores followed by patient's level of depression, co-morbid physical conditions and age in years all making a significant unique contributions to the variance in overall HRQoL scores.

Figure 19 below presents the findings from the multi-regression models to predict anxiety symptom scores and overall HRQoL in a simple diagram. The findings from the current study lend only partial support to both the Wilson & Cleary (1996) and Ferrans et al (2005) revised HRQoL models. Both models postulate that symptom status and functional status are core influencing variables on patient's perceived HRQoL. Characteristics of the individual (including anxiety and depression) and characteristics of the environment (social support) are thought to affect patient's symptom status and functional status but are not reported to be direct determinants of perceived HRQoL in the Wilson & Cleary and Ferrans HRQoL models. However, evidence from the current research only partially supports the models, in that patient's physical symptoms have been found to be a primary determinant of patient report HRQoL. However, the findings from the study also show that depression, although not anxiety, was also a key determinant of patient reported HRQoL, suggesting a stronger influence of characteristics of the individual than is currently represented in the models. However, in the original Wilson & Cleary model, it is possible to see how depression and anxiety, as symptoms, could be conceptualised under the category of symptom status, not characteristics of the individual, which would place them in a more central, influencing role in the models.

The finds from the current study do loosely support a model of HRQoL proposed by Rector (2006), which postulates that physical symptoms exert a dominant influence over HRQoL, but acknowledges the role of emotional factors. Although anxiety was not found to be a significant predictor of HRQoL in the current study it is acknowledged that the low levels reported in the current research may have influenced this outcome.

Figure 22: Diagram to represent the main findings from the regression models conducted in the survey



Clinical Implications

Identification of anxiety in clinical practice

Research has suggested that mental health conditions are under-identified in clinical practice (Coventry et al, 2011; Lesman-Leegte, 2007). Reasons for this are many but include a lack of understanding of the association between mental health conditions and LTCs, a lack of confidence in identifying and assessing anxiety and depression and uncertainty as to how best to refer/treat common mental health conditions in patients with a LTC. The research conducted here indicates the importance of attention to and identification of symptoms of anxiety and depression in HF patients as the prevalence of both conditions is high and the influence of depression in determining HRQoL in this patient group is considerable. Regardless of a lack of association found between anxiety and HRQoL, it is clear that a significant proportion of HF patients are experiencing levels of anxiety that could benefit from psychological therapies in order to reduce the emotional and physical distress brought on by this condition. Recent findings from a year one report from the Increasing Access to Psychological Therapies (IAPT) initiative in the UK indicate that IAPT services, including watchful waiting, Cognitive Behavioural Therapy (CBT), computer delivered CBT (cCBT), guided self help, pure self help, and psychoeducational groups can be benficial to paitent with a range of clinical presentations from mild through to severe (IAPTs, 2011). NICE guidelines for Generalised Anxiety Disorder, no. 113 (NICE 2011) encourage the identification and treatment of subthreshold anxiety, which suggests that patients with even low levels of anxiety symptoms should be targeted for management of anxiety. It is important for clinicians to appropriately screen for anxiety and depression in HF samples and consider the potential for co- morbidity if a patient is diagnosed with either anxiety or depression in isolation, in order to access the appropriate services and allow the patient to receive the correct treatment.

Clinicans in both primary care and specialist secondary care services must take care to investigate symptoms of mental health conditions in HF patient popualtions , as if the anxiety/depression component of a patient's problem is not detected or is misattributed to their cardiac condition they may not receive the correct treatment and may undergo unnecessary and costly investigations, in particular for their physical symptoms (Hales *et al.*, 1997).

Measurement of anxiety and depression

Clinicians may be unsure of the most appropriate tool to use to identify anxiety and depression in busy clinical practice. The systematic review revealed that a number of tools are being used to identify anxiety in a research setting, some of which are more appropriate than others for use in this patient population. Interestingly, few studies in the review conceptualised anxiety. In using the tools identified in the studies however that rely on patient's self-reporting of symptomology, researchers are implicitly conceptualising anxiety using a medical model. However, using symptoms of common mental health conditions to identify their presence in patient populations with concurrent physical LTCs has been shown to be challenging, due primarily to the overlap in somatic symptoms across anxiety, depression and a range of LTCs including HF. Therefore, the selection of measurement tools in this area of research and clinical practice becomes crucial in order to obtain valid findings; accurate identification of anxiety and depression.

In the UK NICE guidelines for anxiety (GAD) recommend using DSM-IV criteria for sign and symptoms, however many medical professionals may not feel suitably trained to do this, may not have the time or may misattribute symptoms of anxiety and depression to the medical condition they are treating. In the UK the HADS and the GAD-7 are primarily used to screen HF patients for anxiety and the HADS and PHQ-9 are used to identify depression. Recently the validity of the HADS to accurately measure anxiety and depression has been questioned and the use of the total HADS score is proposed (Cosco et al, 2012). Post-hoc analysis in the survey indicated that total HADS distress scores were independent significant predictors of HRQoL in HF. However, the clinical utility of identifying a total distress score in HF patients would require consideration. Treatment, both pharmacological and psychological, for anxiety and depression differs and so it may not be entirely appropriate to identify patients with general distress; unless the purpose was to screen for distress and then refer patients to more specialist mental health services for further assessment of separate clinical anxiety and depression. As research has shown, symptoms of anxiety and depression do overlap, but to date research indicates that the two conditions are distinct and separate pathologies. Furthermore, in relation to the HADS, although evidence of a single-factor, three-factor and four-factor loading of items does exist, so too does a vast amount of evidence to support a two-factor loading of items. The HADS is a widely used, reliable tool and is cuurently one of the best tools we have for assessing levels of anxious and depressive symptomology in clinical populations.

With such debate surrounding the measurement of anxiety and depression is no wonder medical professionals are unsure of how best to assess common mental health coinditions in busy clinical practice with so many measures available and controversy relating to their psychometric properties. Currently the HADS, the GAD-7 and the PHQ-9 appear to be the most validated, brief and clinically useful tools for routine screening of anxiety and depression in clinical practice and for patient self-monitoring in the community.

Factors and considerations for interventions to improve HRQoL and anxiety in heart failuire patient populations.

A wide range of physical symptoms, not isolated to the condition of HF were found to influence both HRQoL scores and anxiety symptom scores. Symptoms of dyspena and fatigue are key symptoms of HF that are routinely assessed in clinical practice and form the basis for classification using NYHA functional class. However, the findings from the current study suggest that patients with HF are experiencing a wider range of physical symptoms than the primary HF symptoms of dysponea and fatigue. Symptoms of dry mouth, weak legs, dizziness, sleep disturbances and many more were rated as frequent and burdensome by the sample. This may reflect the presence of a number of LTCs impacting on patient's overall health and supports the need for holistic, collaborative care for patients with LTCs. Interventions to target dysponea and fatigue may have limited impact on patient's psychological well-being and HRQoL as they fail to consider other important physical symptoms.

In addition, an increased rate of co-morbid conditions was found to predict poorer HRQoL in the study. Again this finding adds weight to the need for collaborative care across services and a holitic appraoch to the care of patients with LTCs.

Both depression and social support were associated with anxiety. As with all the associations identified using cross-sectional methods the direction of these relationships can not be inferred; however it is reasonable to assume that interventions that involve psychological components and peer-support may help to improve both the emotional well-being and HRQoL of HF patients.

Recommendations for future research

There is still no agreed upon, recognised and standardised way to measure anxiety and depression in clinical practice. Further research is required to investigate the use of the total HADS score for identifying psychological distress in LTC patient samples.The use of the GAD-7 and PHQ-9 to identifying anxiety and depression in HF samples also requires further research, as currently few studies have adopted these methods of assessment. The GAD-7 is free to use and very brief (7 items). It contains no questions relating to somatic complaints and can distinguish between anxiety and depression, making its use in cardiac populations appropriate (Spitzer et al., 2006). Scores over 10 have been found to correspond to caseness of moderate to severe anxiety (Spitzer et al, 2006) that can impact individual's ability to perform everyday activities, cause marked distress but responds well to psychological interventions (NICE, 2011; IAPT Toolkit, 2008). Additional research using a variety of HF samples will help to establish the validity of this measure in HF samples.

The KCCQ has proved a useful tool to measure overall HRQoL in the current sample. Its use in HF patient populations is increasing and its further application in determining factors associated with HRQoL in HF patient populations should be considered.

Although the models tested in the study are comprehensive and account for a large proportion of variance in both anxiety symptom scores and HRQoL they do not account for all of the variance It is acknowledge that some variance in measurement will be due to error however addional factors such as medication, care setting, self-efficacy, previous mentalhealth history and percieved control could also be tested in combination with significant predictors found in the current study to more fully understand predictors of variance in HRQoL in HF patient populations. Further to this, the HRQoL models referred to in the thisis may require revisin, with further elaboration of the details of categories. In order to inform revisions further research is required to test the relationships within the models; currently very little ersearch on HRQoL in HF is informed by theoretical models.

An interesting observation was that levels of anxiety in the current sample were moderate and that social support was found to account for a significant proportion of variance in anxiety scores. Concordently, the health care that HF patients in the current sample received may not be considered representative of the standard care provided across both primary and secondary care service in the UK. Postulating, it may be that service

provisions play a cruicial role in supporting patients' emotional needs . Future research, both quantative and qualitative in nature, would be beneficial, to explore the potential impact of health care provisions on HF patients' emotional symptoms, including depression and anxiety. This work could include the assessment of more collaborative care to manage patients across services, irrespective of physical and emotional conditions.

Conclusions

The findings from both the systematic review and survey are presented in this chapter. A wide range of prevalence rates of anxiety exist in the literature. The review found that these rates are predominantly an artefact of measurement as opposed to reflecting actual differences in the levels of anxiety in HF patient samples. Individuals with a diagnosis of HF experience levels of anxiety that may cause distress. The routine identification of anxiety in clinical practice should be encouraged; it may be that financial incentives are required to priorities such screening, particularly in primary care settings. The identification of symptoms of both anxiety and depression may prove to be the most effective way to screen patients for referral to appropriate psychological services.

Depression, social support and physical symptoms accounted for the largest amount of variance in anxiety symptoms in HF patients. Interventions featuring components that improve these variables need to be developed and tested further in representative samples in order to improve patients' psychological well-being. Anxiety did not account for significant unique variance in HRQoL in the current sample, however, interventions that address patients' levels of depression and physical symptom burden will impact not only on levels of anxiety but also their reported levels of HRQoL. It is proposed that a holistic, collaborative care model will be the most effective way to manage HF patient's HRQoL given that a broad range of physical symptoms not exclusive to a HF condition and co-morbid medical conditions also impacted significantly on patients reported disease specific HRQoL outcome.

The research presented in this thesis contributes significantly to the body of knowledge in the area of common mental health conditions co-morbid to physical LTCs. In addition the research raises some very interesting and important questions about the measurement and screening of anxiety and depression in a clinical context.

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Appendix 1 Prevalence of Heart Failure from notable UK and USA studies.

Study	Sample, Findings & Limitations
Framingham Heart Study (Kannel & Belanger, 1991; Kannel, 2000)	- Longitudinal sample, small town in America. Original cohort from 1948 consisted of 5,209 participants. Additional cohort of 5,124 offspring added in 1971. - Looked for development of HF over the years. - Prevalence 0.8% in 50 to 59 year olds, rising to 7.3% in persons 80 to 89 years old. - Only signs and symptoms, so asymptomatic omitted.
MONICA (McDonagh et al, 1997)	- Cross-sectional survey of 1640 randomly selected men and women aged 25-74 from North Glasgow - Assessed LVSD based ejection fraction <40% using echocardiography - 65-74 years old 3.4% prevalence rates, 2.9% overall. - Younger sample than previous studies - Diastolic omitted - Half sample asymptomatic. - Younger age and strict criteria (not all HF subtypes) may account for lower rates found
Hillingdon Heart Study (Cowie et al, 1999)	- Population sample of urban West London PCT from 1995-1996 - Looking at diagnosis of HF following acute hospital admission or referral from GP using objective clinical assessment - 25 to 64 years ranged from 0.02% to 1.2%. 85 years and over 11.6% - 80% acute admissions omits stable chronic HF
ECHOES study (Davies et al, 2001)	- Cross-sectional survey of 3960 randomly selected men and women aged 45-85 years and over from West Midlands - Assessed LVSD and HF using objective methods - Definite HF diagnosed in 2.3% overall, ranging from 2.9% in those 65-74 yrs to 15.2% in those 85 yrs and over. - LVSD in 1.8% overall, half of whom were asymptomatic. - Diastolic omitted - Lower rates found but strict diagnostic criteria applied
National Health Interview Survey (NHIS) (Hanyu, 2003)	- Large scale survey conducted with 30,801 American adults - Self-report, asked if had been told they had HF by doctor - Prevalence 3.6% in 65 to 74 year old and 5.5% in 75-105 year olds - Not validated, no idea what types of HF - Hospitalised and those in assisted living not sampled

Primary Care management of HF following NSF CHD guidelines (Majeed, Williams, de Lusignan, & Chan, 2005)	- A recent UK survey of HF management in selected southern English GP's with a combined list size of 256,188 patients - Cross-sectional - Prevalence rates increased with age, from 0.2 per 1000 in people aged under 35 years of age to 125 per 1000 in those aged 85 years and over - Found an average prevalence of 8.3 per 1,000 population.
Heart failure in the family practice (Carmona et al, 2011)	- Based on the electronic medical records from 2007 of 198,670 PC patients at 34 health centres Madrid, Spain - International Classification of Primary Care (ICPC) - 198, 670 patients: 52% females, 48% males (47.65%) - 6.9% prevalence overall (60% females and 40% males) - Under 40yrs 0.3%, 75% over 80yrs

Appendix 2 Advisory group contributions

Consideration	Advisory group contribution	Action
Choice of sites	The advisory group discussed the choice of Manchester MRI and Wythenshawe Hospital as study sites for recruiting patients. Recruiting HF patients from three sites, rather than the two selected was initially an option. A HF specialist nurse, who was a member of the advisory group, runs HF clinics and provides community appointments in Lancashire PCT.	The two sites included in the final survey demonstrated the capacity to provide sufficient numbers of patients to meet the sample size required to power the planned statistical analysis. In addition R and D approval for the two Manchester sites took over three months to obtain and so adding a further site with no theoretical rationale was deemed inappropriate.
	An academic member of the advisory group voiced methodological concerns over selecting multiple sites for recruitment. It was suggested that selecting one site alone and describing the sample in detail may hold more merit methodologically than mixing patients from two sites, selected for no other reason than convenience.	Selecting one site alone was however problematic. The MRI sees a wide range of HF patient types, but they run fewer clinics than Wythenshawe and over a period of time would see fewer patients. Wythenshawe in contrast runs clinics every morning with the exception of Mondays and sees a large number of patients relative to the MRI. They do however define HF as LVEF only and so the types of

		HF patients treated at the centre with a recorded diagnosis of HF would have been less varied if the site had been selected as a standalone site
Survey aims and variables under investigation	The concept of measuring patient care as a variable for inclusion in the study was suggested by a clinical member of the advisory group. The suggestion was that frequency and length of appointments, the location of follow-ups (home or hospital), and the professional seen, may influence patient's levels of anxiety.	This idea is interesting and was given thought, however by introducing this angle to the research the focus of study would have altered, the sampling and site inclusion would have required further attention, as would the number of participants required to power the analyses. The concept of looking at service delivery as an impact factor on the levels of anxiety in HF patients may be an interesting option for future research in this area.
	Medication was also raised as a potential variable for investigation at an advisory meeting and subsequently through emails with clinician members of the group. Medication is often a variable featured in HF research. The potential influence of the number and types of medication that patients are prescribed could be a factor that potentially influences the levels	It would have been interesting to investigate the interaction between medication, anxiety, and patients self reported physical and mental symptoms. However, this area of investigation was deemed outside the scope of the current study and other factors such as social support were considered in this instance to be of greater relevance for the investigation.

	of anxiety in HF patients, particularly as Beta blockers (a class of drugs now prescribed to HF patients to reduce their heart rate) have been shown to be effective for the treatment of anxiety, although the mechanism of action is unknown (Tryler, 1992).	
Measurement tools	Prior to applying for ethical approval debate occurred around the selection of a symptom severity tool for the study. It was suggested that a new symptom severity measure be developed by a clinical member of the team and myself.	This idea did not progress beyond a brainstorming session of content for the tool as the task was considered outside of the scope of the PhD, particularly as the development of an outcome tool was not within the aims of the PhD and the validity of the measure could not be tested.
Recruitment and Procedure	Initially measurement tools were to be administered by the researcher in person with patients at the time of their appointments at clinical sites. However, this presented ethical issues, as patients should be given twenty-four hours to consider the research and their participation in it prior to active involvement in a study. A way around this was to pre-inform patients of the research prior to their clinic appointments with a	It was decided that data would not be collected in person (face-to-face) by the research at the time or on the day of patient's clinics appointments. This left the options of travelling to see patients in their homes to administer questionnaires, collecting data over the telephone or having patients self complete questionnaires in their own time and post them back to the researcher. The most cost-effective use of time and money was to have participants complete measured themselves in their own time.

cover letter and information sheet. This too presented challenges as it was unclear who could send out information to patients and have access to their addresses prior to consent being obtained for access to such information. Additionally a member of the advisory group was cautious about pre-informing patients of the research, suggesting it may increase their levels of anxiety prior to their appointments.

Even if patients could be pre-informed of the it would be difficult to collect data from patients at the time of their appointments or on the day of their appointment in the hospital site due to the number of patients seen per clinic and the times taken to complete the questionnaire.

Furthermore service-user members of the advisory group voiced concerns over the issue of keeping patients waiting following their appointments, even if they were seen immediately after their appointments as parking fees at hospital sites are high. The service-

	user advisory group members felt that the added burden of cost as well as time to patients' participation in the study would impact on response rates.	
Informing patients about their levels of anxiety	One of the clinical sites indicated that they would like to be informed if patients were identified as having clinically significant anxiety during the survey in order for them to be offered support. However the psychiatrist on the advisory committee disagreed with this request, primarily as the study is observational and changing a patient's treatment based on the findings of the survey before all data had been collected may have impacted on findings.	The decision not to inform clinicians of patients mental health status whilst research was ongoing was justified in a number of ways. First, all patients passing through the clinic have access to usual primary and secondary care services and participation in the survey did not reduce the availability of conventional services to patients. Second, there is currently no evidence that offering advice on anxiety in this tertiary care population provides any benefit to anxiety or that even if it does this improvement is sustained and provides benefit to HRQoL. Therefore the benefit of informing HF nurses would be minimal. It was decided that any patient who is visibly distressed through anxiety or who asks for advice for anxiety would be referred to the appropriate person in the clinic.

Appendix 3 Definitions of conditions and interventions featured in the inclusion and exclusion criteria of the systematic review

Condition or Intervention	Definition
Acquired left-sided ischaemic and non-ischaemic heart failure	Acquired structural and functional changes of the left side of the heart, that impair the heart's ability to fill and contract to handle blood volume and meet the metabolic needs of the body. Impairment of the heart can be due to ischaemic damage from coronary heart disease, or due to non-ischaemic causes.
Dilated cardiomyopathy	Condition where ventricles of the heart become enlarged and poorly contractile
Congenital heart disease	Conditions where there are abnormalities of the structure of the heart or major blood vessels, present from birth and may be hereditary
Isolated right-sided heart failure	Inefficient pumping of the right side of the heart in isolation from the left side. Produces symptoms of swollen ankles and feet. Mostly commonly caused by lung disease
Pulmonary hypertension	Increase in blood pressure in the pulmonary arteries
Cor pulmonale	Enlargement of the right side of the heart in response to resistance or high blood pressure in the lungs
Implantable Cardioverter Defibrillator (ICD)	Procedure that involves implanting leads into the heart and a pacemaker/defbrillator a device into chest wall. Monitors heart rhythm, senses severe rhythm disturbance and paces and/or delivers an electrical shock to correct it.
Purcutaneous coronary intervention (PCI)	Procedure to widen narrowed coronary arteries. Involves inflation of balloons inside the artery or

	the placing of stents to maintain the lumen of the artery.
Coronary resynchronisation therapy (CRT)	Biventricular pacemaker that synchronises contraction of the left and right ventricles
Coronary artery bypass graft (CABG)	Operation to bypass a narrowed section/s of coronary arteries and improve bloody supply to the heart

Appendix 4 Search strategy

Ovid MEDLINE (1950-2009), CINAL (1982 -2008), BNI (1985-2009), and Embase (1980-2009)

1. Heart Failure/
2. cardiac adj failure.mp.
3. heart adj failure adj congestive.mp.
4. heart adj decompensation.mp.
5. decompensated adj heart.mp.
6. heart adj failure adj left adj sided.mp.
7. left adj sided adj heart adj failure.mp.
8. myocardial adj failure.mp.
9. cardiomyopathies/
10. cardiac adj patient$.mp.
11. coronary adj patient$.mp.
12. heart adj failure .mp.
13. or/ 1-12
14. Anxiety disorders/
15. anxiety adj disorders.mp.
16. anxieties.mp
17. anxiety adj symptoms.mp.
18. nervousness.mp.
19. worry.mp.
20. mental health.mp. or Mental Health/
21. mood disorders.mp. or Mood Disorders/
22. anxiety.mp. or Anxiety/
23. affective adj disorder$.mp.
24. stress adj psychological.mp.
25. stress adj disorder.mp.
26. psychological adj stress.mp.
27. emotional adj factors.mp.
28. emotional adj stress.mp.
29. panic disorder.mp. or Panic Disorder/
30. Phobic disorders.mp. or Phobic Disorders/
31. obsessive adj compulsive adj disorder.mp
32. agoraphobia.mp or Agoraphobia/
33. post-traumatic adj stress adj disorder.mp
34. or/ 14-33
35. 13 and 34 (heart failure and anxiety)
36. quality of life.mp or “Quality of Life”/
37. health adj related adj quality adj of adj life.mp
38. HRQOL.mp
39. life adj quality$.mp
40. well adj being.mp
41. life adj satisfaction.mp
42. or/36-41

43. 13 and 42 (heart failure and quality of life
44. prevalence.mp. or Prevalence/
45. 13 and 34 and 44 (heart failure and anxiety and prevalence)
46. 35 or 43 or 45 (heart failure and anxiety or heart failure and QoL or heart failure, anx, and prevalence)
47. limit 46 to (English language and humans)

Search strategy for PsycINFO (1967-2009)

1. heart adj failure.mp.
2. cardiac adj failure.mp.
3. congestive adj heat adj failure.mp.
4. decompensated adj heart.mp.
5. myocardial adj failure.mp.
6. cardiomyopathies.mp.
7. cardiac adj patient$.mp.
8. coronary adj patient$.mp.
9. or/1-8
10. exp SOCIAL ANXIETY/ or exp ANXIETY DISORDERS/ or exp ANXIETY/ or exp GENERALIZED ANXIETY DISORDER/ or anxiety.mp.
11. exp Phobias/ or anxiety symptoms.mp.
12. anxieties.mp.
13. nervousness.mp. or exp NERVOUSNESS/
14. worry.mp.
15. exp Mental Health/
16. exp Affective Disorders/
17. mood adj disorders.mp.
18. exp Psychological Stress/
19. emotional adj factors.mp.
20. emotional adj stress.mp.
21. exp AGORAPHOBIA/
22. exp Panic Disorder/
23. exp Social Phobia/
24. Obsessive Compulsive Disorder/
25. exp Posttraumatic Stress Disorder/
26. or/10-25
27. 9-26 (heart failure and anxiety)
28. exp “Quality of Life”/
29. exp Psychological Factors/ or exp Well Being/
30. health adj related adj quality adj of adj life.mp.
31. life adj satisfaction.mp.
32. life adj quality$.mp.
33. or/28-32
34. 9 and 33 (heart failure and quality of life)
35. prevalence.mp.
36. 9 and 26 and 35 (heart failure and anxiety and prevalence)
37. 27 or 34 or 36 (heart failure and anxiety or heart failure and QoL or heart failure, anx and prevalence)
38. limit 37 to (human and English language)

Appendix 5 Formulae for mean and standard deviation

Formulae for mean and standard deviation (Mean = Sum / no of case)

So if the reported means are m1 and m2, and the numbers of cases in the groups are n1 and n2, then the sums within the groups are

sum1 = m1 * n1

sum2 = m2 * n2

Overall sum = sum1 + sum2

Overall mean = overall sum / (n1 + n2)

SD (pooled estimate) = square root of {[sum of squares of (x - suitable mean)]/(no of cases - 1)}

So if the reported SDs are SD1, SD2, then

sum_of_squares1 = (n1 - 1) * SD1 * SD1

sum_of_squares2 = (n2 - 1) * SD1 * SD2

Total sum of squares = sum_of_squares1 + sum_of_squares2

Estimate of overall SD = square root of {[Total sum of squares]/(n1-1 + n2-1)}

Appendix 6 Systematic review extraction form

SYSTEMATIC REVIEW DATA EXTRACTION FORM

INSTRUCTIONS

- Please enter data in each BLANK shaded data entry field
- Use the TAB key to move DOWN from one data entry field to the next one
- Use SHIFT+TAB together to move UP from one data entry field to the previous one
- Boxes will expand to fit additional data
- If data is not available, please enter 'Not clear'
- When the data extraction is completed, please save the file with the following filename:
    - [First author] [Date] [Reviewer initials].doc
    - e.g. Scogin 2005 PB.doc
    - If two studies share the same identifier, please use 2001a, 2001b etc

GENERAL INFORMATION

Extractor ID

Date

Study ID (First author + Year)

Publication (volume, pages)

Country where data collected

Recruitment context (e.g. out-patients, community based, primary care, specialist service, hospital in-patient, other)

Sample Recruitment (Consecutive, random, purposive)

Data Collection (cross-sections, longitudinal, retrospective, prospective)

STUDY POPULATION

Inclusion criteria (list all)

Exclusion criteria (list all)

How have heart failure patients been identified? (Medical records, inpatients, attendance at clinics, part of larger trial)

How has HF been described? (Ejection fraction, peak oxygen consumption, ECG, chest x-ray, bloods, NYHA functional class, six minute walk test)

Sample size

Attrition rate/drop outs

Demographics and clinical information

Means (sd), percentages for study group and control/comparison group if included

Aetiology of Heart failure

severity of illness (NYHA functional class, peak oxygen flow, ejection fraction)

sex

age

ethnicity

DESIGN

Design (RCT, Controlled pre-post, none-controlled pre-post, cohort)

Were the comparison group and experimental (heart failure) group comparable (If comparison group included)?

