Improving care for patients with non-cardiac chest pain

– Description of psychological distress and costs, and evaluation of an Internet-delivered intervention

Ghassan Mourad

Division of Health, Activity, and Care
Department of Social and Welfare Studies
Linköping University, Sweden

LINKÖPING UNIVERSITY

Linköping 2015

Improving care for patients with non-cardiac chest pain – Description of psychological distress and costs, and evaluation of an Internet-delivered intervention

To my family
Maria, Elin and Emma

And to my parents
Gabro and Vergin

Av alla passioner är fruktan den som mest försvagar omdömet
Of all the passions, fear is the one that weakens our judgement the most
(Paul de Gondi Retz, 1613-1679)

CONTENTS

ABBREVIATIONS

AMI	Acute Myocardial Infarction
AP	Angina Pectoris
BSQ	Body Sensations Questionnaire
CAQ	Cardiac Anxiety Questionnaire
CBT	Cognitive Behavioural Therapy
CDW	Care Data Warehouse
CPP	Cost Per Patient
ICD	International Classification of Diseases
IHD	Ischemic Heart Disease
MADRS	Montgomery Åsberg Depression Rating Scale
NCCP	Non-cardiac Chest Pain
PHQ-9	Patient Health Questionnaire-9
SQ-3	Screening Questions-3

ABSTRACT

Introduction

More than half of all patients seeking care for chest pain do not have a cardiac cause for this pain. Despite recurrent episodes of chest pain, many patients are discharged without a clear explanation of the cause for their pain. A lack of explanation may result in a misinterpretation of the pain as being cardiac-related, causing worry and uncertainty, which in turn leads to substantial use of healthcare resources. Psychological distress has been associated with non-cardiac chest pain (NCCP), but there is limited research regarding the relationship between different psychological factors and their association with healthcare utilization. There is a need for interventions to support patients to manage their chest pain, decrease psychological distress, and reduce healthcare utilization and costs.

Aim

The overall aim of this thesis was to improve care for patients with non-cardiac chest pain by describing related psychological distress, healthcare utilization and societal costs, and by evaluating an Internet-delivered cognitive behavioural intervention.

Designs and methods

This thesis presents results from four quantitative studies. Studies I and II had a longitudinal descriptive and comparative design. The studies used the same initial cohort. Patients were consecutively approached within 2 weeks from the day of discharge from a general hospital in southeast Sweden. In study I, 267 patients participated (131 with NCCP, 66 with acute myocardial infarction (AMI), and 70 with angina pectoris (AP)). Out of these, 199 patients (99 with NCCP, 51 with AMI, 49 with AP) participated in study II. Participants were predominantly male (about 60 %) with a mean age of 67 years. Data was collected on depressive symptoms (Study I), healthcare utilization (Study I, II), and societal costs (Study II).

Study III had a cross-sectional explorative and descriptive design. Data was collected consecutively on depressive symptoms, cardiac anxiety and fear of body sensations in 552 patients discharged with diagnoses of NCCP (51 % women, mean age 64 years) from four hospitals in southeast Sweden. Patients were approached within one month from the day of discharge. Study IV was a pilot randomized controlled study including nine men and six women with a median age of 66 years, who were randomly assigned to an intervention (n=7) or control group

(n=8). The intervention consisted of a four-session guided Internet-delivered cognitive behavioural therapy (CBT) program containing psychoeducation, exposure to physical activity, and relaxation. The control group received usual care. Data was collected on chest pain frequency, cardiac anxiety, fear of body sensations, and depressive symptoms.

Results

Depressive symptoms were prevalent in 20 % (Study IV) and 25 % (Study I, III) of the patients, and more than half of the patients still experienced depressive symptoms one year later (Study I). There were no significant differences in prevalence and severity of depressive symptoms between patients diagnosed with NCCP, AMI or AP. Living alone and younger age were independently related to more depressive symptoms (Study I). Cardiac anxiety was reported by 42 % of the patients in study III and 67 % of the patients in study IV. Fear of body sensations was reported by 62 % of the patients in study III and 93 % of the patients in study IV.

On average, patients with NCCP had 54 contacts with primary care or the outpatient clinic per patient during the two-year study period. This was comparable to the number of contacts among patients with AMI (50 contacts) and AP (65). Patients with NCCP had on average 2.6 hospital admissions during the two years, compared to 3.6 for patients with AMI and 3.9 for patients with AP (Study II). Four out of ten patients reported seeking healthcare at least twice during the last year due to chest pain (Study III). On average, 14 % of patients with NCCP were on sick-leave annually, compared to 18 % for patient with AMI and 25 % for patient with AP. About 11-12 % in each group received a disability pension. The mean annual societal costs for patients with NCCP, AMI and AP were €10,068, €15,989 and €14,737 (Study II). Depressive symptoms (Study I, III), cardiac anxiety (Study III) and fear of body sensations (Study III) were related to healthcare utilization. Cardiac anxiety was the only variable independently associated with healthcare utilization (Study III).

In the intervention study (Study IV), almost all patients in both the intervention and control groups improved with regard to chest pain frequency, cardiac anxiety, fear of body sensations, and depressive symptoms. There was no significant difference between the groups. The intervention was perceived as feasible and easy to manage, with comprehensible language, adequate and varied content, and manageable homework assignments.

Conclusions

Patients with NCCP experienced recurrent and persistent chest pain and psychological distress in terms of depressive symptoms, cardiac anxiety and fear

of body sensations. The prevalence and severity of depressive symptoms in patients with NCCP did not differ from patients with AMI and patients with AP. NCCP was significantly associated with healthcare utilization and patients had similar amount of primary care and outpatient clinic contacts as patients with AMI. The estimated cumulative annual national societal cost for patients with NCCP was more than double that of patients with AMI and patients with AP, due to a larger number of patients with NCCP. Depressive symptoms, cardiac anxiety and fear of body sensations were related to increased healthcare utilization, but cardiac anxiety was the only variable independently associated with healthcare utilization.

These findings imply that screening and treatment of psychological distress should be considered for implementation in the care of patients with NCCP. By reducing cardiac anxiety, patients may be better prepared to handle chest pain. A short guided Internet-delivered CBT program seems to be feasible. In the pilot study, patients improved with regard to chest pain frequency, cardiac anxiety, fear of body sensations, and depressive symptoms, but this did not differ from the patients in the control group who received usual care. Larger studies with longer follow-up are needed to evaluate both the short and long- term effects of this intervention.

LIST OF PAPERS

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals;

I. Mourad G, Jaarsma T, Hallert C, Strömberg A. Depressive symptoms and healthcare utilization in patients with noncardiac chest pain compared to patients with ischemic heart disease. Heart Lung 2012 Sep; 41(5):446-455. PMID: 22652167.

II. Mourad G, Alwin J, Strömberg A, Jaarsma T. Societal costs of non-cardiac chest pain compared with ischemic heart disease – a longitudinal study. BMC Health Serv Res 2013 Oct 9; 13:403-6963-13-403. PMID: 24107009.

III. Mourad G, Strömberg A, Johansson P, Jaarsma T. Depressive Symptoms, Cardiac Anxiety, and Fear of Body Sensations in Patients with Non-Cardiac Chest Pain, and Their Relation to Healthcare-Seeking Behavior: A Cross-Sectional Study. Patient 2015 Apr 4. [Epub ahead of print] PMID: 25840677.

IV. Mourad G, Strömberg A, Jonsbu E, Gustafsson M, Johansson P, Jaarsma T. Guided Internet-delivered cognitive behavioural therapy in patients with non-cardiac chest pain – a pilot randomized controlled study. (Submitted).

PREFACE

As a newly graduated nurse I was full of anticipation to start my new profession. My first and only clinical workplace was the cardiac unit at Vrinnevi hospital in Norrköping, where I worked for about 7 years. At this unit, I had many talented colleagues who were very passionate about their profession. I had a lot to learn and I was inspired to do my work with great enthusiasm.

I soon discovered that there was a large flow of patients, of whom many required advanced medical care. I also discovered that healthcare resources were limited and this led to an overfilled unit, short treatments and usually relatively quick discharges. In order to give patients the best possible care I had to prioritize my work carefully, and hence some non-urgent problems had to stand back. When the diagnosis of acute cardiac disease was ruled out in patients with acute chest pain, the treatment of these patients was considered to be complete and they were discharged. This applied particularly to patients with non-cardiac chest pain who often did not have/receive a clear physical explanation for their chest pain. I understood that some patients were not really pleased being discharged without an explanation for their chest pain and that they were worried about what could be wrong, but I probably never realized quite how big an impact chest pain had on some of them.

In retrospect, I could have asked these patients more questions about their psychological well-being and how they were affected by their chest pain. Where appropriate, I could have discussed any psychological distress with the team, particularly the physician, and pointed out the importance of screening and follow-up of these patients. Perhaps this might have reduced the suffering for some of the patients and their families, and led to fewer healthcare contacts, and hence lower healthcare costs. Though, these patients are not only found in cardiac care, the majority of them appear within primary care and emergency care departments. In order to achieve an improvement, everyone who meets patients with non-cardiac chest pain needs to keep in mind that the care process does not end once the diagnosis of acute cardiac disease is ruled out.

INTRODUCTION

Acute chest pain is a symptom that may indicate a serious and life-threatening condition that requires urgent medical attention. The severity of the pain is not a reliable indicator for the seriousness of the condition. Therefore, it is important to rapidly identify patients with potentially dangerous conditions for diagnosis and treatment (1). The majority of the patients seeking care with chest pain are admitted for in-hospital cardiac rule out observation, resulting in large costs (2, 3). Yet, not all chest pain is cardiac-related (4, 5). At least half of patients with chest pain have non-cardiac causes for their chest pain (4, 6, 7). Furthermore, patients with history of Ischemic heart disease (IHD) report other chest pain that is clearly non-cardiac (4, 8, 9).

As cardiac disease needs acute treatment and every minute's delay can have serious consequences, physicians are afraid of missing a cardiac diagnosis and therefore tend to overestimate the risk (10). This could lead to reinforcement of patients' beliefs of having a cardiac disease. Due to recurrent chest pain, many patients with NCCP are not satisfied or convinced by the 'ruled out' cardiac diagnosis, as they have not received another explanation for the chest pain (11, 12). They therefore tend to misinterpret their pain as cardiac-related and react with fear and avoidance of activities, leading to disability, impaired quality of life, cardiac-related anxiety, increased chest pain, and high and inappropriate use of medical care (4, 5, 13, 14). Avoidance behaviour can lead to maintenance and exacerbation of fear and pain (15, 16). Thus, these patients need support to change their perception of their chest pain and learn how to manage it, which can be accomplished with psychological interventions (17, 18).

Several studies have demonstrated an association between depressive symptoms, anxiety, fear of body sensations and NCCP, and highlighted the negative impact these factors have on patients' health-related quality of life, daily life, pain experience, and healthcare seeking behaviour (13, 14, 19-22). However, the relationship between these psychological factors and their association with healthcare seeking behaviour needs further exploration. There is also limited research regarding the course of NCCP with regard to healthcare utilization and the societal costs related to patients with NCCP. Gaining an insight into these aspects would be of great value and provide key knowledge that can be used to design interventions aiming to improve patient outcomes and avoid unnecessary suffering, but also to reduce healthcare utilization and costs in the long run.

BACKGROUND

NON-CARDIAC CHEST PAIN

Chest pain is the underlying reason for approximately 1 % of all primary care consultations (23, 24) and 20-30 % of all medical admissions (4, 25). More than half of the patients consulting the emergency department due to chest pain are diagnosed as non-cardiac (4, 6, 7), which constitutes 2-5 % of all emergency department presentations (26, 27). The population prevalence of NCCP is 25-35 % in Sweden, USA, and Australia (28, 29).

Non-cardiac chest pain (NCCP) can be defined as "pain that has not been diagnosed as acute myocardial infarction (AMI) or IHD by a doctor" (6, p. 911). In this thesis, NCCP has been classified as being discharged with the diagnostic International Classification of Diseases (ICD)-10 codes: R07.2, precordial chest pain (Study III, IV); R07.3, other chest pain (Study III, IV); R07.4, chest pain unspecified (Study I-IV); and Z03.4, observation for suspected myocardial infarction (Study I-IV). In the literature, NCCP is also referred to as non-specific (7), atypical (25), functional (30), and unexplained chest pain (31). In this thesis, NCCP is used as the nomenclature including the other concepts.

The causes for NCCP often overlap, but in many studies only one cause for the chest pain is considered (26). Common causes for NCCP are gastro-intestinal diseases, musculoskeletal disorders, pulmonary disorders, chest wall syndromes, pleural and pericardial conditions, but also panic disorder and other psychiatric conditions (1, 9, 24, 29). Despite this, many patients are discharged without a diagnosis (25, 32), and although they have continuous chest pain, many of them still remain undiagnosed one year later (25).

According to a study on the trends in incidence of NCCP in Swedish non-AMI patients between 1987 and 2006, NCCP increased in patients aged 25-74 years from the early 1990s and stabilized during the last years of the data collection (33). In general, patients suffering from NCCP are younger, have lower educational level, comprise a higher percentage of immigrants and do not differ regarding sex distribution compared to patients with IHD or a population-based reference group (6, 34, 35). In some studies, women have more often reported NCCP (20, 21). Significantly fewer women than men are engaged in regular physical activity, and about 25 % of both men and women have reported having a sedentary leisure time. Women with NCCP are also more often on sick-leave (36) compared to men.

Patients with NCCP have reported greater pain intensity and more pain at rest compared to patients with IHD. Increased chest pain due to activity has been reported by 31 % of the NCCP group and 33 % of the IHD group (37), but there is no difference between men and women with NCCP. Neither are there any differences regarding how pain is experienced between men and women. Half of them experience their chest pain as intermittent and the other half as continuous (36, 37). Patients with IHD have reported more intermittent than continuous pain (37).

In NCCP, pain is often rated as mild or moderate (34, 38), with conflicting reports regarding pain duration. This varies between 1-4 minutes (34), 5-20 minutes (14, 19), and 15-30 minutes, compared to severe pain that lasts 5-15 minutes in cardiac patients (39), and is mainly not effort related (37). Patients with NCCP experience the pain as sharp, pressing, aching, stabbing and cramping (34, 37, 39), and they describe it as worrying, frightening and troublesome (37), compared to stinging, pressing, tearing, intolerable and terrifying as in patients with AMI (1). NCCP patients have often reported pain in the central and the upper chest, whereas those with cardiac pain report pain in the left chest and arm (39). This is in conflict with data from other studies reporting NCCP being primarily located to the left chest region and to the central chest (34). The pain could also be located to the front middle left chest region with some radiation to the left upper back region, compared to central chest pain with no radiation in cardiac patients (36, 37). Although there are some differences, the location of the pain is relatively similar in patients with NCCP and patients with cardiac chest pain, which makes it difficult to distinguish between these patients based on the location of the pain alone (39).

The prognosis of NCCP seems to be benign with low 1-year mortality rates of 1-3 %, which does not differ from a general population (7, 33, 40). In their review, Ruddox et al (7) concluded that the mean 1-year readmission rate for patients with NCCP was 17.5 %. They also found that patients with NCCP with pre-existing IHD had poor prognosis compared to those without IHD, although they had much lower 1-year mortality than patients with IHD. Opposite results were found in another study (41), where the course of chest pain over a 4-year period in 126 patients with NCCP and 71 with cardiac chest pain was examined. The authors found that patients with NCCP did not differ from cardiac patients with regards to mortality, although mortality rates for these patients were 5.5 % and 11 % respectively. Almost all deaths among the NCCP patients were due to AMI, and age was the only predictor of mortality. Many of the patients in this study did not undergo coronary angiography to definitively rule out cardiac disease which could have led to misclassification bias, which the authors brought up as a limitation.

CARDIAC CHEST PAIN

In this thesis, outcomes in patients with NCCP are compared with outcomes in patients with cardiac chest pain, such as AMI and angina pectoris (AP). Acute myocardial infarction with chest pain as the main characteristic symptom is defined as *"myocardial cell death due to prolonged ischemia"* (42, p. 277). In 2013, about 28,000 people suffered an AMI in Sweden, which corresponded with a population prevalence of about 3 ‰. In general, the trends in incidence of AMI attacks have decreased significantly in the last 25 years (43, 44). The incidence of AMI and related mortality is higher in men than in women, despite excess of AP in women (43-45).

Angina pectoris, a type of chest pain, which is a common sign of cardiovascular disease is mainly due to insufficient oxygen supply from the coronary arteries. The onset of angina increases the risk of cardiovascular death and recurrent myocardial infarction, but also has a significant impact on functional capacity and quality of life (46). According to a systematic review and meta-analysis including data from 31 countries, the population prevalence of AP is about 6 % in men and 7 % in women (45).

THE IMPACT OF NON-CARDIAC CHEST PAIN

NCCP negatively influences patients' quality of life and everyday life (35, 47-49), including interruption of daily activities and absence from work (6). Compared to other patients with chronic pain, such as AP, fibromyalgia and whiplash injury, patients with NCCP and fibromyalgia have the most impaired quality of life, particularly in the pain and mental dimensions (31).

Non-cardiac chest pain has been associated with psychological distress (8, 20, 22, 50, 51), particularly anxiety (21). Patients with NCCP have been shown to experience similar levels of psychological distress (20, 52) or higher levels than cardiac patients (53-55). Psychological distress includes fear, anxiety, depression, uncertainty, mental strain at work, stress, loss of strength (47, 49, 54-56), as well as sleep problems and negative life events (serious illness or death of a close relative) (49, 57). The uncertainty and stress could partly be due to different explanations of the chest pain by different doctors or no adequate explanation at all (47, 58).

Patients with NCCP perceive themselves as having less control over their situation and less understanding for their chest pain compared to patients with cardiac pain, despite having undergone a cardiac evaluation (55, 59). They experience

unfulfilled information needs, including unanswered questions and healthcare providers not focusing on their individual problems (60). Many of them are not convinced by their negative cardiac diagnosis (11, 18, 26, 60, 61), and continue to experience symptoms, worry about heart disease, avoid activities that they think might be harmful to their heart, and seek medical help (4, 61). These patients often seek care due to recurrent and persistent chest pain (5, 12, 41, 62), but also because of symptom anxiety, anxiety due to possible serious disease and symptom severity (26, 34). The high level of healthcare utilization contributes to high costs for the healthcare system and the society (2, 3, 26, 63, 64).

Psychological distress

This thesis focuses on the prevalence of psychological distress such as depressive symptoms, cardiac anxiety, and fear of body sensations. Therefore, these conditions are explained further below.