What was the main study outcome? (Describe) Was it stated a priori? (Y/N)

How has anxiety been measured? e.g. self-report measure, clinical interview, medical records

What measure has been used to assess anxiety?

If health related quality of life has been measured how has it been assessed? Global or disease specific measure? Specify measure

What other variables/secondary outcomes were included? list

OUTCOMES 1

Overall prevalence rate of anxiety (%, mean scores (SD))

Have anxiety scores been associated or correlated with any variables? (Demographics, clinical characteristics, psychosocial variables)

OUTCOMES 2

HRQoL scores for HF patients (broken down into global and specific if available)

Are HRQoL scores associated with any variables? (demographics, clinical characteristics, psychosocial)

CONCLUSIONS

Any relevant comments made in conclusion

Are limitations acknowledged (Y/N) describe

Any other comments/limitations not addressed

QUALITY CRITERIA

Are objectives clearly stated?

Are outcomes stated a priori?

Is the sample size adequate (10:1 patient variable ratio)?

Are power calculations reported/discussed?

Are the target population defined?

Was probability sampling used?

Where demographics of sample descried adequately?

Do characteristics of respondents match target population?

Does study have a comparison sample (health older adults/chronic)?

Is data collection standardised?

Are instruments used reliable?

Are instruments used valid?

Has appropriate analysis been conducted?

Are CI's included for relevant statistics?

Are conclusions justified?

Are any crucial limitations acknowledged?

Score of 0 if responses to items are no/insufficiently information;
score of 1 if response to item is yes/adequate information
Score 2 if not relevant

Appendix 7 Excluded studies from systematic review

Reference	Reason for exclusion
Ai et al (2012)	Anxiety measured too soon pre/post invasive procedure
Aimonino (2007)	Anxiety not measured
Amiaz et al (2012)	Unable to locate conference abstract
Angermann (2007)	Not primary research
Anunziato et al (2009)	Unable to locate paper
Arestedt, Argren & Stromberg (2011)	Unable to locate conference abstract
Artinian, (2004)	Not primary research
Astley, (2008)	Not heart failure patients
Ayanian et al (1995)	General MH measure
Aydemir et al (1997)	Not heart failure patients
Baas et al (1999)	Condition too severe/unstable
Barbareschi et al (2011)	Anxiety not measured
Barnason et al (2003)	Not valid anxiety measure
Barnes et al (2006)	Not valid anxiety measure
Basile et al (2009)	Unable to locate paper
Baumbauer et al (2005)	Not heart failure patients
Bean et al (2009)	Not primary research
Bedi and Brown (2005)	General MH measure
Beery et al (2007)	Not heart failure patients
Bennett et al (1998)	Not valid anxiety measure
*Ben-Zur et al (2000)	Not heart failure patients
Biddiss et al (2009)	Not valid anxiety measure

Birket-Smith & Rasmussen (2008)	Not heart failure patients
Blackwood (1984)	Not valid anxiety measure
Blinderman et al (2008)	Anxiety not measured
Bocalini et al (2008)	Anxiety not measured
*Bohachick (1984)	Not heart failure patients
Bouras, Vanger & Bridges (1986)	Not heart failure patients
Brezinka et al (1998)	Not heart failure patients
Brezinka et al (2001)	Not heart failure patients
Brontons et al (2009)	Anxiety not measured
Brouwers et al (2013)	Anxiety not measured
Buls (1995)	Not heart failure patients
Cameron et al (2009)	Anxiety not measured
Carels et al (2004)	Not valid anxiety measure
*Carless et al (2006)	Not heart failure patients
Castels et al (2009)	Anxiety not measured
Chignon et al (1993	Not heart failure patients
Chu & Pei (1999)	General MH measure
Chung, Moser & Lennie (2012)	Not HF patients
Cole et al (2006)	Anxiety not measured
Comin-Colet et al (2012)	Anxiety not measured
Comin-Colet et al (2013)	Not valid anxiety measure
Compare et al (2012)	Not primary research
Cote et al (1976)	Not heart failure patients
Craney et al (1996)	Not heart failure patients
Cully et al (2009)	Unable to locate paper
Damen et al (2011)	Not HF patients

Dannerman et al (2010)	Not HF patients
De Leon et al (2009)	Not heart failure patients
Denollet & Pedersen (2009)	Not primary research
Denollet & Pedersen (2009)	Not primary research
Denollet (1991)	Not heart failure patients
Dixon et al (2000)	Not valid anxiety measure
Dogar et al (2008)	Not heart failure patients
Dougherty et al (2005)	Not heart failure patients
Dowling (1980)	Not primary research
Dunbar & Summerville (1997)	Not primary research
Dunbar (2005)	Not primary research
Dunbar et al (2009)	Not heart failure patients
*Edelman et al (2007)	Not heart failure patients
Ege, Yilmaz,& Yilmar (2011)	Not primary research
Eichenauer et al (2010)	Not HF patients
Emery et al (2003)	Not heart failure patients
Emons et al (2012)	Not HF patients
Engebretson et al (1999)	Not heart failure patients
Evangelista et al (2001)	Not valid anxiety measure
Evangelista et al (2006)	Anxiety not measured
Evangelista et al (2008)	Anxiety not measured
Ferketich & Binkley (2005)	Not valid anxiety measure
Fifer et al (1994)	Not heart failure patients
Fontelonga Bento et al (2011)	Not valid anxiety measure
Frasure – Smith et al (2012)	Anxiety not measured
Freidman (2003)	Anxiety not measured

Friedberg et al (2009)	Not HF patients
Froese et al (1975)	Not heart failure patients
Frost et al (1975)	General MH measure
Gallagher et al (2004)	Anxiety measured too soon after invasive procedure
Gavin et al (2000)	Not heart failure patients
Gellis et al (2012)	Anxiety not measured
Gerber et al (2009)	Not heart failure patients
Giannuzzi et al (2008)	Not heart failure patients
Graveley-Wiite (2009)	Not HF patients
Griez et al (2000)	Condition too severe/unstable
Guo et al (2012)	Not HF patients
Gupta et al (2005)	Unable to locate publication
Gupta et al (2006)	Unable to locate publication
Habibovic et al (2012)	Not HF patients
Hambridge et al (2009)	Not HF patients
Harkness et al (2011)	Not HF patients
Hermann-Lingen & Pieske (2008)	Not primary research
Hermann-Lingen (2011)	Not primary research
Hevey et al (2007)	Not heart failure patients
*Hervey et al (2003)	Not heart failure patients
Hiiatt et al (1984)	Not heart failure patients
Hinz et al (2011)	Not HF patients
Hodges (2009)	Anxiety not measured
Huang et al (2010)	Anxiety not measured
Hughes et al (2004)	Not heart failure patients
Hughes et al (2007)	Not heart failure patients

Hunt-Skanks et al (2009)	Not heart failure patients
Hunts-Shanks et al (2010)	Not HF patients
Ibatov et al (2011a)	Not HF patients
*Ingle (2006)	Not heart failure patients
Ingle et al (2006)	Not valid measure of anxiety
*Ingram et al (2006)	Not heart failure patients
Jenkins & McSweeney (2001)	Not valid measure of anxiety
Johnson et al (2011)	Condition too severe/unstable
Jolly et al (2009)	Not heart failure patients
Jones et al (2006)	Not heart failure patients
Jonsdottir & Baldursdottir (1998)	Not heart failure patients
Jurgens et al (2009)	Not valid anxiety measure
Kahn et al (1987)	Condition too severe/unstable
Karavidas et al (2010)	Anxiety not measured
Karlsson (2000)	Anxiety not measured
Karve & Candrilli (2012)	Not HF patients
Klocel et al (2005)	Not valid measure of anxiety
Koivula (2002)	Not heart failure patients
Komorovsky et al (2008)	Not heart failure patients
Kornerup, Zwisler & Prescott (2011)	Not HF patients
Kotianova et al (2008)	Not heart failure patients
Kuchibhatla & Fillenbaum (2011)	Anxiety not measured
Ladwig (2000)	Not heart failure patients
Ladwig et al (2008)	Not heart failure patients
Lam et al (2009)	Not heart failure patients
Le Grande et al (2012)	Anxiety not measured

Levenson et al (2000)	Condition to severe/unstable
Majani et al (1999)	Condition to severe/unstable
Maryniak et al (2009)	Not heart failure patients
McGirr et al (1990	Not heart failure patients
McLauchlan et al (1992)	Not heart failure patients
McLaughlin et al (2005)	Not heart failure patients
Mercer et al (2011)	Unable to locate conference abstract
Messerli-Burgy et al (2012)	Not HF patients
Millan-Calenti et al (2011)	Anxiety not measured
*Mittag (2006)	Not heart failure patients
Molchany & Peterson (1994)	Not heart failure patients
Mommersteeg et al (2011)	Not HF patients
Moser et al (2012a)	Anxiety not measured
Moser et al (2012b)	Not HF patients
Mutwalli et al (2012)	Not HF patients
Nickel et al (1990)	Not heart failure patients
*Okkonen & Vanhanen (2006)	Not heart failure patients
*Okkonen (2006)	Not heart failure patients
O'Reilly (2004)	Not heart failure patients
Pedersen et al (2008a)	Anxiety measured too soon after invasive procedure
Pedersen et al (2008b)	Not heart failure patients
Pedersen et al (2010)	Not HF patients
Pelle et al (2010)	General MH measure
Penninx (1996)	Not heart failure patients
Peters-Klimm (2007)	Not primary research
Philip (1987)	Not heart failure patients

Plach et al (2008a)	Unable to locate publication
Prosser et al (1981)	Not heart failure patients
Rathore et al (2008)	Anxiety not measured
Roberts, 2001	Not heart failure patients
Rohrbaugh (2002)	General MH measure
Saskia, Pasteuning & Walpot (2012)	Unable to locate conference abstract
Schrader (2004)	Not heart failure patients
Schuster et al (1998)	Not heart failure patients
Sears (2000)	Not heart failure patients
Sherbourne et al (1998)	Not heart failure patients
Shiell, (1991)	Not heart failure patients
Skodova et al (2009)	Not heart failure patients
Smeulders, (2006)	Not primary research
Spertus et al (2002)	Not primary research
Stein et al (1990)	Not heart failure patients
Stromberg & Jaarsma (2008)	Not valid anxiety measure
Thomas et al (2006)	Anxiety measured too soon after invasive procedure
Thomas et al (2008)	Anxiety measured too soon after invasive procedure
Thompson & Webster (1989)	Not heart failure patients
Tooth, 97	Not heart failure patients
Trzcieniecka-Green (1996)	Not heart failure patients
Trzcieniecka-Green et al (1994)	Not heart failure patients
Turner, 2002	Not heart failure patients
Valliant & Laith (1986)	Not heart failure patients
Van et al (2009)	Unable to locate paper
Vazquez-baruero, 85	Not heart failure patients

West et al (1995)	Not heart failure patients
Worcester et al (2011)	Anxiety not measured
Worcester et al (2011)	Anxiety not measured

*** indicates excluded following consultation with supervisors**

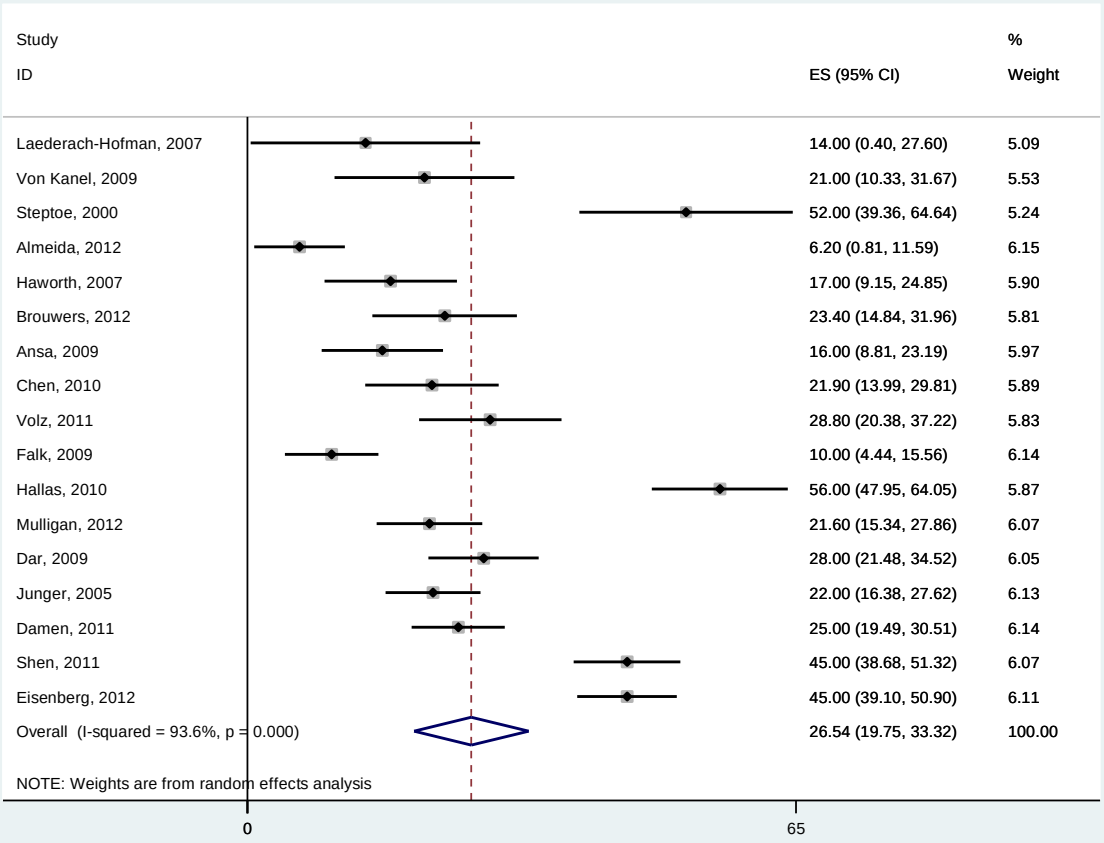
Appendix 8 Studies that met inclusion criteria for the review but that were not entered into synthesis

Reference	Reason for exclusion from analysis
Angermann (current trial)	No data yet
Ansa et al, 2009	No/insufficient/unclear data
Arnous et al, 2011	No/insufficient/unclear data
Baumeister et al, 2010	No/insufficient/unclear data
Benetar et al (2003)	No/insufficient/unclear data
Brenes (2007)	No/insufficient/unclear data
Carroll & Hamilton (2008)	No/insufficient/unclear data
Celano et al, 2012	No/insufficient/unclear data
Cheok et al (2003)	No/insufficient/unclear data
Cowie (current trial)	Duplicate study
Cully et al (2008)	Duplicate paper
Dastirdar & Jiang, 2012	No/insufficient/unclear data
DeJong et al (2008)	Duplicate paper
Franklin et al (current trial)	No data yet
Freitas et al, 2011	No/insufficient/unclear data
Fritzsche et al (2007)	No/insufficient/unclear data
Gorkin et al (1993)	No/insufficient/unclear data
Hamilton & Carroll (2004)	No/insufficient/unclear data
Harkness et al (2009)	No/insufficient/unclear data
Haworth et al (2005)	Duplicate paper
Hedemalm et al, 2010	No/insufficient/unclear data
Heish & Chen (1986)	No/insufficient/unclear data
Heo et al (2007a)	Duplicate paper
Heo et al (2007b)	Duplicate paper
Hermann-Lingen et al (1997)	No/insufficient/unclear data
Hofer et al (2008)	No/insufficient/unclear data
Holly et al (2012)	No/insufficient/unclear data
Hwang et al, 2012	No/insufficient/unclear data
Ibatov et al, 2011	No/insufficient/unclear data
Ibishi et al (2010)	No/insufficient/unclear data
Johansen et al (2008)	No/insufficient/unclear data
Katz & McHorney (2002)	No/insufficient/unclear data
Kaya et al, 2012	No/insufficient/unclear data
Konstam et al (1999)	No/insufficient/unclear data
Kornerup et al, 2011	No/insufficient/unclear data
Kovacs et al (2006)	No/insufficient/unclear data
Krishna et al (2009)	No/insufficient/unclear data
Lee et al (2005a)	No/insufficient/unclear data
Lee et al, 2011a	No/insufficient/unclear data
Lee et al, 2011b	No/insufficient/unclear data
Luskin et al (2002)	No/insufficient/unclear data

Matsumori (current trial)	No/insufficient/unclear data
McGrady et al, 2009	No/insufficient/unclear data
Miche et al (2003)	No/insufficient/unclear data
Miche et al (2008)	No/insufficient/unclear data
Miche et al, 2009	No/insufficient/unclear data
Muller-Tasch (current trial)	No data yet
Nahlen et al, 2012	No/insufficient/unclear data
O'Donoghe (current trial)	No/insufficient/unclear data
Pedersen et al (2008c)	No/insufficient/unclear data
Pedersen et al (2009)	No/insufficient/unclear data
Pelle et al (2009)	No/insufficient/unclear data
Podgorna et al (2007)	No/insufficient/unclear data
Reigel et al, 2011	Duplicate sample Moser et al, 2005, Huang 2012
Reynolds et al (2007)	No/insufficient/unclear data
Riedinger et al (2001)	No/insufficient/unclear data
Riedinger et al (2002)	No/insufficient/unclear data
Scherer et al (2007)	Duplicate paper
Scott et al (2004)	No/insufficient/unclear data
Smeulders (current trial)	No/insufficient/unclear data
Spinder et al (2009b)	No/insufficient/unclear data
Spindler et al (2009a)	No/insufficient/unclear data
Stewart et al (1994)	No/insufficient/unclear data
Svansdottir et al, 2012	No/Insufficient/unclear data
Szekely et al (2007)	No/insufficient/unclear data
Thomas et al, 2009	Duplicate sample Friedmann et al, 2006 & Thomas et al, 2006
Tsuchihashi et al (2004)	No/insufficient/unclear data
Walke et al (2007)	No/insufficient/unclear data
Wereteka (current trial)	No/insufficient/unclear data
Yu et al (2004)	Duplicate paper
Yu et al (2007a)	Duplicate paper
Yu et al, 2012	Duplicate sample of Huang et al, 2012

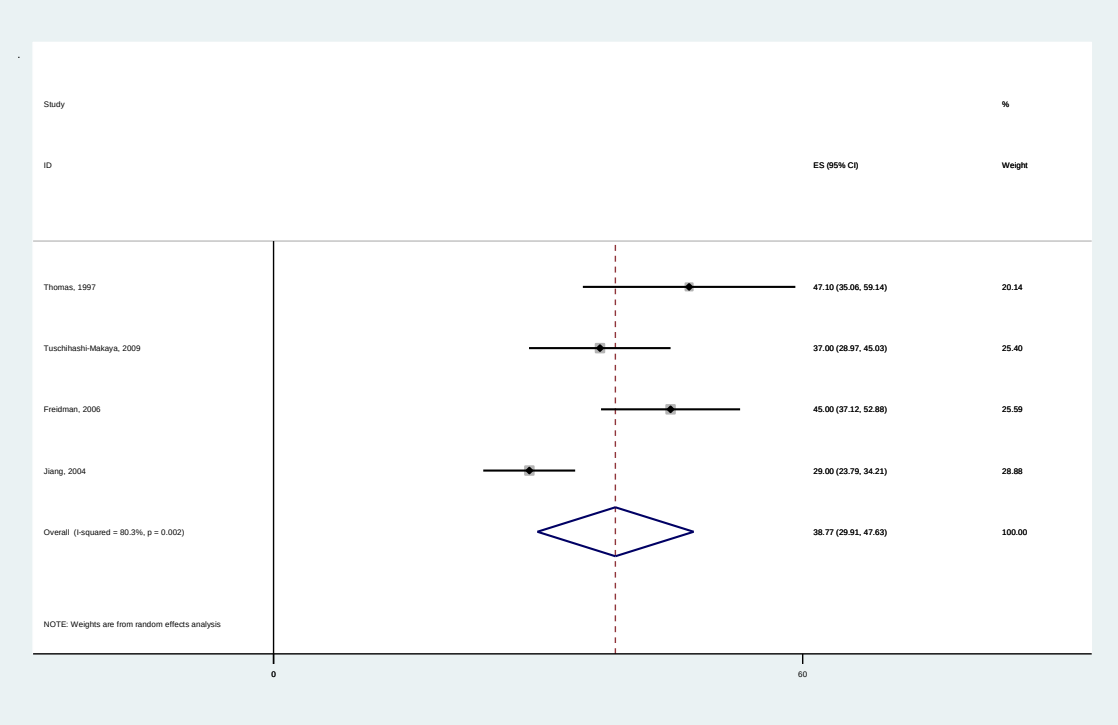
Appendix 9 Forest plots of prevalence of anxiety by anxiety measurement tools

A forest plot to show the results of random effects meta-analysis on HADS prevalence rates



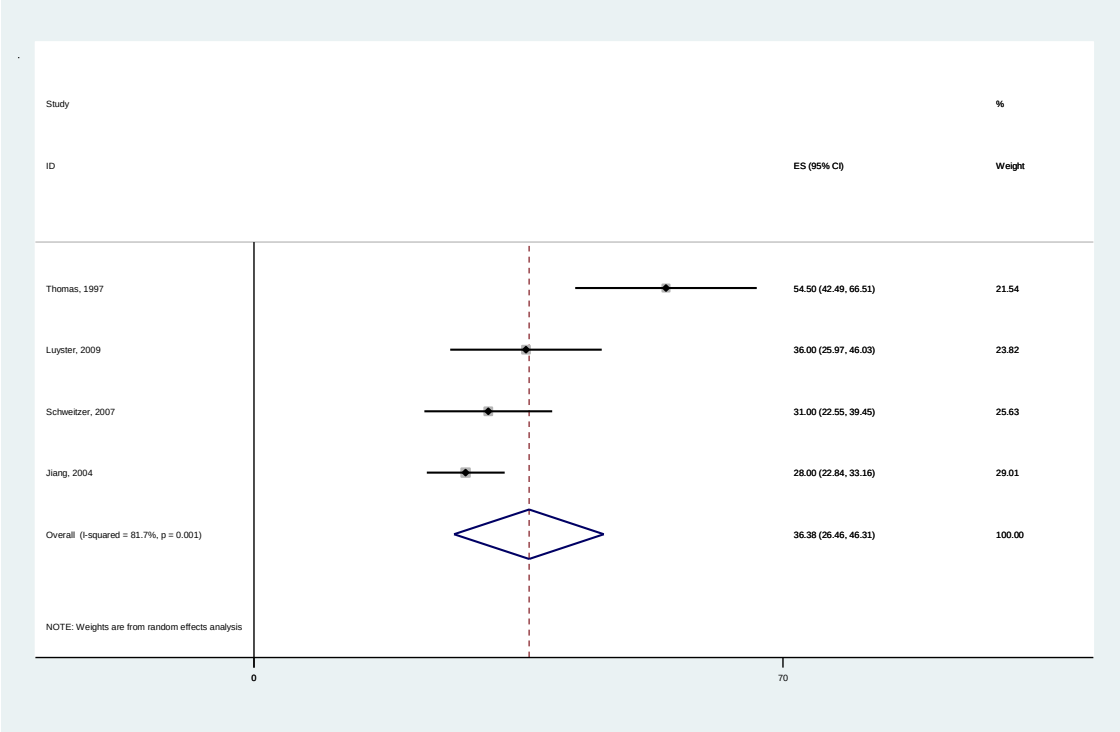
Heterogeneity chi-squared = 249.43 (d.f. = 16) p = 0.000
I-squared (variation in ES attributable to heterogeneity) = 93.6%
Estimate of between-study variance Tau-squared = 187.1390
Test of ES=0: z= 7.67 p = 0.000

A forest plot to show the results of random effects meta-analysis on STAI-S prevalence rates



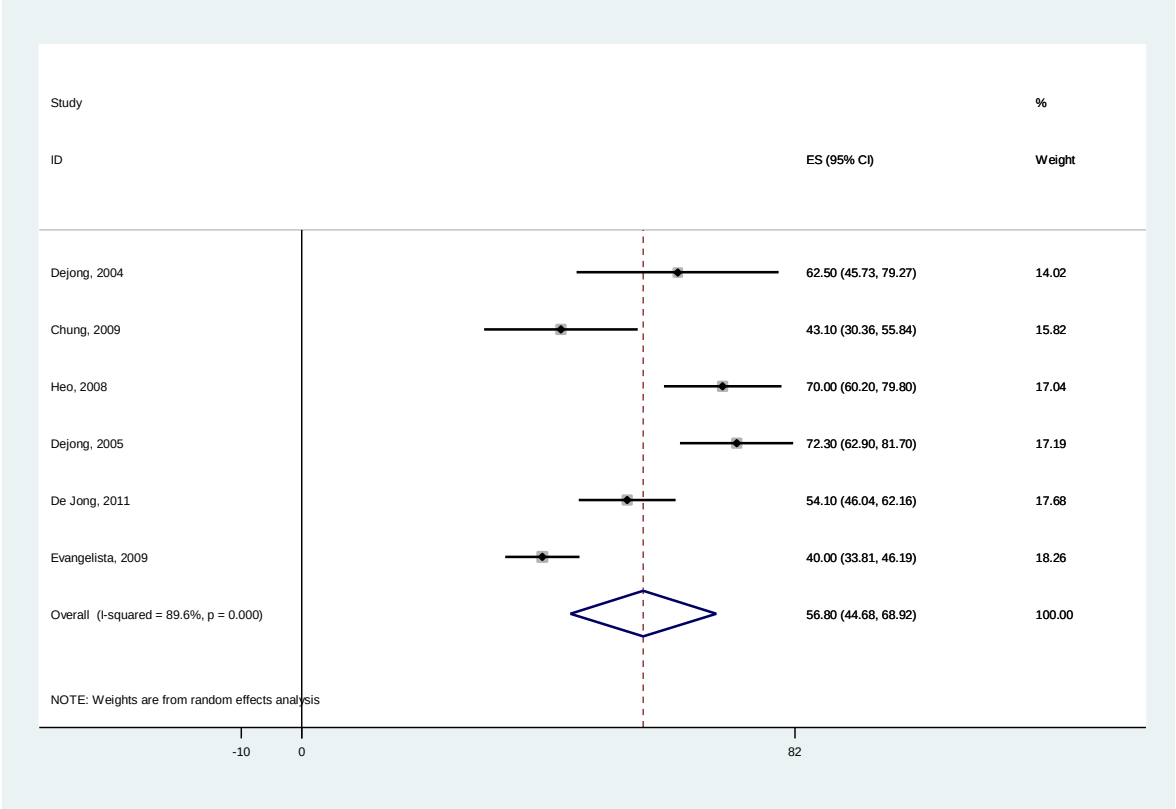
Heterogeneity chi-squared = 15.23 (d.f. = 3) p = 0.002
I-squared (variation in ES attributable to heterogeneity) = 80.3%
Estimate of between-study variance Tau-squared = 63.6236
Test of ES=0: z= 8.58 p = 0.000

A forest plot to show the results of random effects meta-analysis on STAI-T prevalence rates



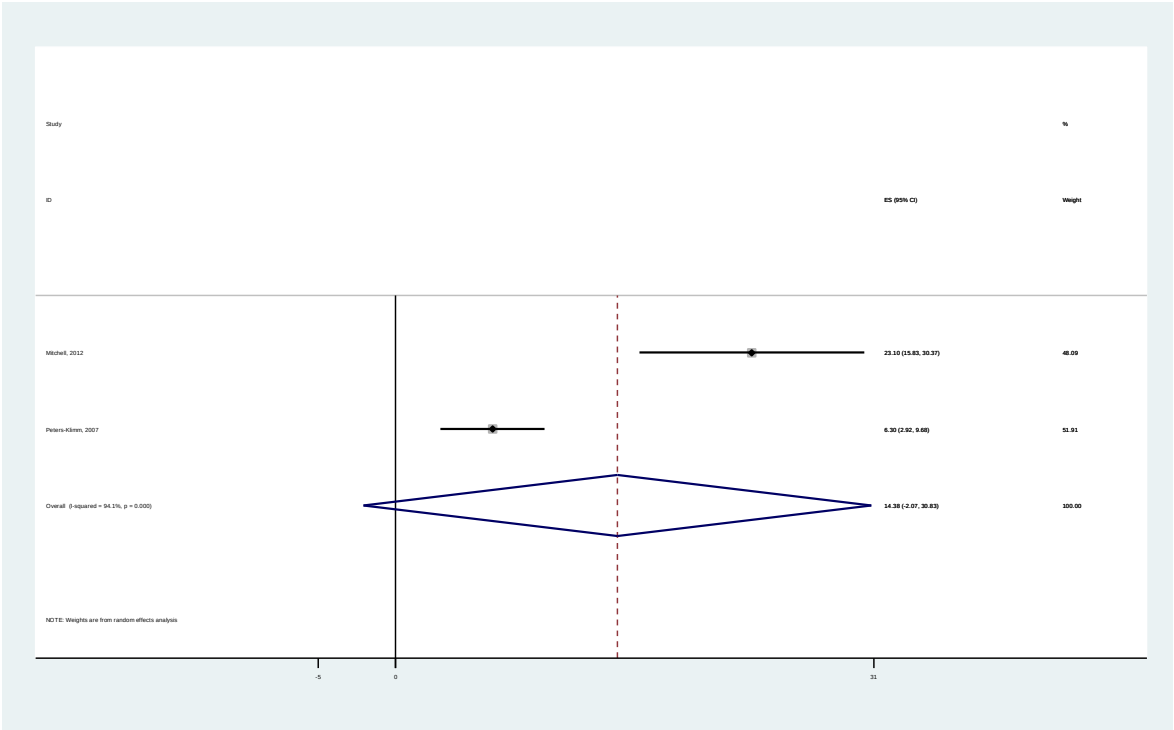
Heterogeneity chi-squared = 16.39 (d.f. = 3) p = 0.001
I-squared (variation in ES attributable to heterogeneity) = 81.7%
Estimate of between-study variance Tau-squared = 81.4507
Test of ES=0: z= 7.19 p = 0.000

A forest plot to show the results of random effects meta-analysis on BSI –a prevalence rates



Heterogeneity chi-squared = 48.23 (d.f. = 5) p = 0.000
I-squared (variation in ES attributable to heterogeneity) = 89.6%
Estimate of between-study variance Tau-squared = 199.3862
Test of ES=0: z= 9.19, p = 0.000

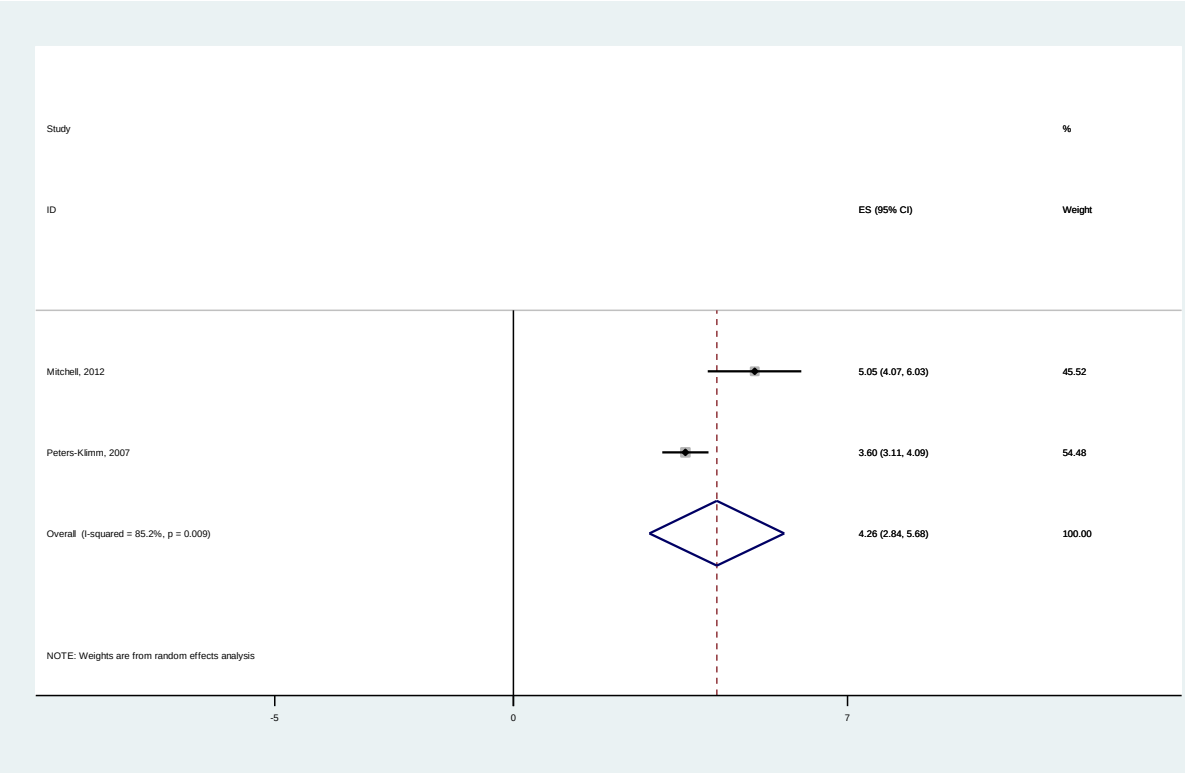
A forest plot to show the results of random effects meta-analysis on GAD-7 prevalence rates



Heterogeneity chi-squared = 6.75 (d.f. = 1) p = 0.009
I-squared (variation in ES attributable to heterogeneity) = 85.2%
Estimate of between-study variance Tau-squared = 0.8954
Test of ES=0: z= 5.90, p = 0.000

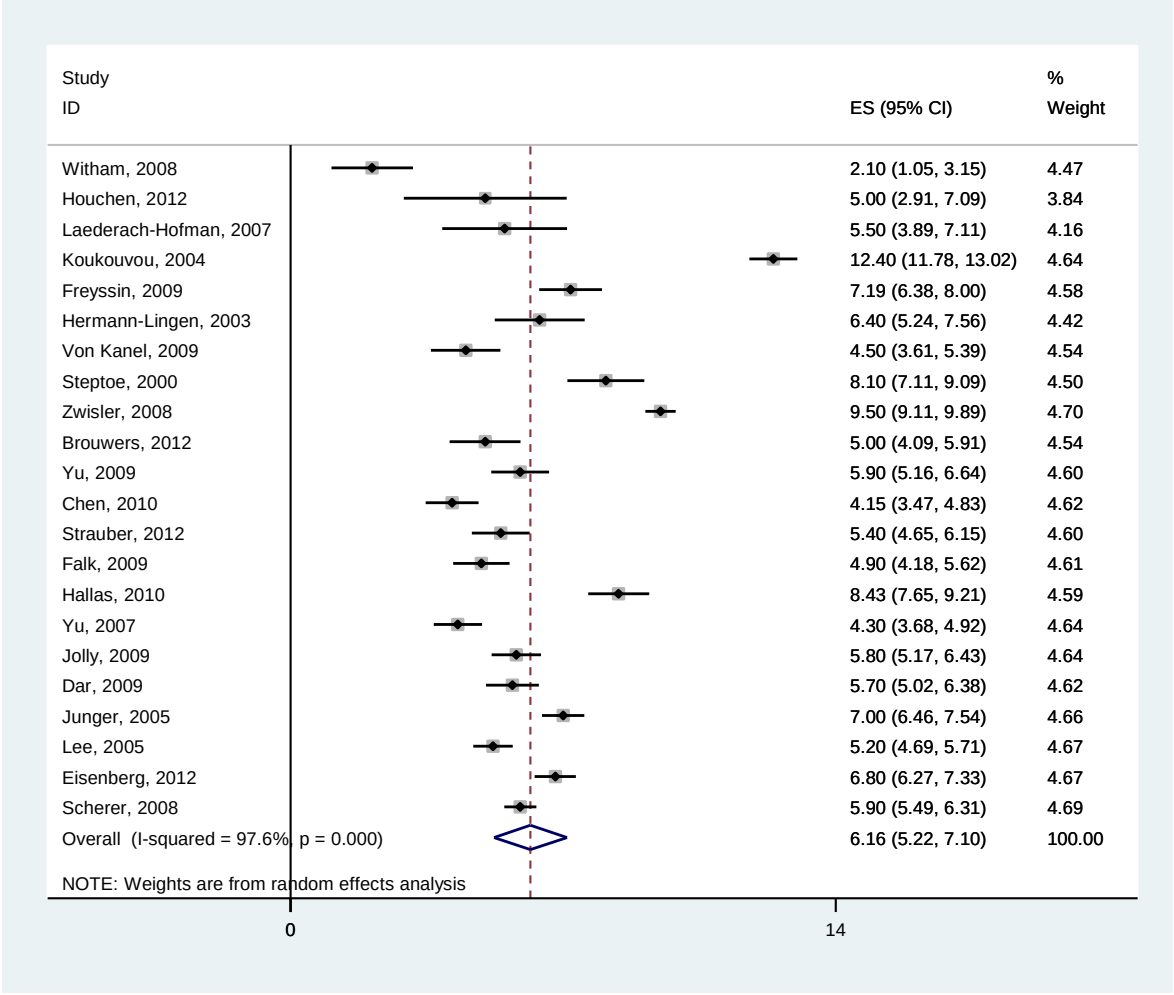
Appendix 10 Forest plots of anxiety severity (mean, SD) by anxiety measurement tool

A forest plot to show the results of random effects meta-analysis on GAD-7 mean symptom score



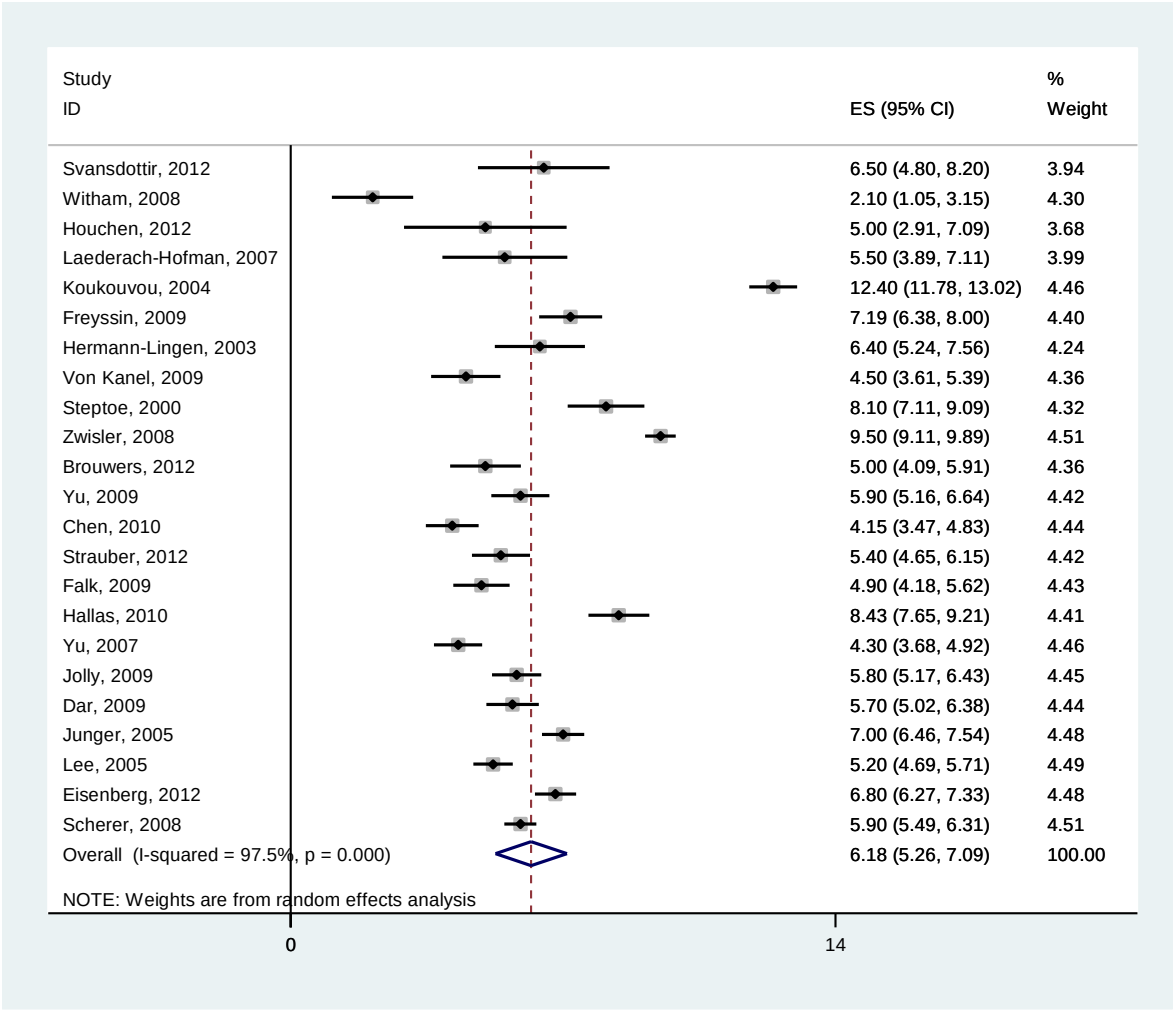
Heterogeneity chi-squared = 6.75 (d.f. = 1) p = 0.009
I-squared (variation in ES attributable to heterogeneity) = 85.2%
Estimate of between-study variance Tau-squared = 0.8954
Test of ES=0: z= 5.90. p = 0.000

A forest plot to show the results of random effects meta-analysis on HADS-A mean symptom score



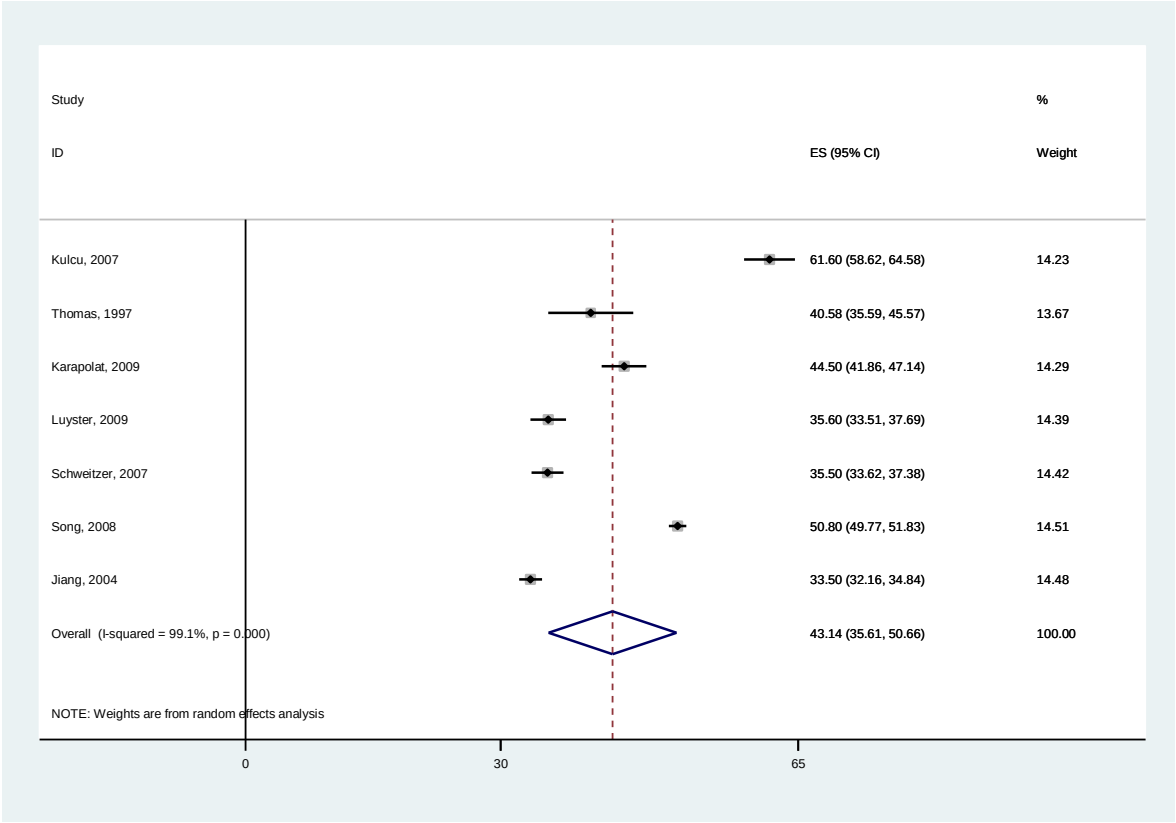
Heterogeneity chi-squared = 888.19 (d.f. = 21) p = 0.000
I-squared (variation in ES attributable to heterogeneity) = 97.6%
Estimate of between-study variance Tau-squared = 4.8497
Test of ES=0: z= 12.86 p = 0.000

A forest plot to show the results of random effects meta-analysis on STAI –S mean anxiety symptom scores



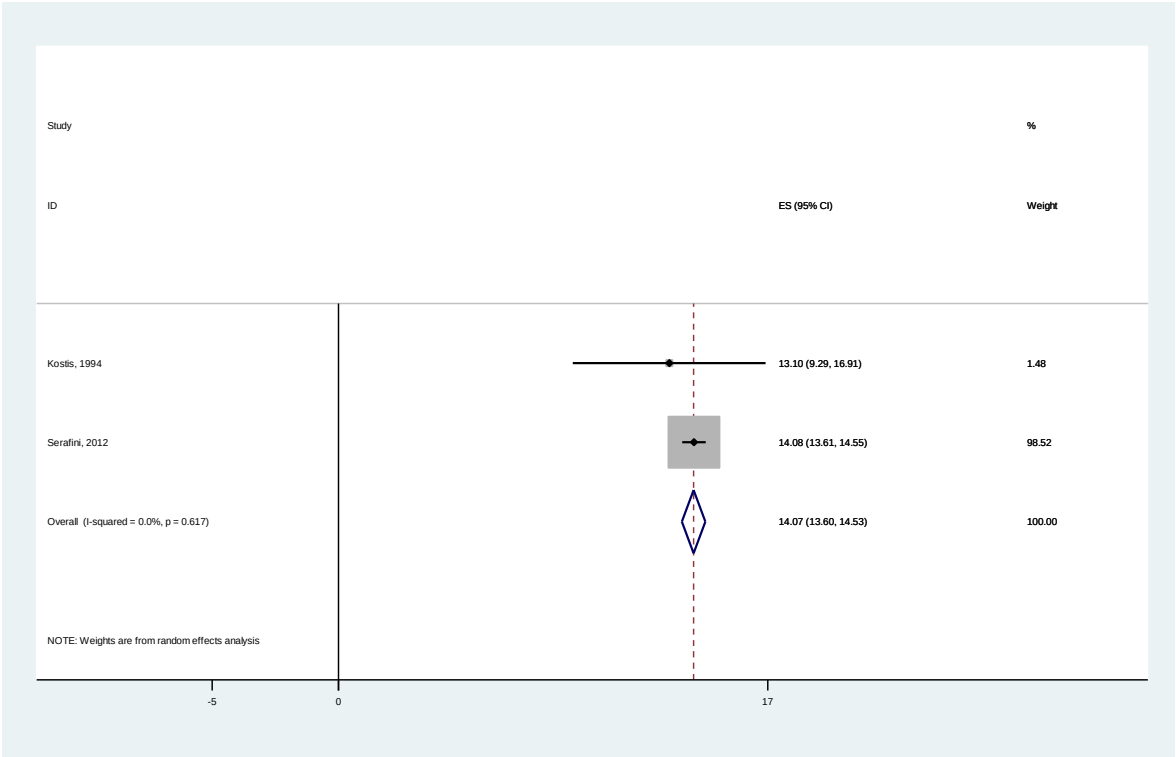
Heterogeneity chi-squared = 5145.52 (d.f. = 7) p = 0.000
I-squared (variation in ES attributable to heterogeneity) = 99.9%
Estimate of between-study variance Tau-squared = 210.0553
Test of ES=0: z= 7.3 p = 0.000

A forest plot to show the results of random effects meta-analysis on STAI-T mean anxiety symptom scores



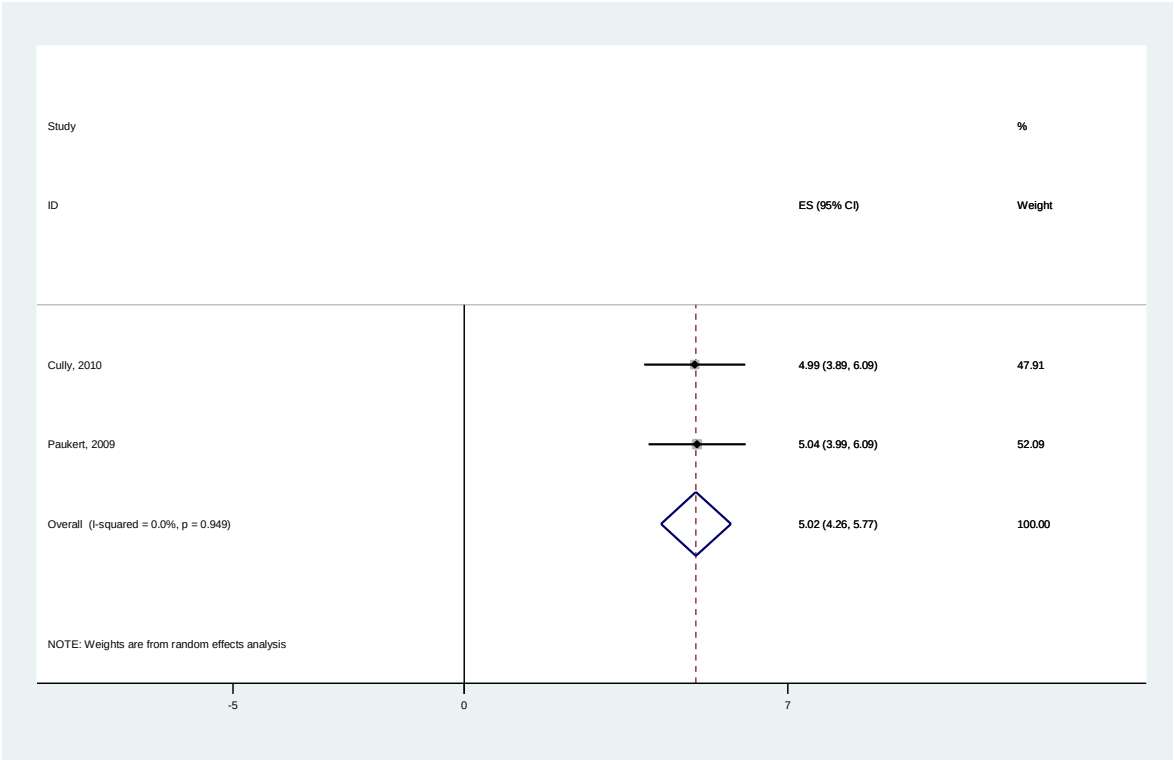
Heterogeneity chi-squared = 670.99 (d.f. = 6) p = 0.000
I-squared (variation in ES attributable to heterogeneity) = 99.1%
Estimate of between-study variance Tau-squared = 101.2919
Test of ES=0: z= 11.24, p = 0.000

A forest plot to show the results of fixed effects meta-analysis on HARS mean anxiety symptoms scores