Depressive symptoms
The World Health Organization defines depression as a "common mental disorder, characterized by sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, feelings of tiredness, and poor concentration" (65). According to the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, DSM-V, suffering from a major depression implies five or more symptoms including at least depressed mood or decreased interest or pleasure in daily activities for a 2-week period, with a significant impact on the person's daily life. Other commonly prevalent symptoms are weight loss/gain, sleep problems, agitation, fatigue, feeling of worthlessness/guilt, problems with thinking/concentration, and suicide thoughts (66). Depression can be long-lasting or recurrent, and have a substantial impact on the individual's ability to function in daily life activities. When mild, the individual can be disturbed but able to carry on normal activities. When moderate or severe, the individual may need medication and professional talking treatments. At its most severe, depression can lead to suicide (65). Depression is among the leading causes of ill-health, loss of productivity and disability worldwide. Depression aggravates many physical illnesses, worsens their prognosis (67, 68), and affects quality of life and overall health negatively (69).

The prevalence of major depression in a general population in Sweden in the early 2000 was 18 % and an additional 12 % suffered from minor depression (70). In patients with NCCP, more than half had a depressive disorder (52), and the prevalence of a lifetime major depression was about 20 % (62). Patients with depression are more often women, younger, living alone (70), unemployed and

more likely to be receiving state benefits (71). Depression is common in patients with chronic pain and can affect their pain threshold and tolerance (72). Depression is also associated with continued chest pain in patients with NCCP (19, 22). On the other hand, many patients with depression have pain (72), and there is a significant correlation between chest pain severity and increased depression (41, 72). This can result in worse outcomes for the patients and greater healthcare utilization (72).

Cardiac anxiety

Anxiety is a response to anticipation of a future threat (66). Anxiety disorders are common among patients with chronic pain (73). About four out of ten of patients with NCCP have an anxiety disorder (19, 52, 74), and about 35-55 % have a lifetime anxiety disorder (19, 62). Patients with multiple pain conditions experience more severe anxiety, worse physical performance, and bodily symptoms (73). Uncertainty about the cause for the pain can lead to anxiety (73, 75). Anxiety disorders are a risk factor for future development of depression (75) and are associated with healthcare utilization (13). Anxiety is also related to continued chest pain in patients with NCCP (22) and increased attention to cardiopulmonary symptoms (38, 62).

Cardiac anxiety, which can be described as fear of cardiac-related stimuli and sensations, is very common among patients with NCCP (38, 76). Cardiac anxiety increases with increasing age due to an awareness of the increased risk of cardiovascular diseases in older age (77). It can be mediated by fear due to activities that cause bodily sensations (38). NCCP patients' fear of AMI resulted in greater body awareness and avoidance of physical activity as they felt unsafe (47). Fear of body sensations is part of anxiety sensitivity and can lead to anxiety (75). When comparing non-cardiac and cardiac patients, those with non-cardiac diagnoses reported more anxiety (55) and scored significantly higher on the fear and heart-focused attention subscales (78). Decreased cardiac anxiety can mediate the effect of cognitive behavioural therapy (CBT) on pain (79).

Fear of body sensations and fear avoidance

Fear is an emotional response to an either real or perceived threat (66). Fear of body sensations is fear related to different body symptoms such as palpitations, dizziness and sweating (80). Fear of body sensations, particularly cardiopulmonary sensations, is common in patients with NCCP who attribute their pain to heart disease (62, 81).

The experience of severe pain involves both pain sensation and an emotional reaction. The emotional reaction is primarily characterized by fear, which is a

normal response to the threat of pain. There are two extreme responses to fear, namely confrontation or avoidance (15). Confrontation leads to reduction of fear, while avoidance leads to maintenance and exacerbation of fear (15, 16). The way patients perceive and interpret their chest pain have an impact on their recovery from NCCP (82). If the patients perceive their acute pain as non-threatening, it will not affect their daily activities. In contrast, a vicious circle may be created if patients catastrophize their pain, which gives rise to pain-related fear and safety seeking behaviour, such as avoidance (16, 83). Pain catastrophizing refers to pain being interpreted as extremely threatening (16), and there is a tendency to magnify the pain sensation and feel helpless and unable to inhibit pain-related thoughts (84, 85). Pain catastrophizing is associated with both physical and psychosocial disability (84).

Pain-related fear is related to anxiety sensitivity (16, 86). It is also associated with decreased participation in activities, greater perceived disability and more frequent periods of sick-leave (16). Pain-related fear is also strongly associated with decreased physical health (14), and it predicts increased healthcare utilization in NCCP (13). Fearful patients are more likely to misinterpret ambiguous physical sensations as threatening or painful, and therefore have an increased risk to experience pain (16). Furthermore, patients with anxiety disorders often interpret ambiguous stimuli as more threatening. Decreased anxiety sensitivity makes the patient more tolerant to non-harmful physical symptoms and able to break the vicious circle that maintains anxiety and pain (75).

Avoidance behaviour prevents the patients from discovering that activities may be harmless, and it can be reflected in decreased activity in order to prevent an aversive situation from occurring (16). Although patients with NCCP rarely describe having chest pain during exercise, many of them avoid physical activity as they feel that this could threaten their life and health (87). Avoidance of physical activity can also be due to high levels of fear of body symptoms (62), as physical activity can lead to somatic symptoms such as hyperventilation, tachycardia, palpitations and sweating. Patients tend to interpret these in a catastrophic way and are therefore likely to avoid situations causing these symptoms (88). This behaviour may affect daily living negatively and lead to disability and maintenance of pain, but also contribute to chronic pain if associated with pain-related fear (16).

Cost-of-illness of non-cardiac chest pain

It is hypothesized that patients with NCCP suffer from psychological distress, leading to many contacts with healthcare providers and increased sick-leave, resulting in high costs for the society.

For a better insight into the societal costs incurred by patients with NCCP, a "cost-of-illness" calculation can be used. When estimating cost-of-illness, the cost-generating components should be identified and attributed a monetary value. This can be done using different perspectives, e.g. a healthcare or a societal perspective. The healthcare perspective only includes direct costs related to healthcare utilization. The societal perspective includes all costs associated with the illness and mainly comprises direct costs related to healthcare utilization and indirect costs related to productivity loss due to morbidity or mortality (89-91). Psychosocial costs of illness, such as pain and suffering, and costs for family members caring for the individual (traditionally referred to as intangible costs), are omitted from this approach (90, 92).

The productivity loss can be estimated using either the "human capital approach" or the "friction cost method". In the human capital approach, the estimates are based on gross earnings including employment overheads and benefits of the individuals in employment, and in some cases also of those not in paid employment, e.g. individuals who are unemployed or on parental leave. By using this method, adjustments are made for the opportunity cost of the production an individual could have contributed with if being at work (89, 90, 92). The friction cost method is based on the idea that the amount of productivity loss is dependent on the time it takes to replace the person and restore the initial production level (89), which is about 6 months (93). The human capital approach takes the patient's perspective by counting hours not worked as lost hours, while the friction cost method takes the employer's perspective and only counts the lost hours until another employee replaces the absent one (93). This approach yields significantly lower indirect costs compared to the human capital approach (89). Despite overestimation of the costs, the human capital approach is the most used one (93, 94). In this thesis, a societal perspective is adopted and the human capital approach is used to estimate the indirect costs.

MANAGEMENT OF NON-CARDIAC CHEST PAIN

When patients present with acute chest pain a clinical assessment is important to quickly identify patients with serious conditions and rapidly provide them with optimal treatment. Once acute cardiac disease has been ruled out, appropriate management of these patients should be investigation and treatment of other serious causes of the NCCP to avoid misdiagnosing of life-threatening disorders. After ruling out these conditions, less serious conditions such as gastro-intestinal disease, and musculoskeletal and psychiatric disorders can be diagnosed and treated, although not as acutely (1). Bass and Mayou (4) highlighted the importance of diagnosing and managing NCCP within primary care. Quick

assessment and treatment are needed to counteract anxiety and disability. Patients should be able to discuss their worries, be advised on how to cope with symptoms, and be encouraged to remain physically active (4). As psychiatric co-morbidity is highly prevalent in patients with NCCP, a psychiatric evaluation in these patients is recommended (95, 96).

Different ways of follow-up of patients with NCCP are suggested, ranging from reassurance and explanation in the cardiac clinic to more intensive individual psychological treatment of underlying psychological problems (97). The treatment should aim at correcting the misattributions regarding chest pain as being harmful. Patients must adopt the belief that psychological factors can cause chest pain and attribute the chest pain to these. This approach focuses on managing stress, reducing cardiac risk factors, and educating the patient on the appropriate use of medical resources. Although treatment is psychological, the focus is to decrease the intensity and frequency of the physical symptoms, as well as to reduce distress and interference associated with the physical symptom. The treatment should be short as many patients refuse to participate in long psychological treatments. In addition, short treatments could suit more patients and have a greater population impact (98).

Although patients with NCCP have normal angiograms, some of them have been told that they suffer from angina and have been treated for this for long periods of time. Therefore, negative investigation of the pain and simple reassurance alone might not be effective. In these patients it is often necessary to combine psychological and physical interventions (83), and focus on the patients' concerns and fears (83, 99). Treatment in NCCP should target patients' misinterpretation of NCCP and improve the understanding of possible causes, provide tools for management of pain, stress, and anxiety, and gradually return to normal daily activities (18, 58, 83, 99). The information should include reassurance, explanation of alternative causes, and advice about symptom management (58). For example, relaxation techniques have been found to be helpful for patients with NCCP to handle stress and chest pain (100, 101), as well as decrease anxiety, somatization, and cardiovascular complaints (102).

There is strong support for CBT in the treatment of a series of conditions, including anxiety, panic, depressive symptoms (103-105), and NCCP (106). A Cochrane review found CBT useful and moderately successful, despite the multifaceted aetiology in NCCP (107). Cognitive behavioural therapy programs, even brief educational sessions, can effectively decrease disability. This might be due to reduced fear avoidance beliefs and pain catastrophizing when performing tasks that the individual misinterpret as threatening. In patients with avoidance behaviour, graded exposure to physical activity is recommended to challenge the

fear of body sensations by convincing the patient that their heart is fit (16). Physical activity has shown to be effective in the treatment of depression and anxiety (88, 108), although patients with panic may experience somatic symptoms after exercise (108).

Cognitive behavioural therapy

Cognitive behavioural therapy is a structured and collaborative process aiming to help patients evaluate their thoughts and behaviours, and to help them think in a more positive way (109). Central parts of CBT are cognitive restructuring strategies, modification of core beliefs, behavioural change strategies, and prevention of relapse (109, 110).

There are a number of randomized controlled CBT studies based on psychoeducation, cognitive restructuring, problem-solving, relaxation and breathing exercises, and exposure to physical activity (61, 79, 96, 111-114), see Table I. These studies have shown positive effects on chest pain frequency and intensity, psychological distress, avoidance of physical activity, and health-related quality of life among patients with NCCP compared to controls.

Several of the randomized controlled CBT studies aimed to anticipate and control symptoms in patients with NCCP, but also to modify inappropriate health beliefs. The treatment offered an alternative, non-cardiac explanation for the patients' chest pain by addressing the problem as a combination of physical, cognitive and behavioural factors, while challenging any catastrophic interpretations of symptoms. Furthermore, patients were taught how to cope with symptoms using relaxation and controlled breathing, and they addressed and managed problems that could maintain symptoms, including stress, anxiety, and inappropriate health beliefs. These studies had a positive impact on chest pain, activity avoidance, and psychological distress (111, 112, 114). An individualized biopsychosocial model with a stepped care, consisting of assessment only, low intensity CBT, or high intensity CBT showed significant improvement in chest pain frequency, pain interference, depressive symptoms, anxiety, avoidance of physical activity, work absenteeism, and healthcare utilization (82).

Face-to-face CBT treatment is effective, but requires experts and is time-consuming (104, 115), which limits its usefulness. Internet-delivered CBT, on the other hand, can be given to more patients as it requires less therapist involvement, is not time dependent, and is cheaper (115). Therapist guided Internet-delivered CBT is similar to face-to-face treatment with regard to treatment effects (115-119), despite different therapist backgrounds (120-122). Guided Internet-delivered CBT

has been proven to be effective in the treatment of mild to moderate symptoms of depression and anxiety (104, 123), and does not differ from face-to-face treatment. However, there is a big difference between guided and unguided Internet-delivered CBT (115, 124). Modern technology, such as smartphones and artificial intelligence, may potentially enhance Internet-delivered CBT (115). A study compared an 8-week long Internet-delivered CBT with a 5-week long Internet-delivered problem solving therapy and a waiting list control group in the treatment of adults with depressive symptoms. A significant improvement over time in depressive symptoms, anxiety and quality of life in the CBT and problem solving therapy groups was found, compared to the wait list group (125). Yet, no Internet-delivered CBT programs have been conducted in patients with NCCP.

Table I: Randomized controlled CBT studies in patients with NCCP				
CBT trials	**Number (n)**	**Intervention**	**Control**	**Improved outcomes**
Klimes et al (1990)	Intervention n=18 Control n=17	Maximum of 11 sessions individual CBT containing relaxation, breathing, cognitive restructuring and problem solving	Explanation and discussion of symptoms, encouragement to increase activity	Chest pain, limitations and disruptions in daily life, autonomic symptoms and psychological distress
Mayou et al (1997)	Intervention n=20 Control n=17	12 sessions of individual CBT containing relaxation, breathing, cognitive restructuring and problem solving	Assessment only	Frequency and distress of symptoms, mood and activity at 3 months, but no more differences at 6 months follow-up
Potts et al (1999)	Intervention n=34 Control n=26	Six sessions of group CBT containing psychoeducation, cognitive restructuring, relaxation, breathing exercises, light physical exercise with graded exposure	Waiting control	Chest pain frequency, anxiety, depression, disability, and exercise tolerance
Van Peski Oosterbaan et al (1999)	Intervention n=32 Control n=33	Up to 12 sessions of individual CBT containing relaxation, breathing, cognitive restructuring and problem solving	Usual care	Frequency and intensity of chest pain
Spinhoven et al (2010)	Intervention n=23 Paroxetine n=23 Placebo n=23	6-12 sessions of individual CBT containing breathing and relaxation techniques, cognitive restructuring, and behavioural experiments to challenge maintaining factors	Placebo or paroxetine	Chest pain frequency
Jonsbu et al (2011)	Intervention n=21 Control n=19	Three sessions of individual CBT containing psychoeducation, exposure to physical activity and cognitive restructuring	Usual care	Fear of body sensations, avoidance of physical activity, depressive symptoms, and some domains of quality of life
Van Beek et al (2013)	Intervention n=60 Control n=53	Six sessions of individual CBT containing psychoeducation, cognitive restructuring, and influencing avoidance behaviour	Usual care	Disease severity, anxiety, and depressive symptoms

CBT Cognitive Behavioural Therapy, *NCCP* Non-Cardiac Chest Pain

RATIONALE FOR THE THESIS

Non-cardiac chest pain is a common condition that has a negative impact on patients' health-related quality of life, daily life, and healthcare seeking behaviour. Previous research has shown that patients with NCCP suffer from psychological distress in terms of depressive symptoms, cardiac anxiety and fear of body sensations, but there is little knowledge about which of these factors drives people to seek healthcare. Knowledge is also lacking regarding the extent of healthcare utilization and the costs these patients incur in relation to patients with cardiac chest pain. The hypothesis of this thesis was that patients who experience recurrent and persistent chest pain and who do not receive an accurate explanation for the cause of the chest pain may perceive the pain as threatening. This can lead to pain-related fear and cardiac anxiety, which in turn can have a negative impact on patients' psychological well-being, and lead to increased levels of healthcare utilization and productivity loss, and therefore result in high costs for the society (Figure I).

Patients might suffer from pain-related fear and anxiety about having a cardiac disease, which make them avoid physical activities in order to prevent an aversive situation from occurring, which in turn might lead to disability and maintenance of pain. Therefore, these patients might need help to modify their beliefs about chest pain, change their cognitive and behavioural strategies and learn how to handle their chest pain. It is hypothesized that targeting cardiac anxiety with CBT can help patients modify their beliefs about chest pain and give them tools to easier handle chest pain (Figure I). To date, there are no Internet-delivered CBT-studies on these patients.
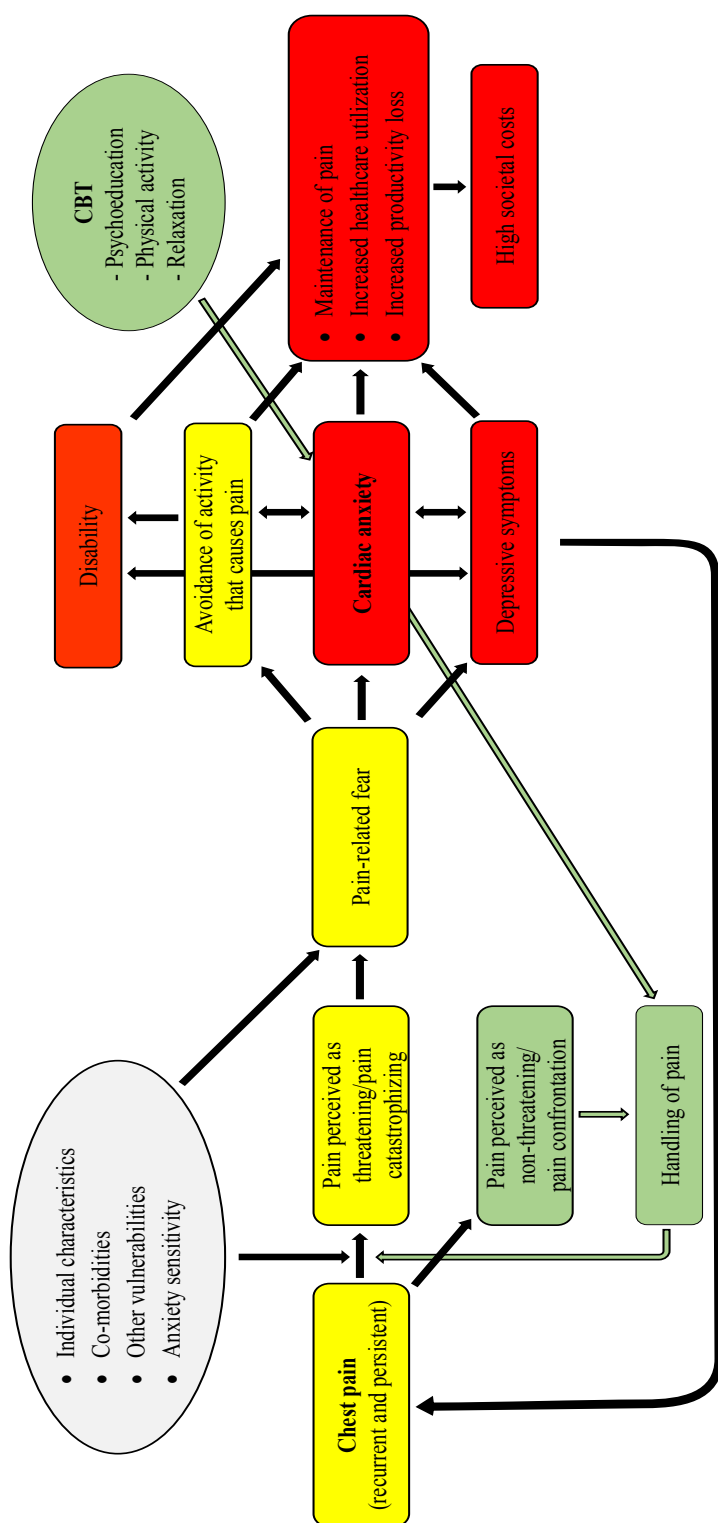
Figure I: As shown in yellow, chest pain that is perceived as threatening can lead to pain-related fear and cardiac anxiety. This can have negative impact on patients' physical (i.e. avoidance of activity that causes pain and maintenance of pain) and psychological wellbeing (i.e. depressive symptoms) and leads to increased healthcare utilization and productivity loss (due to sick-leave and disability pension), resulting in high societal costs (shown in red). As shown in green, targeting cardiac anxiety with Cognitive Behavioural Therapy (CBT) can help patients modify their beliefs about chest pain and give them tools to easier handle chest pain and avoid further pain catastrophizing

AIMS FOR THE THESIS

OVERALL AIM

The overall aim of this thesis was to improve care for patients with non-cardiac chest pain by describing related psychological distress, healthcare utilization and societal costs, and by evaluating an Internet-delivered cognitive behavioural intervention.