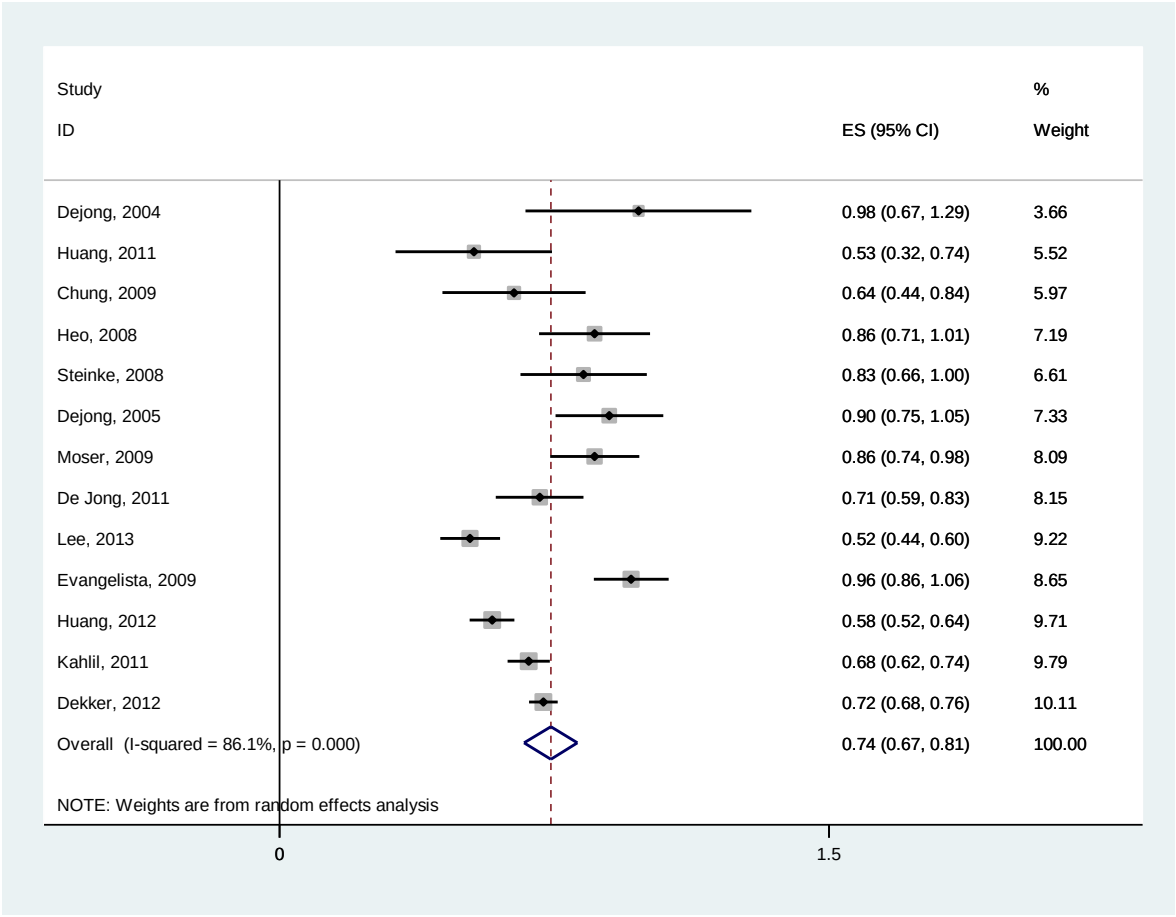
Heterogeneity chi-squared = 0.25 (d.f. = 1) p = 0.617
I-squared (variation in ES attributable to heterogeneity) = 0%
Test of ES=0: z= 59.48 p = 0.000

A forest plot to show the results of fixed effects meta-analysis on GAI mean anxiety symptoms scores



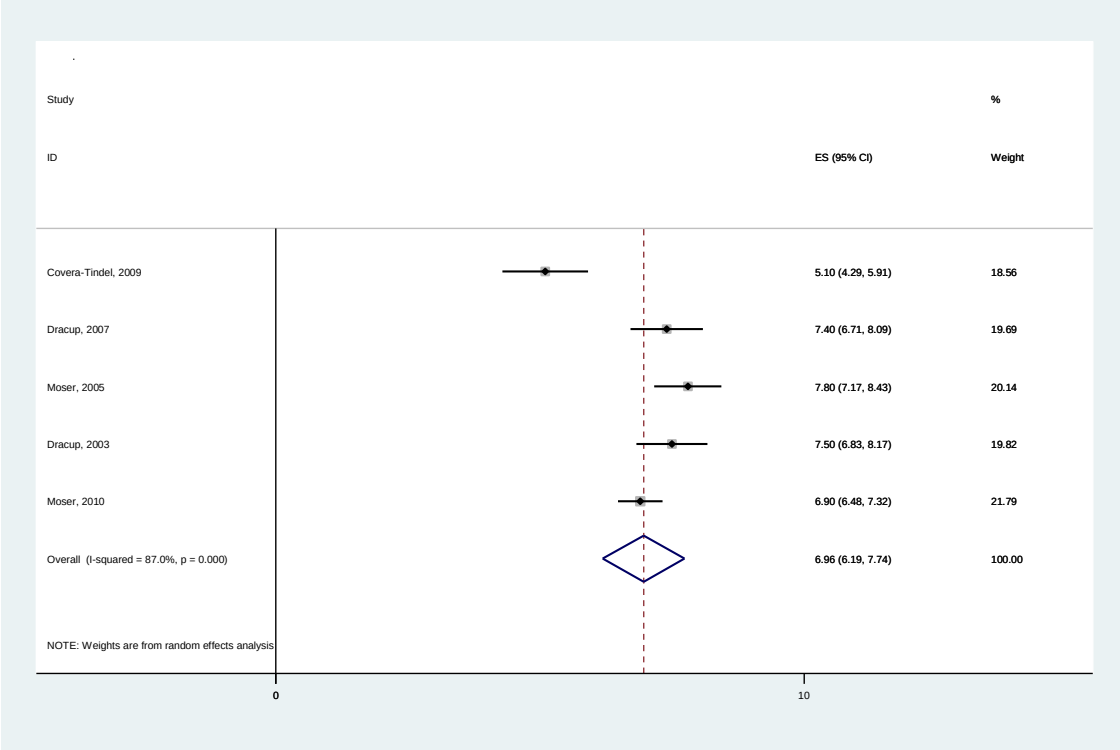
Heterogeneity chi-squared = 0.00 (d.f. = 1) p = 0.949
I-squared (variation in ES attributable to heterogeneity) = 0%
Test of ES=0: z= 12.96 p = 0.000

A forest plot to show the results of fixed effects meta-analysis on BSI –a mean anxiety symptoms scores



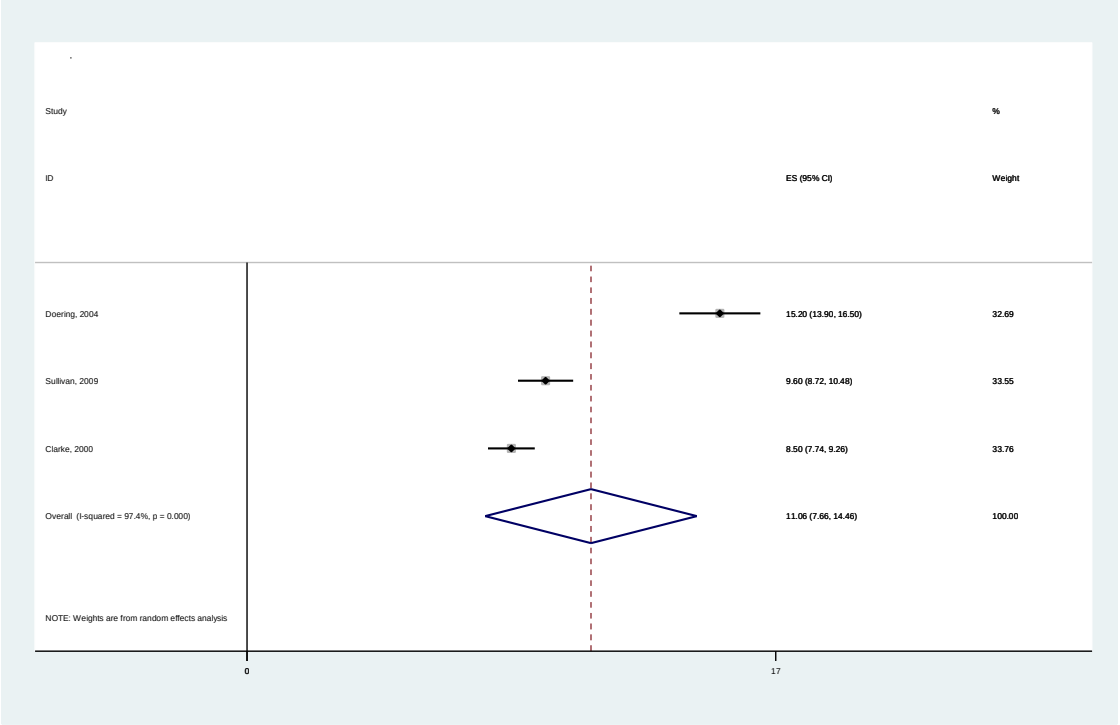
Heterogeneity chi-squared = 86.09 (d.f. = 12) p = 0.000
I-squared (variation in ES attributable to heterogeneity) = 86.1%
Test of ES=0 : z= 19.81 p = 0.000

A forest plot to show the results of random effects meta-analysis on MAACL mean anxiety symptom scores



Heterogeneity chi-squared = 30.87 (d.f. = 4) p = 0.000
I-squared (variation in ES attributable to heterogeneity) = 87.0%
Estimate of between-study variance Tau-squared = 0.6699
Test of ES=0 : z= 17.63 p = 0.000

A forest plot to show the results of random effects meta-analysis on POMS mean anxiety symptom scores



Heterogeneity chi-squared = 77.11 (d.f. = 2) p = 0.000
I-squared (variation in ES attributable to heterogeneity) = 97.4%
Estimate of between-study variance Tau-squared = 8.7848
Test of ES=0: z= 6.37 p = 0.000

Appendix 11 Two factor meta-regression from systematic review

		PrevAllAnx						
		coeff	se	p-value		coeff	se	p-value
Agem		-0.79	0.29	0.009	AnxMes	12.29	5.26	0.026
						38.13	6.23	0.000
Agecat	< 59 yrs versus 60-69	-7.88	5.31	0.148	AnxMes	13.04	6.05	0.039
	< 59 yrs versus 70 +	-7.71	6.63	0.254		39.36	7.06	0.000
Gender	% Male	-0.25	0.18	0.157	AnxMes	11.90	5.80	0.048
						36.85	7.32	0.000
LVEF		0.64	0.51	0.231	AnxMes	17.89	7.87	0.036
						42.85	9.09	0.000
NYHA	Mild vs mod/severe	-15.06	6.98	0.041	AnxMes	18.76	7.35	0.017
	Mild vs Mixed	-6.09	5.44	0.274		47.17	7.69	0.000
Design	RCT vs non-RCT	colin						
	RCT vs Uncontrolled	-9.80	14.16	0.572	AnxMes	13.50	8.06	0.034
	RCT vs Cohort	5.58	9.80	0.574		39.89	7.82	0.000
	RCT vs Case controlled	9.47	12.90	0.469				
	RCT vs Case series	3.97	9.90	0.691				
Setting	Outpatient vs Inpatient	-10.46	9.50	0.280	AnxMes	17.29	6.45	0.012
	Outpatient vs Mixed	-2.83	7.89	0.723		43.31	7.47	0.000
Country	USA vs UK + EU	-11.20	5.48	0.050	AnxMes	17.71	5.89	0.005
	USA vs Asia	-8.30	10.12	0.418		35.54	7.27	0.000
	USA vs Australasia	-6.74	13.51	0.621				
	USA vs Mixed	-12.70	9.99	0.214				
	USA vs Africa	-21.74	13.31	0.113				

Coeff (coefficient); Se error (standard error); P value (probability value); Agem (age mean yrs); Age cat (Age category), LVEF (left ventricular ejection fraction); NYHA (New York Heart Association); Mod (moderate), Anx Meas (Conceptualisation of anxiety), RCT (randomised controlled trial), USA (United states of America), UK (United Kingdom), Eu (Europe)

Appendix 12 Meta regression of anxiety severity by measurement tool

	HADS			STAIs			STAIt			BSI-a			MAACL			POMS		
obs	8-22			6-8 obs			3-7 obs			7-13 obs			4-5 obs			3 obs		
	coeff	se	pval	coeff	se	pval	coeff	se	pval	coeff	se	pval	coeff	se	pval	coeff	se	pval
Agem	-0.13	0.04	0.006	-0.63	0.45	0.209	-0.41	0.54	0.486	0.007	0.01	0.495	-0.08	0.09	0.941	-0.87	0.29	0.203
Agecat	-1.48	1.02	0.162	-10.05	5.97	0.143	-12.92	7.90	0.177	-0.07	0.11	0.528	-1.38	0.91	0.267	[1]		
	-2.78	1.05	0.016	Colin			-17.42	11.13	0.177	0.12	0.19	0.544	0.35	1.11	0.782			
Gender	0.05	0.03	0.135	-0.14	0.14	0.348	0.001	0.35	0.997	0.003	0.005	0.541	-0.05	0.02	0.088	-0.24	0.30	0.569
Setting	1.13	1.70	0.527	[1]			4.05	3.87	0.485	0.12	0.12	0.373	[1]			[1]		
	Colin						2	4.31	0.723	Colin								
LVEF	0.007	0.10	0.943	0.18	0.58	0.771	5.86	3.93	0.377	-0.002	0.01	0.898	-0.17	0.46	0.749	-2.28	2.84	0.569
NYHA	-1.43	2.83	0.623	Colin			Colin			Colin			2.3	0.54	0.147	[1]		
	-0.39	1.53	0.804	-4.05	7.80	0.626	7.11	8.79	0.456	0.02	0.16	0.884	2.56	0.48	0.117			

HADS = hospital Anxiety and Depression Scale; STAI – s = State Trait Anxiety Inventory state scale; STAT – t = State Trait Anxiety Inventory trait scale; BSI-A = Brief Symptom Inventory – anxiety; SCL =r = Symptom Checklist –revised; MAACL = Multiple Affect Adjective Checklist; POMS = Profile of Mood States. Obs (observations), Agem (age mean years), Age cat (age category), LVEF (Left Ventricular Ejection Fraction), NYHA (New York Heart Association).

Appendix 13 Definitions of conditions and interventions featured in the exclusion criteria

Condition or Intervention	Definition
Implantable Cardioverter Defibrillator (ICD)	Invasive procedure that involves implanting leads into the heart and a pacemaker/defibrillator into chest wall. Monitors heart rhythm, senses severe disturbance, paces, and if necessary delivers an electrical shock.
Coronary synchronisation therapy (CRT)	Biventricular pacemaker that synchronises contraction of the left and right ventricles
Coronary artery bypass graft (CABG)	Operation to bypass a narrowed section/s of coronary arteries and improve bloody supply to the heart
Purcutaneous coronary intervention (PCI)	Procedure to widen narrowed coronary arteries. Involves inflation of balloons inside the artery and potentially the placing of stents to maintain the lumen of the artery.

Appendix 14. Patient packs

The University of Manchester

Anxiety symptoms among people with Heart Failure

Dear Sir/Madam,

I am a PhD student in the School of Nursing, Midwifery and Social Work at the University of Manchester. I am interested in identifying factors associated with anxiety symptoms (i.e. worry, tension, fear, chest pains, racing heart) in people with heart failure and discovering whether anxiety affects people's quality of life. The findings from this study will hopefully allow us to identify factors that can be modified to reduce anxiety and improve outcomes for people with heart failure.

Taking part in the study would involve you filling out a set of questionnaires that ask for information on your age, gender, ethnic background, physical symptoms you experience, psychological well-being, social support and quality of life in relation to your heart failure.

I would be grateful if you would consider taking part in this study and I have enclosed an information sheet which will provide you with more details about the study to help you make your decision. You are welcome to contact me to discuss the research – you can find my contact at the bottom of this letter.

If you think you might like to take part I will provide you with a booklet of questionnaires now that can be taken home for you to complete and return in a prepaid addressed envelope that I will also provide you with. I will also ask you for your name and contact telephone number at this time so that I might call you on one occasion in two weeks time if you have not returned your questionnaire to see if you are still interested in taking part. You will not be contacted if you have already returned your booklets. You are under no obligation to complete the questionnaires however and if you later decide you do not wish to participate in the research your contact details will be destroyed and you will not be contacted again in relation to this research.

Thank you for taking the time to read this letter.

Yours faithfully

Katherine Easton
School of Nursing, Midwifery & Social Work
University of Manchester, Jean MacFarlane Building
Oxford Road, Manchester, M13 9PL
Katherine.easton@manchester.ac.uk
0161 306 7890
Mobile number: 07954 309215

Participant Information Sheet

Anxiety symptoms among people with Heart Failure

(Phase 1: questionnaires)

You are being invited to take part in a university research study involving people who attend heart failure clinics. Before you decide whether to take part it is important for you to understand why the research is being done and what it will involve. Please take the time to read this information sheet carefully and feel free to discuss this with friends or family if you wish.

What is the purpose of this study?

This study aims to identify factors that are associated with anxiety symptoms (i.e. worry, tension, fear, chest pains, racing heart) and quality of life in people with heart failure. The study also aims to find out more about people's experiences of living with heart failure. By learning more about the factors that contribute to anxiety and the impact anxiety has on patients' quality of life, we hope to improve the care and treatment of other people who have heart failure.

Why have I been chosen?

You have been chosen as you currently attend a heart failure clinic and your heart failure care team have identified you as a potential candidate for the study. Approximately 176 people who attend specialist clinics for their heart failure care will be studied.

Do I have to take part?

No. It is up to you to decide if you want to take part in the study. If you do wish to participate, you will be given this information sheet to keep and be asked to sign a consent form. You are still free to withdraw at any time during the study without giving a reason. The standard of your care will not be affected if you withdraw from the study, or if you decide not to part.

What will happen to me if I take part?

After your clinic appointment you will be given a pack of information and a questionnaire booklet to take home with you. This pack will contain information sheets for you to read that will tell you about the study. If you decide to take part you will need to sign both consent forms provided and send ONE of the consent forms back along with your completed booklet of questionnaires in the freepost addressed envelope provided. There are six questionnaires to complete, they ask you for your age, gender, ethnic background, about your physical symptoms, the number of times you have been in hospital the past year as a result of your condition, whether you have been feeling anxious or depressed, your quality of life, and social support. They may take about an hour to complete and can be filled in at home in your own time. You will also be asked for your contact details after your clinics appointment. If after two weeks you have not returned your questionnaire booklets and consent form you will be contacted to see whether you would still like to participate. You are under no obligation to participate and can withdraw at any time. If you do not wish to participate or if you decide not to fill in the questionnaires after this phone call your details will be destroyed and I will not contact you again about this research. If you have any questions or problems filling in the questionnaires you can contact the researcher who will be able to help you with this on 0161 306 7890.

What are the possible disadvantages and risks of taking part?

As this study only involves filling out questionnaires and a small number of interviews, there is no disadvantage in taking part. If you feel upset or concerned while completing the questionnaires you can stop and contact the researcher on 0161 306 7890.

What are the possible benefits of taking part?

We can not promise that the study will help you but the information we get from the study might help improve the care and treatment of other people like you with heart failure. In addition participants who score over 12 on the psychological assessment measure (HADS) will be referred to their GP, which may lead to a follow up and further assessment of your mental health needs.

What happens when the research study stops?

When the study is complete you will receive a summary of the results.

What if there is a problem?

If you have any concerns about any part of the study, you should ask to speak with the researcher who will do her best to answer your questions. You can contact Katherine Easton on 0161 306 7890. If they are unable to resolve your concern or you wish to make a complaint regarding the study, please contact a University Research Practice and Governance Co-ordinator on 0161 2757583 or 0161 2758093 or by email to research-governance@manchester.ac.uk.

Will my taking part in the study be kept confidential?

All information collected about you during the course of the study will be kept strictly confidential and stored in secure premises at the University. Any information about you that leaves the hospital will have your name and address removed so that you cannot be recognised from it. All information related to the study will be kept for 10 years and then confidentially destroyed.

Who is organising and funding the research?

This study is funded by a Medical Research Council (MRC) and Economics and Social Research Council (ESRC) interdisciplinary award. The MRC is based at 20 Park Crescent, London, W1B 1AL. Telephone: +44 (0)20 7636 5422.

Who has reviewed this study?

This study was given a favourable ethical opinion for conduct in the NHS by Northwest 11 Research Ethics Committee - Preston.

Contact details

The researcher for this study is Miss Katherine Easton who is based at the School of Nursing, Midwifery & Social Work at the University of Manchester. If you have any questions about this study please contact Miss Easton on: 0161 306 7890 OR 07954 309215

Thank you for taking the time to read this information sheet.

Participant Identification Number: 350

CONSENT FORM

Anxiety symptoms among people with Heart Failure (Phase 1: questionnaires)

Name of Researcher: Katherine Easton

Please initial box

1. I confirm that I have read and understand the information sheet dated 05/05/2010 (Version 3) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected ☐

3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the University of Manchester, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I give my permission for my GP to be informed if my scores on the psychological assessment measure (HADS) are high. ☐

5. I agree to take part in the above study. ☐

_____	_____	_____
Name of Patient	Date	Signature
Katherine Easton	9/09/2010	**K. Easton**
Researcher		

Participant booklet

Booklet containing self-completion questionnaires for participants taking part in the research study:

Anxiety symptoms among people with Heart Failure

We would be grateful if you could give us some information about yourself

All information will be kept confidential and your name will not be used in any way. Please circle the responses most relevant to you, or write you response in the spaces provided.

Age ……

Gender Male Female

Ethnic background

White British
White Irish
White other

Mixed – White and Black African
Mixed – White and Black Caribbean
Mixed – White and Asian
Mixed – Other background

Black or Black British – African
Black or Black British –Caribbean
Other Black background

Chinese

Asian or Asian British – Pakistani
Asian or Asian British –Bangladeshi
Other Asian Background

Other ethnic Background
Not known
Not specified

How many times in the past year have you been admitted to hospital as a result of your heart failure?.....

Thank you for answering these questions

Physical Symptom Incidence and Distress Scale

Instructions: Please describe how much you have been BOTHERED within the PAST WEEK by each of the following symptoms by circling the number which best describes your experience.

		Not at all	A little	Moderately	A lot
1.	Feeling hot all over	0	1	2	3
2.	Sweating all over	0	1	2	3
3.	Dizziness	0	1	2	3
4.	Blurring of vision	0	1	2	3
5.	Heart beating louder	0	1	2	3
6.	Feeling faint or tired	0	1	2	3
7.	Nausea	0	1	2	3
8.	Heart rate increasing	0	1	2	3
9.	Chest pain or discomfort	0	1	2	3
10.	Churning in stomach	0	1	2	3
11.	Pain or discomfort other than in chest	0	1	2	3
12.	Difficulty breathing	0	1	2	3
13.	Mouth becoming dry	0	1	2	3
14.	Diarrhoea	0	1	2	3
15.	Constipation	0	1	2	3
16.	Legs feeling weak	0	1	2	3
17.	Heart misses beats	0	1	2	3
18.	Pulses in neck	0	1	2	3
19.	Muscles twitching and jumping	0	1	2	3
20.	Tense feeling in neck or jaw	0	1	2	3

21.	Swelling in ankles	0	1	2	3

Thank you for answering these questions

Hospital Anxiety and Depression Scale (HADS)

GL assessment
the measure of potential

Name: _____ Date: _____

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more.

This questionnaire is designed to help your clinician to know how you feel. Read each item below and **underline the reply** which comes closest to how you have been feeling in the past week. Ignore the numbers printed at the edge of the questionnaire.

Don't take too long over your replies, your immediate reaction to each item will probably be more accurate than a long, thought-out response.

FOLD HERE

FOLD HERE

A	D			A	D
		I feel tense or 'wound up'	**I feel as if I am slowed down**		
3		Most of the time	Nearly all the time		3
2		A lot of the time	Very often		2
1		From time to time, occasionally	Sometimes		1
0		Not at all	Not at all		0
		I still enjoy the things I used to enjoy	**I get a sort of frightened feeling like 'butterflies' in the stomach**		
	0	Definitely as much	Not at all	0	
	1	Not quite so much	Occasionally	1	
	2	Only a little	Quite often	2	
	3	Hardly at all	Very often	3	
		I get a sort of frightened feeling as if something awful is about to happen	**I have lost interest in my appearance**		
3		Very definitely and quite badly	Definitely		3
2		Yes, but not too badly	I don't take as much care as I should		2
1		A little, but it doesn't worry me	I may not take quite as much care		1
0		Not at all	I take just as much care as ever		0
		I can laugh and see the funny side of things	**I feel restless as if I have to be on the move**		
	0	As much as I always could	Very much indeed	3	
	1	Not quite so much now	Quite a lot	2	
	2	Definitely not so much now	Not very much	1	
	3	Not at all	Not at all	0	
		Worrying thoughts go through my mind			
3		A great deal of the time	**I look forward with enjoyment to things**		
2		A lot of the time	As much as I ever did		0
1		Not too often	Rather less than I used to		1
0		Very little	Definitely less than I used to		2
		I feel cheerful	Hardly at all		3
	3	Never	**I get sudden feelings of panic**		
	2	Not often	Very often indeed	3	
	1	Sometimes	Quite often	2	
	0	Most of the time	Not very often	1	
		I can sit at ease and feel relaxed	Not at all	0	
0		Definitely	**I can enjoy a good book or radio or television programme**		
1		Usually	Often		0
2		Not often	Sometimes		1
3		Not at all	Not often		2
			Very seldom		3

Now check that you have answered all the questions

A	D

TOTAL

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SF-12v2™ Health Survey

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Answer every question by selecting the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

---

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
○	○	○	○	○

---

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

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a <u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○	○	○
b Climbing <u>several</u> flights of stairs	○	○	○

---

3. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?

All of the time	Most of the time	Some of the time	A little of the time	None of the time

a	Accomplished less than you would like	○	○	○	○	○
b	Were limited in the kind of work or other activities	○	○	○	○	○

---

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

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Accomplished less than you would like	○	○	○	○	○
b Did work or activities less carefully than usual	○	○	○	○	○

---

5. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
○	○	○	○	○

---

6. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time

a	Have you felt calm and peaceful?	○	○	○	○	○
b	Did you have a lot of energy?	○	○	○	○	○
c	Have you felt downhearted and depressed?	○	○	○	○	○

---

7. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
○	○	○	○	○

Thank you for completing these questions!

ENRICHD Social Support questionnaire

Please circle your answer:

1	**Is there someone available to whom you can count on to listen to when you need to talk?**				
	None of the time	A little of the time	Some of the time	Most of the time	All of the time
2	**Is there someone available to give you good advice about a problem?**				
	None of the time	A little of the time	Some of the time	Most of the time	All of the time
3	**Is there someone available who shows you love and affection?**				
	None of the time	A little of the time	Some of the time	Most of the time	All of the time
4	**Is there someone to help with daily chores?**				
	None of the time	A little of the time	Some of the time	Most of the time	All of the time
5	**Can you count on anyone to provide you with emotional support (talking over problems or helping you make a difficult decision)?**				
	None of the time	A little of the time	Some of the time	Most of the time	All of the time
6	**Do you have as much contact as you would like with someone you feel close to, someone in whom you can trust and confide in?**				
	None of the time	A little of the time	Some of the time	Most of the time	All of the time

7 Are you currently married or living with a partner?

Yes No

Thank you for taking the time to answer these questions

Cardiomyopathy Questionnaire (Kansas City)

The following questions refer to your **heart failure** and how it may affect your life. Please read and complete the following questions. There are no right or wrong answers. Please mark the answer that best applies to you.

1. **Heart failure** affects different people in different ways. Some may mainly feel shortness of breath while others mainly fatigue. Please indicate how limited you have been by **heart failure** (for example, shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

Please put an X in one box on each line

Activity	**Extremely** limited	**Quite a bit** limited	**Moderately** limited	**Slightly** limited	**Not at all** limited	**Limited for other reasons or did not do the activity**
Dressing yourself	☐	☐	☐	☐	☐	☐
Showering or having a bath	☐	☐	☐	☐	☐	☐
Walking 100 yards on level ground	☐	☐	☐	☐	☐	☐
Doing gardening, housework or carrying groceries	☐	☐	☐	☐	☐	☐
Climbing a flight of stairs without stopping	☐	☐	☐	☐	☐	☐
Jogging or hurrying (as if to catch a bus)	☐	☐	☐	☐	☐	☐

2. Compared with 2 weeks ago, have your symptoms of **heart failure** (for example, shortness of breath, fatigue, or ankle swelling) changed?

My symptoms of **heart failure** are now...

Much worse	Slightly worse	Not changed	Slightly better	Much better	I've had no symptoms over the last 2 weeks
☐	☐	☐	☐	☐	☐

KCCQ - UK/English

3. Over the past 2 weeks, how many times have you had **swelling** in your feet, ankles or legs when you woke up in the morning?

Every morning	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐

4. Over the past 2 weeks, how much has **swelling** in your feet, ankles or legs bothered you?

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no swelling**
☐	☐	☐	☐	☐	☐

5. Over the past 2 weeks, on average, how many times has **fatigue** limited your ability to do what you wanted?

All of the time	Several times a day	At least once a day	3 or more times a week but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐	☐	☐

6. Over the past 2 weeks, how much has your **fatigue** bothered you?

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no fatigue**
☐	☐	☐	☐	☐	☐

7. Over the past 2 weeks, on average, how many times has **shortness of breath** limited your ability to do what you wanted?

All of the time	Several times a day	At least once a day	3 or more times a week but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐	☐	☐

8. Over the past 2 weeks, how much has your **shortness of breath** bothered you?

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no shortness of breath**
☐	☐	☐	☐	☐	☐

9. Over the past 2 weeks, on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of **shortness of breath**?

Every night	3 or more times a week, but not every night	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐

10. **Heart failure** symptoms can worsen for a number of reasons. How sure are you that you know what to do, or whom to call, if your **heart failure** gets worse?

Not at all sure	**Not very** sure	**Somewhat** sure	**Mostly** sure	**Completely** sure
☐	☐	☐	☐	☐

11. How well do you understand what things you are able to do to keep your **heart failure** symptoms from getting worse (for example, regularly weighing yourself, eating a low salt diet etc.)?

Do not understand at all	Do not understand very well	Somewhat understand	Mostly understand	Completely understand
☐	☐	☐	☐	☐

12. Over the past 2 weeks, how much has your **heart failure** limited your enjoyment of life?

It has **extremely** limited my enjoyment of life	It has limited my enjoyment of life **quite a bit**	It has **moderately** limited my enjoyment of life	It has **slightly** limited my enjoyment of life	It has **not limited** my enjoyment of life at all
☐	☐	☐	☐	☐

13. If you had to spend the rest of your life with your **heart failure** the way it is right now, how would you feel about this?

Completely dissatisfied	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

14. Over the past 2 weeks, how often have you felt discouraged or down in the dumps because of your **heart failure**?

I have felt that way **all of the time**	I have felt that way **most of the time**	I have **occasionally** felt that way	I have **rarely** felt that way	I have **never** felt that way
☐	☐	☐	☐	☐

15. How much does your **heart failure** affect your lifestyle? Please indicate how your **heart failure** may have limited your participation in the following activities over the past 2 weeks.

Please put an **X** in one box on each line

Activity	**Extremely** limited	**Quite a bit** limited	**Moderately** limited	**Slightly** limited	**Not at all** limited	**Limited for other reasons or did not do the activity**
Hobbies, recreational activities	☐	☐	☐	☐	☐	☐
Working or doing household chores	☐	☐	☐	☐	☐	☐
Visiting family or friends	☐	☐	☐	☐	☐	☐
Intimate or sexual relationships	☐	☐	☐	☐	☐	☐

Appendix 15 Protocol for distressed participants

If the participant becomes distressed:

1. No pressure should be placed on participants to complete the research if they become distressed. In this circumstance, pick up all the information that you can about their current mental state and make notes on this.

2. A lack of affect as well as nihilistic ideas and existential angst are all signs of severe depression in addition to negativity.

3. Other problems to look out for are hopelessness and strange behaviour (grandiosity, loss of sleep, risk-taking, formal thought disorder, hostility & aggression).

If, during the research process, the person is telling you that they are very unhappy, make reassuring and sympathetic noises all the way through.

At an appropriate point, say something like:
"I've noticed that you seem to be quite unhappy with things at the moment, and I'm a little worried about you. We would be really pleased it you felt able to continue with the research, but the last thing I want to do is make you do something you don't feel up to. Do you think you might like to keep going with the research?"

Talk with the participant to see how they feel about it, and if they want to tell you more, and then listen.

If the person sounds very distressed, ask:

"It is clear that you are extremely unhappy at the moment. Is this the worst you've ever felt? Can you imagine this feeling going away, and you getting back to your normal happy self?"

Asking about hopelessness and self-harm:
Hopelessness:

"Do you think the way you feel now is a temporary thing? Can you imagine it getting better in the future?"

"Can you think of a reason for why you are feeling this bad? I there anything you can think of that you could do to make yourself feel better?"

"How do you see yourself in a year's time? Is there anything in life that you could look forward to?"

Hopelessness is the most important risk factor for self-harm/suicide – be vigilant.

"When people feel as distressed as you seem to, they sometimes try to hurt themselves, or even worse. I am so worried about you that I must ask you whether you have ever thought about, or ever actually harmed yourself, for example by cutting your arms?"

a) If they say it has entered their mind, but they would never do it, it's probably safe.
b) Ask "Have you gone as far as to think about how you might do it? Did you ever devise a plan to hurt or even kill yourself?"
c) Ask "Have you told anybody about how you feel? Your friends or family? I know it can be very difficult to explain to people close to you how you are really feeling – would you like me to tell somebody for you?"
d) Ask about impediments: "Is there anything that's stopping you from actually carrying out the actions? Who would be upset? How do you think your parents would react?" "Do you have religious beliefs?"
e) Ask "Have you ever sought any help for the way you feel? Who from?" If not, offer to find help via their GP or the student counselling service.

Risk Assessment:

If the person is mildly dysphoric, ask them if they feel up to continuing with the study. Explain that their participation is particularly valued, and they would be making a wonderful contribution

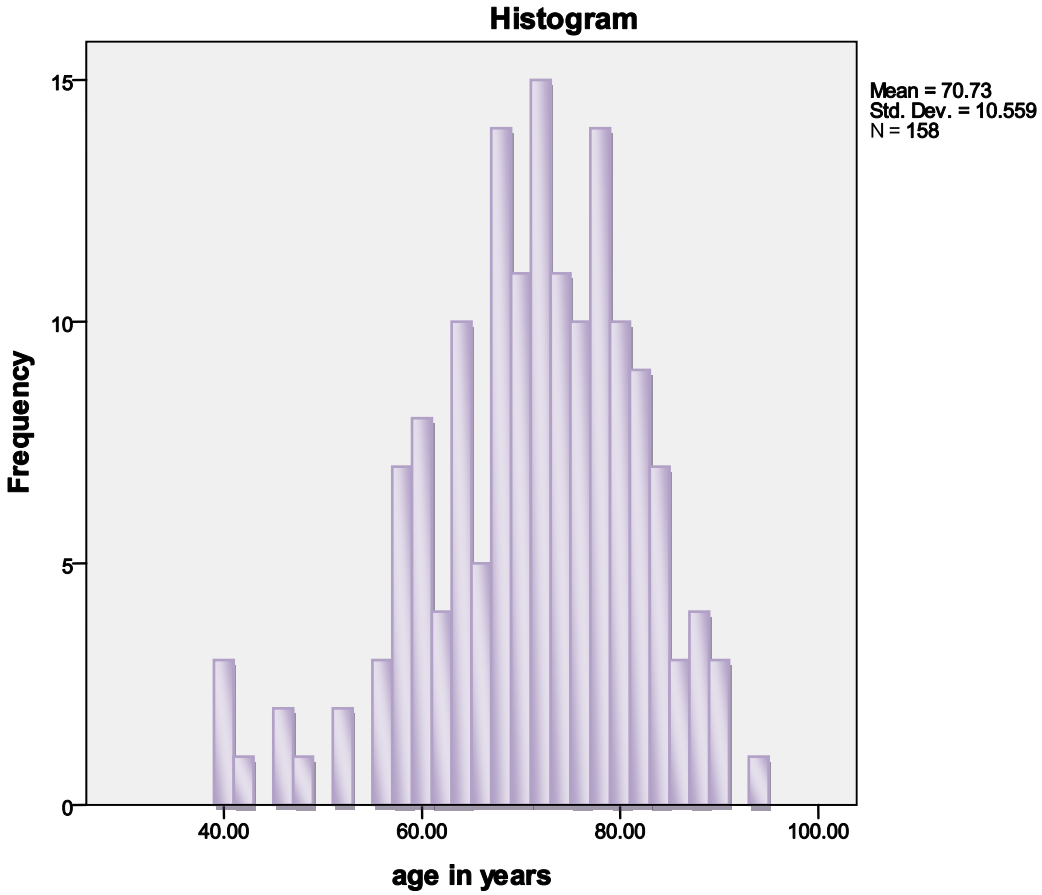
If the person is clearly heading for a severe mood episode, ask them if they have seen a doctor, psychologist, or a counsellor. Offer to contact their GP, or a student counselling service for them.

If the person is dysphoric but not presenting any obvious danger to themselves also check whether they are getting any help. If not, offer to point them in the right direction.

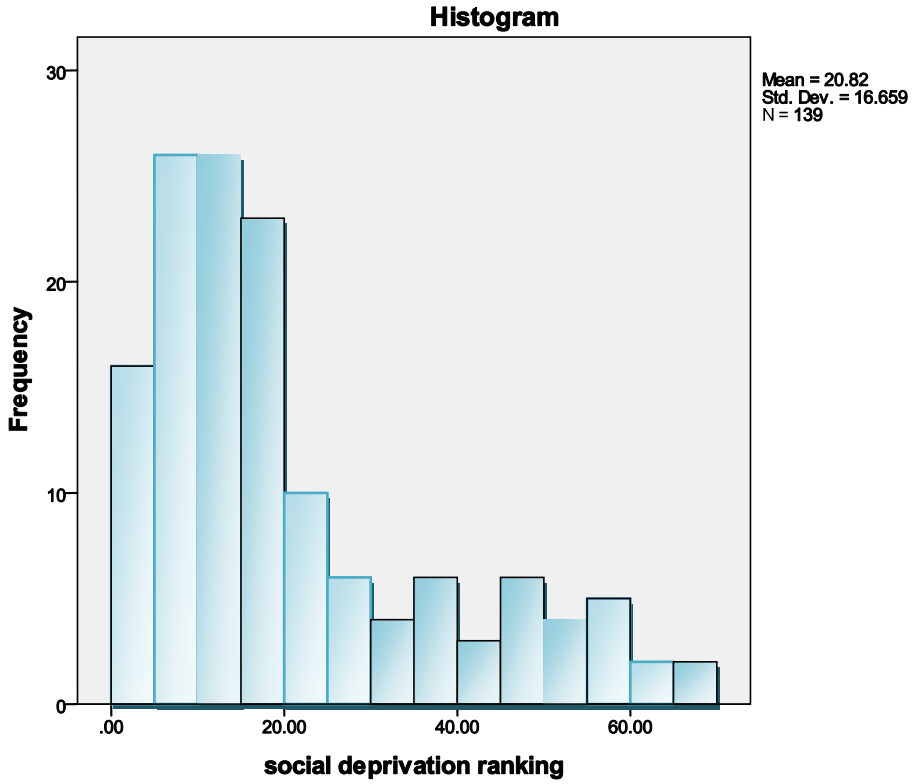
If you think there is a real danger of self-harm/suicide contact immediately and say "I am so worried about you that I would like to contact one of my colleagues who you could talk to about your worries if that would help.

Appendix 16. Histograms to show distribution of data

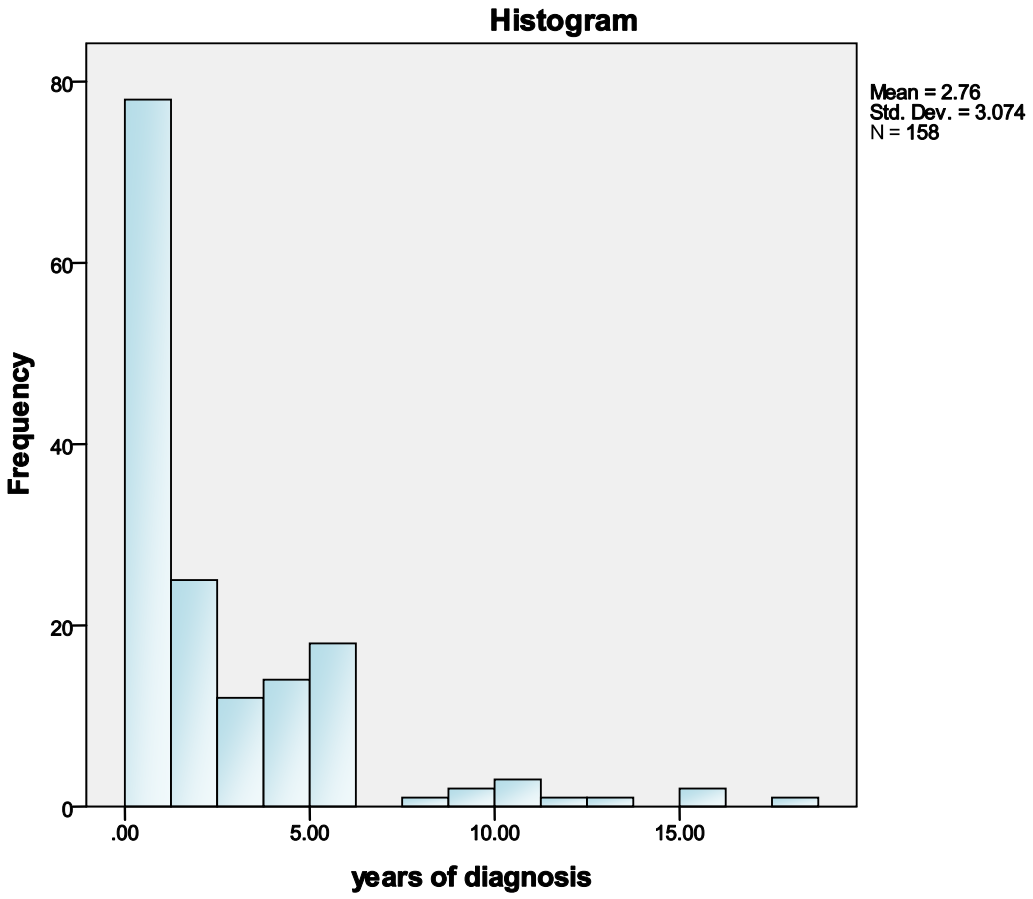
Histogram to show the distribution of age data



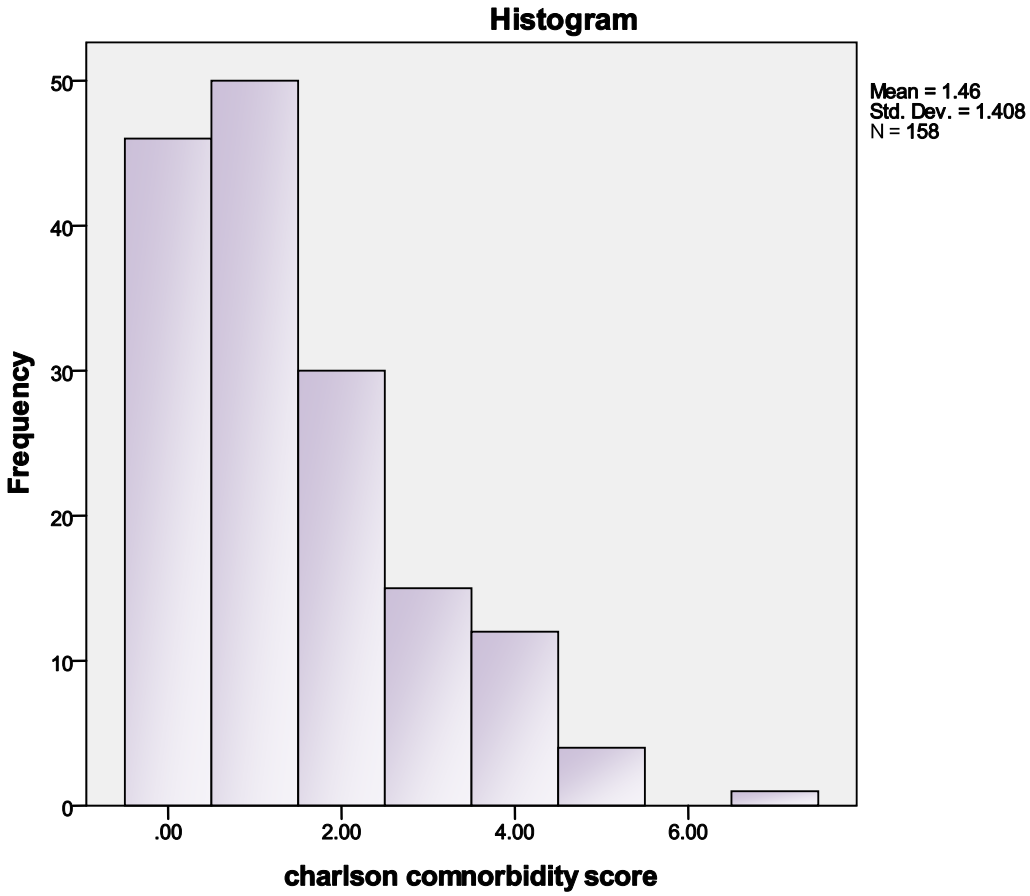
Histogram to show the distribution of social deprivation score data



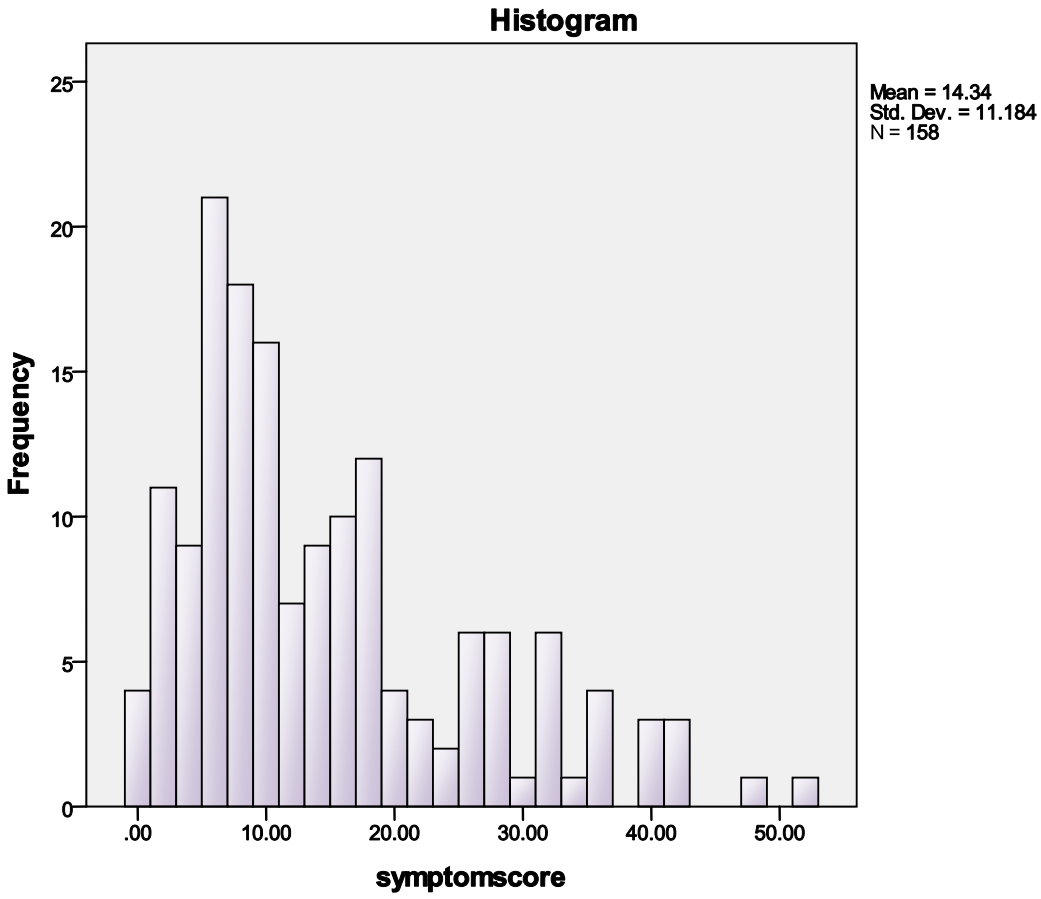
Histogram to show the distribution of years since diagnosis data



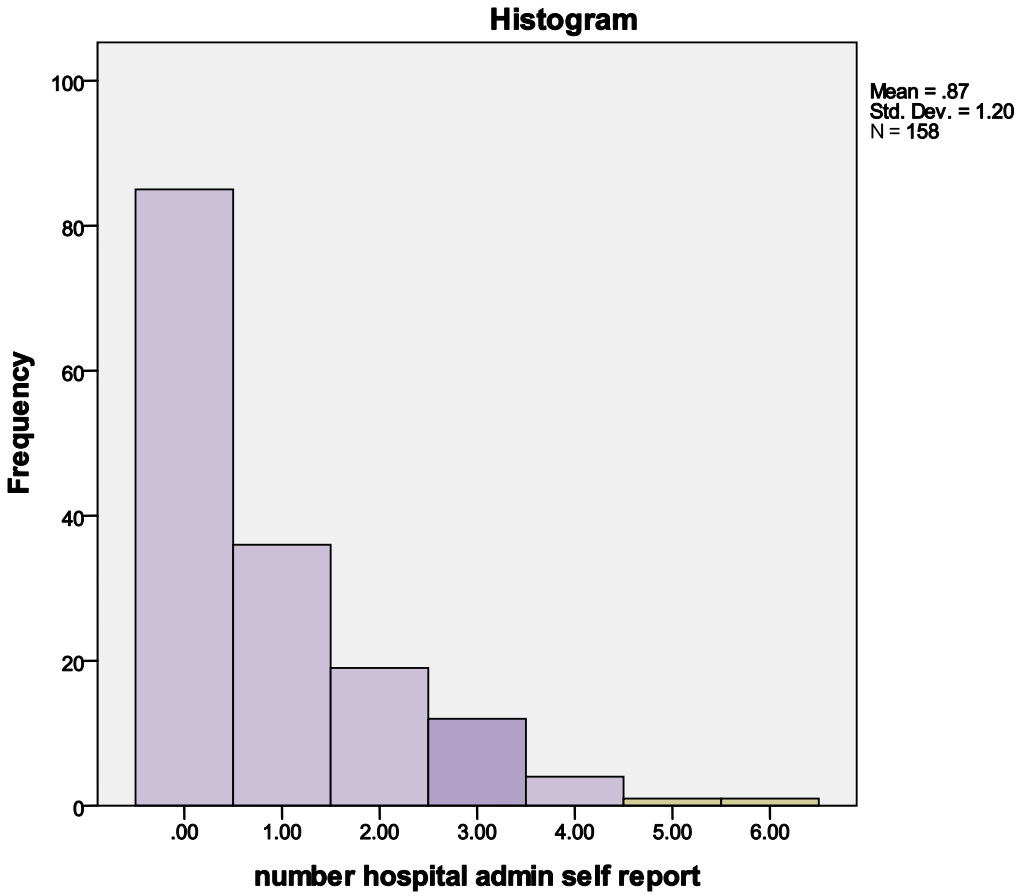
Histogram to show the distribution of co- morbidity score data