SPECIFIC AIMS OF THE STUDIES

- To compare depressive symptoms and healthcare utilization in patients admitted for later proven NCCP, compared to patients with IHD presenting with acute myocardial infarction (AMI) and angina pectoris (AP) during a 1-year follow-up after an acute chest pain event (Study I).

- To present a detailed description of the costs of patients with NCCP compared to patients with AMI and Angina Pectoris (AP) from a societal perspective (Study II).

- To explore the prevalence of depressive symptoms, cardiac anxiety, and fear of body sensations in patients who were admitted to hospital because of chest pain and discharged with a NCCP diagnosis. Further, we aimed to describe how depressive symptoms, cardiac anxiety and fear of body sensations are related to each other and to healthcare-seeking behavior (Study III).

- To test the feasibility of a short guided Internet-delivered CBT intervention and the effects on chest pain, cardiac anxiety, fear of body sensations, and depressive symptoms in patients with NCCP compared to usual care (Study IV).

METHODS AND MATERIALS

DESIGNS AND SETTINGS

This thesis comprises four quantitative studies. Table II contains an overview of the methods and materials used in studies I-IV.

Studies I and II had a longitudinal descriptive and comparative design. Participants were recruited consecutively among patients discharged from a county hospital in southeast Sweden after hospitalization due to acute chest pain and with diagnoses of NCCP (ICD 10-code R07.4, chest pain unspecified; and ICD 10-code Z03.4, observation for suspected myocardial infarction), AMI (ICD 10-code I21), or AP (ICD 10-code I20). This information was provided from a regional care database. Patients were excluded if they could not complete questionnaires, and/or were living in a nursing home. Patients were approached within 2 weeks from the day of discharge, and data was collected between July and December 2008 and at the 1-year follow-up (Study I). In study II, two-year data was collected from registers.

Study III had a cross-sectional explorative and descriptive design. Data was collected consecutively between October 2013 and January 2014. Eligible participants for this study were patients 18 years or older who were discharged with any NCCP diagnoses (ICD 10-code R07.2, precordial chest pain; ICD 10-code R07.3, other chest pain; ICD 10-code R07.4, chest pain unspecified; and ICD 10-code Z03.4, observation for suspected myocardial infarction). Patients were approached within one month from the day of discharge from the emergency, medical, or cardiac departments at three county hospitals and one university hospital within a region in southeast Sweden. Patients who reported a cardiac cause for their chest pain were excluded. Compared to studies I and II, ICD 10-codes R07.2, and R07.3 were added to include a broader range of patients with NCCP. Most patients still had ICD 10-codes R07.4 and Z03.4.

Study IV was designed as a pilot randomized controlled study and was conducted February-March 2015. Eligible participants were patients 18 years or older who had sought medical care at least three times during the last 6 months because of chest pain of non-cardiac origin (ICD 10-codes: R07.2, precordial chest pain; R07.3, other chest pain; R07.4, chest pain unspecified; and Z03.4, observation for suspected myocardial infarction). Eligible patients were identified using a regional care database. Included patients suffered from cardiac anxiety ($\geq$ 24 points on the Cardiac Anxiety Questionnaire (CAQ)), or fear of body sensations ($\geq$ 28 on the Body Sensations Questionnaire (BSQ)). Patients who had no easy access to a

computer/tablet with an Internet connection, those with physical constraints leading to inability to perform physical activity/bicycle stress test, difficulties to read and understand the Swedish language, and/or severe depressive symptoms according to cut-off (≥ 20) on the Patient health Questionaire-9 (PHQ-9), were excluded.

Table II: Overview of study methods and materials (Studies I-IV)				
	Study I	**Study II**	**Study III**	**Study IV**
Study design	Longitudinal descriptive and comparative	Longitudinal descriptive and comparative	Cross-sectional explorative and descriptive	Pilot randomized controlled study
Participants	267 patients (131 NCCP, 66 AMI, 70 AP)	199 patients (99 NCCP, 51 AMI, 49 AP)	552 patients with NCCP	15 patients with NCCP (7 intervention, 8 control)
Data source	Questionnaires and registers	Registers	Questionnaires	Questionnaires
Data collection date	July-December, 2008 and 2009	July-December, 2009	October, 2013- January, 2014	January-February, and March-April, 2015
Measurements	Depressive symptoms and healthcare utilization, one year before index admission and one year after	Healthcare utilization, sick-leave, disability pension, and societal costs (direct healthcare costs and indirect costs due to productivity loss), one year including index admission and one year after	Number of healthcare visits, depressive symptoms, cardiac anxiety, and fear of body sensations	Feasibility of intervention, chest pain frequency, cardiac anxiety, fear of body sensations, and depressive symptoms before and after the intervention
Instruments and registers	SQ-3, MADRS, CDW	CDW, CPP, Social Insurance Agency database	Question regarding number of healthcare visits, PHQ-9, CAQ, BSQ	Question regarding chest pain frequency, CAQ, BSQ, PHQ-9
Cronbach's α coefficient in this thesis	SQ-3 = 0.81 MADRS = 0.86		PHQ-9 = 0.87 CAQ = 0.90 -Fear = 0.84 -Avoidance = 0.89 -Heart focused attention = 0.76 BSQ = 0.93	PHQ-9 = 0.85 CAQ = 0.83 -Fear = 0.83 -Avoidance = 0.87 -Heart focused attention = 0.65 BSQ = 0.92
Data analysis	Kuder Richardson-20 coefficient of reliability, Cronbach's α, One-way ANOVA with Bonferroni's post hoc test, Chi-square test, Student's t-test, Multiple linear regression, paired t-test, Kruskal Wallis test, Mann-Whitney U test, Wilcoxon signed rank test	One-way ANOVA, Bonferroni's post hoc test, Chi-square test, Wilcoxon signed rank test	Cronbach's α, Chi-square test, Student's t-test, Mann-Whitney U test, Kruskal Wallis test, Spearman correlation, Multivariate logistic regression	Cronbach's α, Chi-square test, Mann-Whitney U test

AMI Acute Myocardial Infarction, *AP* Angina Pectoris, *BSQ* Body Sensations Questionnaire, *CAQ* Cardiac Anxiety Questionnaire, *CDW* Care Data Warehouse, *CPP* Cost Per Patient database, *MADRS* Montgomery Åsberg Depression Rating Scale, *NCCP* Non-cardiac Chest Pain, *PHQ-9* Patient Health Questionnaire-9, *SQ-3* Screening questions-3

The pilot randomized controlled intervention is described according to the Template for Intervention Description and Replication (TIDieR) checklist (126) in Table III.

Table III: Description of the pilot randomized controlled intervention according to the Template for Intervention Description and Replication (TIDieR) checklist.	
Brief name	Internet-delivered CBT for NCCP patients - a pilot study
Rationale	NCCP patients who experience recurrent and persistent chest pain and do not receive an explanation for the cause of the chest pain may perceive the pain as threatening, leading to pain-related fear and cardiac anxiety, resulting in avoidance of physical activity in order to prevent an aversive situation from occurring. It was hypothesized that targeting cardiac anxiety with CBT could help patients modify their beliefs about chest pain and learn how to handle their chest pain. An additional hypothesis was that a short guided Internet-delivered CBT program would be preferred by the patients and easier to implement in healthcare settings than a long face-to-face program.
Materials	Patients received practical information about the Internet platform (i.e., website URL, login details, and how to manage the program). The Internet platform offered introductory information about the goals and the content of the program, how to handle the program, names and photos of the study team, as well as contact details for the study provider. The program comprised text materials, figures, and video and audio files. One video showed two patients talking about their experiences of NCCP, and the other one included information and instructions about physical activity given by a physiotherapist. The audio file contained a breathing-based relaxation exercise.
Procedures	Eligible patients (≥18 years old with at least 3 healthcare consultations due to NCCP during the last 6 months) who were interested in participation were screened for cardiac anxiety and/or fear of body sensations before study inclusion. Patients reporting cardiac anxiety (≥ 24 points on the CAQ) or fear of body sensations (≥ 28 on the BSQ), were included in the study and randomized into an intervention or control group. The intervention group received four sessions of Internet-delivered CBT and the control group received care as usual.
Intervention provider	A cardiac nurse provided the intervention with support from a research team including three cardiac nurses, one psychiatrist, one cardiologist, and one physiotherapist.
Mode of delivery	Guided Internet-delivered.
Location for the intervention	Prior to the study start, the patients made one visit at the clinic to perform a bicycle stress test and receive study information. The rest of the program was delivered via the Internet.
Length of intervention	The CBT program was conducted February-March 2015 and contained four sessions to be completed within four weeks. Patients could access one session each week. On average, about 45-60 minutes daily engagement was required to complete the program.
Fidelity	Planned: The intervention was based on a theoretical basis (i.e. avoidance of physical activity due to cardiac anxiety). The intervention was designed together with experts from different areas, such as nursing, psychiatry, medicine, and physiotherapy, and was validated before implementation. All patients received the same intervention and were guided by the same person, ensuring that the same intervention was delivered and that patients were adhering to the study protocol and understanding what was expected from them.
	Actual: There were some differences in the amount of guidance as some patients needed more guidance and support.

BSQ Body Sensations Questionnaire, *CAQ* Cardiac Anxiety Questionnaire, *CBT* Cognitive Behavioural Therapy, *NCCP* Non-Cardiac Chest Pain

Internet-delivered cognitive behavioural therapy program

The CBT program contained four sessions to be completed within four weeks. The program was delivered using an Internet platform specifically developed for this study by the study provider (GM) and a computer technician. Beside the content of the program, the Internet platform offered introductory information about the goals and the content of the program, how to handle the program, names and photos of the study team, as well as contact details for the study provider (GM). The program was arranged similarly to the intervention by Jonsbu et al (61), which consisted of three weeks CBT with psychoeducation (about NCCP and avoidance behaviour) and exposure to physical activity. Their intervention resulted in a greater improvement in fear of body sensations, avoidance of physical activity, depression, and some quality of life measures compared to usual care, and the effects were maintained at the 12- month follow-up. The CBT program explored in this thesis lasted for four weeks and contained exposure to physical activity (including a bicycle stress test) and psychoeducation (about NCCP and avoidance behaviour), but also a breathing-based relaxation exercise as it has positive effects on stress and anxiety. In addition, patients formulated goals to be achieved and had weekly homework assignments. The program comprised text materials, figures, and video and audio files. One video showed two patients talking about their experiences of NCCP, and the other one included information and instructions about physical activity given by a physiotherapist. The audio file contained the breathing-based relaxation exercise. Before implementation, the content was validated individually by a general practitioner and two patients with long experience of NCCP.

Figure II shows an overview of the content in each session/week. Before the start of session one, patients randomized to the CBT group performed a bicycle stress test. On that same occasion, patients received information about website URL, login details, and how to manage the program. This is referred to as week 0 in Figure II. Once logged in, patients could access one session each week.

Session one included goal setting and psychoeducation, including a homework assignment about NCCP. The content of session two was psychoeducation and practical exercises and homework assignments about relaxation and physical activity. The relaxation and physical activity exercises with related homework assignments continued during the rest of the program. However, in session three, patients were provided with psychoeducation about avoidance behaviour, and in session four they received additional information and further advice about management of chest pain. The intention was that patients would gradually increase the intensity to be able to perform moderate physical activity for at least 30 minutes per day, 5 days per week. This was in accordance with the "Physical Activity in the Prevention and Treatment of Diseases" (127), but has also been

recommended in earlier research (108). Patients were also instructed to perform the relaxation exercise using the audio file at least 5 days per week. Every session started with a summary of the key knowledge from the previous session and the content of the following session. Goals were evaluated during the program.
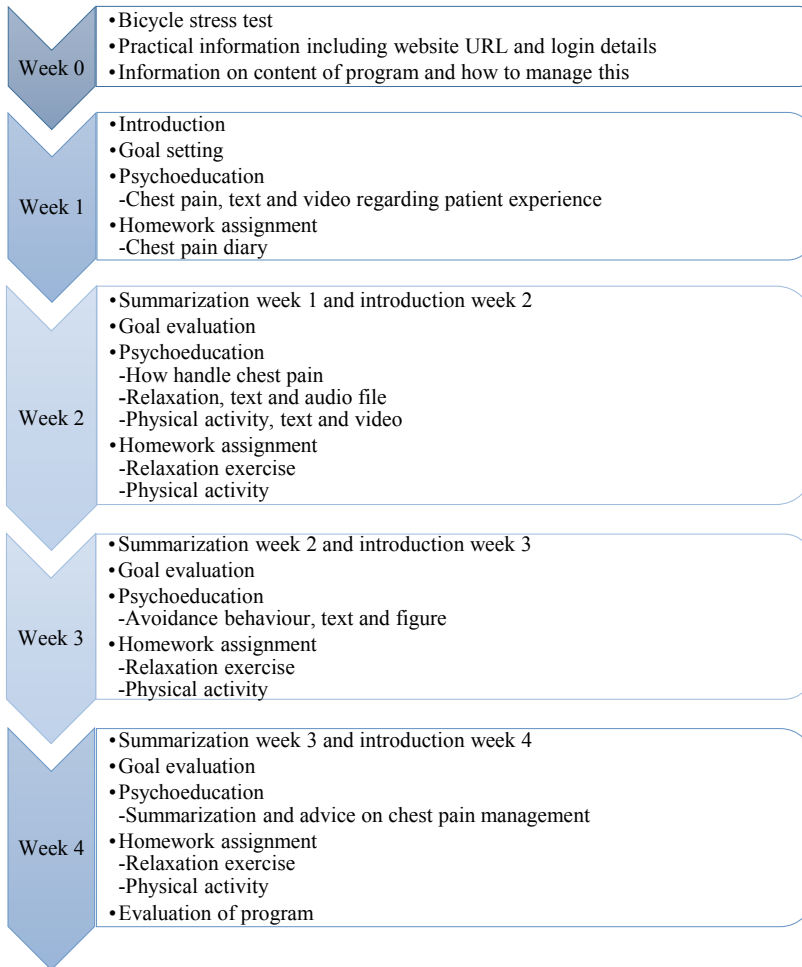
Week 0
- Bicycle stress test
- Practical information including website URL and login details
- Information on content of program and how to manage this

Week 1
- Introduction
- Goal setting
- Psychoeducation
  -Chest pain, text and video regarding patient experience
- Homework assignment
  -Chest pain diary

Week 2
- Summarization week 1 and introduction week 2
- Goal evaluation
- Psychoeducation
  -How handle chest pain
  -Relaxation, text and audio file
  -Physical activity, text and video
- Homework assignment
  -Relaxation exercise
  -Physical activity

Week 3
- Summarization week 2 and introduction week 3
- Goal evaluation
- Psychoeducation
  -Avoidance behaviour, text and figure
- Homework assignment
  -Relaxation exercise
  -Physical activity

Week 4
- Summarization week 3 and introduction week 4
- Goal evaluation
- Psychoeducation
  -Summarization and advice on chest pain management
- Homework assignment
  -Relaxation exercise
  -Physical activity
- Evaluation of program

Figure II: Content of the Cognitive Behavioural Therapy program, four sessions/weeks

STUDY PARTICIPANTS

The basic demographics are rather similar in all four studies, see Table IV. In study I, 267 patients participated (131 with NCCP, 66 with AMI and 70 with AP). Of these 267 patients, a total of 199 (99 with NCCP, 51 with AMI and 49 with AP) agreed to participate in study II. In these studies, patients were predominantly male

(about 60 %) and had a mean age of 67 years. Study III included 552 patients with a mean age of 64 years and with similar gender distribution. In study IV, nine men and six women between the age of 22 and 76 (median age of 66 years, q1-q3 57-73) participated.

Table IV: Demographic and clinical characteristics for study participants (Study I-IV)				
	Study I N=267*	Study II N=199*	Study III N=552	Study IV N=15
Age year, mean ±SD	67±14	67±13	64±17	Median 66 (q1-q3 57-73)
Sex, n (%)				
Females	112 (42)	82 (41)	281 (51)	6 (40)
Males	155 (58)	117 (59)	271 (49)	9 (60)
Married/cohabiting, n (%)	187 (70)	144 (72)	370 (67)	10 (67)
Educational level, n (%)				
Compulsory school	118 (44)	82 (41)	165 (30)	2 (13)
High school	103 (39)	78 (39)	216 (39)	7 (47)
University	46 (17)	39 (20)	150 (27)	6 (40)
Other	-	-	20 (4)	-
Work status, n (%)				
Workers	69 (26)	55 (28)	152 (28)	6 (40)
Retired	164 (61)	120 (60)	302 (55)	5 (33)
Sick-leave/disability pension	21 (8)	14 (7)	40 (7)	4 (27)
Unemployed	-	8 (4)	21 (4)	-
Students	-	2 (1)	19 (3)	-
Other	13 (5)	-	17 (3)	-

*Studies I and II are based on the same cohort

Of the approached patients 53 % (Study I), 77 % (Study II), 30 % (Study III), and 15 % (Study IV) agreed to participate. Many of the non-participants did not fulfil the inclusion or exclusion criteria, did not respond to our study invitation or declined study participation. Non-participants did not differ significantly in sex and age compared to study participants (Study I, IV). In study II, non-participants were comparable to study participants with regard to sex, but patients with NCCP were significantly younger, and those with AP were significantly older. In study III, those who did not respond were significantly younger and tended to more often be males, while those who declined participation were significantly older than the study participants.

DATA COLLECTION AND MEASUREMENTS

In this thesis, data was collected using standardized self-administered questionnaires (Studies I, III, IV) and registers (Study I, II). Demographic data including age, sex, marital status, educational level, work status, income level (Study I, II), medical diagnosis (I, III, IV), birth country, body mass index (BMI), smoking habits, alcohol consumption, and exercise level (Study III, IV) was collected. In Table IV, only demographic data collected in all studies is presented.

Data was also collected regarding depressive symptoms (Study I, III, IV), cardiac anxiety (Study III, IV), fear of body sensation (Study III, IV), healthcare utilization (Study I, II, III), societal costs (i.e. direct healthcare costs and indirect costs due to productivity loss) (Study II), and chest pain frequency, and feasibility of the CBT intervention (Study IV). In study I, two-year data was collected one year before index admission (i.e. admission when patients were recruited) and one year after index admission. The index admission and administrative contacts were not included in the analysis. In study II, two-year data was also collected, but in this study the index admission was included in year 1. All contacts within primary care and outpatient clinics, including administrative contacts, were included in the analysis. In study IV, data was collected before randomization and after the end of the CBT program. Data regarding feasibility of the program was collected at the end of the CBT program.

Instruments and registers

Depressive symptoms

In study I, a two-step procedure was used to collect data on depressive symptoms. First, the patients were asked to answer the following three screening questions (SQ-3):

1. *During the past month, have you often been bothered by little interest or pleasure in doing things?* ("no" or "yes")

2. *During the past month, have you often been bothered by feeling down, depressed or hopeless?* ("no" or "yes")

3. *Is this something with which you would like help?* ("no"; "yes, but not today" or "yes")

Two of the three screening questions were derived from the original Primary care evaluation of Mental Disorders (Prime MD), and were validated by Arroll et al after the addition of a "help"-question. The SQ-3 has high sensitivity and specificity (128, 129). Cronbach's α coefficient was 0.81 in this thesis.

Patients who answered positively to any of the three questions were considered at risk for depressive symptoms and were therefore instructed to complete the Montgomery Åsberg Depression Rating Scale (MADRS). The MADRS is a valid and reliable depression rating scale (130-132), comprising 9 items with item scores between 0 and 6 points. Higher scores reflect more severe depressive symptoms, and scores of 12 and above imply at least moderately severe depression (130). In this thesis, Cronbach's α coefficient was 0.86.

In studies III and IV, depressive symptoms were measured with the PHQ-9, which is a 9-item questionnaire with item scores between 0 (not at all) and 3 (nearly every day) points. A score of 10 or above indicates at least moderate depressive symptoms. The PHQ-9 has demonstrated good psychometric properties (133). Cronbach's α coefficient was 0.85-0.87 in this thesis.

Cardiac anxiety

Cardiac anxiety was measured with the CAQ (Study III, IV). The CAQ contains 18 items ranging from 0 (never) to 4 (always) points. For example, items can be formulated as: "I pay attention to my heart beat" or "I avoid exercise or other physical work". The CAQ consists of three subscales for Fear, Avoidance, and Heart-focused attention. A sum and a mean total score can be calculated for the CAQ. For the subscales, the mean score of the items included in each subscale can be calculated. Mean values are recommended for an easier comparison of scores from the total CAQ and the subscales. Higher scores indicate greater cardiac anxiety and for the subscales greater fear, avoidance and heart-focused attention (76). In accordance with the grading of the questionnaire, a mean score of two indicates that cardiac anxiety is sometimes prevalent. It was therefore classified as moderate cardiac anxiety.

The CAQ has demonstrated good psychometric properties (76). Cronbach's α coefficients in this thesis were 0.83-0.90 for the total CAQ, 0.83-0.84 for the fear subscale, 0.87-0.89 for the avoidance subscale, and 0.65-0.76 for the heart-focused attention subscale.

Fear of body sensations

Fear of body sensations was measured with the BSQ (Study III, IV). This is a 17-item scale used to measure fear of body sensations, such as palpitations, dizziness and sweating. Item scores range from 1 (not frightened or worried by this sensation) to 5 (extremely frightened by this sensation) points. The total score is computed as the mean value of all items, with higher scores indicating more fear of body sensations. In this thesis, a mean score of two was classified as having some degree of fear of body sensations. The BSQ is reliable and valid (80), and sensitive to changes in fear of body sensations in patients with NCCP undergoing CBT (61). Cronbach's α coefficient was 0.92-0.93 in this thesis.

Healthcare utilization and societal costs

Healthcare utilization data (Study I, II) (i.e. primary care, outpatient clinic contacts, and hospital admissions) was collected from the Care Data Warehouse (CDW) database. This is a population-based diagnosis-related administrative database that contains information about almost all healthcare contacts within primary care, out-patient clinics and hospital care. The CDW database is run by Östergötland County Council (134-136). In study III, the number of healthcare visits was self-reported by the patients by answering the following self-developed question: *"In the last year, how many times did you seek care due to chest pain?"* Patients could choose between the categories: "1, 2-3, or >3".

Data on the direct healthcare costs (Study II) was collected from the Cost Per Patient (CPP) database, which provides patient-related cost information about almost all healthcare in the county of Östergötland, based on information from the CDW. The CPP database is also run by Östergötland County Council (134-136). The indirect costs (Study II) were mainly based on productivity loss due to sick-leave, as well as productivity loss due to disability pension in cases of prolonged reduced work capacity. Data on the indirect costs was collected from the Social Insurance Agency database (137). The Social Insurance Agency has been tasked by the government to be responsible for the official statistics in the areas of support in disease and disability.

Chest pain frequency

Chest pain frequency was self-reported by the patients before and after the intervention (Study IV) by answering the following self-developed question: *"During the last month, how often have you experienced non-cardiac chest pain?*

Feasibility of cognitive behavioural therapy intervention

In study IV, feasibility of the CBT intervention was determined based on the user-friendliness of the Internet platform, the time and amount of guiding needed to manage the program, the accessibility of the content, and the patients' perception of the program. Feasibility was assessed using a questionnaire developed by the study team and contained both open and closed questions and statements. Some of the questions/statements were:

- *The educational section was sufficient.* Patients could choose between "Totally agree", "Agree", "Partly agree", "Do not agree".

- *The tools (e.g. physical activity and relaxation exercise) were sufficient.* Patients could choose between "Totally agree", "Agree", "Partly agree", "Do not agree".

- *I lack information about the following:* _____

- *To which extent do you think the program was easy to use?* Patients could choose between "To a large extent", "To a sufficient extent", "To a small extent", "Not at all".

- *How much time did you spend on the program per day?* _____

- *To which extent do you think the program helped you fulfil your goals?* Patients could choose between "To a large extent", "To a sufficient extent", "To a small extent", "Not at all".

- *How satisfied are you with the guiding?* Patients could choose between "Very satisfied", "Satisfied", "Neither satisfied nor dissatisfied", "Dissatisfied", "Very dissatisfied".

PROCEDURES

Study participants were identified using lists of patients that were provided by the secretaries at the different departments (Study I-III), or at the CDW (Study IV). These lists were derived based on the inclusion criteria in the studies. Study information, written informed consent form, questionnaires, and a pre-stamped envelope were sent to all eligible patients (Study I-III). The invited patients were offered to contact the research team in case of questions or remarks. Patients consented to study participation (Study I-III) and gave permission to data being

collected from the databases (Study II) by signing and returning the written informed consent form together with the completed questionnaires.

In study IV, patients were initially contacted by phone and informed about the study, and those interested in participation received written study information, a written informed consent form, questionnaires, and a pre-stamped envelope. Patients who returned a signed written informed consent were screened for cardiac anxiety and/or fear of body sensations before randomization. Patients reporting cardiac anxiety ($\geq$ 24 points on the CAQ) or fear of body sensations ($\geq$ 28 on the BSQ) were included in the study.

In studies I and III, 1 and 2 reminders were sent to those who had not replied within 2 and 3 weeks respectively. Patients not willing to participate and those under investigation to rule out cardiac disease were not contacted further. A scratch card worth 1 Euro was sent to study participants to thank them for completing the questionnaires (Study III).

STATISTICAL ANALYSIS

The statistical analysis was performed using the Statistical Package for Social Science (SPSS) version 18.0 (Study I), IBM SPSS Statistics 20 (Study II), and IBM SPSS Statistics 22 (Study III, IV).

Kuder Richardson-20 coefficient of reliability was used to calculate the reliability coefficient for the SQ-3 (Study I), and Cronbach's α coefficient was used to calculate the reliability coefficient for the MADRS (Study I), and PHQ-9, CAQ, and BSQ (Study III, IV). Categorical variables are described as frequencies and percentages. Continuous variables are described as mean values and standard deviations (Study I-III), and medians and interquartile range due to small sample (Study IV). Normally distributed data was analyzed with Student's t-test. Skewed data was analyzed with Mann-Whitney U test and Kruskal Wallis test (Study I-IV). Between-group differences regarding socio-demographic variables were calculated using One-way ANOVA with Bonferroni's post hoc test for continuous variables and Chi-square test for categorical variables (Study I, II).

Multiple linear regression analysis was used to explore the relationship between healthcare utilization, depressive symptoms and socio-demographic variables. Kruskal Wallis test and Mann-Whitney U test were used to explore differences regarding changes in depressive symptoms in relation to socio-demographic variables. Differences within groups between baseline and follow-up were analyzed with paired T-test for normally distributed variables and Wilcoxon signed

rank test for skewed variables. For differences between groups, One-way ANOVA and Student's t-test were used for normally distributed data, and Kruskal Wallis test and Mann-Whitney U test for skewed data (Study I). Wilcoxon signed rank test was used to analyze differences within groups between year 1 and 2 regarding healthcare utilization and costs. A rough estimate of the index admission costs was made by dividing the total hospital cost for the first year with the number of admissions (Study II). Spearman correlation coefficient was used to describe the relationship between depressive symptoms, cardiac anxiety and fear of body sensations. Chi-square test was used to explore co-existence of depressive symptoms, cardiac anxiety and fear of body sensations in the participants. The independent relationship between depressive symptoms, cardiac anxiety, fear of body sensations, and healthcare seeking behaviour was determined using a multivariate logistic regression. Age, sex and multi-morbidity were controlled for. No problems with multicollinearity between the independent variables were detected according to the variance inflation factor (range 1.5-1.6) (Study III). In study IV, Mann-Whitney U test was used to compare the CBT and control groups regarding mean differences in cardiac anxiety, fear of body sensations and depressive symptoms between baseline and the end of the program. Analyses were done based on intention to treat. Differences were considered significant at $p<0.05$ (Study I-IV).

ETHICAL CONSIDERATIONS

All studies were approved by the Regional Ethical Review Board in Linköping, code M12-08 and M12-08 T118-09 (Study I, II)), code 2013/223-31 (Study III), and code 2014/377-31 (Study IV). The studies were carried out in accordance with the Declaration of Helsinki (138). Written informed consent was obtained from all participants. Patients were informed that study participation was voluntary, and that they could withdraw from participation whenever they wished without any consequences. The researchers were not involved in the care of the participants (Study I-IV). The data collection was also approved by all clinic managers (Study I, III).

To ensure patient' safety, patients scoring more than 20 on the MADRS (Study I), indicating severe depressive symptoms, were contacted by a physician for an evaluation of further examination and treatment. When using the Internet in study IV, security was ensured by making the program accessible only for those who received the website URL and login details. For login, a two-factor authentication was applied using Google Authenticator. Data was collected using a secure web-based questionnaire requiring both username and password for login.

Study participation, including the intervention was free of cost. In all cases where patients were expected to send any material to the research team, they were provided with pre-stamped envelopes so that they did not have to pay by themselves.

The data collection included several questionnaires (Study III, IV), which could possibly be perceived as burdensome to the patients. Therefore, patients were informed about the possibility to complete the questionnaires in more than one sitting, although these were distributed electronically (Study IV).

Participation in the intervention (Study IV) may have resulted in a big commitment for the patients, who had to dedicate about one hour per day for the program. In return, patients were examined and followed-up for their chest pain. They also received a free CBT program aiming to improve knowledge about chest pain and how to manage it.

RESULTS

PSYCHOLOGICAL DISTRESS

Depressive symptoms

Depressive symptoms were reported by more than 25 % of the participants in studies I and III, and in 20 % of the participants in study IV. There were no significant differences between patients with NCCP, AMI or AP regarding either prevalence or severity of depressive symptoms. Single marital status (p<0.05, Beta=0.20) and younger age (p<0.01, Beta=-0.30) were independently related to more depressive symptoms at the baseline measurement. Experiencing depressive symptoms at baseline was also independently related to more depressive symptoms at the follow-up (p<0.001, Beta=0.74) (Study I).

In patients with NCCP, 7 % of those with depressive symptoms at baseline had no depressive symptoms at follow-up. In total, 21 % had depressive symptoms both at baseline and follow-up, and 11 % had depressive symptoms at follow-up, but not at baseline (see Figure III). There were no significant differences in depressive symptom changes between diagnosis groups or between several socio-demographics (Study I). Nine percent of follow-up data was missing due to declined participation at the 1-year follow-up.
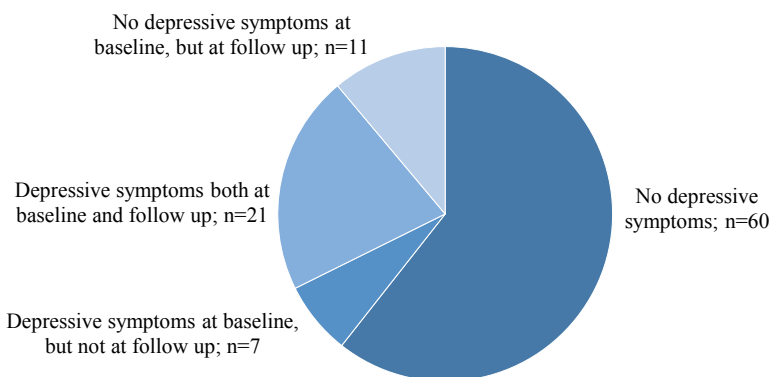

No depressive symptoms at baseline, but at follow up; n=11

Depressive symptoms both at baseline and follow up; n=21

Depressive symptoms at baseline, but not at follow up; n=7

No depressive symptoms; n=60

Figure III: Comparisons of depressive symptom prevalence in patients with NCCP between baseline and follow-up in study I (N=99)

Cardiac anxiety

In study III, the total CAQ score was 24.6±13.0 and the mean score was 1.4±0.7. In study IV, these scores were 31.7±10.5 and 1.8±0.6. About 42 % of the patients in study III, and 67 % of the patients in study IV scored at least two, indicating at least moderate cardiac anxiety.

The scores in the CAQ, including the subscales fear, avoidance, and heart-focused attention are presented by the number of healthcare seeking occasions in Table V. The more healthcare seeking occasions, the higher scores indicating greater cardiac anxiety, fear, avoidance, and heart-focused attention.

Table V: Cardiac Anxiety Questionnaire scores in patients with non-cardiac chest pain, based on the number of healthcare seeking occasions, mean±SD. Higher scores indicate greater cardiac anxiety, fear, avoidance, and heart-focused attention (Study III, IV)

	Study III			Study IV
	Patients with 1 healthcare seeking occasion/year (n=331)	Patients with 2-3 healthcare seeking occasions/year (n=145)	Patients with >3 healthcare seeking occasions/year (n=76)	Patients with ≥3 healthcare seeking occasions/6 month (n=15)
Total score	20.0±11.1	29.2±11.8	36.1±12.5	31.7±10.5
Mean score	1.1±0.6	1.6±0.7	2.0±0.7	1.8±0.6
- Fear	1.4±0.8	1.9±0.7	2.3±0.7	2.2±0.8
- Avoidance	1.0±0.9	1.5±1.0	1.9±1.0	1.5±0.9
- Heart-focused attention	0.8±0.6	1.3±0.7	1.7±0.8	1.4±0.7

Multivariate logistic regression analysis showed that cardiac anxiety was the only variable independently related to healthcare seeking behaviour, also after adjusting for multi-morbidity (OR 1.08, CI 1.06-1.10, p<0.001) (Study III), see Table VI.

Table VI: The independent relationship between psychological distress and healthcare seeking behaviour based on multivariate logistic regression analysis, after adjusting for multi-morbidity (Study III)

	Healthcare seeking behaviour		
Explanatory variables	**Odds Ratio**	**95 % Confidence interval**	**p-value**
Cardiac anxiety	1.08	1.06-1.10	**<0.001**
Depressive symptoms	1.02	0.98-1.06	0.423
Fear of body sensations	0.99	0.97-1.01	0.172

(Goodness of fit Hosmer-Lemeshow chi-square coefficient = 10.9, p-value = 0.208)

Fear of body sensations

The total score in the BSQ was 31.4±12.1 and the mean score was 1.9±0.7 (Study III). In study IV, these scores were 43.9±12.9 and 2.6±0.8. In total, 62 % of the patients in study III, and 93 % of the patients in study IV scored at least two, indicating at least some degree of fear of body sensations.

The BSQ scores are reported by the number of healthcare seeking occasions in Table VII. The scores in the BSQ increased in relation to increased number of healthcare seeking occasions, indicating higher fear of body sensations in patients with more healthcare seeking occasions.

Table VII: Body Sensations Questionnaire scores in patients with non-cardiac chest pain, based on the number of healthcare seeking occasions, mean±SD. Higher scores indicate greater fear of body sensations (Study III, IV)

	Study III			Study IV
	Patients with 1 healthcare seeking occasion/year (n=331)	Patients with 2-3 healthcare seeking occasions/year (n=145)	Patients with >3 healthcare seeking occasions/year (n=76)	Patients with ≥3 healthcare seeking occasions/6 month (n=15)
Total score	29.3±11.3	32.7±12.0	37. 9±13.1	43.9±12.9
Mean score	1.7±0.7	1.9±0.7	2.2±0.8	2.6±0.8

Relationship between depressive symptoms, cardiac anxiety and fear of body sensations

In study III, the relationship between depressive symptoms, cardiac anxiety, and fear of body sensations was examined. There was a strong positive relationship between depressive symptoms and cardiac anxiety (r_s=0.49, p<0.01), depressive symptoms and fear of body sensations (r_s=0.50, p<0.01), and cardiac anxiety and fear of body sensations (r_s=0.56, p<0.01).