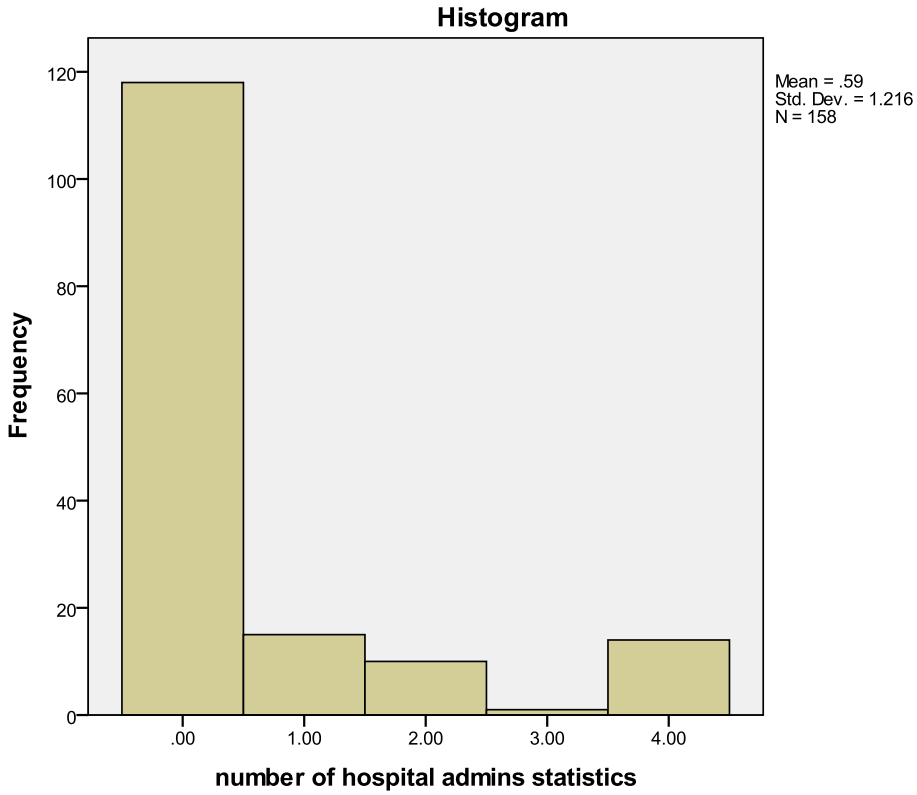
Histogram to show the distribution of physical symptom score data



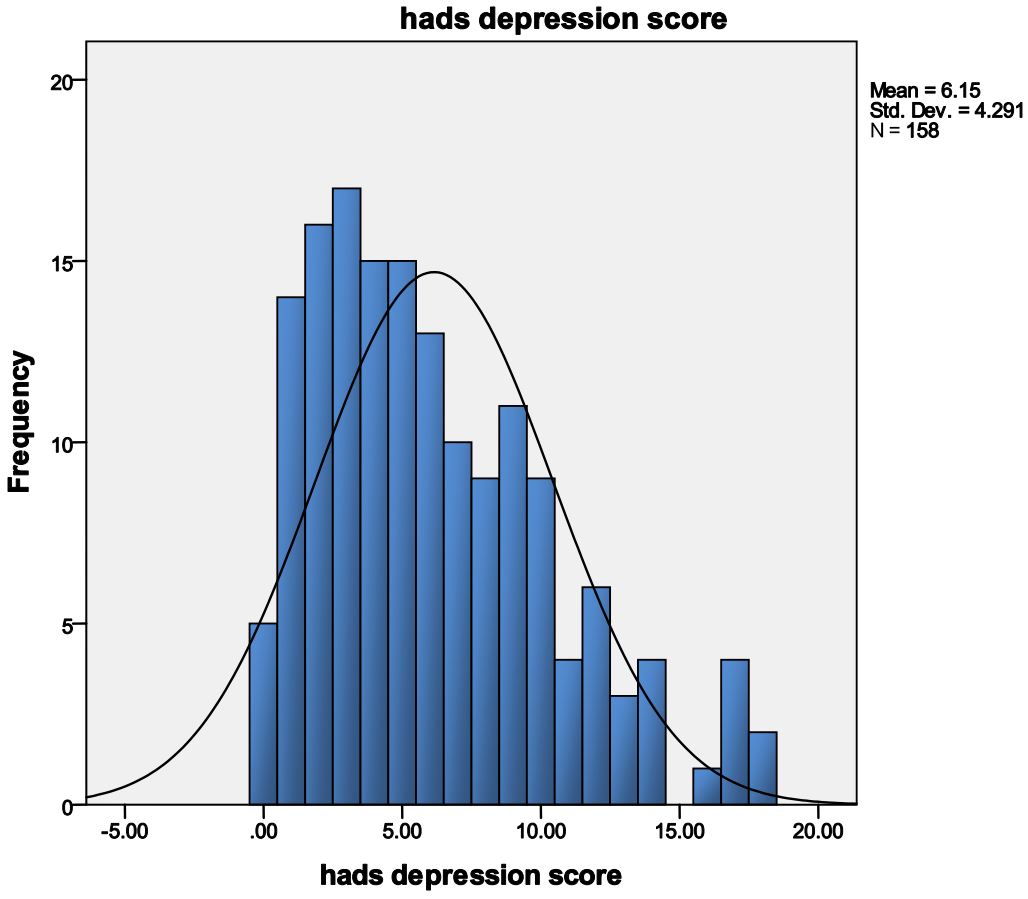
Histogram to show the distribution of self-report hospital admission data



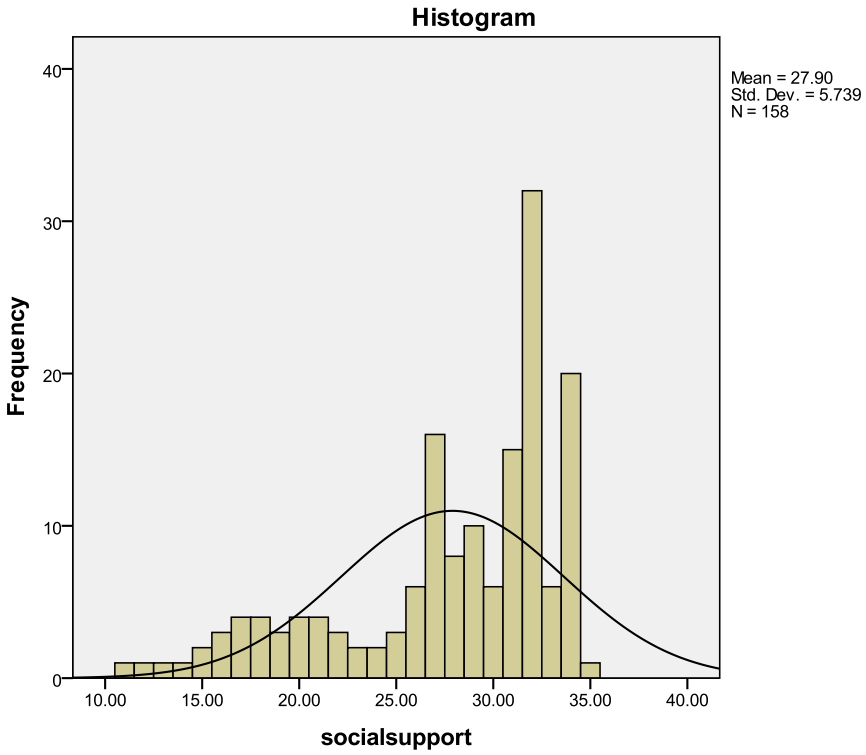
Histogram to show the distribution on hospital recorded admission



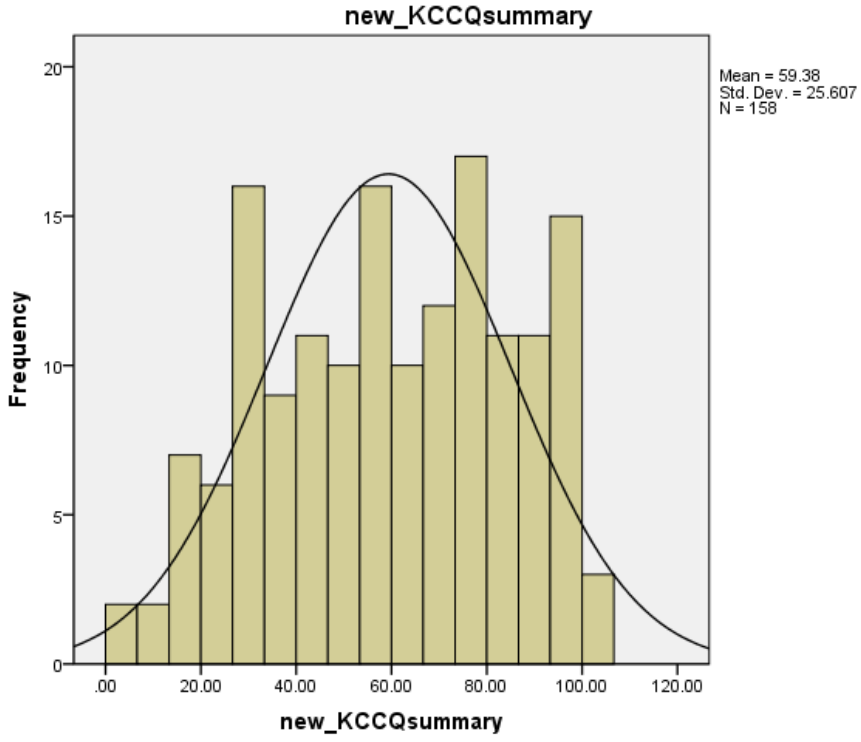
Histogram to show the distribution of HADS depression scores



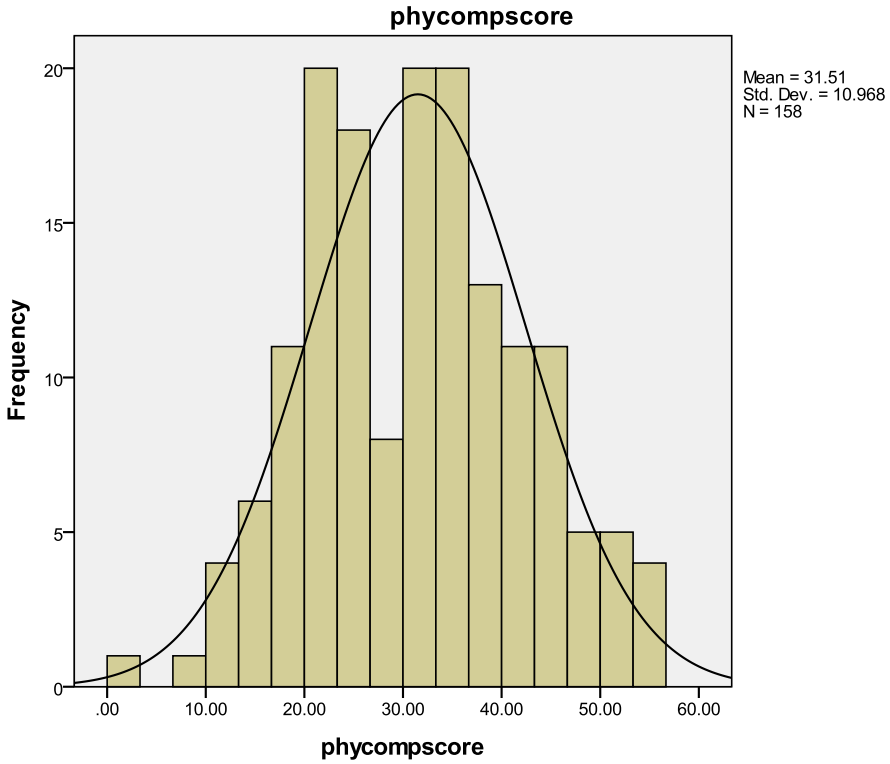
Histogram to show the distribution of perceived social support



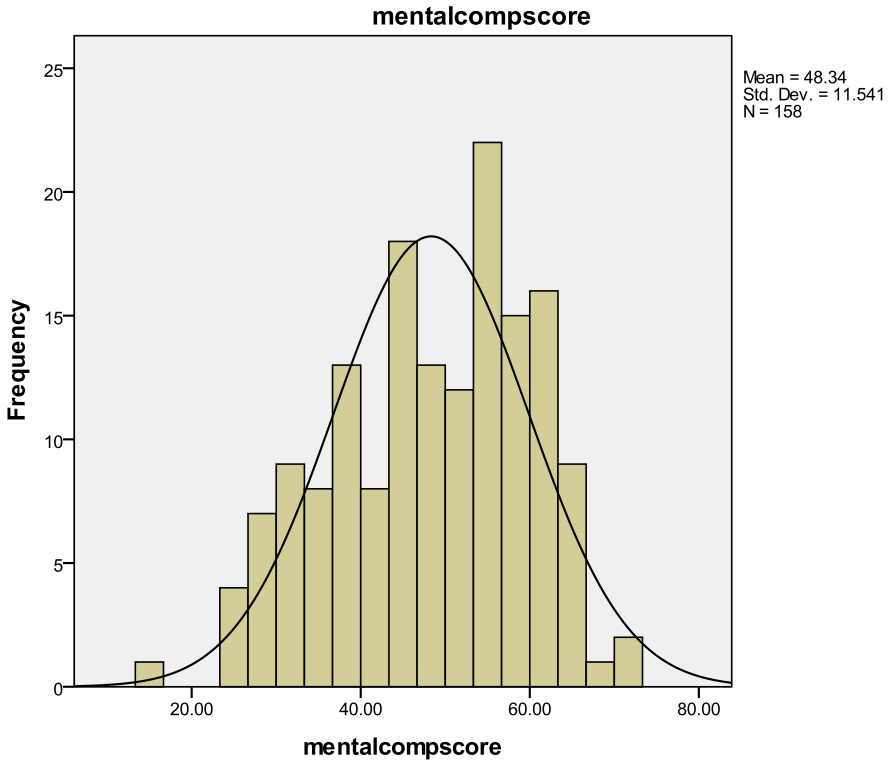
Histogram to show the distribution of KCCQ Summary scores



Histogram to show the distribution of SF12 PCS

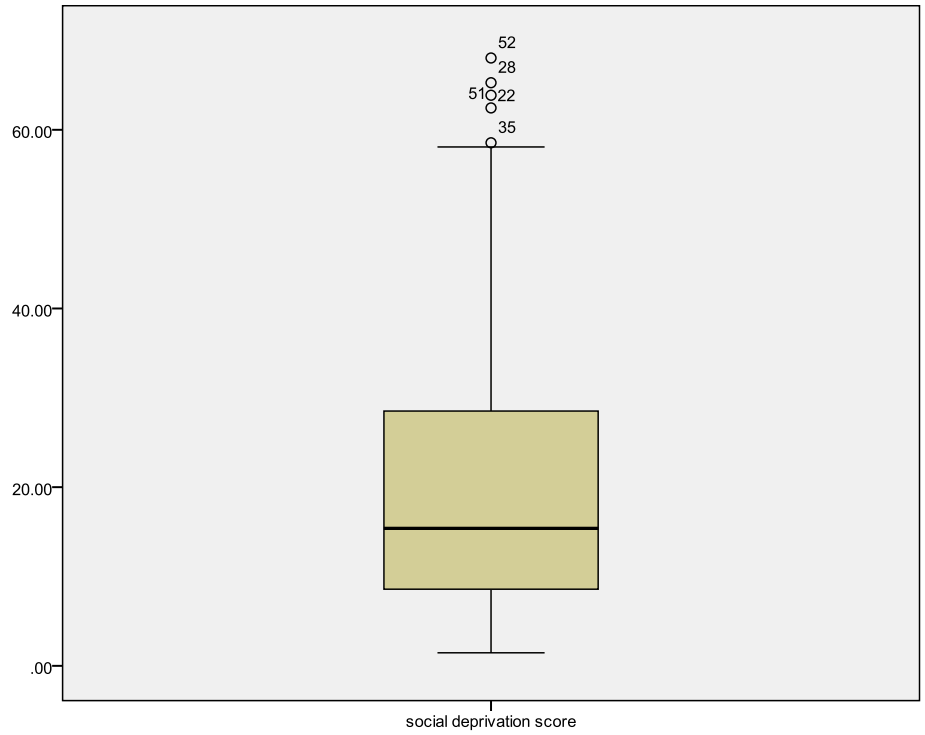


Histogram to show the distribution of SF12 MCS

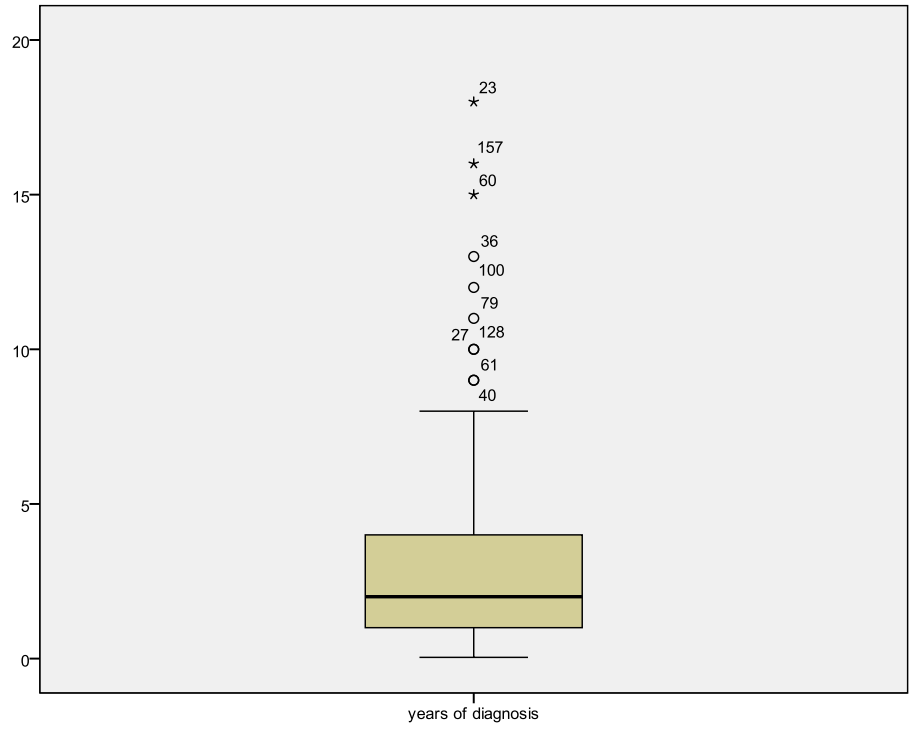


Appendix 16 Box plots to show outliers in data

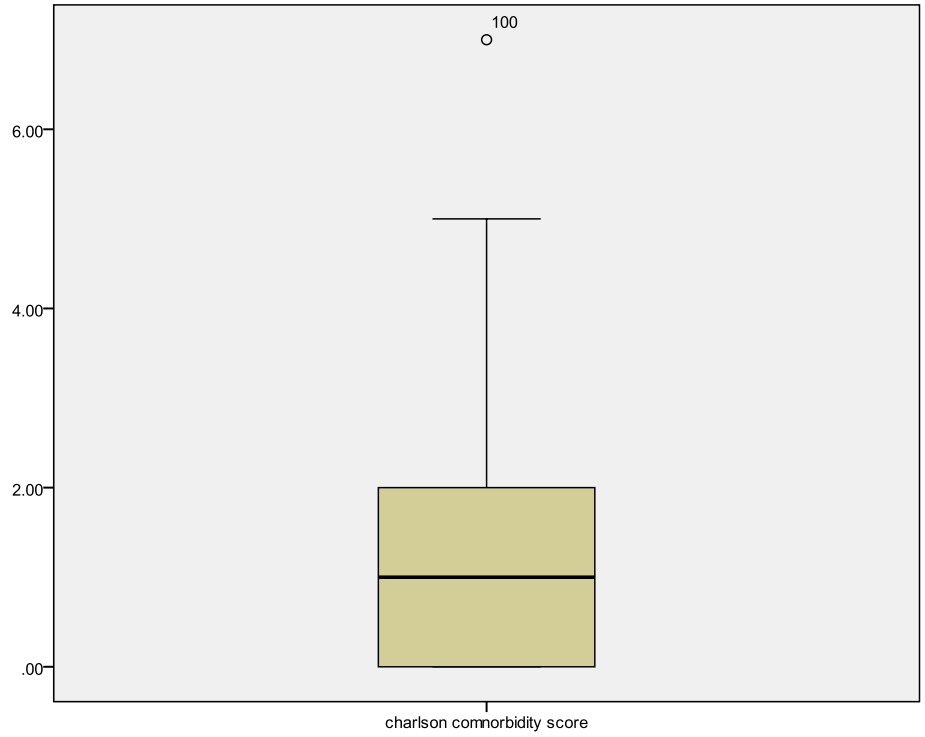
Box plot to identify outliers in social deprivation data



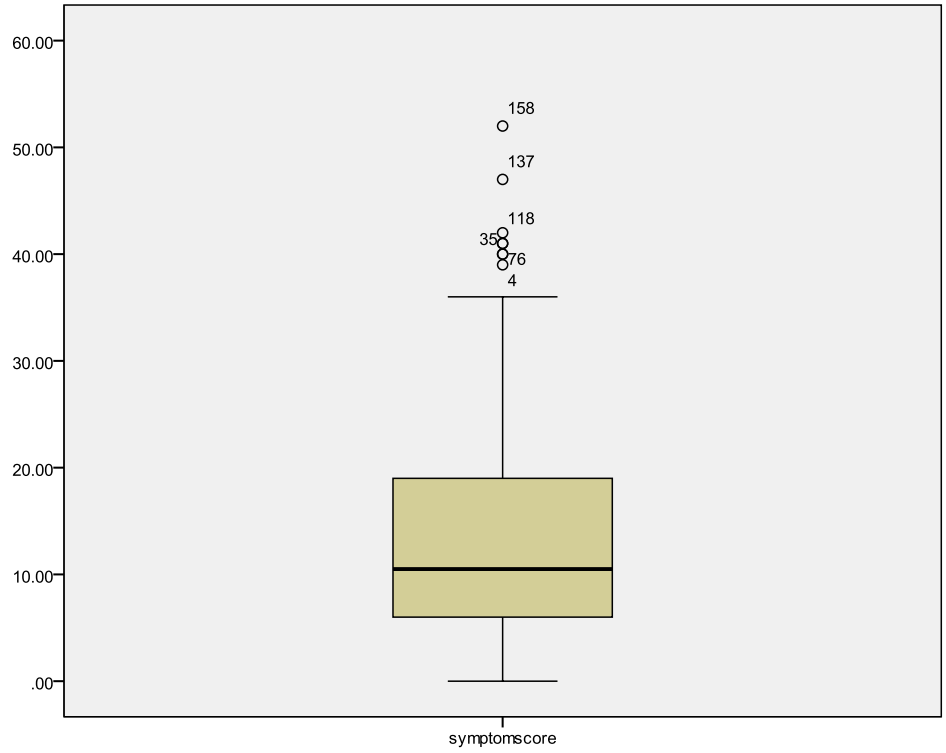
Box plot to show outliers in yrs of diagnosis data



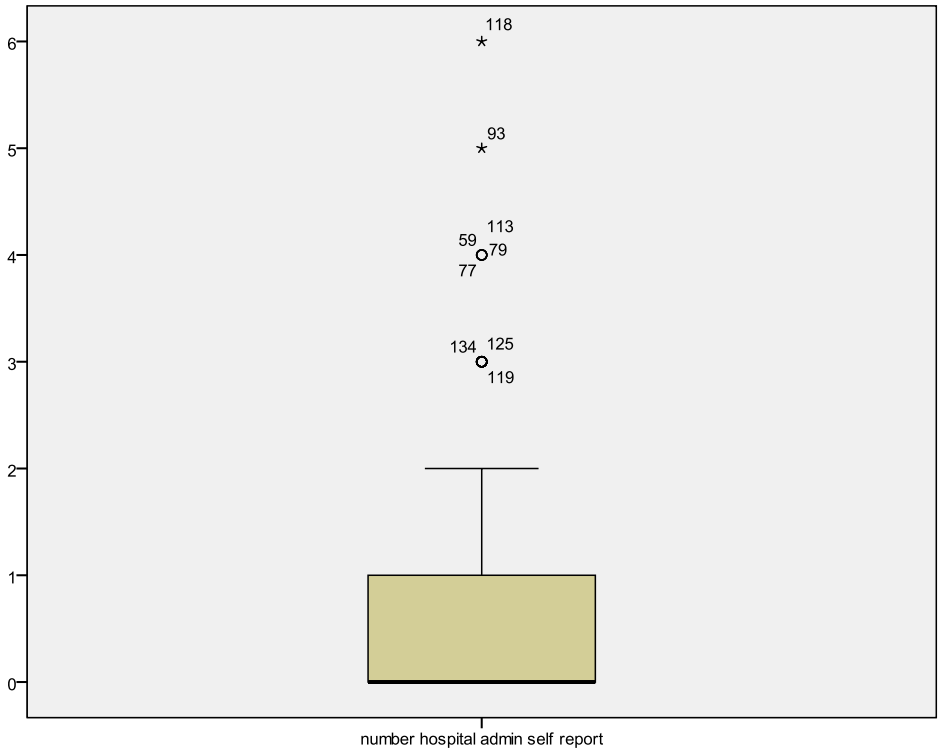
Box plot to show outliers in co-morbidity data