In total, 112 patients (20 %) scored above both the cut-off of 10 in the PHQ-9 and the median score of 24 in the CAQ. A total of 103 (19 %) patients scored both above the cut-off of 10 in the PHQ-9 and the median score of 28 in the BSQ, and 195 (35 %) scored above the medians of both the CAQ and BSQ. Moreover, 93 (17 %) of all patients scored above the cut-off of 10 in the PHQ-9 and the medians of both the CAQ and BSQ, indicating that they suffered from all three conditions, see Figure IV.
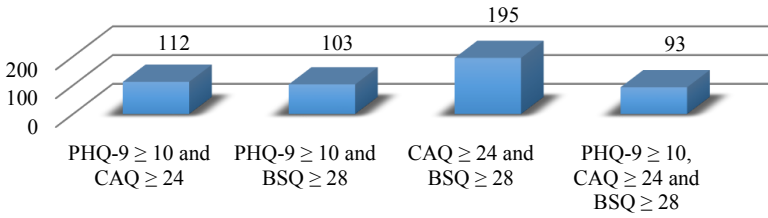
Figure IV: Co-existence of depressive symptoms (PHQ-9 score ≥ 10), cardiac anxiety (CAQ score ≥ 24) and fear of body sensations (BSQ score ≥ 28) in patients with non-cardiac chest pain, N=552 (Study III)

HEALTHCARE UTILIZATION

Contacts within primary care and outpatient clinics

Patients with NCCP, AMI, and AP had many contacts with primary care and outpatient clinics (Study I, II). For example, patients with NCCP had 54 contacts and patients with AMI or AP had 50 and 65 contacts registered respectively during the two-year study period (Study II), see Figure V. The causes for these contacts varied and were not only related to the NCCP, AMI or AP diagnoses. In all groups, the most common type of contact was individual clinic visits, followed by telephone contacts. The most common care givers were physicians and primary care nurses. All groups had significantly more contacts the year after the index admission than the year before (p<0.05) (Study I, II). Based on the total number of contacts over the two years, patients with AP contacted healthcare providers significantly more than NCCP and AMI patients. A multiple linear regression analysis showed that patients with depressive symptoms at baseline had more contacts with healthcare providers the year before index admission (p<0.01, Beta=0.27) (Study I).
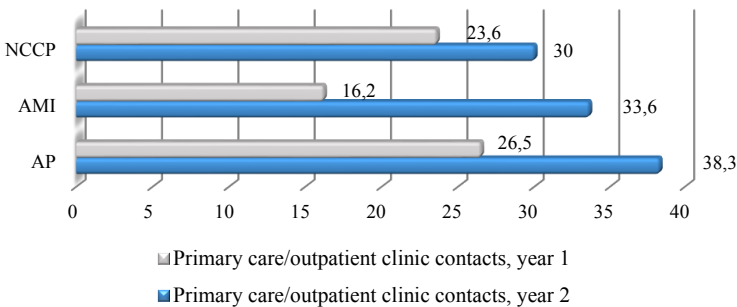

Figure V: Number of primary care and outpatient clinic contacts the year including index admission (year 1) and the year after index admission (year 2) per patient with NCCP, AMI, and AP (Study II)

Hospital admissions and length of hospital stay

Patients with NCCP, AMI and AP had 2.6, 3.6, and 3.9 admissions per patient respectively during the two-year study period (Study II), see Figure VI. Patients with NCCP had significantly fewer hospital admissions than both patients with AMI and patients with AP ($p<0.001$) the year before index admission (Study I). Patients with AP also had significantly fewer hospital admissions than patients with AMI ($p<0.05$). The year after the index admission, patients with AP had more hospital admissions than both NCCP ($p<0.01$) and AMI patients ($p<0.05$), but no difference was found between NCCP and AMI patients ($p=0.474$). All three groups had significantly fewer admissions ($P<0.001$) the year after index admission than the year before (Study II). The causes for the admissions were directly related to the NCCP, AMI and AP diagnoses in almost all admissions in all groups.
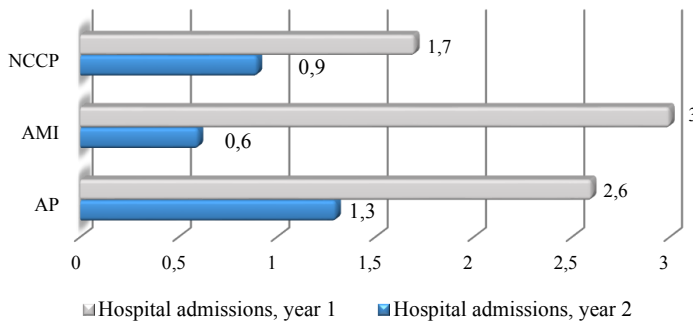

Figure VI: Number of hospital admissions the year including index admission (year 1) and the year after index admission (year 2) per patient with NCCP, AMI, and AP (Study II)

Sixty-six percent of the patients with NCCP did not have any hospital admissions the year before index admission, compared to 17 % for patients with AMI and 36 % for patients with AP. In contrast to patients with AMI, a small number of patients (n=7), both in the NCCP and AP groups, had the most admissions. Multiple linear regression revealed a relationship between the number of hospital admissions the year before index admission and diagnosis and baseline depressive symptoms. Baseline depressive symptoms were also independently related to more hospital admissions the year after index admission, as was older age (Study I), see Table VIII.

	Hospital admissions, 2 years[A]		Hospital admissions, the year before index admission[B]		Hospital admissions, the year after index admission[C]	
Explanatory variables	Beta	p-value	Beta	p-value	Beta	p-value
Diagnosis*	-0.05	0.57	**-0.24**	0.015	0.10	0.27
Age	**0.25**	0.03	0.13	0.28	**0.29**	0.015
Depressive symptoms	**0.27**	0.008	**0.26**	0.012	**0.21**	0.039

Table VIII: Multiple linear regression analysis of factors related to hospital admissions (Study I)

A: $R^2=0.17$, F=2.46, p=0.018; **B**: $R^2=0.17$, F=2.42, p=0.02; **C**: $R^2=0.18$, F=2.63, p=0.012
* = Non-cardiac chest pain was coded as 0, angina pectoris was coded as 1, and acute myocardial infarction was coded as 2

On average, patients with NCCP were hospitalized 6.3 days during the two-year study period, compared to 10.9 for patients with AMI and 10.5 for patients with AP (Study II), see Figure VII. The year before index admission, patients with NCCP were hospitalized for significantly shorter periods of time than patients with AMI and patients with AP (p<0.001) (Study I). The year after index admission, NCCP patients were hospitalized for significantly shorter periods of time than patients with AP (p<0.01), but did not differ significantly from patients with AMI. Patients with baseline depressive symptoms had longer hospital stay the year before index admission (p<0.05, Beta=0.21) than patients with no baseline depressive symptoms. All three groups had significantly shorter hospital stays the second year compared to the first (p<0.01) (Study II).
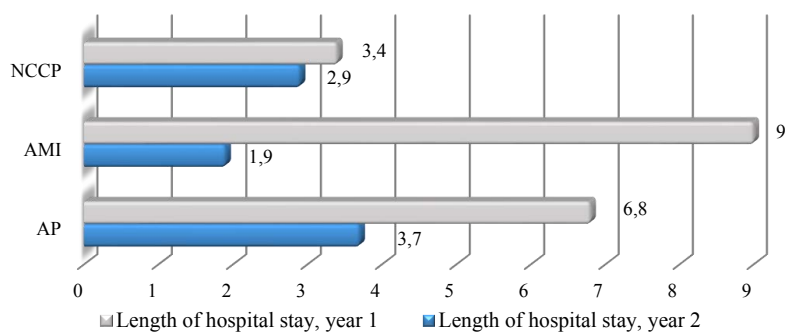

Figure VII: Length of hospital stay in days the year including index admission (year 1) and the year after index admission (year 2) per patient with NCCP, AMI, and AP (Study II)

SOCIETAL COSTS

Direct costs

The direct costs include all costs within primary care, out-patient clinics and hospital care. The costs for the two-year study period are presented per patient in Table IX. The annual costs for primary care and outpatient clinics were higher the second year compared to the first in patients with NCCP ($p<0.05$) and AMI ($p<0.01$).

The annual costs for hospital care were lower during the second year compared to the first in patients with AMI and patients with AP ($p<0.01$), but did not differ in patients with NCCP. A rough estimate of the costs of the index admission resulted in sums of €2237, €5462, and €4148 per patient for patients with NCCP, AMI and AP respectively (Study II).

Table IX: Direct and indirect costs of patients with NCCP, AMI and AP the year including (year 1) and the year after (year 2) index admission, in Euros (€) (Study II)							
	Direct cost: Primary care and outpatient clinics		**Direct cost: Hospital care**		**Indirect cost: Sick-leave and disability pension**			
	Total costs per patient		Total costs per patient		Total costs per patient		**Total mean annual cost per patient**	Cumulative annual national cost
	Year 1	Year 2	Year 1	Year 2	Year 1	Year 2		
NCCP	€ 3212	€ 3616[*]	€ 3803	€ 2963	€ 3527	€ 3014	**€ 10,068**	€817 million
AMI	€ 2024	€ 3112[**]	€ 16,387[**]	€ 3103	€ 3670	€ 3682	**€ 15,989**	€364 million
AP	€ 3089	€ 3348	€ 10,785[**]	€ 4084	€ 3652	€ 4516	**€ 14,737**	€408 million

Comparison between year 1 and 2, [*] = $p<0.05$; [**] = $p<0.01$

Indirect costs

The indirect costs include productivity loss due to sick-leave and disability pension, see Table IX.

About 21 % of the study patients were on sick-leave during the year including index admission and 16 % during the following year. On average, fewer patients with NCCP were on sick-leave compared to patients with AMI and patients with AP. The number of annual sick-leave days for patients with NCCP, AMI and AP were 103, 54 and 94 respectively. In patients with NCCP, the mean annual cost per patient due to productivity loss because of sick-leave was €1233, compared to €903 for patients with AMI and €1989 for patients with AP.

Between 10 % and 14 % of the study patients received a disability pension during the year including index admission, and between 9 % and 12 % received a disability pension the following year. On average, patients with NCCP, AMI and AP received a disability pension for 338, 348 and 295 days per year respectively. The mean annual cost per patient due to productivity loss because of disability in patients with NCCP was €2038, compared to €2773 in patients with AMI, and €2095 in patients with AP. There were no significant differences between year 1 and year 2 in any of the groups regarding either sick-leave or disability pension (Study II).

Total annual societal costs of patients with non-cardiac chest pain, acute myocardial infarction and angina pectoris

The mean total annual societal cost per patient with NCCP, including both direct and indirect costs, was about €10,068. For a patient with AMI, the cost was €15,989 and for a patient with AP, this was €14,737.

These costs were extrapolated to a national context to gain a better understanding of the potential burden these patient groups constituted to society. In 2010, the number of patients diagnosed with NCCP was 81,121. The number of patients with AMI was 22,836, and the number of patients with AP was 27,683 (27). Based on the great number of patients with NCCP, the cumulative annual national cost of these patients would be about €817 million if all patients incurred the same costs as in our study. The corresponding costs for patients with AMI and patients with AP would then be about €364 million and €408 million respectively, see Table IX (Study II).

EFFECTS OF THE INTERNET-DELIVERED COGNITIVE BEHAVIOURAL THERAPY PROGRAM COMPARED TO USUAL CARE

Chest pain frequency

Patients' reports of chest pain before the intervention are presented in Table X. After completing the CBT program, two patients reported less chest pain, but five remained unchanged. In the control group, one patient reported less chest pain, one reported more chest pain, but six remained unchanged.

Table X: Reports of chest pain frequency before the intervention, N=15		
	Intervention group, n=7	Control group, n=8
Chest pain frequency	**Before program**	**Before program**
Daily	3	4
Twice per week	2	1
Sporadically	2	3

Cardiac anxiety, fear of body sensations, and depressive symptoms

Patients in both the intervention and control groups reported lower scores regarding cardiac anxiety, fear of body sensations, and depressive symptoms after the end of the program (Figures VIII-IX). After completing the CBT program, five patients reported lower CAQ scores, one reported higher scores, and one remained unchanged. In the control group, five patients reported lower CAQ scores and three patients reported higher CAQ scores. No significant differences were found between the intervention and control groups regarding mean score differences between the measurements.
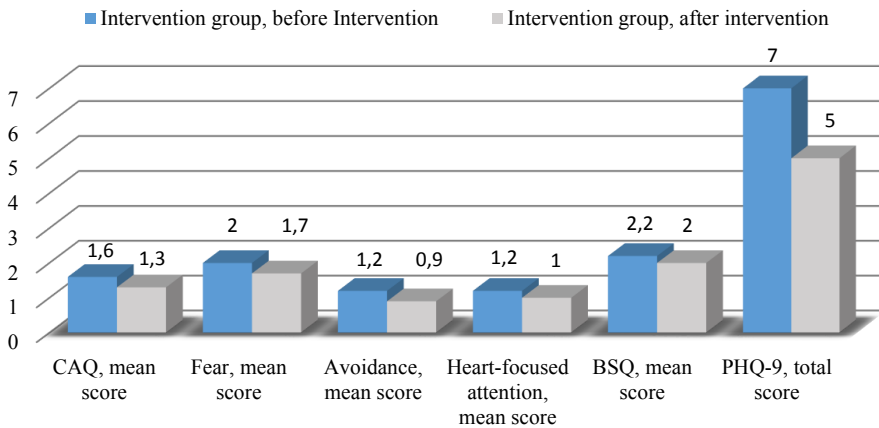
Figure VIII: scores of cardiac anxiety, fear of body sensations, and depressive symptoms before and after the intervention, intervention group n=7 (Study IV)
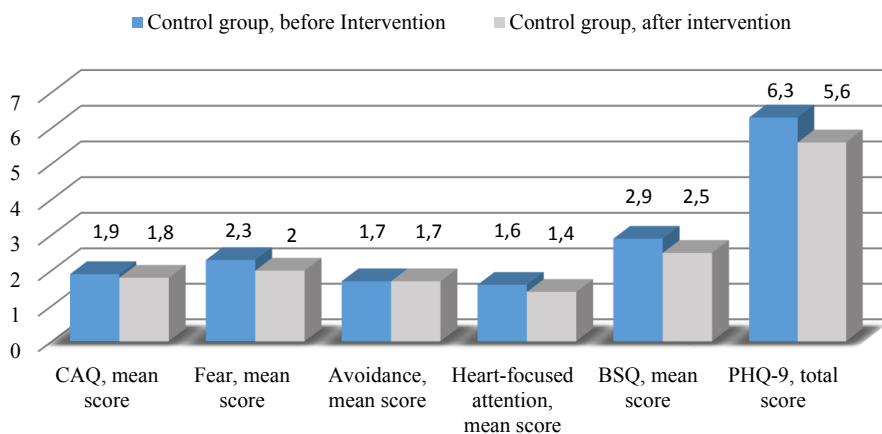
Figure IX: scores of cardiac anxiety, fear of body sensations, and depressive symptoms before and after the intervention, control group n=8 (Study IV)

FEASIBILITY OF THE INTERNET-DELIVERED CBT PROGRAM

Of the seven patients randomized to the intervention group, five completed all sessions. One patient joined the whole program but completed only parts of it, despite several reminders and one week's extended intervention time (5 weeks in total). This patient reported having little chest pain and stated that he did not need to do all parts, but he still wanted to stay in the program. Another patient who had been very active during the start of the intervention ceased her participation after 1.5 weeks/sessions because of stress due to the computer use and technology problems.

The CBT program was reported to be user-friendly by all patients who joined the whole program. Patients reported that it was worth the time and effort they invested in the program. Most of them were satisfied with the overall program and were happy to recommend it to others. Almost all patients described that the program had met their expectations, that they had learned a lot from it, and could gain from the different pieces of knowledge and exercises. The program was perceived as easy to manage, with comprehensible language, adequate and varied content (i.e. text, and video and audio files), and manageable homework assignments. Still, some patients needed some technology support (e.g. how to download and use the two-factor authentication for login, how to switch between the different parts of the program and how to fill in and submit the forms). Two patients requested more varied and differently tailored exercises and assignments. On average, about 22 minutes' weekly therapist time was required to guide, support, and give feedback

to each patient throughout the program. The two patients who were inactive required about 35 minutes each due to repeated contacts and reminders.

Four patients reported that they reached their goals to a great extent after completing the program. Some patients reported that the program reassured them that their hearts tolerated physical activity, which led to decreased worries and anxiety about the chest pain. Study participation was viewed in various ways among the patients. Some reported that participating in a program, particularly being guided and supported, motivated and empowered them to be active and manage the program. Others reported that they felt an obligation to complete the program because they were surveyed, which they did despite sometimes feeling tired and not in the mood.

DISCUSSION

DISCUSSION OF THE RESULTS

The overall aim of this thesis was to improve care for patients with NCCP. This was done by identifying and describing related psychological distress, healthcare utilization and societal costs, and by evaluating the feasibility and effects of the first guided Internet-delivered cognitive behavioural intervention on chest pain and psychological distress.

This thesis shows that patients with NCCP experience psychological distress in terms of depressive symptoms, cardiac anxiety and fear of body sensations. The prevalence and severity of depressive symptoms did not differ from patients with AMI and patients with AP. Depressive symptoms, cardiac anxiety and fear of body sensations were all related to increased healthcare utilization, but cardiac anxiety was the driving factor. Patients with NCCP utilized a significant amount of healthcare resources. The number of primary care and outpatient clinic contacts in these patients did not differ from patients with AMI. This thesis provides a unique and detailed description of the annual societal costs, including direct healthcare costs and indirect costs due to productivity loss, for patients with NCCP, AMI and AP. The annual societal cost per patient with NCCP was substantial and the estimated cumulative annual national costs for patients with NCCP, €817 million, were equivalent to more than double the cost for patients with AMI and patients with AP. This implies that patients' negative interpretation of their chest pain and fear of having a cardiac disease made them seek healthcare repeatedly and that they presumably stayed at home from work, resulting in large costs for society. A short guided Internet-delivered CBT program seems to be feasible and showed the potential to help patients with NCCP improve regarding chest pain frequency and psychological distress, although this was not significantly different from the control group that received usual care.

Psychological distress, healthcare utilization and societal costs

Depressive symptoms were common (20-25 %) among patients with NCCP and most of them still had depressive symptoms at the follow-up after one year. This is in line with previous research on depressive symptoms in patients with NCCP (20). Patients with NCCP did not differ significantly from patients with cardiac chest pain regarding prevalence or severity of depressive symptoms. This confirms previous findings describing the common prevalence of anxiety and depressive

symptoms in patients with NCCP as similar to or greater than in patients with cardiac chest pain (52, 55). Cardiac anxiety and fear of body sensations were prevalent in more than half of the patients, who reported higher cardiac anxiety scores than in a general population (77). Moreover, many patients suffered from a combination of depressive symptoms, cardiac anxiety and fear of body sensations. This finding adds to the evidence of high prevalence of co-morbid psychological distress in patients with NCCP, with about 70 % having at least one psychiatric diagnosis (14, 64, 139), and about half having at least two (64, 139).

The patients with NCCP who were recruited to our studies were all discharged without screening for psychological distress or any planned follow-up for their chest pain. Bearing in mind that many of these patients screened positively for either depressive symptoms, cardiac anxiety or fear of body sensations, it is not surprising that they were re-admitted with new episodes of chest pain. Psychological distress has earlier been associated with maintained or worsened chest pain (4). Increased chest pain frequency has in turn been correlated with decreased general health, higher level of psychological distress and care-seeking behaviour (41). This thesis reveals significant relationships between increased healthcare utilization and the different types of psychological distress, particularly cardiac anxiety.

Non-cardiac chest pain is recognized as a benign condition (7, 33, 40) compared to AMI, which is life-threatening and requires intensive and expensive healthcare resources. Surprisingly, the patients with NCCP utilized similar amounts of resources within primary care and outpatient clinics during the two-year study period and hospital care resources during the year after index admission as patients with AMI. As hospitals often are short-staffed and overfilled with patients, thorough investigations and follow-ups of patients with NCCP may not be a priority. These patients are often discharged without any treatment or clear explanation of the cause for their chest pain (47, 58), and often fall between the cracks because they have no obvious organic causes for their chest pain. This could result in a feeling of not being taken seriously, despite continuous complaints and concerns.

There are various causes for chest pain in patients with NCCP. Clinically relevant adverse cardiac events are rare in patients with NCCP and, therefore, they should not be admitted to hospital (140). However, patients are involved in time-consuming and expensive assessments at the emergency departments or hospitalized and treated within cardiac units, even though the pain is not caused by a cardiac disease. This is not cost-effective (2, 3, 141, 142), but can partly be explained by the fact that many physicians are afraid of missing a cardiac diagnosis and therefore tend to overestimate the risk (10), in addition to the fact that even

cardiac patients can have NCCP (4, 8, 9). By comparing the costs associated with patients with NCCP, who have a less severe condition, to patients with a more severe cardiac disease, the intention was to highlight the extent of the costs these patients incur, despite the good prognosis they are assigned in different research (7, 33, 40). Furthermore, the intention was to emphasize the importance of early diagnostics and treatment for these patients, which may impact healthcare utilization and costs positively. This thesis shows that patients with NCCP incurred more than double the societal costs annually as patients with AMI and patients with AP, as patients with NCCP are more than three times as many. Similar findings have been reported, although only regarding direct costs (142). Based on these findings, it is important that the care of these patients is structured differently and that actions are taken to reduce healthcare utilization and costs.

As patients with NCCP are generally treated within cardiology, where formal screening for e.g. anxiety and depression is not a part of the routine care, there is a risk that psychological distress can go unrecognized. In the absence of formal screening, healthcare providers tend to underestimate depression (71, 143) and anxiety (74). Yet, patients experience recurrent chest pain that they think is cardiac-related and seek care repeatedly, leading to great costs. Therefore, after ruling out acute cardiac disease and other physical diagnoses in patients with recurrent NCCP, these patients should be screened for psychological distress using valid and reliable instruments. Although cardiac anxiety was found to be the main driving factor for healthcare utilization, it is important that also depressive symptoms and fear of body symptoms are screened for and treated if prevalent, as these conditions were so common in these patients and related to healthcare utilization. Previous studies have also shown a relationship between depressive symptoms, continued chest pain, and healthcare utilization in patients with NCCP (19, 22).

Fear of body sensations was prevalent in many of the patients in this thesis. Relatively recent studies have shown that negative illness perception is associated with psychological distress and chest pain (22, 59, 144), and that the way patients perceive and interpret their chest pain has an impact on the management of NCCP (82). Fear of cardiac sensations may increase pain, disability and avoidance behaviour (81). Changes in how body sensations are interpreted can mediate the treatment effect on depression, avoidance of physical activity (61), and anxiety (145). Changes in perceptions can be achieved when thoughts are repeatedly challenged and become weaker and less frightening, or replaced by other more appropriate thoughts (146). The bicycle stress test that was used as an exposure was useful to reassure patients that their hearts tolerate physical activity, thus leading to less worry and anxiety. Although stress tests may not be advocated for a diagnostic purpose in these patients, they could demonstrate the ability to exercise safely (106). Modification of thoughts and behaviours can lead to

decreased avoidance of physical activity, less anxiety, and also less chest pain in these patients (16).

Effects of the Internet-delivered CBT program

The CBT program showed the potential to decrease chest pain frequency, cardiac anxiety, fear of body sensations, and depressive symptoms in patients with NCCP immediately after the end of the program. However, there were no significant differences compared to the control group that received usual care. No information was collected regarding the care received by patients from healthcare providers during the intervention, or whether patients in the control group received care that had an impact on their progress. An early study by Sanders et al (147), using a brief CBT-intervention containing psychoeducation and breathing and relaxation exercises had similar results with no differences between the treatment and control groups at the 3-month follow-up. This was partly explained by many drop-outs, resulting in a small sample, the intervention taking place too soon after coronary angiography, and the fact that many patients considered the intervention too psychological and did not use the behavioural techniques.

Possible explanations for the lack of effect could be:

1. Small sample size, target group, and modes of delivery

   As the study was a pilot and included small groups, it might be difficult to find significant differences in the outcomes compared to the control. Another explanation could be that despite randomization, patients in the intervention group had lower baseline scores in both the CAQ and BSQ and could therefore not decrease as much compared with the control group. If the groups had been larger, such differences might have evened out. As mentioned earlier, a small sample was one of the explanations for the lack of effect in another CBT-intervention (147).

   According to previous research in other groups there were no differences between face-to-face and Internet-delivered CBT (115, 116, 118, 119). Still, delivering the intervention via the Internet resulted in many patients declining or not being able to participate in the study.

2. Duration of intervention

   The duration of the intervention was four weeks, which is relatively short compared to the average length of face-to-face CBT programs that is about 8-12 weeks (118). It can be discussed whether a period of four weeks was too

short to enable patients to modify their thoughts and change their behaviours or if the process of change just started, although one study was successful despite one week shorter program (61). Nevertheless, it is crucial that short and effective programs are developed as they are more easily accepted by patients and implemented in the healthcare system.

3. Short follow-up

An early follow-up might have made it difficult to capture the real effects of the intervention, particularly in combination with the short duration of the intervention. Future studies should consider having several follow-up measurements to evaluate both the short and long- term effects of the intervention.

Feasibility of the Internet-delivered CBT program

As for feasibility of the program, the patients were satisfied with the program and perceived it as adequate and relevant, including the exercises and homework assignments. The Internet platform was perceived as user-friendly, although some patients needed technical support. Therefore, it is important that patients have someone to ask for help, which they could in this study. Otherwise, an un-guided program might lose patients due to technology issues.

The average therapist time needed to guide, support and give feedback to an ordinary patient was 22 minutes per week. Internet-delivered CBT studies in other groups of patients have reported feedback time of between 9 and 20 minutes (125, 148, 149). This is a bit shorter, but it seems that it only concerns time for feedback and not guidance and support. Cardiac nurses have sufficient knowledge and skills to embrace the role of a therapist in Internet-delivered programs for patients with NCCP. They can learn to provide education, simple psychological interventions and follow-ups, but specialist treatment should be considered if symptoms continue (4). In this study, running a new intervention guided by a cardiac nurse not skilled in CBT was not a challenge, but may have influenced time expenditure. Research has shown that performance improves over time and with more experience (150).

METHODOLOGICAL CONSIDERATIONS

Recruitment, drop-out, and generalizability

Recruitment to the studies was a challenge. Using lists and registers to approach patients with whom the researcher did not have a care-relation could have affected patients' willingness to participate. As no permission was given from the ethical committee to review patients' medical records for suitable patients, also patients with e.g. cognitive impairment and language difficulties were approached. This gave an inaccurate picture of the participation rates in the studies. To bypass these aspects, future studies should recruit patients prospectively in connection with the healthcare encounter.

Another aspect that may have had an impact on recruitment is that patients were asked about psychological distress while they experienced chest pain that they thought was cardiac-related, and probably did not perceive themselves as suitable candidates. Moreover, patients may have considered the intervention too psychological and chose to decline participation (147). This is illustrated by one of our unexpected findings showing an inconsistency between the information concerning the patients' final diagnosis, which was also recorded in patients' medical records, and the information received/perceived by patients. For example, when recruiting patients who had been discharged with a NCCP diagnosis (Study III), more than 13 % (n=156) of those who responded reported that they had received a cardiac explanation for their chest pain or were under investigation for cardiac disease. Similar findings were reported by Spalding et al (25). Some other factors that may have had a negative impact on the response rate were examination of a sensitive topic, long questionnaires, and not providing the patients with a second battery of questionnaires together with the reminder. Monetary incentives, on the other hand, are known to have positive effects on response rate (151, 152). In study III, a scratch card was sent to patients who agreed to participate, but still only 30 % agreed to participate. Using gifts or scratch cards to maximize response rate has been tested in previous research examining similar groups of patients (14, 34, 61), with various effects. Of these three studies, only one had a large number of responders. The extent of drop-out at the 1-year follow-up (Studies I, II) was probably due to the long period of time between the points of data collection.

Despite recruitment and drop-out issues, external validity is considered acceptable as the findings and conclusions in studies I-III are based on sufficiently large samples with similar characteristics throughout all studies. The study samples are considered representative and findings can be generalized to other patients with NCCP. Although there were few differences between participants and non-participants, there could be some selection bias related to those of a younger age

declining participation, particularly in study III. In study IV, there could also be selection bias despite randomization as baseline scores differed between patients in the intervention and control groups. The findings in study IV should be interpreted with caution as they were based on a small sample. As the control group improved similarly to the intervention group, the effects in the intervention group could partly be due to maturation rather than just the intervention. The control group may have improved because they were included in a study and attention was given to their chest pain. On the other hand, the analyses were based on intention to treat, including data for patients who did not complete the intervention. Therefore, the effects of the intervention could have been underestimated.

Validity, reliability, and fidelity

Valid and reliable instruments were used in all the studies in this thesis, and the scores of these instruments were handled in accordance with the given instructions. However, additional questions were developed by the research team to measure the number of healthcare visits (Study III) and chest pain frequency (Study IV), but these questions were only used in a descriptive way. The registers/databases (CDW, CPP, Social Insurance Agency) used in this thesis are considered reliable. Data from these databases is precise and reflects the exact amount of healthcare use and societal costs.

Different questionnaires were used to assess prevalence of depressive symptoms; SQ-3 and MADRS in study I, and PHQ-9 in study III and IV. The short SQ-3 was used as a screening tool and MADRS was then used to assess only those who screened positive according to SQ-3 as this was considered to be time-saving and less burdensome for the patients. The use of different questionnaires strengthens our findings, as similar proportions of depressive symptoms were found in the different samples, despite of the questionnaire used.

When computing the costs (Study II), all direct and indirect costs incurred by the patients were included in the analysis, although these may not have been directly related to NCCP, AMI or AP. This was considered to be the optimal way as it would be difficult to exclude non-related costs. The cost estimation in this thesis gives a clear overview of the total costs incurred by these patients, although it might have caused a slight overestimation. However, this was done for all patients and not only for those with NCCP. The human capital approach was used for estimation of the indirect costs. This approach has been criticized for overestimating the costs as productivity loss due to morbidity or premature mortality can be replaced by existing unemployed people. On the other hand, it tends to underestimate costs because it values life based on market earnings, which

yields very low values for children and retired people. It also undervalues life if labour market deficiencies exist and wages do not reflect true abilities. In addition, as intangible costs, i.e. psychosocial costs of illness, such as pain and suffering, and costs for family members caring for the individual are omitted from this approach (90, 92), and thus not included in our analysis, the total societal costs presented in this thesis might be underestimated.

Fidelity in the intervention (Study IV) was ensured based on several aspects. First, a theoretical basis for the intervention was identified (i.e. avoidance of physical activity due to cardiac anxiety). The content and structure of the intervention were designed together with experts from different areas, such as nursing, psychiatry, medicine, and physiotherapy and were validated before implementation. The content of the intervention was the same for all patients, who received the same number of sessions. The patients were guided by the same person, ensuring that the same intervention was delivered and that patients were adhering to the study protocol and understanding what was expected from them. There were some differences in the amount of guidance as some patients needed more guidance and support. No data was collected regarding the care received by patients from healthcare providers during the intervention. The differences in the amount of guidance, and not collecting data on received care might have contaminated the results of the intervention.

Feasibility of the Internet-delivered CBT program

The CBT intervention (Study IV) seemed feasible. Still, few patients were interested in participation. As mentioned before, patients may have considered the intervention too psychological and burdensome due to the content or way of delivery. Non-adherence and non-completion of Internet-delivered interventions are very common (14, 116, 118, 125, 153). Moreover, the delivery over the Internet made patients with no access to a computer/tablet with an Internet connection ineligible, leading to fewer patients that could be recruited. Those who participated had various levels of knowledge, needs and preferences for treatment and technology. Technology issues have been pointed out as one of the disadvantages with Internet-delivered treatments (116). Therefore, support is needed for those who experience technology-related difficulties. Patients who participated in the intervention perceived it as feasible and needed little therapist guidance. The intervention is valid with realistic conditions and could easily be implemented in the healthcare settings. As it needs to be evaluated in larger groups, the challenge would be to find eligible patients and make them participate in the program.

CLINICAL IMPLICATIONS

The findings of this thesis contribute to a better understanding of patients with NCCP and what to address in the healthcare encounter. Psychological distress, particularly cardiac anxiety is common and independently related to healthcare utilization among patients with NCCP. These patients experience recurrent chest pain and consult healthcare providers repeatedly because of worries and fear of having a cardiac disease. Nevertheless, patients are often discharged without any explanation or investigation of psychological distress as formal screening for this is not part of routine care after ruling out acute cardiac disease. Healthcare providers should keep in mind that psychological distress may be the reason for patients' chest pain and care-seeking behaviour and should assess this, either by direct questioning or with assessment instruments. Patients with psychological distress should be referred for further investigation and treatment.

Patients with recurrent NCCP and repeated healthcare visits could benefit from undergoing a bicycle stress test to be reassured that their hearts tolerate physical activity. Healthcare providers should encourage patients to be physically active despite chest pain, and not only tell them that their pain is not cardiac-related. This can lead to decreased and less prominent symptoms of NCCP. A cardiac nurse can provide education, simple psychological interventions and follow-ups. In case of persistent symptoms, specialist treatment should be considered. Our Internet-delivered CBT treatment showed the potential to help patients improve in chest pain frequency and psychological distress, but it needs to be tested in larger groups and with longer follow-up.

FUTURE RESEARCH

During the work with this thesis, new ideas for future research developed. Some of them originate from findings in the studies, and the rest have evolved from the research gaps found while searching for literature.

Suggested future research:

- Evaluate the effects of Internet-delivered CBT in patients with NCCP in larger groups and with longer follow-up. Our program might also suit other groups of patients, particularly those with anxiety.

- Study the effect of stress test on reassurance in patients with repeated care-seeking occasions due to NCCP.

- Study how patients with repeated care-seeking occasions perceive their situation and self-image.

- Study the experience of living with a family member with NCCP.

- Study the perception of the encounter with healthcare providers among patients with repeated care-seeking occasions.

- Structure the care for patients with NCCP using a multidisciplinary team including cardiologists, nurses, psychologists and physiotherapists that can handle all steps in the care process of these patients within a specialized chest pain clinic. Both short and long- term effects of the intervention with regard to pain, psychological distress, healthcare utilization, and costs should be evaluated. This is tested in e.g. the United Kingdom and seems to show good potential.

CONCLUSIONS

Patients with NCCP experienced recurrent and persistent chest pain and psychological distress in terms of depressive symptoms, cardiac anxiety and fear of body sensations. The prevalence and severity of depressive symptoms did not differ from patients with AMI or patients with AP.

Non-cardiac chest pain was associated with significant healthcare utilization. The number of primary care and outpatient clinic contacts in these patients did not differ from patients with AMI. The annual societal cost per patient with NCCP was substantial. As there is a great number of patients with NCCP, the estimated cumulative annual national costs of these patients, €817 million, correspond with more than the double of the annual national costs for patients with AMI and patients with AP.

Depressive symptoms, cardiac anxiety and fear of body sensations were related to increased healthcare utilization, but cardiac anxiety was the only variable independently associated with healthcare utilization. Screening and treatment of psychological distress should therefore be considered for implementation in the care of patients with NCCP. By reducing cardiac anxiety, patients may be better prepared to handle chest pain, which could also lead to decreased and less prominent symptoms of NCCP.

A short guided Internet-delivered CBT program seems to be feasible. In this thesis, almost all patients who received CBT improved with regard to chest pain frequency, cardiac anxiety, fear of body sensations, and depressive symptoms based on the first follow-up immediately after the end of the program. However, there were no differences compared to the control group that received usual care. Larger studies with longer follow-up are needed to further evaluate the short and long- term effects of such interventions.

SVENSK SAMMANFATTNING

Fler än hälften av alla patienter som söker vård för akut bröstsmärta har ingen kardiell orsak till bröstsmärtan. Trots återkommande smärta skrivs många patienter ut efter en sjukhusvistelse utan en tydlig förklaring till bröstsmärtan. Detta kan leda till att fortsatt smärta misstolkas som hjärtrelaterad, vilket kan orsaka oro och osäkerhet, samt leda till ökad vårdkonsumtion. Psykisk ohälsa och icke-kardiell bröstsmärta är starkt relaterade, men det finns för lite forskning kring sambanden mellan olika typer av psykisk ohälsa, samt deras inverkan på vårdkonsumtion. Det finns behov av att utveckla interventioner som kan hjälpa patienter hantera sin bröstsmärta, vilket kan leda till minskad psykisk ohälsa, lägre vårdkonsumtion och kostnader.

Avhandlingens övergripande syfte var att förbättra vården av patienter med icke-kardiell bröstsmärta genom att beskriva relaterad psykisk ohälsa, vårdkonsumtion och sociala kostnader, samt genom att utvärdera en internet-baserad kognitiv beteende-intervention.

Avhandlingen bygger på resultat från fyra kvantitativa delstudier. Studierna I och II hade en longitudinell deskriptiv och jämförande design. Båda studierna var baserande på samma initiala patienturval. Patienterna rekryterades konsekutivt inom 2 veckor från utskrivningsdatum från ett allmänsjukhus i sydöstra Sverige. I studie I deltog 267 patienter (131 med icke-kardiell bröstsmärta, 66 med akut hjärtinfarkt, samt 70 med angina pectoris). Av dessa deltog 199 patienter (99 med icke-kardiell bröstsmärta, 51 med hjärtinfarkt, 49 med angina pectoris) i studie II. Majoriteten av patienterna var män (ca 60 %) med en medelålder av 67 år. Data samlades in avseende depressiva symtom (Studie I), vårdkonsumtion (Studie I, II), samt samhällskostnader (Studie II).

Studie III hade en explorativ och beskrivande tvärsnittsdesign. Data avseende depressiva symtom, hjärtrelaterad ångest och rädsla för kroppsliga sensationer samlades konsekutivt in bland 552 patienter med icke-kardiell bröstsmärta (51 % kvinnor, medelålder 64 år) på fyra sjukhus i sydöstra Sverige. Patienterna rekryterades inom en månad från utskrivningsdatumet. Studie IV var en randomiserad kontrollerad pilotstudie som inkluderade nio män och sex kvinnor med en medianålder av 66 år. Dessa randomiserades in i interventions- (n=7) eller kontrollgrupp (n=8). Interventionsprogrammet omfattade fyra sessioner av guidad internet-baserad kognitiv beteendeterapi innehållande utbildning om icke-kardiell bröstsmärta, exponering för fysisk aktivitet, samt avslappning. Kontrollgruppen

erhöll rutinvård. Data samlades in avseende frekvens av bröstsmärta, hjärtrelaterad ångest, rädsla för kroppsliga sensationer och depressiva symtom.