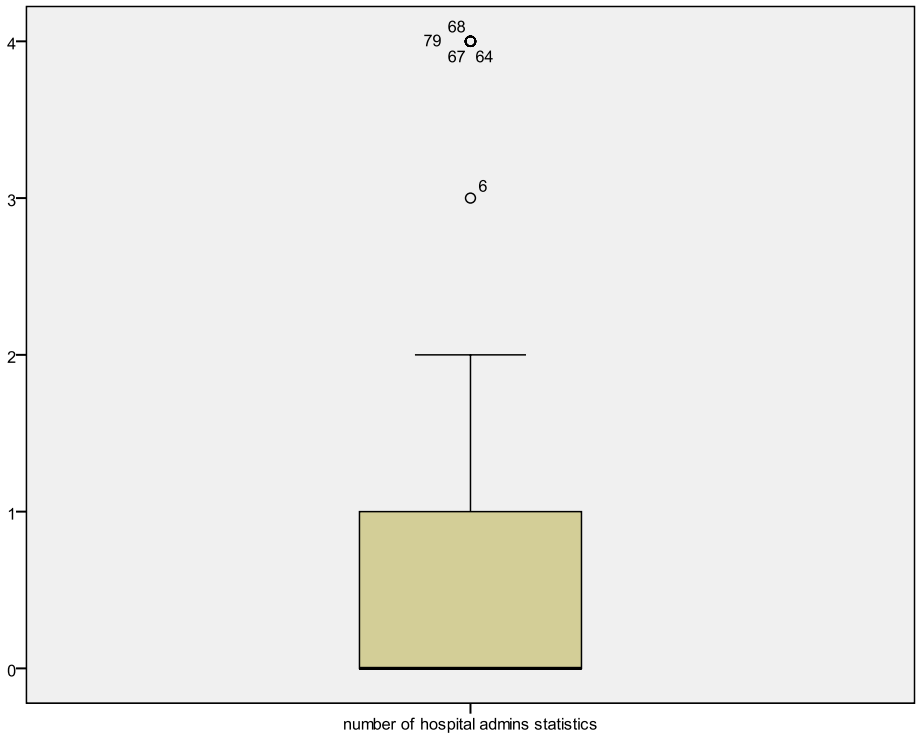
Box plot to identify outliers in physical symptom score data



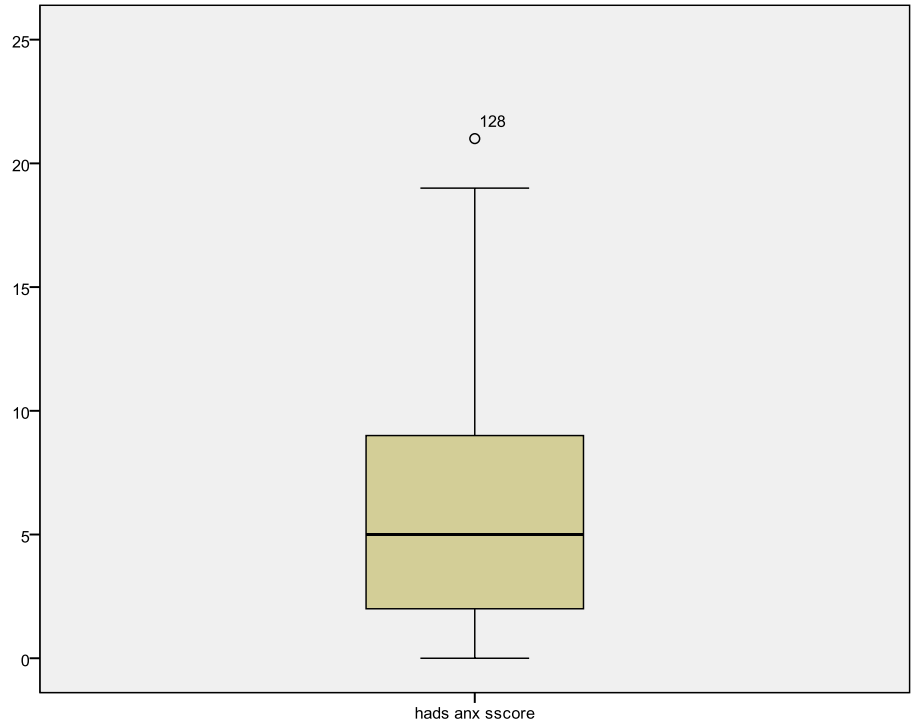
Box plot to show outliers in the number of self- reported hospital admissions for exacerbations of HF in the past year



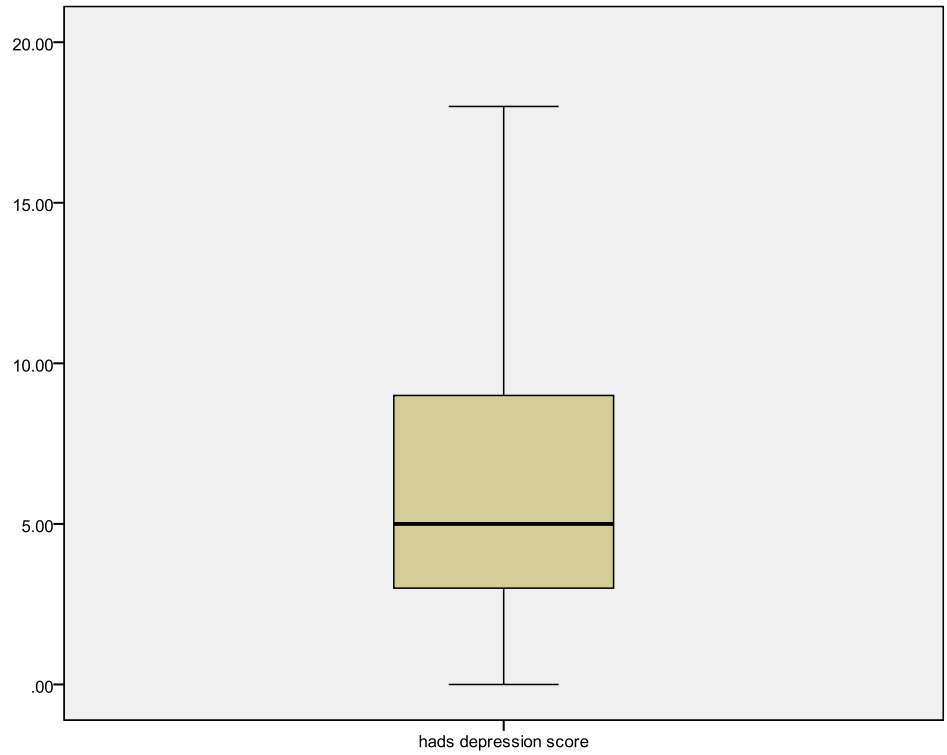
Box plot to show outliers in hospital recorded HF admissions in the previous 12 months



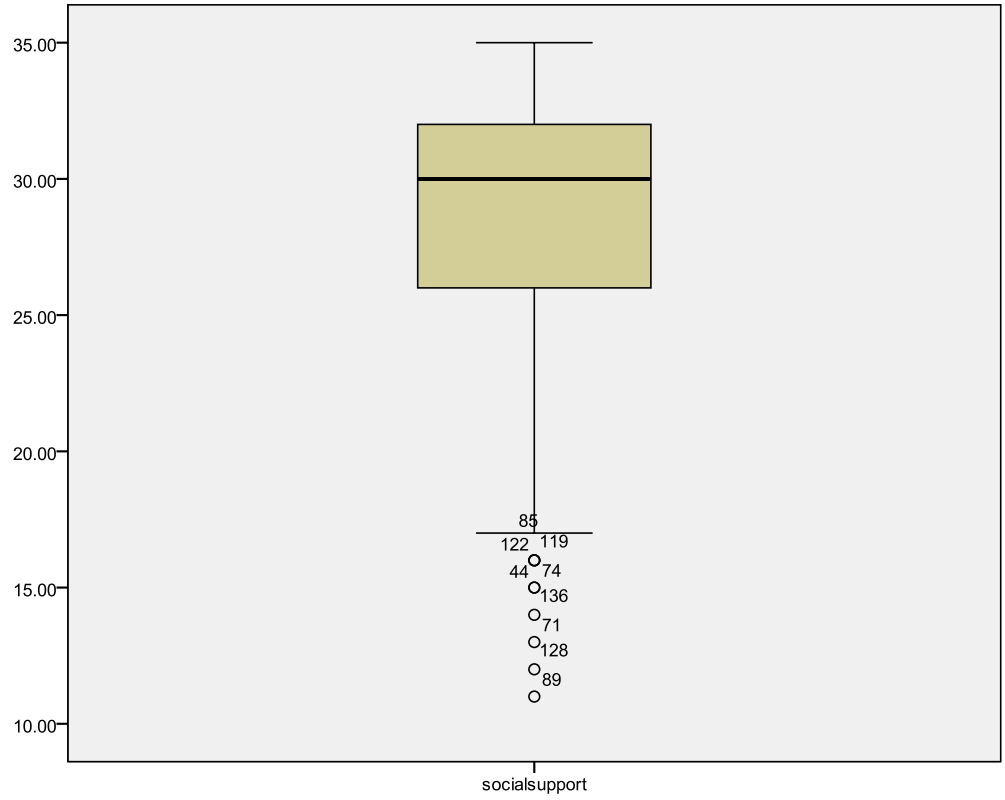
Box plot to identify outliers in HADS anxiety scores



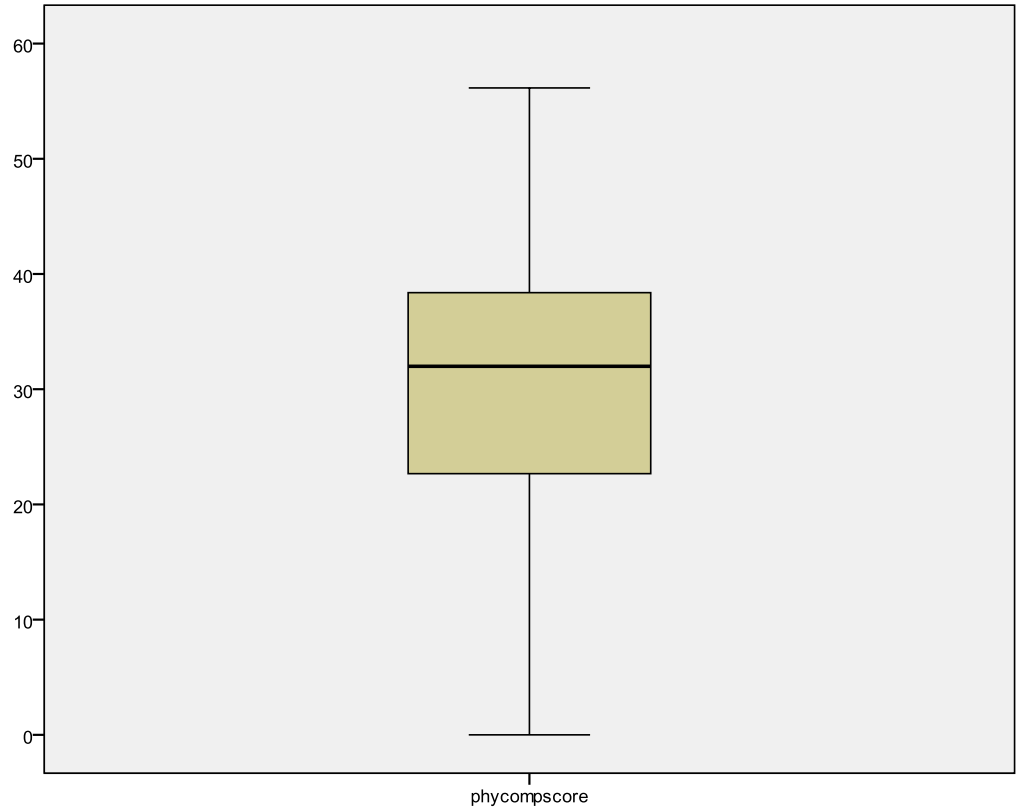
Box plot to show outliers in HADS depression scores



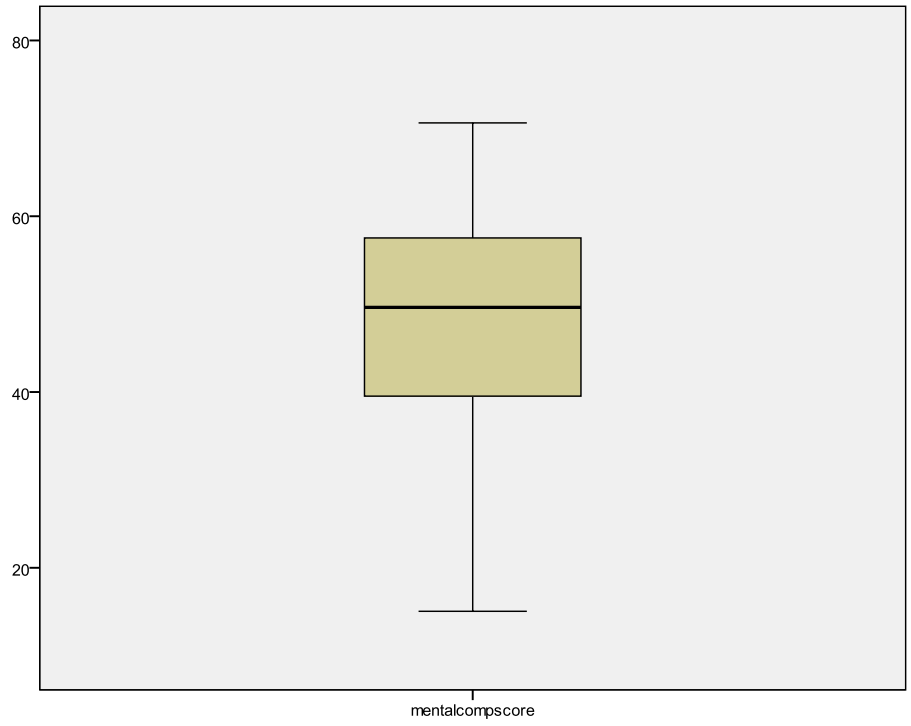
Box plot to show outliers in social support scores



Box plot to show outliers in SF PCS scores

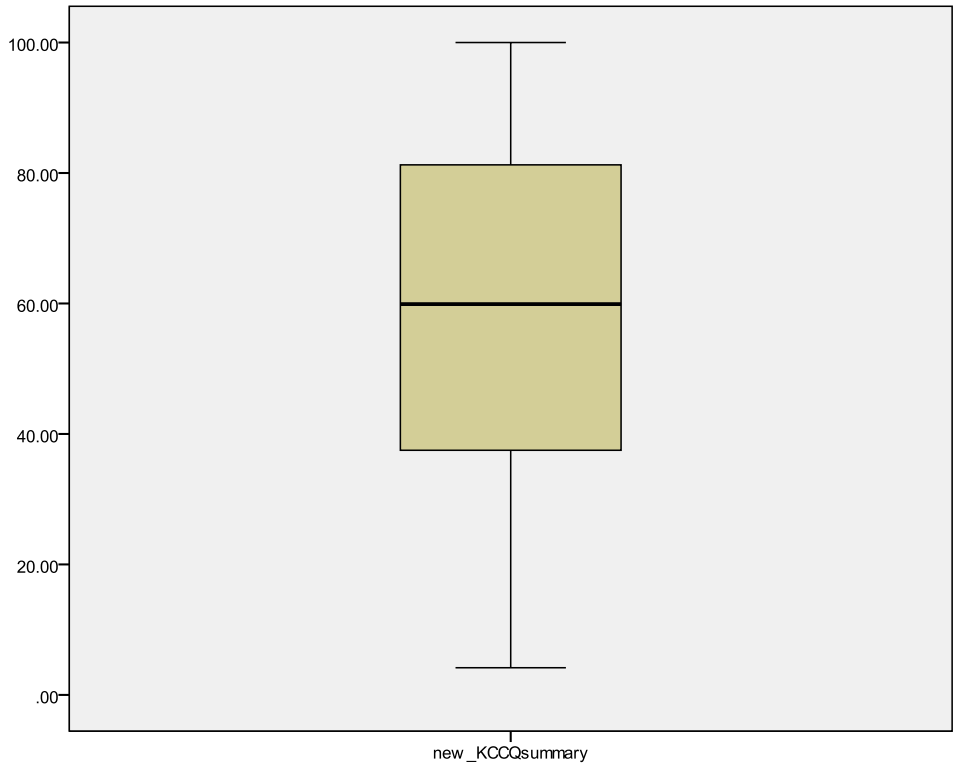


Box plot to show outliers in SF12 MCS scores

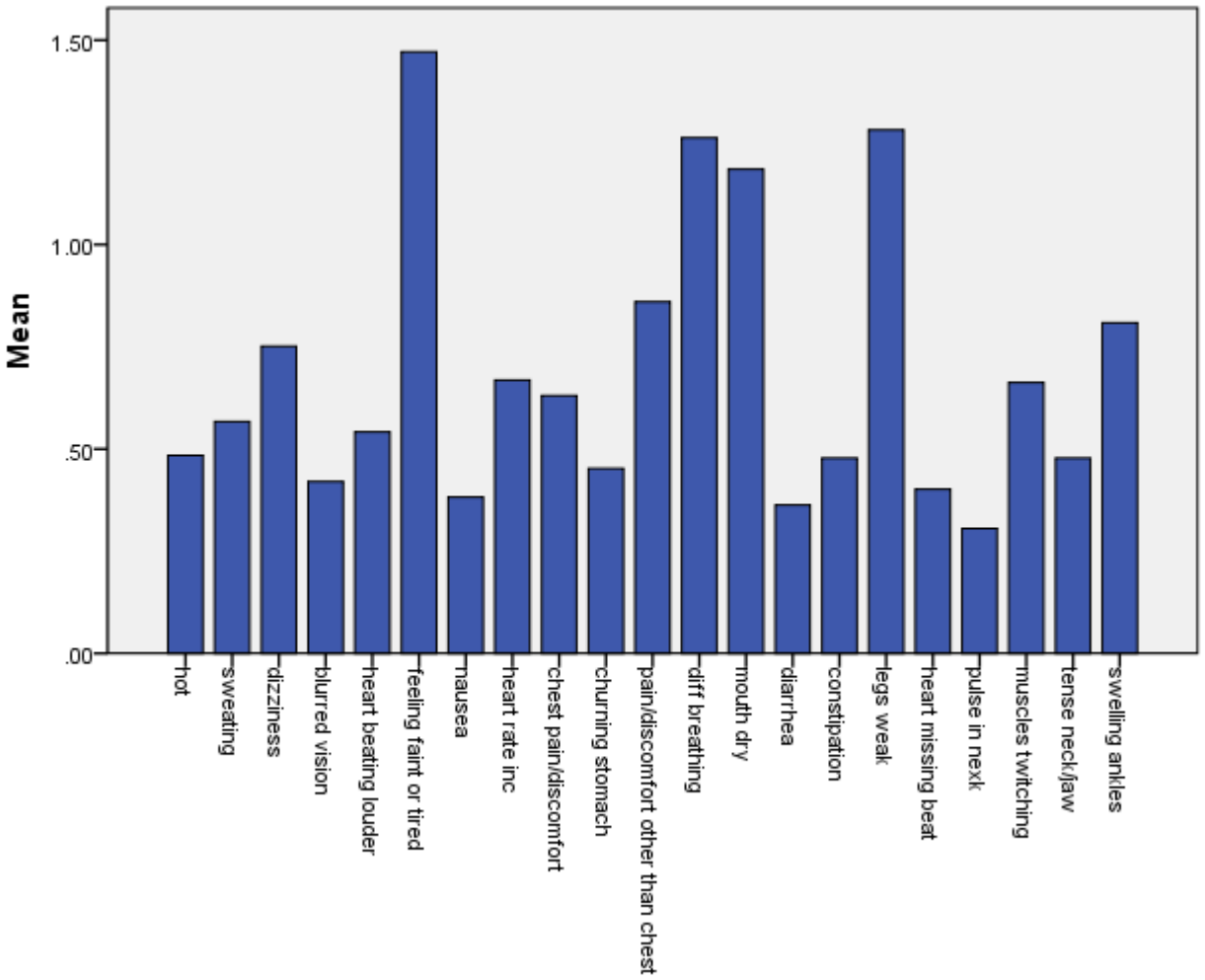


Box plot to show outliers in Overall KCCQ scores

Box plot to show outliers in KCCQ summary scores

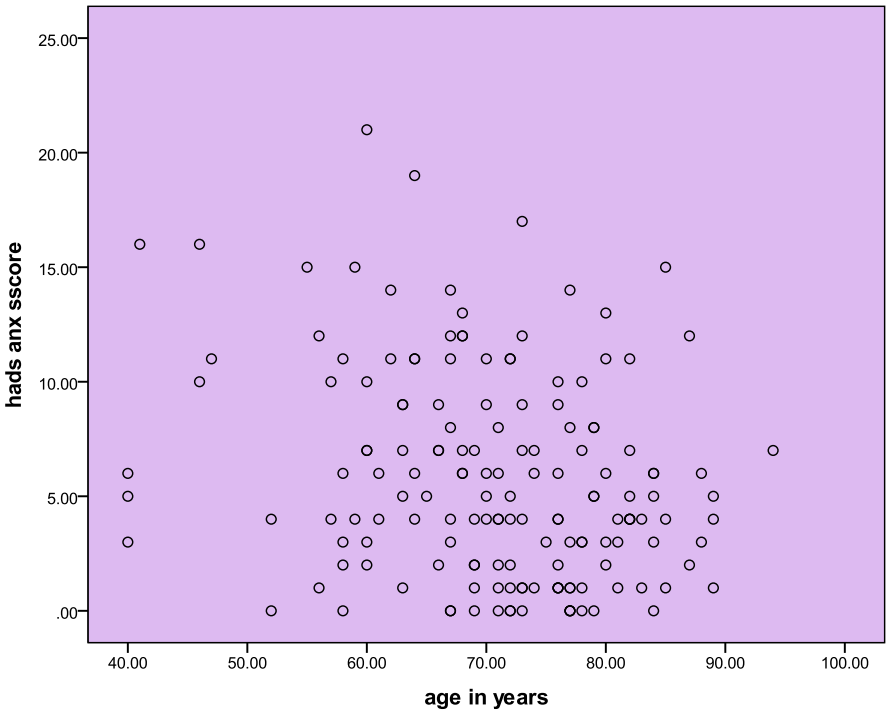


Appendix 18 Graph to show patient reported physical symptom frequency and burden by symptom

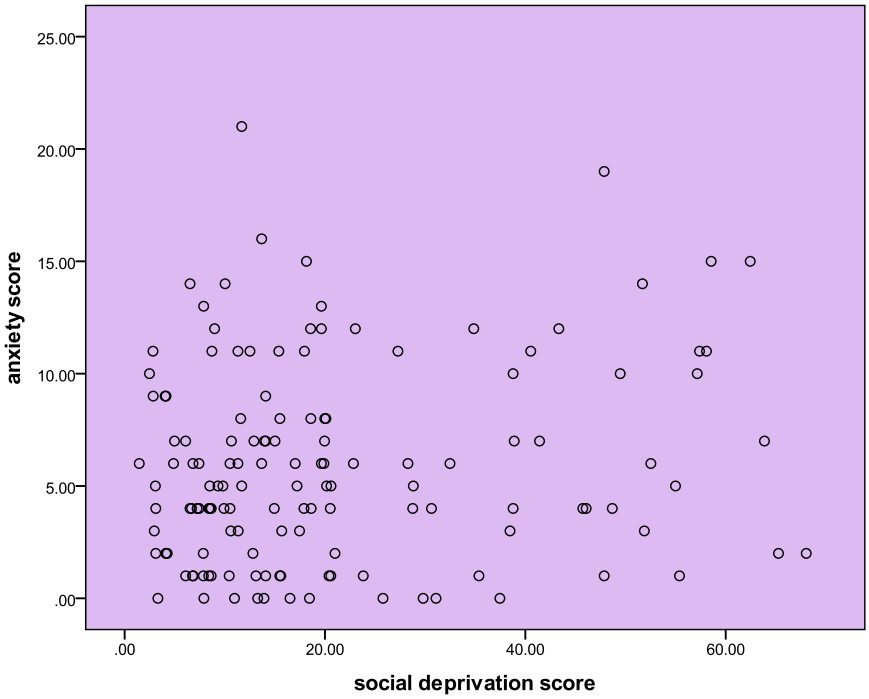


Appendix 19 Scatter plots to show correlations with anxiety data

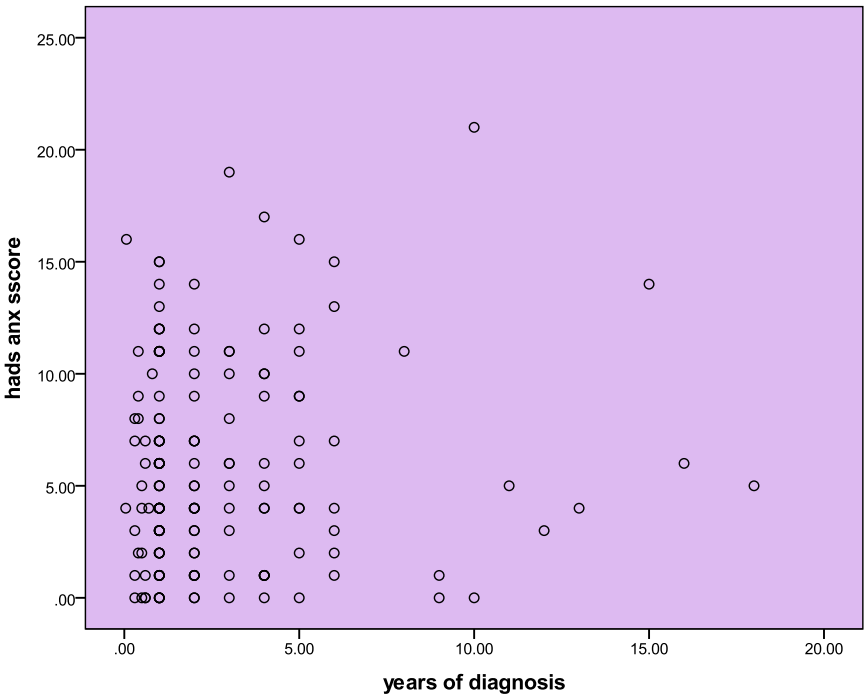
Scatter plot of the correlation between age (yrs) and anxiety symptoms scores



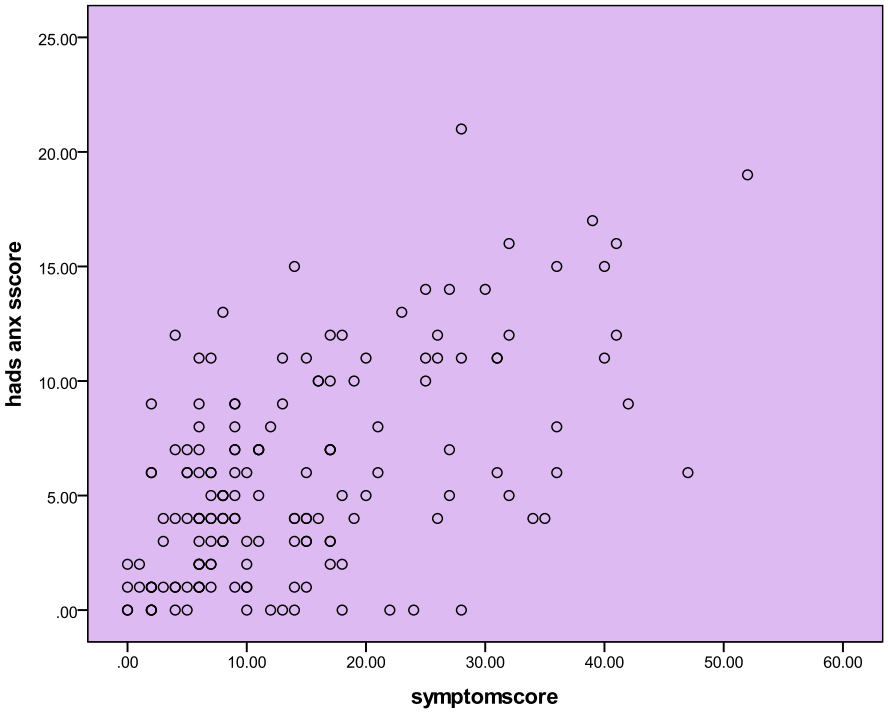
Scatter plot to show the correlation between social deprivation scores and anxiety symptom scores



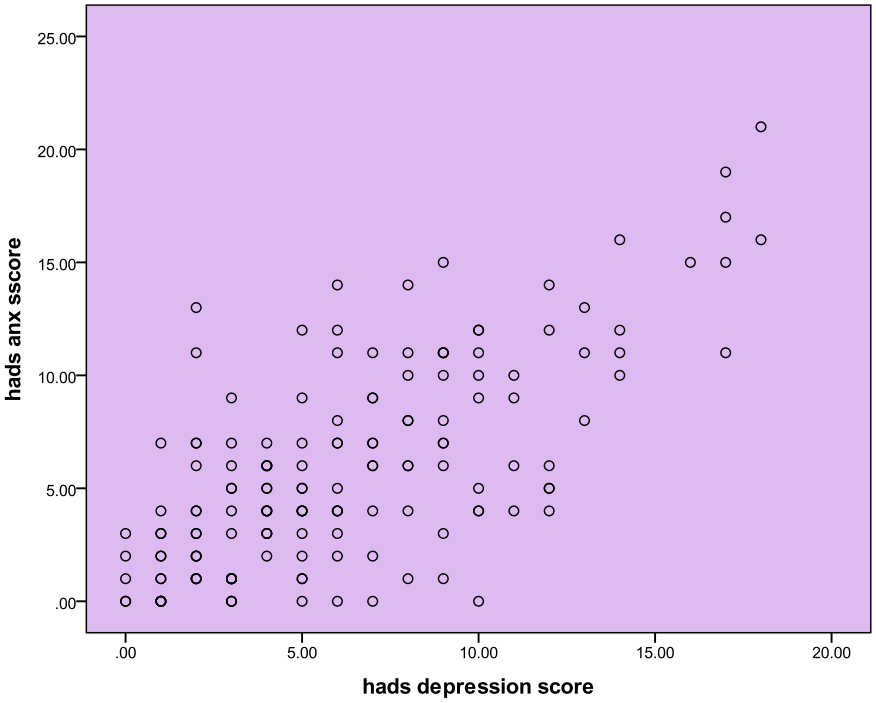
Scatter plot to show the correlation between duration of HF (yrs) and anxiety symptom scores



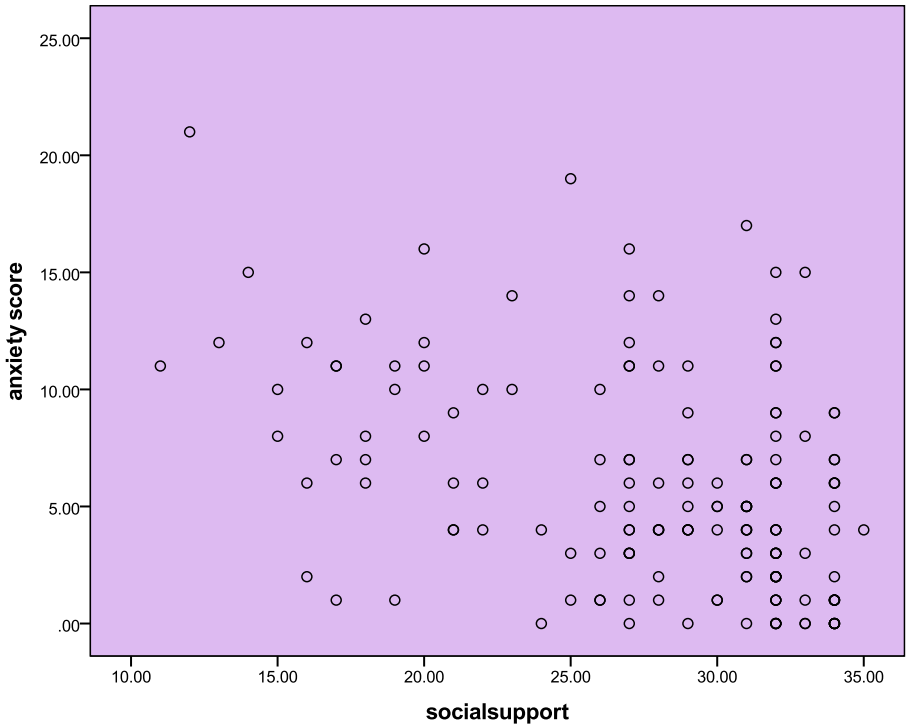
Scatter plot to show the correlation between physical symptom scores and anxiety symptom scores



Scatter plot to show the correlation between depression and anxiety symptom scores.

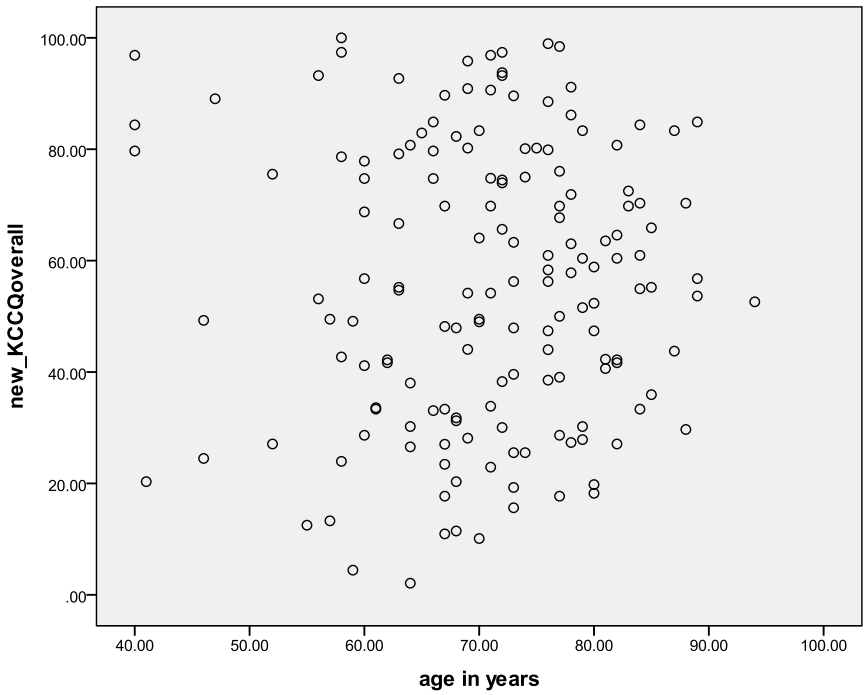


Scatter plot to show the correlation between perceived social support and anxiety symptom scores.

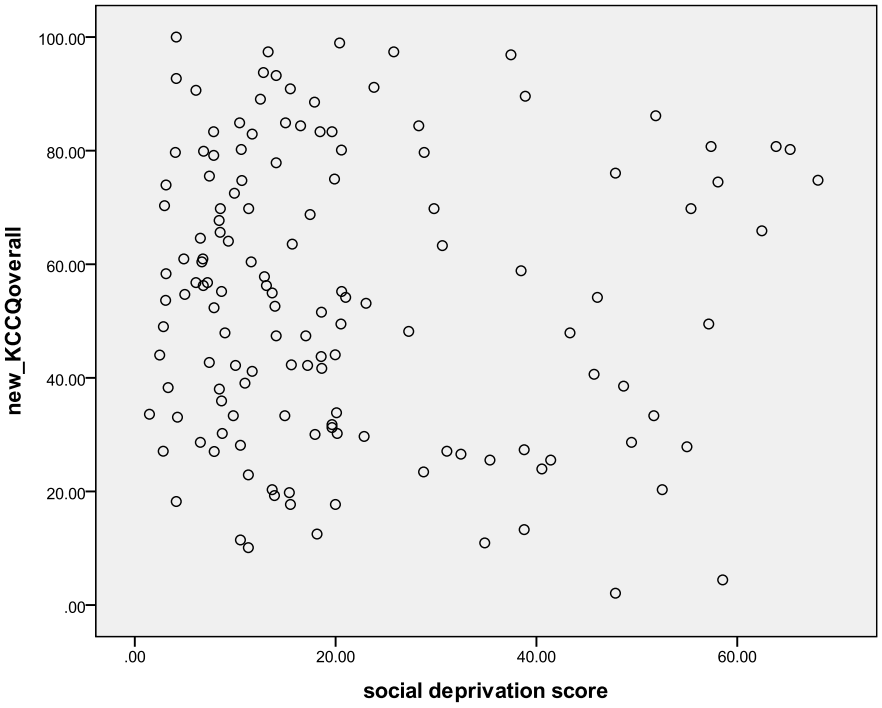


Appendix 20 Scatter plots to show correlations with HRQoL data

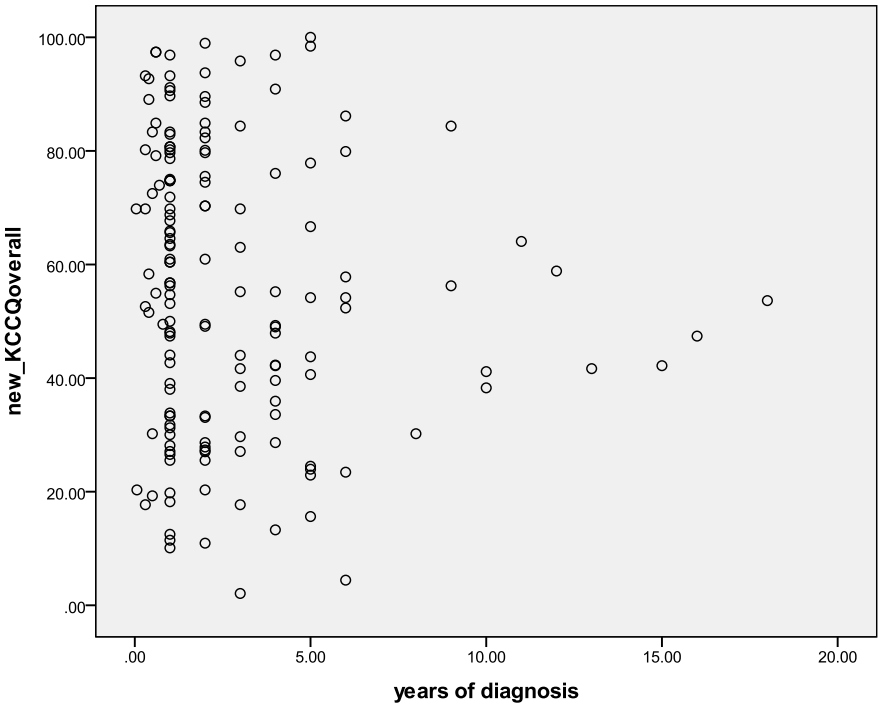
Scatter plot to show the correlations between overall HRQoL and age(yrs)



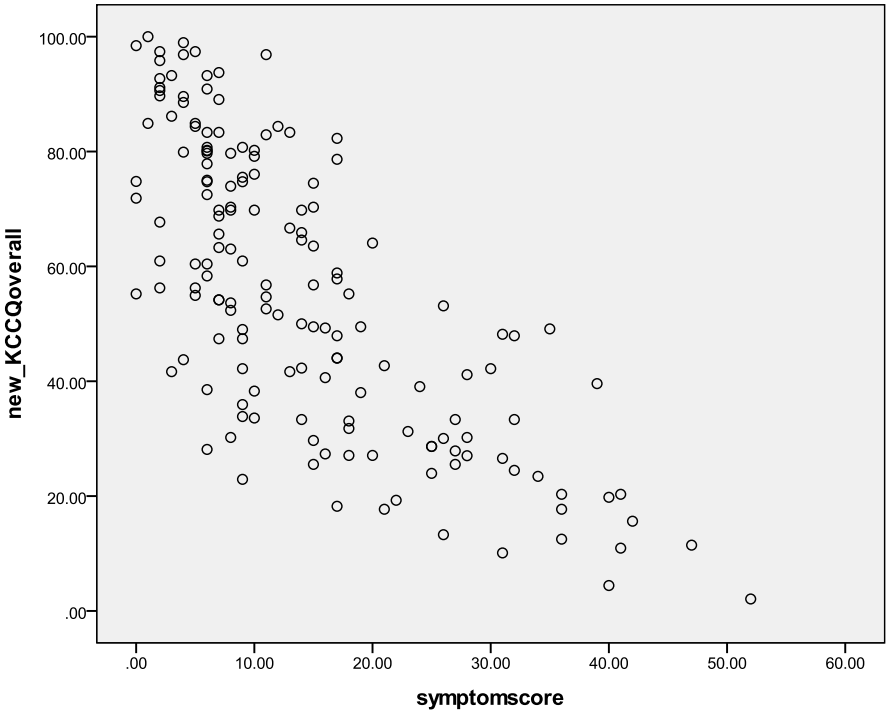
Scatter plot to show the correlations between overall HRQoL and social deprivation scores



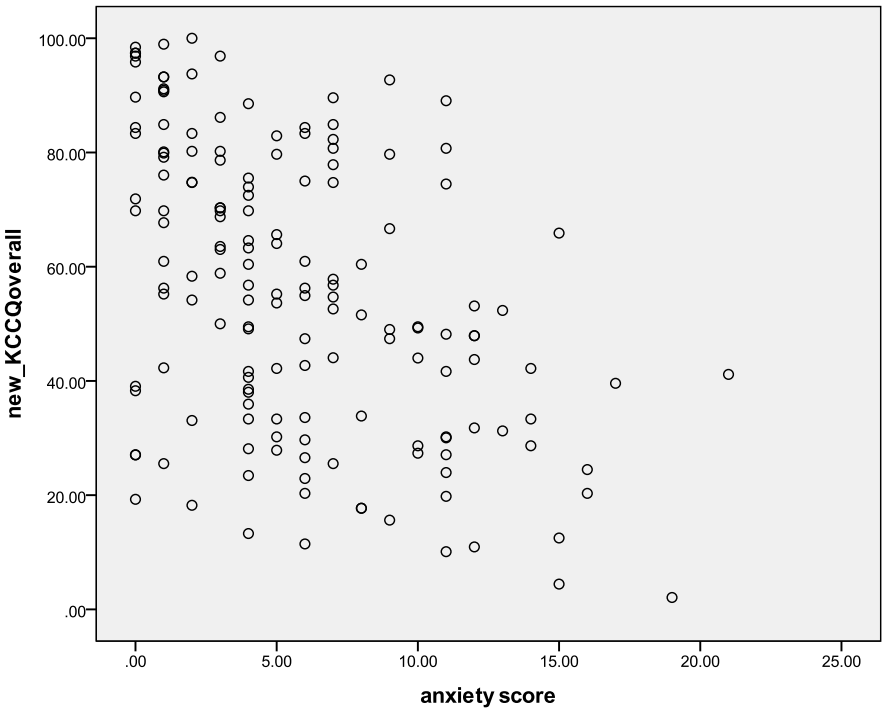
Scatter plot to show the correlation between overall HRQoL and duration of diagnosis (yrs)



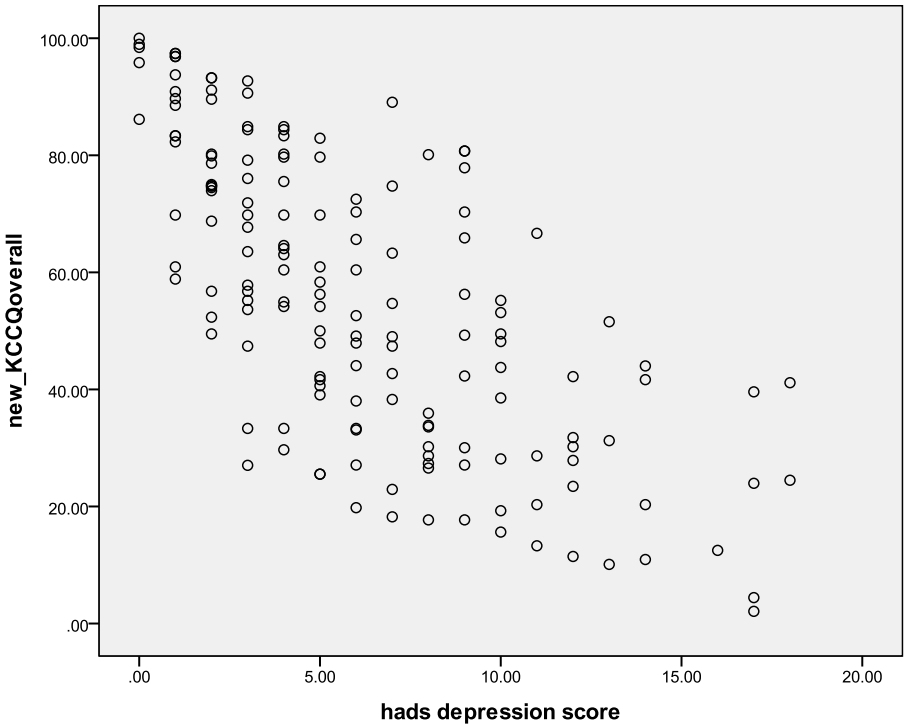
Scatter plot to show the correlation between overall HRQoL and physical symptoms



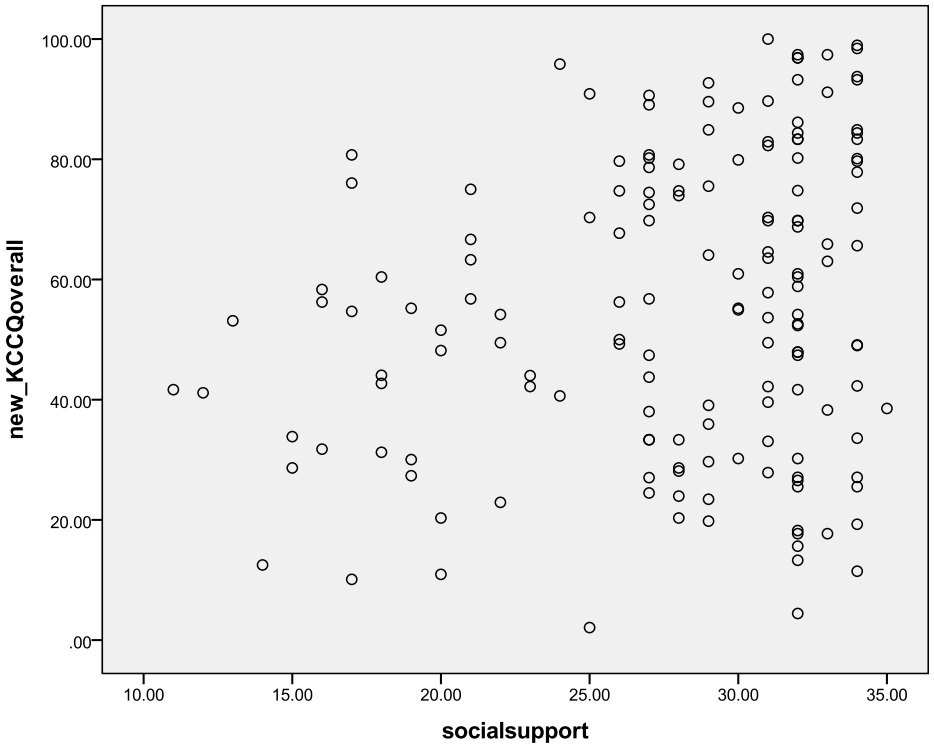
Scatter plot to show the correlation between overall HRQoL and HADS anxiety symptom score



Scatter plot to show the correlation between overall HRQoL and HADS depression score



Scatter plot to show the correlations between overall HRQol and perceived Social Support



Appendix 21 Table to show the regression coefficients of a model to predict overall HRQoL – Collinearity data provided

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B		Collinearity Statistics	
		B	Std. Error	Beta			Lower Bound	Upper Bound	Tolerance	VIF
1	(Constant)	122.027	13.640		8.946	.000	95.032	149.022		
	age in years	-.396	.122	-.167	-3.244	.002	-.638	-.155	.855	1.169
	gender	-.814	2.731	-.015	-.298	.766	-6.219	4.590	.876	1.141
	social deprivation score	.124	.074	.082	1.678	.096	-.022	.269	.944	1.059
	number hospital admin self report	-.735	1.059	-.035	-.693	.489	-2.831	1.362	.880	1.137
	NYHAnew	-3.678	2.829	-.066	-1.300	.196	-9.278	1.921	.879	1.138
	LVEFnew	-.660	2.602	-.013	-.254	.800	-5.809	4.490	.871	1.148
	years of diagnosis	-.163	.416	-.020	-.391	.696	-.985	.660	.872	1.147
	ICDnew	-1.757	3.061	-.030	-.574	.567	-7.815	4.302	.841	1.189
	charlesonHF	-2.592	.932	-.146	-2.780	.006	-4.438	-.747	.826	1.211
	symptomscore	-1.194	.150	-.533	-7.953	.000	-1.492	-.897	.504	1.983
	hads depression score	-2.584	.463	-.442	-5.586	.000	-3.500	-1.669	.361	2.771

	socialsupport	.187	.244	.043	.766	.445	-.296	.670	.725	1.379
	anxiety score	.578	.420	.105	1.375	.172	-.254	1.410	.389	2.572

a. Dependent Variable: new_KCCQoverall

Appendix 22 Regression coefficients to predict overall HRQoL with the exclusion of HADS depression scores

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B		Collinearity Statistics	
		B	Std. Error	Beta			Lower Bound	Upper Bound	Tolerance	VIF
1	(Constant)	104.638	14.786		7.077	.000	75.378	133.899		
	age in years	-.404	.136	-.170	-2.968	.004	-.673	-.135	.855	1.169
	gender	2.172	2.982	.040	.728	.468	-3.729	8.072	.911	1.097
	social deprivation score	.110	.082	.073	1.347	.181	-.052	.273	.945	1.058
	number hospital admin self report	-.893	1.179	-.043	-.757	.450	-3.226	1.441	.880	1.136
	NYHAnew	-3.027	3.147	-.054	-.962	.338	-9.256	3.201	.880	1.136
	LVEFnew	-1.429	2.893	-.028	-.494	.622	-7.155	4.296	.873	1.145
	years of diagnosis	-.029	.462	-.004	-.063	.950	-.943	.885	.875	1.143
	ICDnew	1.382	3.351	.023	.413	.681	-5.249	8.013	.870	1.149
	charlesonHF	-3.304	1.028	-.186	-3.213	.002	-5.340	-1.269	.841	1.189
	symptomscore	-1.533	.153	-.684	-10.021	.000	-1.836	-1.230	.602	1.660
	socialsupport	.513	.264	.118	1.946	.054	-.009	1.036	.769	1.300

anxiety score	-.551	.410	-.100	-1.342	.182	-1.363	.261	.506	1.978

a. Dependent Variable: new_KCCQoverall

Appendix 23 Regression coefficients from a model to predict overall HRQoL featuring Total HADS scores

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B		Collinearity Statistics	
		B	Std. Error	Beta			Lower Bound	Upper Bound	Tolerance	VIF
1	(Constant)	117.454	14.445		8.131	.000	88.868	146.040		
	age in years	-.427	.130	-.180	-3.293	.001	-.683	-.170	.858	1.165
	gender	2.077	2.806	.039	.740	.460	-3.475	7.630	.937	1.067
	social deprivation score	.128	.078	.085	1.637	.104	-.027	.283	.944	1.060
	number hospital admin self report	-.615	1.125	-.029	-.547	.586	-2.842	1.612	.880	1.136
	NYHAnew	-3.943	3.005	-.071	-1.312	.192	-9.891	2.004	.879	1.137
	LVEFnew	-.252	2.763	-.005	-.091	.928	-5.719	5.216	.872	1.147
	years of diagnosis	.058	.438	.007	.132	.895	-.809	.924	.886	1.128
	ICDnew	.912	3.180	.015	.287	.775	-5.382	7.206	.880	1.137
	charlesonHF	-3.214	.978	-.181	-3.286	.001	-5.150	-1.279	.847	1.180
	symptomscore	-1.271	.158	-.567	-8.025	.000	-1.584	-.957	.512	1.953
	socialsupport	.216	.259	.050	.835	.406	-.297	.729	.726	1.378
	TotalHADS	-.903	.238	-.294	-3.785	.000	-1.375	-.431	.425	2.353

Dependent Variable: new_KCCQoveral