Depressiva symtom kunde konstateras hos 20 % (Studie IV) och 25 % (Studie I, III) av patienterna och fler än hälften av dessa hade fortfarande depressiva symtom vid 1-årsuppföljningen (Studie I). Det fanns ingen statistiskt signifikant skillnad mellan patienter med icke-kardiell bröstsmärta, akut hjärtinfarkt och angina pectoris avseende förekomsten och svårighetsgraden av depressiva symtom. Att leva ensam och vara yngre hade oberoende relation till depressiva symtom (Studie I). Hjärtrelaterad ångest rapporterades av 42 % av patienterna i studie III, samt av 67 % av patienterna i studie IV och omkring 62 % av patienterna i studie III och 93 % av patienterna i studie IV rapporterade rädsla för kroppsliga sensationer.

Patienter med icke-kardiell bröstsmärta hade i genomsnitt 54 öppenvårdskontakter, medan patienter med akut hjärtinfarkt och angina pectoris hade 50 respektive 65 öppenvårdskontakter under studieperioden som omfattade två år. Patienterna i de olika diagnosgrupperna hade också 2,6, 3,6 och 3,9 sjukhusinläggningar vardera (Studie II). Fyra av tio patienter i studie III angav att de sökt sjukvård vid minst 2 tillfällen under senaste året på grund av bröstsmärta. Cirka 14 % av patienter med icke-kardiell bröstsmärta, 18 % av de med akut hjärtinfarkt och 25 % av de med angina pectoris var sjukskrivna årligen och ungefär 11-12 % i varje patientgrupp hade förtidspension. Den årliga samhällskostnaden för patienter med icke-kardiell bröstsmärta, akut hjärtinfarkt och angina pectoris motsvarade i snitt 10068, 15989 och 14737 euro per patient i respektive diagnosgrupp (Studie II). Depressiva symtom (Studie I, III), hjärtrelaterad ångest (Studie III) och rädsla för kroppsliga sensationer (Studie III) var alla relaterade till vårdkonsumtion, men hjärtrelaterad ångest var enda faktorn med oberoende relation till vårdkonsumtion (Studie III).

Nästan alla patienter i interventionsstudien (Studie IV), både i interventions- och kontrollgruppen, förbättrades avseende frekvens av bröstsmärta, hjärtrelaterad ångest, rädsla för kroppsliga sensationer och depressiva symtom. Det fanns inga statistiskt signifikanta skillnader mellan grupperna. Interventionen upplevdes som genomförbar och lätt att hantera, hade förståeligt språk, adekvat och varierat innehåll, samt genomförbara hemuppgifter.

Sammanfattningsvis, patienter med icke-kardiell bröstsmärta har återkommande och ihållande bröstsmärta och psykisk ohälsa i termer av depressiva symtom, hjärtrelaterad ångest och rädsla för kroppsliga sensationer. Förekomsten och svårighetsgraden av depressiva symtom skiljde sig inte från patienter med akut hjärtinfarkt eller angina pectoris. Icke-kardiell bröstsmärta var associerad med vårdkonsumtion och patienterna hade lika stort antal primärvårdskontakter som

patienter med akut hjärtinfarkt. Den skattade sammanlagda årliga nationella samhällskostnaden för patienter med icke-kardiell bröstsmärta var mer än den dubbla som för patienter med akut hjärtinfarkt och angina pectoris på grund av större antal patienter med icke-kardiell bröstsmärta.

Psykisk ohälsa var relaterad till ökad vårdkonsumtion, men hjärtrelaterad ångest var enda faktorn med oberoende relation till vårdkonsumtion. Dessa resultat antyder att screening och behandling av psykisk ohälsa i vården av patienter med icke-kardiell bröstsmärta borde övervägas. Genom att reducera hjärtrelaterad ångest kan patienterna få bättre möjlighet att hantera sin bröstsmärta. Ett kort internet-baserat kognitivt beteendeprogram verkar genomförbart. Patienterna i pilotstudien förbättrades avseende frekvens av bröstsmärta, hjärtrelaterad ångest, rädsla för kroppsliga sensationer och depressiva symtom, men skiljde sig inte signifikant från kontrollgruppen som erhöll rutinvård. Studier baserade på större patientgrupper och med längre uppföljning behövs för att utvärdera både korttids- och långtidseffekterna av denna typ av intervention.

Sökord

Depressiva symtom, direkta kostnader, hjärtrelaterad ångest, icke-kardiell bröstsmärta, indirekta kostnader, internet-baserat, ischemisk hjärtsjukdom, kognitiv beteendeterapi, randomiserad kontrollerad studie, rädsla för kroppsliga sensationer, samhällskostnader, sjukhusvård, vårdkonsumtion, öppenvård.

ACKNOWLEDGEMENTS

I want to express my appreciation and gratitude to all of you who in different ways have supported me and contributed to this thesis.

Special thanks to:

All patients, who have devoted time to answer questionnaires and participate in the intervention. Without you, this thesis would not have existed. Thank you!

Tiny Jaarsma, my main supervisor. Thank you for your guidance, support, and encouragement, and for always believing in me and allowing me to grow as a researcher. I really appreciated having you as my supervisor and getting the possibility to learn from all your wisdom and professionalism.

Anna Strömberg, my co-supervisor. Thank you for arousing my interest in research and for the ideas that helped me develop this thesis. You have been a great support with your knowledge, experience, and precision. I have always admired your competence and I have really enjoyed working with you over these years.

Claes Hallert, my co-author and initial supervisor. Thank you for giving me the chance to start with research, helping me create the first study and getting initial funding. Our early work was the seed that now blossoms.

Jenny Alwin, my co-author, for nice discussions and valuable advice, and for your support. I learned so much from you.

Peter Johansson, my co-author. You have been a great support and have contributed with valuable knowledge to the last part of this thesis. Thank you for that and also for all the fun we have had during this journey, not least at the conferences.

Egil Jonsbu, my co-author, for the collaboration and all the stimulating discussions that led to a great project. Thank you for your generosity by welcoming me to Norway and showing me the beautiful Molde.

Mikael Gustafsson, my co-author, for your contribution to the intervention and your valuable advice.

REFERENCES

1. Erhardt L, Herlitz J, Bossaert L, Halinen M, Keltai M, Koster R, et al. Task force on the management of chest pain. Eur Heart J. 2002 Aug;23(15):1153-76.

2. Forberg JL, Henriksen LS, Edenbrandt L, Ekelund U. Direct hospital costs of chest pain patients attending the emergency department: a retrospective study. BMC Emerg Med. 2006 May 4;6:6.

3. Groarke J, O'Brien J, Go G, Susanto M, Owens P, Maree AO. Cost burden of non-specific chest pain admissions. Ir J Med Sci. 2013 Mar;182(1):57-61.

4. Bass C, Mayou R. Chest pain. BMJ. 2002 Sep 14;325(7364):588-91.

5. Glombiewski JA, Rief W, Bosner S, Keller H, Martin A, Donner-Banzhoff N. The course of nonspecific chest pain in primary care: symptom persistence and health care usage. Arch Intern Med. 2010 Feb 8;170(3):251-5.

6. Eslick GD, Talley NJ. Non-cardiac chest pain: predictors of health care seeking, the types of health care professional consulted, work absenteeism and interruption of daily activities. Aliment Pharmacol Ther. 2004 Oct 15;20(8):909-15.

7. Ruddox V, Mathisen M, Otterstad JE. Prevalence and prognosis of non-specific chest pain among patients hospitalized for suspected acute coronary syndrome - a systematic literature search. BMC Med. 2012 Jun 12;10:58,7015-10-58.

8. Sheps DS, Creed F, Clouse RE. Chest pain in patients with cardiac and noncardiac disease. Psychosom Med. 2004 Nov-Dec;66(6):861-7.

9. Lenfant C. Chest pain of cardiac and noncardiac origin. Metabolism. 2010 Oct;59 Suppl 1:S41-6.

10. Kline JA, Stubblefield WB. Clinician gestalt estimate of pretest probability for acute coronary syndrome and pulmonary embolism in patients with chest pain and dyspnea. Ann Emerg Med. 2014 Mar;63(3):275-80.

11. Dumville JC, MacPherson H, Griffith K, Miles JN, Lewin RJ. Non-cardiac chest pain: a retrospective cohort study of patients who attended a Rapid Access Chest Pain Clinic. Fam Pract. 2007 Apr;24(2):152-7.

12. Leise MD, Locke GR,3rd, Dierkhising RA, Zinsmeister AR, Reeder GS, Talley NJ. Patients dismissed from the hospital with a diagnosis of noncardiac chest pain: cardiac outcomes and health care utilization. Mayo Clin Proc. 2010 Apr;85(4):323-30.

13. Hadlandsmyth K, Rosenbaum DL, Craft JM, Gervino EV, White KS. Health care utilisation in patients with non-cardiac chest pain: a longitudinal analysis of chest pain, anxiety and interoceptive fear. Psychol Health. 2013;28(8):849-61.

14. Hadlandsmyth K, White KS, Krone RJ. Quality of life in patients with non-CAD chest pain: associations to fear of pain and psychiatric disorder severity. J Clin Psychol Med Settings. 2013 Sep;20(3):284-93.

15. Lethem J, Slade PD, Troup JD, Bentley G. Outline of a Fear-Avoidance Model of exaggerated pain perception-I. Behav Res Ther. 1983;21(4):401-8.

16. Leeuw M, Goossens ME, Linton SJ, Crombez G, Boersma K, Vlaeyen JW. The fear-avoidance model of musculoskeletal pain: current state of scientific evidence. J Behav Med. 2007 Feb;30(1):77-94.

17. Roditi D, Robinson ME. The role of psychological interventions in the management of patients with chronic pain. Psychol Res Behav Manag. 2011;4:41-9.

18. Webster R, Thompson AR, Norman P. 'Everything's fine, so why does it happen?' A qualitative investigation of patients' perceptions of noncardiac chest pain. J Clin Nurs. 2015 Jul;24(13-14):1936-45.

19. White KS, Raffa SD, Jakle KR, Stoddard JA, Barlow DH, Brown TA, et al. Morbidity of DSM-IV Axis I disorders in patients with noncardiac chest pain: Psychiatric morbidity linked with increased pain and health care utilization. J Consult Clin Psychol. 2008 Jun;76(3):422-30.

20. Webster R, Norman P, Goodacre S, Thompson A. The prevalence and correlates of psychological outcomes in patients with acute non-cardiac chest pain: a systematic review. Emerg Med J. 2012 Apr;29(4):267-73.

21. Smeijers L, van de Pas H, Nyklicek I, Notten PJ, Pedersen SS, Kop WJ. The independent association of anxiety with non-cardiac chest pain. Psychol Health. 2014;29(3):253-63.

22. Webster R, Norman P, Goodacre S, Thompson A, McEachan RR. Illness representations, psychological distress and non-cardiac chest pain in patients attending an emergency department. Psychol Health. 2014 May 15:1-37.

23. Nilsson S. Chest pain and ischemic heart disease : diagnosis and management in primary health care. Linköping: Department of Medical and Health Sciences, Linköpings universitet; 2008.

24. Ruigomez A, Masso-Gonzalez EL, Johansson S, Wallander MA, Garcia-Rodriguez LA. Chest pain without established ischaemic heart disease in primary care patients: associated comorbidities and mortality. Br J Gen Pract. 2009 Mar;59(560):e78-86.

25. Spalding L, Reay E, Kelly C. Cause and outcome of atypical chest pain in patients admitted to hospital. J R Soc Med. 2003 Mar;96(3):122-5.

26. Eslick GD, Coulshed DS, Talley NJ. Review article: the burden of illness of non-cardiac chest pain. Aliment Pharmacol Ther. 2002 Jul;16(7):1217-23.

27. The Swedish National Board of Health and Welfare. Statistics database. 2011; Available from: http://www.socialstyrelsen.se/statistik/statistikdatabas. Accessed 02/01, 2012.

28. Fass R, Dickman R. Non-cardiac chest pain: an update. Neurogastroenterol Motil. 2006 Jun;18(6):408-17.

29. Eslick GD. Classification, natural history, epidemiology, and risk factors of noncardiac chest pain. Dis Mon. 2008 Sep;54(9):593-603.

30. Wang W, Sun YH, Wang YY, Wang YT, Wang W, Li YQ, et al. Treatment of functional chest pain with antidepressants: a meta-analysis. Pain Physician. 2012 Mar-Apr;15(2):E131-42.

31. Jerlock M. Patients with unexplained chest pain: pain experience, stress, coping and health-related quality of life. Göteborg: Institute of Health and Care Sciences, The Sahlgrenska Academy at Göteborg University; 2007.

32. Reid S, Wessely S, Crayford T, Hotopf M. Medically unexplained symptoms in frequent attenders of secondary health care: retrospective cohort study. BMJ. 2001 Mar 31;322(7289):767.

33. Fagring AJ, Lappas G, Kjellgren KI, Welin C, Manhem K, Rosengren A. Twenty-year trends in incidence and 1-year mortality in Swedish patients hospitalised with non-AMI chest pain. Data from 1987-2006 from the Swedish hospital and death registries. Heart. 2010 Jul;96(13):1043-9.

34. Eslick GD, Jones MP, Talley NJ. Non-cardiac chest pain: prevalence, risk factors, impact and consulting-a population-based study. Aliment Pharmacol Ther. 2003 May 1;17(9):1115-24.

35. Fagring AJ, Kjellgren KI, Rosengren A, Lissner L, Manhem K, Welin C. Depression, anxiety, stress, social interaction and health-related quality of life in men and women with unexplained chest pain. BMC Public Health. 2008 May 19;8:165.

36. Fagring AJ, Gaston-Johansson F, Kjellgren KI, Welin C. Unexplained chest pain in relation to psychosocial factors and health-related quality of life in men and women. Eur J Cardiovasc Nurs. 2007 Dec;6(4):329-36.

37. Jerlock M, Welin C, Rosengren A, Gaston-Johansson F. Pain characteristics in patients with unexplained chest pain and patients with ischemic heart disease. Eur J Cardiovasc Nurs. 2007 Jun;6(2):130-6.

38. White KS, Craft JM, Gervino EV. Anxiety and hypervigilance to cardiopulmonary sensations in non-cardiac chest pain patients with and without psychiatric disorders. Behav Res Ther. 2010 May;48(5):394-401.

39. Eslick GD. Usefulness of chest pain character and location as diagnostic indicators of an acute coronary syndrome. Am J Cardiol. 2005 May 15;95(10):1228-31.

40. Di Fiore DP, Beltrame JF. Chest pain in patients with 'normal angiography': could it be cardiac? Int J Evid Based Healthc. 2013 Mar;11(1):56-68.

41. Eslick GD, Talley NJ. Natural history and predictors of outcome for non-cardiac chest pain: a prospective 4-year cohort study. Neurogastroenterol Motil. 2008 Sep;20(9):989-97.

42. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. Glob Heart. 2012 Dec;7(4):275-95.

43. The Swedish National Board of Health and Welfare. Myocardial Infarctions in Sweden 1990–2013. 2014; Available from: http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/19595/2014-11-13.pdf. Accessed 09/12, 2015.

44. Degano IR, Salomaa V, Veronesi G, Ferrieres J, Kirchberger I, Laks T, et al. Twenty-five-year trends in myocardial infarction attack and mortality rates, and case-fatality, in six European populations. Heart. 2015 Sep 1;101(17):1413-21.

45. Hemingway H, Langenberg C, Damant J, Frost C, Pyorala K, Barrett-Connor E. Prevalence of angina in women versus men: a systematic review and meta-analysis of international variations across 31 countries. Circulation. 2008 Mar 25;117(12):1526-36.

46. Scirica BM. Chronic angina: definition, prevalence, and implications for quality of life. Rev Cardiovasc Med. 2009;10 Suppl 1:S3-10.

47. Jerlock M, Gaston-Johansson F, Danielson E. Living with unexplained chest pain. J Clin Nurs. 2005 Sep;14(8):956-64.

48. Eslick GD. Health care seeking behaviors, psychological factors, and quality of life of noncardiac chest pain. Dis Mon. 2008 Sep;54(9):604-12.

49. Jerlock M, Kjellgren KI, Gaston-Johansson F, Lissner L, Manhem K, Rosengren A, et al. Psychosocial profile in men and women with unexplained chest pain. J Intern Med. 2008 Sep;264(3):265-74.

50. Asbury EA, Collins P. Psychosocial factors associated with noncardiac chest pain and cardiac syndrome X. Herz. 2005 Feb;30(1):55-60.

51. Jonsbu E, Dammen T, Morken G, Lied A, Vik-Mo H, Martinsen EW. Cardiac and psychiatric diagnoses among patients referred for chest pain and palpitations. Scand Cardiovasc J. 2009 Aug;43(4):256-9.

52. Eken C, Oktay C, Bacanli A, Gulen B, Koparan C, Ugras SS, et al. Anxiety and depressive disorders in patients presenting with chest pain to the emergency department: a comparison between cardiac and non-cardiac origin. J Emerg Med. 2010 Aug;39(2):144-50.

53. Potts SG, Bass CM. Psychological morbidity in patients with chest pain and normal or near-normal coronary arteries: a long-term follow-up study. Psychol Med. 1995 Mar;25(2):339-47.

54. Goodacre S, Mason S, Arnold J, Angelini K. Psychologic morbidity and health-related quality of life of patients assessed in a chest pain observation unit. Ann Emerg Med. 2001 Oct;38(4):369-76.

55. Robertson N, Javed N, Samani NJ, Khunti K. Psychological morbidity and illness appraisals of patients with cardiac and non-cardiac chest pain attending a rapid access chest pain clinic: a longitudinal cohort study. Heart. 2008 Mar;94(3):e12.

56. Janson Fagring A, Gaston-Johansson F, Danielson E. Description of unexplained chest pain and its influence on daily life in men and women. Eur J Cardiovasc Nurs. 2005 Dec;4(4):337-44.

57. Jerlock M, Gaston-Johansson F, Kjellgren KI, Welin C. Coping strategies, stress, physical activity and sleep in patients with unexplained chest pain. BMC Nurs. 2006 Oct 31;5:7.

58. Mayou R, Bryant B, Forfar C, Clark D. Non-cardiac chest pain and benign palpitations in the cardiac clinic. Br Heart J. 1994 Dec;72(6):548-53.

59. Jonsbu E, Martinsen EW, Morken G, Moum T, Dammen T. Illness perception among patients with chest pain and palpitations before and after negative cardiac evaluation. Biopsychosoc Med. 2012 Sep 27;6(1):19,0759-6-19.

60. Roysland IO, Dysvik E, Furnes B, Friberg F. Exploring the information needs of patients with unexplained chest pain. Patient Prefer Adherence. 2013 Sep 9;7:915-23.

61. Jonsbu E, Dammen T, Morken G, Moum T, Martinsen EW. Short-term cognitive behavioral therapy for non-cardiac chest pain and benign palpitations: a randomized controlled trial. J Psychosom Res. 2011 Feb;70(2):117-23.

62. Jonsbu E, Dammen T, Morken G, Martinsen EW. Patients with noncardiac chest pain and benign palpitations referred for cardiac outpatient investigation: a 6-month follow-up. Gen Hosp Psychiatry. 2010 Jul-Aug;32(4):406-12.

63. Reid S, Wessely S, Crayford T, Hotopf M. Frequent attenders with medically unexplained symptoms: service use and costs in secondary care. Br J Psychiatry. 2002 Mar;180:248-53.

64. Reid S, Crayford T, Patel A, Wessely S, Hotopf M. Frequent attenders in secondary care: a 3-year follow-up study of patients with medically unexplained symptoms. Psychol Med. 2003 Apr;33(3):519-24.

65. World Health Organization. Depression. 2013. Available from: http://www.who.int/mental_health/management/depression/en/. Accessed 02/12, 2013.

66. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, Va.: American Psychiatric Publishing; 2013.

67. The Swedish Council on Technology. Treatment of depression a systematic review. Stockholm: 2004. Available from: http://www.sbu.se/upload/Publikationer/Content1/1/SBU_Treatment_depression.pdf. Accessed 07/03, 2009.

68. Herlofson J, Ekselius L. Psykiatri. 1 uppl ed. Lund: Studentlitteratur; 2009.

69. Ruo B, Rumsfeld JS, Hlatky MA, Liu H, Browner WS, Whooley MA. Depressive symptoms and health-related quality of life: the Heart and Soul Study. JAMA. 2003 Jul 9;290(2):215-21.

70. Al-Windi A. Depression in general practice. Nord J Psychiatry. 2005;59(4):272-7.

71. Shiels C, Gabbay M, Dowrick C, Hulbert C. Depression in men attending a rural general practice: factors associated with prevalence of depressive symptoms and diagnosis. Br J Psychiatry. 2004 Sep;185:239-44.

72. Williams LJ, Jacka FN, Pasco JA, Dodd S, Berk M. Depression and pain: an overview. Acta Neuropsychiatrica. 2006;18:79-87.

73. Gureje O. Comorbidity of pain and anxiety disorders. Curr Psychiatry Rep. 2008 Aug;10(4):318-22.

74. Foldes-Busque G, Marchand A, Chauny JM, Poitras J, Diodati J, Denis I, et al. Unexplained chest pain in the ED: could it be panic? Am J Emerg Med. 2011 Sep;29(7):743-51.

75. Jordan KD, Okifuji A. Anxiety disorders: differential diagnosis and their relationship to chronic pain. J Pain Palliat Care Pharmacother. 2011;25(3):231-45.

76. Eifert GH, Thompson RN, Zvolensky MJ, Edwards K, Frazer NL, Haddad JW, et al. The cardiac anxiety questionnaire: development and preliminary validity. Behav Res Ther. 2000 Oct;38(10):1039-53.

77. Fischer D, Kindermann I, Karbach J, Herzberg PY, Ukena C, Barth C, et al. Heart-focused anxiety in the general population. Clin Res Cardiol. 2012 Feb;101(2):109-16.

78. Marker CD, Carmin CN, Ownby RL. Cardiac anxiety in people with and without coronary atherosclerosis. Depress Anxiety. 2008;25(10):824-31.

79. Spinhoven P, Van der Does AJ, Van Dijk E, Van Rood YR. Heart-focused anxiety as a mediating variable in the treatment of noncardiac chest pain by cognitive-behavioral therapy and paroxetine. J Psychosom Res. 2010 Sep;69(3):227-35.

80. Chambless DL, Caputo GC, Bright P, Gallagher R. Assessment of fear of fear in agoraphobics: the body sensations questionnaire and the agoraphobic cognitions questionnaire. J Consult Clin Psychol. 1984 Dec;52(6):1090-7.

81. Aikens JE, Zvolensky MJ, Eifert GH. Differential fear of cardiopulmonary sensations in emergency room noncardiac chest pain patients. J Behav Med. 2001 Apr;24(2):155-67.

82. Chambers JB, Marks EM, Russell V, Hunter MS. A multidisciplinary, biopsychosocial treatment for non-cardiac chest pain. Int J Clin Pract. 2014 Oct 31.

83. Mayou R. Chest pain, palpitations and panic. J Psychosom Res. 1998 Jan;44(1):53-70.

84. Shelby RA, Somers TJ, Keefe FJ, Silva SG, McKee DC, She L, et al. Pain catastrophizing in patients with noncardiac chest pain: relationships with pain, anxiety, and disability. Psychosom Med. 2009 Oct;71(8):861-8.

85. Quartana PJ, Campbell CM, Edwards RR. Pain catastrophizing: a critical review. Expert Rev Neurother. 2009 May;9(5):745-58.

86. Ocanez KL, McHugh RK, Otto MW. A meta-analytic review of the association between anxiety sensitivity and pain. Depress Anxiety. 2010 Aug;27(8):760-7.

87. Roysland IO, Friberg F. Unexplained Chest Pain and Physical Activity: Balancing Between Existential Uncertainty and Certainty. Qual Health Res. 2015 Feb 6.

88. Martinsen EW. Physical activity in the prevention and treatment of anxiety and depression. Nord J Psychiatry. 2008;62 Suppl 47:25-9.

89. Drummond MF. Methods for the economic evaluation of health care programmes. 3, [updat a rev] ed. Oxford: Oxford University Press; 2005.

90. Tarricone R. Cost-of-illness analysis. What room in health economics? Health Policy. 2006 Jun;77(1):51-63.

91. The Swedish Council on Technology. Utvärdering av metoder i hälso- och sjukvården- en handbok. Stockholm: 2012. Available from: http://www.sbu.se/upload/ebm/metodbok/SBUsHandbok.pdf. Accessed 04/02, 2013.

92. Rice DP. Cost of illness studies: what is good about them? Inj Prev. 2000 Sep;6(3):177-9.

93. van den Hout WB. The value of productivity: human-capital versus friction-cost method. Ann Rheum Dis. 2010 Jan;69 Suppl 1:i89-91.

94. Koopmanschap MA. Cost-of-illness studies. Useful for health policy? Pharmacoeconomics. 1998 Aug;14(2):143-8.

95. Hocaoglu C, Gulec MY, Durmus I. Psychiatric comorbidity in patients with chest pain without a cardiac etiology. Isr J Psychiatry Relat Sci. 2008;45(1):49-54.

96. van Beek MH, Oude Voshaar RC, Beek AM, van Zijderveld GA, Visser S, Speckens AE, et al. A brief cognitive-behavioral intervention for treating depression and panic disorder in patients with noncardiac chest pain: a 24-week randomized controlled trial. Depress Anxiety. 2013 Jul;30(7):670-8.

97. Mayou RA, Bass CM, Bryant BM. Management of non-cardiac chest pain: from research to clinical practice. Heart. 1999 Apr;81(4):387-92.

98. Esler JL, Bock BC. Psychological treatments for noncardiac chest pain: recommendations for a new approach. J Psychosom Res. 2004 Mar;56(3):263-9.

99. Chambers J, Bass C. Atypical chest pain: looking beyond the heart. QJM. 1998 Mar;91(3):239-44.

100. Jerlock M, Bjorkelund C. A cognitive behavior intervention program in women with unexplained chest pain-a pilot study. Eur J Cardiovasc Nurs. 2012 Jun;11(2):183-9.

101. Boettcher J, Astrom V, Pahlsson D, Schenstrom O, Andersson G, Carlbring P. Internet-based mindfulness treatment for anxiety disorders: a randomized controlled trial. Behav Ther. 2014 Mar;45(2):241-53.

102. Lahmann C, Loew TH, Tritt K, Nickel M. Efficacy of functional relaxation and patient education in the treatment of somatoform heart disorders: a randomized, controlled clinical investigation. Psychosomatics. 2008 Sep-Oct;49(5):378-85.

103. The Swedish National Board of Health and Welfare. National Guidelines for Care in cases of Depression and Anxiety Disorders - summary. 2010; available from: https://www.socialstyrelsen.se/nationalguidelines/nationalguidelinesforcareincasesofdepressionandanxietydisorders. Accessed 27/11, 2014.

104. Hoifodt RS, Strom C, Kolstrup N, Eisemann M, Waterloo K. Effectiveness of cognitive behavioural therapy in primary health care: a review. Fam Pract. 2011 Oct;28(5):489-504.

105. Hofmann SG, Asnaani A, Vonk IJ, Sawyer AT, Fang A. The Efficacy of Cognitive Behavioral Therapy: A Review of Meta-analyses. Cognit Ther Res. 2012 Oct 1;36(5):427-40.

106. Chambers JB, Marks EM, Hunter MS. The head says yes but the heart says no: what is non-cardiac chest pain and how is it managed? Heart. 2015 Apr 16.

107. Kisely SR, Campbell LA, Yelland MJ, Paydar A. Psychological interventions for symptomatic management of non-specific chest pain in patients with normal coronary anatomy. Cochrane Database Syst Rev. 2012 Jun 13;6:CD004101.

108. Strohle A. Physical activity, exercise, depression and anxiety disorders. J Neural Transm. 2009 Jun;116(6):777-84.

109. Beck AT, Dozois DJ. Cognitive therapy: current status and future directions. Annu Rev Med. 2011;62:397-409.

110. Linton SJ, Landström Flink I. 12 verktyg i KBT: från teori till färdighet. 1 utg ed. Stockholm: Natur & kultur; 2011.

111. Klimes I, Mayou RA, Pearce MJ, Coles L, Fagg JR. Psychological treatment for atypical non-cardiac chest pain: a controlled evaluation. Psychol Med. 1990 Aug;20(3):605-11.

112. Mayou RA, Bryant BM, Sanders D, Bass C, Klimes I, Forfar C. A controlled trial of cognitive behavioural therapy for non-cardiac chest pain. Psychol Med. 1997 Sep;27(5):1021-31.

113. Potts SG, Lewin R, Fox KA, Johnstone EC. Group psychological treatment for chest pain with normal coronary arteries. QJM. 1999 Feb;92(2):81-6.

114. van Peski-Oosterbaan AS, Spinhoven P, van Rood Y, van der Does JW, Bruschke AV, Rooijmans HG. Cognitive-behavioral therapy for noncardiac chest pain: a randomized trial. Am J Med. 1999 Apr;106(4):424-9.

115. Johansson R, Andersson G. Internet-based psychological treatments for depression. Expert Rev Neurother. 2012 Jul;12(7):861-70.

116. Cuijpers P, Marks IM, van Straten A, Cavanagh K, Gega L, Andersson G. Computer-aided psychotherapy for anxiety disorders: a meta-analytic review. Cogn Behav Ther. 2009;38(2):66-82.

117. Andrews G, Cuijpers P, Craske MG, McEvoy P, Titov N. Computer therapy for the anxiety and depressive disorders is effective, acceptable and practical health care: a meta-analysis. PLoS One. 2010 Oct 13;5(10):e13196.

118. Cuijpers P, Donker T, van Straten A, Li J, Andersson G. Is guided self-help as effective as face-to-face psychotherapy for depression and anxiety disorders? A systematic review and meta-analysis of comparative outcome studies. Psychol Med. 2010 Dec;40(12):1943-57.

119. Zou JB, Dear BF, Titov N, Lorian CN, Johnston L, Spence J, et al. Brief internet-delivered cognitive behavioral therapy for anxiety in older adults: a feasibility trial. J Anxiety Disord. 2012 Aug;26(6):650-5.

120. Andersson G. Using the Internet to provide cognitive behaviour therapy. Behav Res Ther. 2009 Mar;47(3):175-80.

121. Robinson E, Titov N, Andrews G, McIntyre K, Schwencke G, Solley K. Internet treatment for generalized anxiety disorder: a randomized controlled trial comparing clinician vs. technician assistance. PLoS One. 2010 Jun 3;5(6):e10942.

122. Stanley MA, Wilson NL, Amspoker AB, Kraus-Schuman C, Wagener PD, Calleo JS, et al. Lay providers can deliver effective cognitive behavior therapy for older adults with generalized anxiety disorder: a randomized trial. Depress Anxiety. 2014 May;31(5):391-401.

123. Dear BF, Zou JB, Ali S, Lorian CN, Johnston L, Sheehan J, et al. Clinical and cost-effectiveness of therapist-guided Internet-delivered cognitive behavior therapy for older adults with symptoms of anxiety: a randomized controlled trial. Behav Ther. 2015 Mar;46(2):206-17.

124. Spek V, Cuijpers P, Nyklicek I, Riper H, Keyzer J, Pop V. Internet-based cognitive behaviour therapy for symptoms of depression and anxiety: a meta-analysis. Psychol Med. 2007 Mar;37(3):319-28.

125. Warmerdam L, van Straten A, Twisk J, Riper H, Cuijpers P. Internet-based treatment for adults with depressive symptoms: randomized controlled trial. J Med Internet Res. 2008 Nov 20;10(4):e44.

126. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ. 2014 Mar 7;348:g1687.

127. Swedish National Institute of Public Health. Physical Activity in the Prevention and Treatment of Diseases. 2011; Available from: http://www.fyss.se/wp-content/uploads/2011/02/fyss_2010_english.pdf. Accessed 30/05, 2014.

128. Arroll B, Khin N, Kerse N. Screening for depression in primary care with two verbally asked questions: cross sectional study. BMJ. 2003 Nov 15;327(7424):1144-6.

129. Arroll B, Goodyear-Smith F, Kerse N, Fishman T, Gunn J. Effect of the addition of a "help" question to two screening questions on specificity for diagnosis of depression in general practice: diagnostic validity study. BMJ. 2005 Oct 15;331(7521):884.

130. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979 Apr;134:382-9.

131. Mulder RT, Joyce PR, Frampton C. Relationships among measures of treatment outcome in depressed patients. J Affect Disord. 2003 Sep;76(1-3):127-35.

132. Muller MJ, Himmerich H, Kienzle B, Szegedi A. Differentiating moderate and severe depression using the Montgomery-Asberg depression rating scale (MADRS). J Affect Disord. 2003 Dec;77(3):255-60.

133. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001 Sep;16(9):606-13.

134. Wirehn AB, Karlsson HM, Carstensen JM. Estimating disease prevalence using a population-based administrative healthcare database. Scand J Public Health. 2007;35(4):424-31.

135. Heintz E, Wirehn AB, Peebo BB, Rosenqvist U, Levin LA. Prevalence and healthcare costs of diabetic retinopathy: a population-based register study in Sweden. Diabetologia. 2010 Oct;53(10):2147-54.

136. Swedish Association of Local Authorities and Regions (SALAR). CPP – Cost Per Patient. 2011; Available from: http://www.skl.se/vi_arbetar_med/statistik/sjukvard/kpp. Accessed 20/02, 2012.

137. The Social Insurance Office. Statistics and analysis. 2012; Available from: http://www.forsakringskassan.se/omfk/statistik_och_analys. Accessed 20/02, 2012.

138. WMA. Declaration of Helsinki. Ethical principles of medical research involving human subjects. 2013; Available from: http://www.wma.net/en/30publications/10policies/b3/. Accessed 20/04, 2014.

139. Kuijpers PM, Denollet J, Wellens HJ, Crijns HM, Honig A. Noncardiac chest pain in the emergency department: the role of cardiac history, anxiety or depression and Type D personality. Eur J Cardiovasc Prev Rehabil. 2007 Apr;14(2):273-9.

140. Weinstock MB, Weingart S, Orth F, VanFossen D, Kaide C, Anderson J, et al. Risk for Clinically Relevant Adverse Cardiac Events in Patients With Chest Pain at Hospital Admission. JAMA Intern Med. 2015 Jul;175(7):1207-12.

141. Goodacre S, Calvert N. Cost effectiveness of diagnostic strategies for patients with acute, undifferentiated chest pain. Emerg Med J. 2003 Sep;20(5):429-33.

142. Cullen L, Greenslade J, Merollini K, Graves N, Hammett CJ, Hawkins T, et al. Cost and outcomes of assessing patients with chest pain in an Australian emergency department. Med J Aust. 2015 May 4;202(8):427-32.

143. Ziegelstein RC, Kim SY, Kao D, Fauerbach JA, Thombs BD, McCann U, et al. Can doctors and nurses recognize depression in patients hospitalized with an acute myocardial infarction in the absence of formal screening? Psychosom Med. 2005 May-Jun;67(3):393-7.

144. Israel JI, White KS, Gervino EV. Illness perceptions, negative emotions, and pain in patients with noncardiac chest pain. J Clin Psychol Med Settings. 2015 Mar;22(1):77-89.

145. Hedman E, Andersson E, Andersson G, Lindefors N, Lekander M, Ruck C, et al. Mediators in internet-based cognitive behavior therapy for severe health anxiety. PLoS One. 2013 Oct 17;8(10):e77752.

146. Jonsbu E, Martinsen EW, Morken G, Moum T, Dammen T. Change and impact of illness perceptions among patients with non-cardiac chest pain or benign palpitations following three sessions of CBT. Behav Cogn Psychother. 2013 Jul;41(4):398-407.

147. Sanders D, Bass C, Mayou RA, Goodwin S, Bryant BM, Tyndel S. Non-cardiac chest pain: why was a brief intervention apparently ineffective? Psychol Med. 1997 Sep;27(5):1033-40.

148. Hedman E, Andersson G, Andersson E, Ljotsson B, Ruck C, Asmundson GJ, et al. Internet-based cognitive-behavioural therapy for severe health anxiety: randomised controlled trial. Br J Psychiatry. 2011 Mar;198(3):230-6.

149. Lundgren J, Andersson G, Dahlstrom O, Jaarsma T, Kohler AK, Johansson P. Internet-based cognitive behavior therapy for patients with heart failure and depressive symptoms: A proof of concept study. Patient Educ Couns. 2015 Apr 27.

150. Campbell M, Fitzpatrick R, Haines A, Kinmonth AL, Sandercock P, Spiegelhalter D, et al. Framework for design and evaluation of complex interventions to improve health. BMJ. 2000 Sep 16;321(7262):694-6.

151. Nakash RA, Hutton JL, Jorstad-Stein EC, Gates S, Lamb SE. Maximising response to postal questionnaires-a systematic review of randomised trials in health research. BMC Med Res Methodol. 2006 Feb 23;6:5.

152. Edwards P, Roberts I, Clarke M, DiGuiseppi C, Pratap S, Wentz R, et al. Methods to increase response rates to postal questionnaires. Cochrane Database Syst Rev. 2007 Apr 18;(2):MR000008.

153. Christensen H, Griffiths KM, Farrer L. Adherence in internet interventions for anxiety and depression. J Med Internet Res. 2009 Apr 24;11(2):e13.

Papers

The articles associated with this thesis have been removed for copyright reasons. For more details about these see: