Egil Jonsbu

Chest Pain and Palpitations in a Cardiac Setting; Psychological Factors, Outcome and Treatment

Thesis for the degree of Philosophiae Doctor

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Norwegian University of Science and Technology
Faculty of Medicine
Department of Neuroscience

NTNU
Norwegian University of Science and Technology

HELSE NORDMØRE OG ROMSDAL

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Brystsmerter og hjertebank ved kardiologisk poliklinikk; psykologiske faktorer, forløp etter undersøkelsen og psykologisk behandling for plagene.

Brystsmerter og hjertebank som kan være symptom på alvorlig hjertesykdom, er vanlige plager i befolkningen. Forløpet etter hjerteundersøkelsen for de som ikke får påvist hjertesykdom, er ofte dårlig. Mange fortsetter å bekymre seg for symptomene og har begrensninger i sine liv og nedsatt livskvalitet. Det er en utfordring å fange opp pasientene som trenger behandling og å utvikle gode behandlingsopplegg

Formålet med studien var å beskrive hvor mange av pasientene henvist til kardiologisk poliklinikk som hadde hjertesykdom, hvor mange som hadde psykiatrisk lidelse, hvordan det gikk med pasientene uten hjertesykdom de kommende 6 månedene og til sist å gjøre en randomisert kontrollert behandlingsstudie av pasientene med vedvarende plager.

Alle pasientene mellom 18 og 65 år som ble henvist fra allmennlege pga brystsmerter eller hjertebank til kardiologisk poliklinikk ved Molde sykehus og som ikke tidligere hadde fått diagnostisert hjertesjukdom, fikk tilbud om å delta. Av de 160 pasientene som ble inkludert, var det kun 4 % som fikk påvist behandlingstrengende hjertesjukdom, mens ca 40 % av pasientene uten hjertesjukdom hadde en psykiatrisk lidelse. De vanligste var; panikklidelse (14%), somatiseringslidelse (14%), spesifikke fobier (20%) og depresjon (5%).

Seks måneder etter hjerteundersøkelsen hadde 43% av pasientene med normal hjerteundersøkelse betydelige plager relatert til brystsmerter og hjertebank, og 70% unngikk fysisk aktivitet en sjelden gang eller oftere fordi de var bekymret for hjertet. Pasientene hadde mer depressive symptomer og var mer redd for sine kroppslige symptomer seks måneder etter enn før hjerteundersøkelsen. Høy score på depresjonstest forut for hjerteundersøkelsen predikerte dårlig prognose. Omtrent 60% av pasientene, med betydelige plager relatert til brystsmerter og hjertebank seks måneder etter normal hjerteundersøkelse, ønsket psykologisk behandling for plagene. De som ønsket behandling var mer redd for kroppslige plager og var mer begrenset av plagene enn andre. De trudde også i større grad før hjerteundersøkelsen at deres plager skyldes hjertesjukdom.

Som en del av studien utviklet vi en behandling som besto av tre sesjoner med kognitiv terapi der eksponering for fysisk aktivitet var et av elementene. Behandlingen ble prøvd ut i en randomisert kontrollert studie (RCT) til 40 pasienter med oppfølgingstid på ett år etter avsluttet behandling. Behandlingen hadde positiv effekt på frykt for kroppslige symptomer, på depressive symptomer, unngåelse av fysisk aktivitet og flere områder av helserelatert livskvalitet. Endringen i frykt for kroppslige symptomer syntes å være en viktig faktor for hele behandlingseffekten.

Konklusjon: Få av pasientene med brystsmerter og hjertebank som henvises elektivt til kardiologisk poliklinikk har hjertesykdom, mange av pasientene uten hjertesykdom har vedvarende plager med funksjonsreduksjon i månedene etter hjerteundersøkelsen. Mange av disse har effekt av tre timer med kognitiv terapi der eksponering for fysisk belastning på ergometersykkel er inkludert.

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Acknowledgements

The process towards this thesis has been demanding in regard of time and energy. Since I am a former long distance runner I have seen this process as a race. In a long distance race there are some important things you have to keep in mind: Stay focussed during the whole race, try to enjoy the journey, it is over when the goal is reached. As the speed is dependent of many factors which you only control some of, rather focus on how you run. Do not focus too much on the other runners, find your own speed. The art is to spend the right amount of energy at each stage, to much or too little will ruin the race. Cheating will spoil the pleasure of reaching the goal. Since long distance running is mentally a cheerful and familiar thing for me, I have enjoyed this race. Later, especially during the submitting process, I have realized that maybe a better way of looking at the work, is as a biathlon race. There are some penalty laps, but anyhow, you are moving towards the goal.

This thesis is based on the study carried out at Cardiac and Psychiatric departments at Molde Hospital.

I wish to express my sincere gratitude to everyone who have helped me and been supportive throughout the process of this thesis.

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I am also grateful to my parents, *Ragne and Hans Magnus,* for their support during life and especially for their contribution in making me safe enough to do things my own way. My

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List of papers

I. Jonsbu, E., Dammen, T., Morken, G., Lied, A., Vik-Mo, H. & Martinsen, E. W. (2009). Cardiac and psychiatric diagnoses among patients referred for chest pain and palpitations. *Scandinavian Cardiovascular Journal,* 43, 256-259.

II. Jonsbu, E., Dammen, T., Morken, G. & Martinsen, E. W. (2010). Patients with noncardiac chest pain and benign palpitations referred for cardiac outpatient investigation: a 6-month follow-up. *General Hospital Psychiatry*, 32, 406-412.

III. Jonsbu, E., Dammen, T., Morken, G., Moum, T. & Martinsen, E. W. Short-term cognitive behavioral therapy for non-cardiac chest pain and benign palpitations: A randomized controlled trial. *Journal of psychosomatic research,* In press.

Abbreviations

ANCOVA	Analysis of covariance
BDI	Beck Depression Inventory
BSQ	Body Sensation Questionnaire
CAD	Coronary artery disease
CBT	Cognitive behavioural therapy
CHD	Coronary heart disease
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CRP	C-reactive protein
DSM-IV	Diagnostic and Statistical manual of Mental Disorders, 4th edition
ECG	Electrocardiogram
fT4	Free T4
GAD	Generalized anxiety disorder
GAF	Global Assessment of Function Scale
HRQOL	Health related quality of life
MI	The Mobility Inventory
OR	Odds ratio
PD	Panic disorder
RCT	Randomized controlled trial
SCID-I	Structured Clinical Interview for DSM-IV axis I disorders
SD	Standard deviation
SF-36	The 36-item Short Form Health Survey
SPSS	Statistical Package for Social Sciences
TSH	Thyroid-stimulating hormone
vs	Versus

Chest pain and palpitations in a cardiac setting; psychological factors, outcome and treatment

General introduction

In internal medicine the main focus is identification and treatment of well defined physical illnesses. In psychosomatic medicine a bio-psycho-social focus is more common. The reason for attending the health care system might be complex, and physical illness might play a minor role or not be present at all. One of the fields in internal medicine, where psychological factors are important, is cardiology. The experience of cardiac complaints may range from living with a severe cardiac disorder to the fear of having this, even when no somatic disorder may be detected. Chest pain and palpitations are the two most common complaints which are associated with heart disorder. Since chest pain and palpitations potentially are symptoms of serious cardiac disorders, a main focus for cardiologists is to evaluate whether there is a cardiac condition present that may explain the symptoms. When a cardiac diagnosis, such as myocardial infarction, angina pectoris or arrhythmias, is made, the treatment is often standardized and well documented. However, in cardiac as well as in primary health care settings a high proportion of patients who present chest pain or palpitations as main symptoms do not have any heart disease or other medical disorders. (Mayou, Bryant, Forfar & Clark 1994; Weber & Kapoor 1996; Dammen, Arnesen, Ekeberg et al. 1999, Kroenke & Mangelsdorff 1989). Non-cardiac chest pain and benign palpitations are diagnoses of exclusion, defined as respectively, recurrent episodes of retrosternal pain/discomfort or unpleasant sensations of heartbeat in the absence of cardiac disease. These conditions are poorly understood and routines for treatments are lacking (Bass & Mayou 2002; Mayou 1998).

The main focus of this thesis was to a) estimate the prevalence of cardiac and psychiatric diagnoses of patients who were referred to cardiac outpatient evaluation with chest pain or palpitations, b) evaluate the six-month outcome, predictors of poor outcome, and the interest in psychological treatment among those where no cardiac condition was detected and c) develop a treatment manual for patients with non-cardiac chest pain or benign palpitations and evaluate the effect of the treatment by conducting a randomized controlled trial.

1.1.1. Epidemiology

In population-based studies the lifetime-prevalence of chest pain has been estimated to vary between 20-39% (Eslick, Jones & Talley 2003; Wong, Lam, Cheng et al. 2004)**,** while 11% reported that palpitations had a significant influence on their subjective well being (Rief, Hessel & Braehler 2001). Palpitations and chest pain are among the most common symptoms in primary care settings (Kroenke, Arrington & Mangelsdorff 1990), and the two most common reasons for referral to cardiologist (Mayou 1998).

1.1.2. Aetiology of chest pain or palpitations

Various conditions may be associated with chest pain. In one review Eslick (2004) reported the prevalence of the following conditions: ischemic heart disease 7-31%, gastrointestinal reflux 9-88%, psychiatric disorders 1-79% and musculoskeletal disorders 11-23%. The large ranges in prevalence rates may to some extent be explained by different

populations being investigated (population-based, hospital-based and out-patient based) and differences in assessment methods.

In a study addressing the aetiology of palpitations, Mayou et al. (Mayou, Sprigings, Birkhead & Price 2003) found that palpitations were associated with detected or probable arrhythmias in 34% of the patients, detected or probable extra systoles in 41%, and awareness of sinus rhythm and no detection of arrhythmias in 26%. Barsky et al. (Barsky, Delamater Clancy et al. 1996) and Weber et al. (1996) found almost similar prevalence of cardiac etiology among patients referred for palpitations by reporting prevalence of clinically significant arrhythmias as 34% and prevalence of cardiac etiology of the palpitations as 43%, respectively.

The reasons for development and maintenance of non-cardiac chest pain or benign palpitations are not well understood. Gastroesophageal reflux, oesophageal dysmotility, musculoskeletal disorders, panic disorder (PD) and benign arrhythmias are assumed to be the cause in some patients. Often, however, multiple factors may explain the symptoms. Mayou has proposed a multifactorial model for the development and maintenance of non-cardiac chest pain and benign palpitations. A central component is the attribution or cognitive appraisal, whereby physiological or minor pathological symptoms are misinterpreted as evidence of serious illness. A hypochondriacal tendency, psychiatric disorders, inappropriate illness beliefs and previous experience of illness may all predispose to misinterpretation of symptoms. The most important maintaining factors are the persistence of bodily misperception, anxiety or other psychiatric disorders, and a continuing belief that the symptoms are caused by a serious physical disorder (Mayou 1998).

1.1.3. Health-related quality of life

The Short Form 36 (SF-36) has been developed for the assessment of health-related quality of life (HRQOL). It measures the patients' own perception of psychological and physical distress and functional ability, and is suitable for use both in physical and psychiatric disorders. This makes it useful in fields like cardiology (Schenkeveld, Pedersen, van Nierop et al. 2010), where the potential consequences of physical disorders are huge and consequently the mental perspective is important. Since the instrument measures both psychological and physical consequences of a disorder, it gives the opportunity to compare the disability of similar diagnoses in different settings. Dammen et al. (Dammen, Ekeberg, Arnesen & Friis 2008) evaluated 66 non-cardiac patients with PD in a cardiac outpatient clinic and found that these were as impaired as PD patients in psychiatric settings regarding HRQOL. Moreover, in a recent review Eslick (Eslick 2008) reported that HRQOL was substantially lower among patients with non-cardiac chest pain compared to the general population. To our knowledge no previous study has explored HRQOL (SF-36) in patients with palpitations.

Introduction to paper I

1.2.0. Prevalence of cardiac and psychiatric diagnoses among patients with chest pain or palpitations

Symptoms associated with cardiac disorders are often unspecific and their origin is difficult to detect without extensive evaluation. As a consequence more than 50% of patients visiting cardiac units with chest pain or palpitations do not have any cardiac disorder (Dammen et al. 1999; Mayou et al. 1994; Bass & Mayou 2002).

Previous studies in cardiac settings have reported that non-cardiac chest pain and benign palpitations are associated with psychiatric disorders (Dammen et al. 1999; Ehlers,

Mayou, Sprigings & Birkhead 2000; Barsky, Cleary, Coeytaux & Ruskin 1994). The most commonly reported psychiatric disorder is panic disorder (PD), and both chest pain and palpitations are common symptom during panic attacks (Table 1). However, probably because of the focus on the physical symptoms, these patients seldom receive psychiatric diagnoses and adequate treatment. One study in a cardiac setting reported that only in 3 out of 76 PD patients were identified and given adequate treatment prior to referral (Dammen et al. 1999). This is in line with a study where only 2% of the patients with PD were recognized as suffering from PD when attending emergency department cardiologists (Fleet, Dupuis, Marchand et al. 1996). In addition to PD the prevalences of generalized anxiety disorder (GAD), specific phobias, somatisation disorder and depression have also been reported to be high among patients referred for chest pain, compared to the general population (Dammen et al. 1999; Fleet, Dupuis, Marchant et al. 1998; White, Raffa, Jakle et al. 2008).

During the past decade there has been a change in hospitalization policy for patients with acute coronary syndrome. Most patients with new onset angina are now urgently hospitalized and not referred for outpatient evaluation. This change might have influenced the prevalence of cardiac as well as psychiatric disorders in the outpatient clinics. A recent study (White et al. 2008) investigated 147 patients with non-cardiac chest pain seeking evaluation at a cardiological centre. The prevalence of any anxiety disorder was 41%, and the prevalences of the specific disorders were PD 12%, social phobia 16%, GAD 13%, specific phobias 14%, and depression 8%. The prevalence rate of PD differs from previous studies, in which the rates have been reported to be at least 25% in various cardiac settings (Dammen et al. 1999; Fleet et al. 1998). This tendency might reflect the changes in referral policy. Since panic attacks in most patients present with acute and dramatic symptoms, it is likely that more patients with panic disorder are sent to the emergency units.

Less is known about the prevalence of psychiatric disorders among patients with benign palpitations, but studies conducted before change in hospitalization policy have estimated the prevalence of panic disorder to 14-23% (Barsky et al. 1994; Ehlers et al. 2000).

1.2.1. Substance abuse or dependence

One review reported the prevalence of additional alcohol and/or substance abuse or dependence to be about 20 % among patients with panic disorder (Sansone, Griffith & Sansone 2005). Dammen et al. (1999) reported a prevalence of 5% of alcohol/drug abuse in patients with PD referred to a cardiac outpatient clinic for chest pain. This may indicate that alcohol/drug abuse is a smaller problem among patients referred to cardiological units compared to patients with PD in general, but this subject is sparsely investigated.

Introduction to paper II

1.3.0. Follow-up studies

Follow-up studies of patients with non-cardiac chest pain or benign palpitations show discouraging results; maintenance of symptoms that affect daily living, worrying about the heart, reduced HRQOL, and increased use of health care services are common. Potts et al. (Potts & Bass 1995) investigated patients with normal (n=31) or near to normal coronary arteries (n=15) eleven years after coronary angiography. At follow up 74% reported continuous chest pain, 39% experienced this at least once a week. Outcome of chest pain was associated with reduced functional capacity as measured by Global Assessment of Function Scale (GAF). Anxiety disorders were common, with panic disorder (15%) as the most prevalent diagnosis. Bringager et al. (Bringager, Friis, Arnesen & Dammen 2008) carried out

a nine- year follow-up study of patients with non-cardiac chest pain (n=150) diagnosed at an outpatient cardiac unit. Of the 55 patients with PD at baseline, 14 (25%) still met the criteria for PD during the month before the interview. The patients with PD at baseline had significantly higher levels of self-reported depression, somatization, anxiety cognitions and hypochondriac concerns at follow-up, as well as generally low HRQOL. In a study by Mayou et al. (Mayou, Sprigings & Gilbert 1999), 81 patients referred for palpitations were evaluated at the time of ECG-monitoring and 18 months later. Forty-six had a normal heart (no arrhythmias or other cardiac disorders detected by 24-hour ECG). Limitations in everyday life were substantial. Only a minority reported improvement at follow-up, and there were few differences between those with normal and abnormal heart (cardiologically significant arrhythmias, cardiac enlargement, or cardiomyopathy). Furthermore, Mayou et al. (1994) investigated patients with non-cardiac chest pain (n=33) or benign palpitations (n=18) six months and three years after the cardiac evaluation. A substantial proportion reported continuing symptoms, emotional stress, limitations in everyday activities, and concern about the heart.

In these previous follow-up studies some interesting information is lacking: Does fear of bodily symptoms change following a normal heart test (pre cardiac evaluation compared to six-month after). Will patients avoid physical and other activities because of worry about cardiac illness, despite negative tests? Do fear of bodily symptoms and symptoms of depression at attendance predict outcome? Will the outcome in terms of HRQOL differ between those with non-cardiac chest pain and those with benign palpitations?

1.3.1. Non-cardiac chest pain vs benign palpitations

Comparison of psychological factors in non-cardiac chest pain and benign palpitations

Limited empirical evidence supports the common assumption that patients with non-cardiac chest pain and benign palpitations have similar psychological characteristics and may be regarded as one group. The assessment of the similarities and differences between patients with these complaints may be important both for the understanding of the complaints and for the development of intervention strategies. The only previous study comparing these two groups (Mayou et al. 1994) found no significant differences in mental distress or prevalence of psychiatric disorders between patients with non-cardiac chest pain (N = 33) and benign palpitations (N = 18). However, patients with palpitations were more likely to be women, younger, report previous psychiatric problems, and have less social disability at the six-month follow-up. This study did not evaluate the degree of fear of the bodily sensations or the HRQOL.

1.3.2. Prediction of poor outcome

Prediction of poor outcome in terms of symptom maintenance, impact of the symptoms, and avoidance of physical activity

It is not stated whether patients should be screened for poor outcome at the cardiac evaluation, or if it is more appropriate to have a system which later identifies those with no cardiac disease and persistent complaints. Mayou and colleagues (Mayou, Bass & Bryant 1999) proposed a stepped care approach. This approach includes: 1) reassurance of the negative results of the cardiological investigation; 2) a six week follow-up to repeat reassurance and to address persisting pain and distress, give alternative explanations to chest pain e.g. musculoskeletal or esophagal problems; 3) a three to six months follow-up to confirm improvement for those with only mild symptoms at the first follow-up; 4) regular follow-up appointments for those with persistent chest pain who are highly distressed and

experience severe disability. For some patients a psychological intervention (cognitive behavioral therapy) or antidepressive treatment may be indicated.

Dammen et al. (Dammen, Ekeberg, Arnesen & Friis 1999) and Fleet et al. (Fleet & Beitman 1997) have developed models to detect PD in cardiac settings. However, previous studies have reported that patients with non-cardiac chest pain, even when psychiatric disorders are detected during the evaluation, are rarely given any specific treatment for such disorders in addition to the cardiac evaluation (Fleet et al. 1996).

As far as we know, none has focused on screening instruments for predicting persistent complaints among these patients. For patients with low back pain a resent review (Chou & Shekelle 2010) has evaluated predictors of persistent disabling low back pain. They reported that maladaptive pain coping behavior including fear avoidance (avoidance of work, movement or other activities due to fear that they will damage or worsening the back) and catastophizing (pain coping characterized by excessively negative thoughts and statements about the future), was predictor of persistent disabling low back pain through one year.

If it is possible to find an appropriate instrument to detect patients at the cardiac evaluation with poor outcome in terms of symptom maintenance, it would be easier to offer these patients adequate treatment. Therefore we wanted to study the screening properties of different variables and to test whether these might be useful as screening instruments.

1.3.3. Symptom attribution

Doubts have been raised whether patients with non-cardiac chest pain or benign palpitations, who are referred to cardiac or other medical units, will accept non-physical explanations of their complaints, and attend effective psychological treatment if available. Dammen et al. found that patients with PD, compared to those without PD, were more likely to believe that their chest pain was caused by heart disease (Dammen et al. 1999). Patients without coronary artery disease (CAD) in general rated it as more likely that their chest pain was caused by psychological distress than CAD (Dammen, Arnesen, Ekeberg & Friis 2004). However, neither the patients nor the cardiologists were convinced about the cause before investigation (general cardiac evaluation and bicycle stress test) was performed. The acceptance of psychological treatment for these patients might be associated with their symptom attribution and fear of the symptoms.

1.3.4. Interest in psychological treatment

Among patients with non-cardiac chest pain, only 40–60% have wanted to enter treatment studies, despite the proven effect of cognitive behavioral therapy (CBT) (Kisely, Campbell, Skerritt, & Yelland 2010). One study (Van Peski Oosterbaan, Spinhoven, Van der Does et al. 1998) found that patients, who were interested in psychological treatment, were more likely to be men, younger, had more limitations in activities and a non-significant tendency to higher frequency of chest pain. They did not differ from patients who did not want treatment regarding duration of complaints or intensity of pain. This study did not evaluate the presence of psychiatric disorders or whether the patients actually were willing to receive psychological treatment. To our knowledge, no previous study has assessed the characteristics of patients who accept psychological treatment for benign palpitations.

1.3.5. The psychological consequences of undergoing normal cardiologic investigation

The general attitude is that there should be a low threshold for cardiac investigation. The main reason for this is the need to detect and treat cardiac disorders as early as possible. It has been generally accepted that information about the test results is sufficient to reassure the patients with normal tests that they do not have a medical problem, however, this assumption is not empirically supported (Bass & Mayou 2002; Potts & Bass 1995). McDonald et al. (McDonald, Daly, Jelinek et al. 1996) have evaluated the effects of reassurance by normal test results one year after the tests. The data were collected during interviews lasting about two hours. All patients who presented with symptoms of palpitations or chest pain (n=10,) were left with anxiety about the heart, despite normal test results and reassurance from cardiologist. Of 28 patients who were referred because of a murmur (no symptoms), 20 became anxious after the detection of the murmur and of these 11 had heart related anxiety at follow-up. The residual anxiety was related to the lack of adequate patient understanding that murmur and symptoms could persist even though the heart was normal. The reduction of anxiety was directly related to improvement of this understanding.

In the present study we wanted to evaluate the fear of bodily symptoms before cardiac evaluation and at six-month follow-up. By comparing the intensity of such fear at baseline and follow-up, we would get an indication about whether the cardiac evaluation led to change in fear of bodily symptoms. Since catastrophic misinterpretations of bodily sensations are supposed to be crucial elements in the aetiology of symptom maintenance, it is important to evaluate the effect of the cardiac investigation on the interpretation of the symptoms.

Introduction to paper III

1.4.0. Treatment of non-cardiac chest pain or benign palpitations

In a recent Cochrane review Kisely et al. (2010) evaluated the effectiveness of psychological interventions for non-cardiac chest pain on the basis of ten randomized controlled trials (RCT). The review included different types of interventions; five studies on individual CBT (Mayou, Bryant, Sanders et al. 1997; Esler, Barlow, Woolard et al. 2003; Sanders, Bass, Mayou et al. 1997; Klimes, Mayou, Pearce et al. 1990; Van Peski-Oosterbaan, Spinhoven, van Rood et al. 1999), one study of group CBT (Potts, Lewin, Fox & Johnstone 1999), one study of hyperventilation control training (De Guire, Gevirtz, Hawkinson & Dixon 1996), one of hypnotherapy (Jones, Cooper, Miller et al. 2006), one of autogenic training (Asbury, Kanji, Ernst et al. 2009) and one study (Tyni-Lenne, Stryjan, Eriksson et al. 2002) focussed on relaxation and physical exercise (cycle ergometer; 30 minutes three times a week for eight weeks)**.** Two studies (Potts et al. 1999; Klimes et al. 1990) had waiting list control groups, where the control patients received s delayed treatment, in one study (Jones et al. 2006) the control group received supportive listening plus placebo medication, otherwise the interventions were compared with treatment as usual/no treatment. The CBT-interventions ranged from one to twelve sessions. The study of hypnotherapy used 12 sessions during 17 weeks with no follow-up measurements (Jones et al. 2006). The review concluded that CBT and hypnotherapy probably were effective in the short term, otherwise the effects of treatment were less clear. CBT interventions with more than one session seemed to have better outcome, especially for more generalised disability. It could not, however, be determined how many sessions were necessary, or what the most important elements in the therapy were. No CBT study had explicitly investigated avoidance of physical activity because of worry about the heart, or included exposure to physical activity in the treatment. The authors called for

new RCT-studies with adequate outcome measures, explicitly described manualized interventions, and at least 12 months follow-up.

Two recent RCT studies, both reporting some effects of the interventions, were not included in the review; one comprised 18 Johrei sessions (energy healing) (Gasiorowska, Navarro-Rodriquez, Dickman et al. 2008) and one studied 11 sessions of functional relaxation and patient education (Lahmann, Loew, Tritt & Nickel 2008). None of these two studies had follow-up measurements. Eighteen sessions of Johrei had significant effect on symptom intensity, but not on any of the eight domains of SF-36. Eleven sessions of functional relaxation and patient education was effective on mean score and two subscales (somatisation and anxiety) of SCL-90, and on cardiovascular complaints of Giesssen Inventory of Complaints.

Some RCT studies have reported beneficial effect of antidepressant medication in patients with non-cardiac chest pain. Imipramine reduced chest pain (Cannon, Quyyumi, Mincemoyer et al. 1994; Cox, Hann & Kaski 1998) and sertraline (Varia, Logue, O'Connor et al. 2000) also had effect on one of eight domains of HRQOL (SF-36). A recent RCT study compared CBT (individual, 6-12 sessions of 45-60 minutes) with sertraline (Spinhoven, Van der Does, Van Dijk & Van Rood 2010). CBT was superior to sertraline in reducing chest pain (combination score from frequency, duration and intensity), but the interventions did not differ significantly regarding change in scores of heart focus anxiety. The follow-up time in these studies was less than three months.

For treatment of benign palpitations only one RCT-study has been published (Mayou, Sprigings, Birkhead & Price 2002). In this study the intervention was based on cognitive behavioural principles, delivered by a cardiac nurse, and varied from one telephone call up to three out-patient visits and telephone calls. At three-month follow-up the there were statistically significant benefits for intervention group as 78% vs 43% in the control group, were classified to have good or excellent activity level. Regarding quality of life, assessed by the Dartmouth Co-op Scale, there was significantly larger improvement in one (physical fitness) of ten subscales.

A recent review (Quartana, Campbell & Edwards 2009) evaluated the different aspects of pain catastrophizing. The study offered evidence to suggest that pain catastrophizing represents an important process factor in pain treatment. Smeets et al. (Smeets, Vlaeyen, Kester & Knottnerus 2006) reported that CBT as well as physical exercise (aerobic, strength and endurance training) were associated with changes in pain catastrophizing, which seemed to mediate the outcome of the treatments among patients with chronic low back pain. Furthermore, in a review about the effect of physical activity on anxiety, Martinsen (Martinsen 2008) stated that physical activity will help patients to normalize their catastrophic interpretation of bodily symptoms.

Patients with non-cardiac chest pain and benign palpitations may have high levels of fear of bodily sensations, and it is assumed that a reduction of this fear will lead to decrease in the patient limitations (Mayou 1998). We therefore assumed that exposure to physical activity, as a part of CBT, would be a useful element, and it was therefore included in the treatment manual.

Since non-cardiac chest pain and benign palpitations have a tendency to poor long term outcome it is important to evaluate the long term effects of treatment. Most previous studies have short follow-ups, and none of the trials using CBT has as long as 12 months follow-up after the end of intervention. Thus, we wanted to conduct a 12 month follow-up study.

1.4.1. Mediator of change

Change in interpretations of symptoms as mediator for depression and avoidance of physical activity

The main goal for RCT studies is to compare the effects of treatments. Process research is dealing with *how* a given intervention works. One way to investigate *how* the intervention works is to measure the association between central elements in the treatment (e.g. symptom perception) and other outcome measures. When analysing the results of a RCT-trial , van Peski-Oosterbaan et al. (Van Peski-Oosterbaan, Spinhoven, Van der Does et al. 1999) found a significant association between interpretation of chest symptoms and chest pain reduction. They did not find similar association for fear of bodily sensations (BSQ) and chest pain reduction. No previous study has analysed whether reductions in BSQ may mediate changes in more general measures like avoidance of physical activity or BDI.

Aims of the study

Paper I

2.1. To estimate the prevalence of cardiac and psychiatric diagnoses among consecutive patients referred to cardiac outpatient evaluation for chest pain or palpitations.

Paper II

2.2. Describe the clinical status prior to cardiac evaluation and at six-month follow-up for patients with non-cardiac chest pain or benign palpitations

2.3. Compare the demographic and psychological characteristics of patients with non-cardiac chest pain and benign palpitations

2.4. Identify factors that predict poor outcome and evaluate their suitability for screening

2.5. Identify factors associated with the patient's interest in psychological treatment

Paper III

2.6. Evaluate the effect of short-term cognitive behavioral therapy for patients with non-cardiac chest pain or benign palpitations with 12 months follow-up

2.7. Evaluate whether changes in depression and avoidance of physical activity were mediated by a reduction in fear of bodily sensations.

Material and methods

3.1.0. Definitions

In this study we have defined non-cardiac chest pain as chest pain where no relevant heart disorder is detected after a proper evaluation (bicycle stress test, and if needed myocardial scintigraphy, and/or coronary angiography), and benign palpitations as a physical sensation of irregularities in the beating of the heart, without detection of serous arrhythmias after a proper evaluation (12-lead resting electrocardiogram (ECG) and Holter monitoring and in addition seven days of ECG monitoring (R-test) when appropriate).

3.1.1. Patients in paper I and II

At attendance

Consecutive patients aged between 18 and 65, who were referred to the cardiac outpatient unit at Molde Hospital, Norway, for evaluation of chest pain or palpitations between May 2006 and May 2007 were asked to participate. The outpatient clinic receives all referrals in a catchment area of about 75 000 inhabitants.

The head of the cardiac unit screened all referrals. The inclusion criteria were: (1) referral for chest pain or arrhythmias, (2) age 18–65 years, and (3) the ability to understand and write Norwegian. The exclusion criteria were: (1) mental retardation, (2) psychosis, and (3) previous organic heart disease confirmed by a cardiologist. Of 219 consecutive patients, 21 cancelled both the cardiological and the psychiatric evaluation, 36 did not want to participate in the study, and two were excluded (one did not speak Norwegian properly and one was mentally retarded). A total of 160/198 patients (81%) completed the study at attendance. Of these, 112 were referred for chest pain and 48 for palpitations. The 36 who did not want to participate in the study did not differ significantly from the participants regarding age, sex, prevalence of CHD (result of the cardiac evaluation), or chest pain/palpitations ratio.

All included patients signed an informed consent form. The recruitment of subjects at attendance is summarized in Figure 1.

Among the 160 patients who participated in psychiatric and cardiac evaluations at attendance, six had coronary heart disease confirmed by the cardiac evaluation (five referred for chest pain and one for palpitations). No arrhythmias in need of treatment were detected.

The non-cardiac sample at attendance consisted of 154 patients, 107 patients were referred because of chest pain and 47 for palpitations.

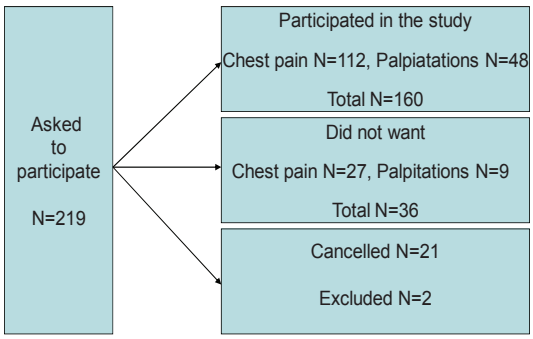

Figure 1 Recruitment of subjects in the study

Sample at six-month follow-up

Of the total sample of 154 patients with non-cardiac chest pain or benign palpitations at attendance, 138 (90%) responded to mailed questionnaires at the six-month follow-up: 95 (89%) in the chest pain group and 43 (91%) in the palpitations group. Those who did not respond at follow-up did not differ from the participants regarding gender, age, prevalence of psychiatric disorders, or scores on any variable with importance for outcome (i.e., depression, anxiety symptoms, and avoidance) at baseline.

3.1.2. Procedure

The cardiologic outpatient unit sent letters with time for evaluation to patients who were routinely referred for cardiac investigation. In the same letters the patients got information about the study. The patients were informed that the purpose of the study was to evaluate psychological distress and prevalence of psychiatric disorders among patients referred for chest pain or palpitations. The psychiatric evaluation and assessments at attendance were performed before the cardiac evaluation; thus, both the interviewer and the patients were blind to the results of the cardiac evaluation. All information about the patients at the six-month follow-up was collected by mail (except for interest in treatment, for which some patients were phoned).

3.1.3. Evaluation and assessments

Sex, age, marital status (married/cohabiting, yes or no), education (vocational school/university, yes or no), work status (main source of income past 6 months; work, sickness benefit, other), duration of symptoms, and number of days on sick leave during the three months prior to consultation were registered at attendance.

Cardiac evaluation

In addition to routine cardiac evaluation, the cardiologist completed a form consisting of risk factors for CHD (smoking habits and blood pressure) and clinical descriptors for chest pain (duration, character, site and radiation of chest pain, and precipitating factors) or palpitations (duration of symptoms, character of arrhythmias or complaints, and syncope). All patients underwent a 12-lead resting electrocardiogram (ECG). Blood samples were taken to analyse fasting blood sugar, CRP, total cholesterol, fT4, and TSH.
The interpretation of the standard bicycle stress test was based on ST-segment deviation, arrhythmias, blood pressure response, and the presence of chest pain. The evaluation was based on the patient's history, ECG, and the results of the stress test. If the cardiologist found the results consistent with CHD, or if there was doubt about this, the patients were referred for myocardial scintigraphy, or coronary angiography.
If there was doubt about the conclusion from the Holter monitoring, the patients also underwent seven days of ECG monitoring (R-test) or a bicycle stress test. A flow diagram shows the participation in the different cardiac investigations (Figure 2).

The cardiac evaluations were performed and administered at the Cardiology unit at Molde Hospital, except for the coronary angiography, which was performed at St. Olav University Hospital, Trondheim.

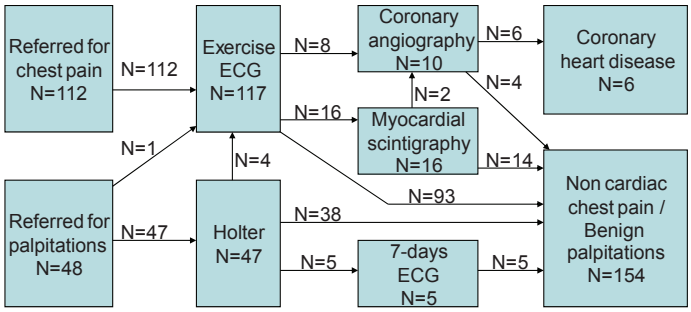

Figure 2 Cardiac evaluation

Cardiac investigators

Three cardiologists and three physicians under supervision by the cardiologist performed the cardiac evaluations. The cardiologists and the physicians were employed at the unit where the study took place.

Psychiatric evaluation

Psychiatric disorders were assessed using the Structured Clinical Interview for DSM-IV axis I disorders, (SCID-I). The interviews were performed by the first author, who is an experienced psychiatrist, who was trained in the use of the instrument. For current diagnoses, the criteria had to be met within one month prior to the interview; for lifetime diagnoses, the criteria had to be met previously or currently.

Fear of bodily sensations, depression, and health related quality of life

The Body Sensations Questionnaire (BSQ) (Chambless, Caputo, Bright & Gallagher 1984) measures fear of body sensations. It consists of 17 different bodily symptoms rated on a 1-5 scale. The questionnaire was noted to be highly internally consistent (Cronbach alpha =0.87). The stability over a period of 31 days was moderately good (r=0.67), and the change with treatment was highly significant. BSQ relations with other indices of relevant psychopathology were also satisfactory (Chambless et al 1984). It is previously used in studies of patients with non-cardiac chest pain and benign palpitations (Dammen et al. 1999; Ehlers et al. 2000).

The Beck Depression Inventory (BDI) (Beck & Steer 1993) measures the level of depression. It consists of 21 items rated on a 0-3 scale, and sum score ranges from 0-63.

The Mobility Inventory (MI) (Chambless, Caputo, Jasin et al. 1985) measures avoidance in 24 different places or situations, and is scored on a 1-5 scale. For each place or situation, the patients score for being alone or accompanied by others.

The 36-item SF-36 (Ware & Sherbourne 1992) measures patient perceptions of HRQOL and their functioning across eight areas of life (domains): physical functioning, physical role limitations (i.e., role limitations because of physical health problems), bodily

pain, general health perception, vitality, social functioning, emotional role limitations (i.e., role limitations because of emotional problems), and mental health. Domain scores range from 0 to 100; higher scores indicate better health. A validated Norwegian translation of the SF-36 was used in the present study (Loge, Kaasa, Hjermstad & kvien 1998; Loge & Kaasa 1998).

All instruments (BSQ, BDI, MI, and SF-36) have sound psychometric properties and are widely used clinically and in research.

Symptom attribution

Patients were asked the following questions: (1) Do you think your symptoms are caused by a heart disease?; and (2) Do you think your symptoms are caused by mental stress or anxiety? The choices of response were: 1. not likely; 2. less likely; 3. most likely; 4. for sure.

Treatment of psychiatric disorders

Psychotherapy was defined as at least one session with psychological treatment/counselling for mental problems during lifetime. The use of the following current medications was registered: antidepressants, anxiolytics, hypnotics, or other psychotropic drugs.

Frequency of symptoms

Symptoms of chest pain or palpitations were recorded on a registration form, developed for the present study. The frequency of symptoms was rated as 1 “daily”, 2 “weekly or more often”, 3 “rare but sometimes”, or 4 “no symptoms in the last 6 months”. For patients who reported both chest pain and palpitations, the highest frequency score was entered in the statistical analyses.

Consequences of chest pain and palpitation

The impact of cardiac symptoms on the domains of family, social, and work life were recorded separately as “very much”, “quite much”, “some”, and “no”, and the highest score (the domain mostly affected) was used.
Avoidance of physical activity was assessed using the following question: “Do you avoid physical activity because of worries about the heart?”. The response categories were “often”, “now and then”, “rare but sometimes”, and “never”.

Clinically significant complaints at follow-up

Clinically significant complaints at follow-up were defined as reports of at least one of the following: At least weekly symptoms; at least moderate impact on family life, social life, or work; or avoiding physical activity now and then because of worries about the heart. Clinically significant complaints were categorized as present or not present. The purpose of the generation of this variable was to identify individuals who were considered to have poor outcome at six-month follow-up. All patients with clinically significant complaints were evaluated as having poor outcome.

Interest in psychological treatment

At the six-month follow-up, all patients were asked the following question: "Do you want to participate in a research project, in which we aim to explore the efficacy of a treatment regimen developed to increase coping ability regarding chest pain and/or palpitations". Response categories were: 1) "yes"; 2) "phone me for more information"; and 3) "no". Of all participants at follow-up 44 patients were interested in psychological treatment, and of these, 11 received information by telephone before making a decision.

Among those who fulfilled the criteria for clinically significant complaints (N=60), 36 (60%) were interested in psychological treatment. When we compared patients who were interested in psychological treatment with patients who were not interested, only patients with clinically significant complaints (N=60) were included in the analyses. In this way only patients who we evaluated as having poor outcome, were compared.

Randomized controlled trial

3.2.0. Patients

At six-month follow-up patients were invited to take part in a treatment study. Eligible patients had 1) no cardiac disease confirmed in the cardiac evaluation, and 2) reports of either at least "weekly" symptoms, at least "some" effects on family life, social life, or work, or at least "rare but sometimes" avoidance of physical activity because of worries about the heart (NB different definition/level of complaints than clinically significant complaints). Ninety-four patients meet the inclusion criteria, and of these 41 (44 %) wanted to participate in the treatment trial. One was excluded because he was seriously ill and died short time thereafter, so 40 patients were included. These patients were randomized to intervention (N=21) and control group (N=19).

There were no significant differences between the intervention and control groups with regard to demographic and clinical data at the time of cardiac evaluation or at the start of treatment (six-month follow-up). The prevalence of PD and any psychiatric disorder (at the cardiac evaluation) for the intervention and control group was 19% vs 36% and 57% vs 42%, respectively.

Participation in the treatment trial and follow-up are summarized in Figure 3.

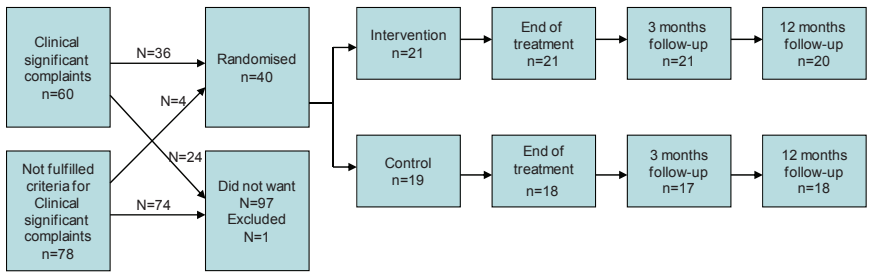

Figure 3 Participation in the treatment trial

3.2.1. Design

Participants were randomly assigned to intervention or control groups by a web module, which offers block randomization. The procedure was performed by the Unit for Applied Clinical Research, NTNU, Norway, which is separate from the intervention location. Patients assigned to the control group received treatment as usual from their general practitioner, and were free to use the health care system when needed. As a reward for each set of questionnaires being returned by mail, the patients received lottery tickets worth about ten Euros.

All patients were assessed at baseline (six months after the cardiological examination), at the end of the intervention and at three- and 12-month after the end of intervention. All assessments were self-report. All assessments in the control group, and the follow-up assessments for the intervention group, were sent to the patients by mail.

3.2.2. Primary and secondary outcome measures

We decided fear of bodily sensations (BSQ) to be the primary outcome measure. Avoidance of physical activity because of worry about the heart, symptoms of depression (BDI), symptom frequency, impact of the symptoms on the domains of family, social, and work, and HRQOL were secondary measures.

Physical assessments during the physical exposure

For assessment of perceived exertion, the experienced strain during physical activity, the Borg scale (Borg, 1970) was used. It is scored on a 6 – 20 scale, where 6 indicates very light and 20 maximally strenuous exercise. This registration was done to secure the intensity of the exposure. In addition, registration of heart rate was done using a pulse monitor (DK City Fitness Polar 5261).

3.2.3. Therapists

All patients received individualised CBT. All patient treatments, except for two, were conducted by the first author (EJ), who is an experienced psychiatrist with formal training in CBT as a therapist and is a licensed CBT supervisor. The remaining two patients were treated by a physician with training in CBT, under the supervision of the first author.

3.2.4. The treatment

The treatment took place at the Psychiatric Outpatient Clinic at Molde Hospital, at the same hospital as the cardiac evaluation was performed. A treatment manual for three sessions of CBT was developed by the first author in cooperation with his co-authors. There is no consensus in the literature about what is the optimal volume of treatment for these conditions, and previous studies have reported number of sessions ranging from 1 to 18. We wanted to develop a program which was extensive enough to cover what we thought were important elements in treatment, and short enough to be useful in a general clinical setting. Three sessions were chosen because this model would give the therapist the opportunity to 1) discuss the patients´ experiences obtained between the sessions and 2) revise, if necessary, their achieved knowledge about their symptoms 3) include a within-session exercise session. Each session lasted 60–90 minutes.

In the first session the results of the previous cardiac evaluation were reviewed in detail, and information about heart diseases, such as coronary heart disease and arrhythmias,

was provided. (Figures of the heart, the coronary arteries, and the electrical impulses which cause heart beats were outlined on a flip-over.) We thought that medical knowledge could be a quick way to achieve safety regarding the heart. If one lacks knowledge, mysterious interpretations might erupt. Subsequently, we focussed on the physical symptoms and how these were interpreted by the patients. If the patients´ interpretations were catastrophic or inappropriate, we helped them, by means of discussion, to find alternative interpretations. For those who had panic disorder (n = 4), the cognitive model of panic was explained (the panic circle). From the start of the treatment, it was emphasized that the therapists considered the patients' complaints to be real and bothersome, but that this did not necessarily prove that they were caused by a serious somatic illness.

In the second session, the patients were exposed to physical activity (up to about 75% of maximal pulse rate) on a treadmill (DK City Fitness Polar 5261) for 12 minutes. During the activity, the patients were asked every second minute to rate their perceived exertion on the 6–20 Borg scale, assess discomfort and worry on a 0–10 scale, and to verbalize all frightening thoughts that emerged. The aim of the session was to give each patient the opportunity to challenge their supposed main worry, whether they could they trust their heart or not. We thought the best way of challenge this fear was to expose them to physical activity in safe and controlled environment. On the treadmill they experienced that physical activity was tolerated and did not harm their hearts.

In the third session, attention was paid to avoidance behaviours and patients' interpretations of their symptoms. Avoidance behaviours, which are maladaptive behaviours to cope with fear, are important to discover and challenge. This is a general principle in treatment of anxiety disorders, and we supposed this was essential among our patients as well. Those who were still anxious about physical activity (avoided physical activity), were given the opportunity to use the treadmill to repeat the exposure. Two patients wanted to use this opportunity.

To gain experience and to maintain what was achieved, all patients were encouraged to engage in physical activity between the sessions.

Reporting of the treatment trial

The treatment trial in this thesis is reported according to the CONSORT statement (Boutron, Moher, Altman et al. 2008).

3.3.0. Statistical analyses

Data were compared between groups using a chi-squared or Fisher's exact test for dichotomous data, the Mann–Whitney for ordinal variables, and Student's *t*-test for continuous variables. Multiple linear regression analysis was used to control for age and sex when comparing patients with chest pain and those with palpitations. The paired-samples *t*-test was used to compare results for continuous variables at attendance and at follow-up. Correlations were calculated as Pearson's r (for pairs of continuous variables), point-biserial (for one dichotomous and one continuous variable), and phi (for two dichotomous variables). Prediction of poor outcome (clinically significant complaints) was analysed using logistic regression. Analyses of covariance (ANCOVAs), using the baseline score of the dependent variable as a linear covariate, were used to test the differences between the intervention and control groups in the amount of change on outcome measures. The variance attributable to the intervention was assessed by partial eta squared for the intervention variable. Differences in the effect of treatment between the chest pain and palpitations groups, and between genders, were examined using ANCOVAs with multiplicative interaction terms between treatment and

diagnosis/gender variables (one pair at a time). Analyses testing the role of BSQ as mediator were performed by ANCOVAs, using the intervention/control variable as the factor, and the difference between baseline and three-month follow-up scores for the assumed mediator (BSQ) as a covariate (in addition to the baseline for the dependent variables). All tests were two-tailed. The alpha level was $p < 0.05$. The Statistical Package for Social Science (SPSS) version 15 or 16 software was used in all analyses.

3.4.0. Ethical aspects

The research protocol was accepted by the Regional Committee for Medical Research Ethics in Trondheim in May 2006 and by the Norwegian Social Science Data Service in Bergen in June 2006. Participation was voluntary and the patient's decision to participate was based on written information. The patients were stimulated to contact the investigator for further information. It was emphasised that the decision to participate or not would not influence on the treatment at the outpatient clinic. One potential adverse effect of the study may be that the patients were asked personal questions both during the diagnostic interview and by the self-rating questionnaires. Exposure to such questions may be a stressful experience. However, no patients complained of these questions and the extensive research battery. Many patients expressed gratitude for the opportunity to discuss psychological/stress issues that they felt might be the reason why they experienced chest pain or palpitations. This is in accordance with the distress reduction during SCID interview found in a study of Scarvalone et al. (Scarvalone, Cloitre, Spielman et al. 1996).One question is if the treatment group and the control group were offered equipoise treatments according to the knowledge before the trial. The opinion of the authors is that even if there were indications of effectiveness of CBT interventions, we introduced exposure to physical activity, used only three consultations and had a long follow-up period after the treatment, which together makes it acceptable to compare with treatment as usual.

The study was registered in the ClinicalTrial.gov with ID NCT00623454

Summary of individual papers

Paper I

Cardiac and psychiatric diagnoses among patients referred for chest pain and palpitations

Scand Cardiovasc J 2009 Aug;43(4):256-9.

The purpose of this study was to assess the prevalence of cardiac and psychiatric diagnoses in patients with chest pain and palpitations. Consecutive patient (N=198), aged between 18 and 65, referred to a cardiac outpatient unit for evaluation for chest pain or palpitations, were asked to participate. Patients with a previous history of heart disease, confirmed by a cardiologist, were excluded. The final sample comprised 160 patients. The psychiatric evaluation consisted of a diagnostic interview (SCID) and self-report questionnaires. The cardiac evaluation comprised a bicycle stress test or Holter monitoring.

The prevalence of coronary heart disease was 4%. No cases of arrhythmia in need of treatment were detected. The prevalence of psychiatric disorders, among those without coronary heart disease, was 39%: 14% panic disorder, 14% somatoform disorders, 5% major depression, 20% simple phobia and 3% any current substance abuse.

Paper II

Patients with noncardiac chest pain and benign palpitations referred for cardiac outpatient investigation: 6-month follow-up

Gen Hosp Psychiatry. 2010 Jul-Aug; 32(4):406-12.

The purposes of this study were to: (1) describe the clinical status prior to cardiac evaluation and at six-month follow-up for patients with non-cardiac chest pain and benign palpitations; (2) compare the psychological characteristics of patients with non-cardiac chest pain and benign palpitations; (3) identify factors that might predict poor outcome and evaluate their suitability for screening, and to (4) identify factors associated with the patients' interest in psychological treatment. The final sample at attendance comprised 154 patients, and 138 (90%) participated at follow-up.

At the six-month follow-up, 43% still had clinically significant complaints. Patients with palpitations were more likely to be female, younger, and less likely to attribute cardiac symptoms to heart disease, but had otherwise similar psychological features to non-cardiac chest pain patients. BDI depression score (five or above) at attendance predicted clinically significant complaints at follow-up, with sensitivity of 64% and specificity of 74%, or a positive predictive value of 66%. Interest in psychological treatment was associated with more fear of bodily sensations, more impaired function, and greater tendency to attribute symptoms to heart disease.

Paper III

Short-term cognitive behavioural therapy for non-cardiac chest pain and benign palpitations. A randomized controlled trial.

Journal of Psychosomatic Research. In press.

The aim of this study was to compare a three-session manualized cognitive behavioural therapy (CBT) intervention with treatment as usual for patients with non-cardiac chest pain or

benign palpitations in a randomized controlled trial. In addition, we wanted to evaluate whether change in scores of Body Sensations Questionnaire mediated changes in depression and avoidance of physical activity scores.
Among eligible patients 40 agreed to participate, and these were randomly assigned to either an intervention (n=21) or control group (n=19). Patients in the intervention group received three manualized sessions with CBT, including one physical activity exposure session. The control group received usual care from their general practitioner. All patients completed the intervention. The dropouts in the intervention and control group at three and 12 month follow-up were 0/21 vs 2/19 and 1/21 vs 1/19, respectively.
There were significantly larger improvements in the treatment group regarding fear of bodily sensations, avoidance of physical activity, depression and some domains of HRQOL during treatment, and at three- and 12-month follow-up. A substantial proportion (about three-quarters) of the intervention effects on depression and avoidance of physical activity could be attributed to (was mediated by) the reduction in fear of bodily sensations.

Discussion

Results

5.1.0. Summary of main results

The prevalence of coronary heart disease among patients referred for chest pain or palpitations was six of 160 patients (4%). No cases of arrhythmia in need of treatment were detected.

The prevalence of psychiatric disorders, among the 154 patients without coronary heart disease, was 39%; 14% panic disorder, 14% somatoform disorders, 5% major depression, 20% specific phobias and 3% any current substance abuse. The majority believed that it was more likely that their symptoms were caused by distress or anxiety than by a cardiac condition. At the six-month follow-up, 43% still had clinically significant complaints. Patients with palpitations were more likely to be female, younger, and less likely to attribute cardiac symptoms to heart disease, but had otherwise similar psychological features to those with non-cardiac chest pain. BDI score at attendance with cut off at five or more was a rather good predictor of clinically significant complaints at follow-up (sensitivity 64%, specificity 74%, positive predictive value 66%, OR= 5.2). Among patients with clinically significant complaints at follow-up, 60% (36/60) were interested in psychological treatment. These had more fear of bodily sensations, more impaired function, and greater tendency to attribute symptoms to heart disease than patients not interested in psychosocial treatment. Three sessions of CBT, including exposure to physical activity, had significant effect on fear of bodily symptoms, depression, avoidance of physical activity because of worry about the heart, and health-related quality of life at three- and 12-month follow-up. Reduction in fear of bodily sensations mediated most of the change in avoidance of physical activity and depression.

5.1.1. Discussion of the main results

Prevalence of cardiac disorders

The prevalence of cardiac disorders (4%) in this study was surprisingly low. Previous studies (Dammen et al. 1999; Mayou et al. 1994 &1999) have also reported low prevalence of cardiac disorders among these patients (16 %- 34%), however, none as low as in the present study. This decline of the prevalence might be a result of the change in hospitalization policy during the past decade for patients with acute coronary symptoms.

Prevalence of psychiatric disorders

The prevalence of panic disorder (PD) in the present study (14%) was in line with another recent study (White et al. 2008), but lower than studies carried out about ten years ago (Dammen et al. 1999; Barsky et al 1994), where the prevalence was at least 25%. This change might reflect the change in hospitalization policy during the past decade, where more patients with acute symptoms are hospitalized. Another explanation for lower prevalence of PD today might be that the GPs are more aware of physical symptoms of PD and therefore send these patients to psychological treatment.

The prevalence of any psychiatric disorder (39%) is still high. One explanation for the high prevalence of mental disorders among patients with non-cardiac chest pain and palpitations, especially anxiety disorders, is that in these disorders dysfunctional thinking is a prominent feature, and this may predispose for misinterpretations of body sensations. This may increase the probability that low intensity symptoms, ignored by the majority, may develop into bothersome and worrying complaints. This is in line with the model developed by Mayou (1998) where catastrophic interpretation of bodily symptoms is the key element in

a cognitive model explaining how the symptoms are maintained. An alternative explanation is that mental problems develop secondarily to the bodily complaints.

The low prevalence of any current substance abuse fits well with the study of Dammen et al. (1999). One way to explain this is that you are less likely to treat your complaints with drug or alcohol if you think you have heart problem, compared to when dealing with anxiety problem.

Treatment of PD among patients with non-cardiac chest pain and benign palpitations

In the present study only 14% of patients with PD had received adequate treatment for their anxiety disorder. Despite low proportion this is higher than in previous studies in cardiac units, where only 4% had their PD detected before and 2% during the cardiac evaluation (Dammen et al. 1999; Fleet et al. 1996). Even when the PD was diagnosed at the cardiac unit, and the patients were informed that PD could be associated with chest pain, only 22% received any treatment during the next year (Dammen, Bringager, Arnesen et al. 2006). Since effective treatment for PD is available (CBT and/or antidepressants), and the prognosis without adequate treatment for a significant proportion is poor, it is an obvious challenge to offer treatment to more of these patients. For patients referred for palpitations, we do not know any study which has evaluated the detection and treatment of the psychiatric disorders. However, based on long-term course for these patients (Mayou et al. 1999; Weber & Kapoor 1996; Barsky, Cleary, Coeytaux & Ruskin 1995) and the similarities with those referred for chest pain, it is likely to suppose that PD often remains undetected among these patients as well.

The natural six-month course for non-cardiac chest pain and benign palpitations

The present study confirms the results of previous studies which report mental distress and sustained complaints for a significant proportion of patients referred for chest pain or palpitations to cardiac units and where no cardiac disorder is detected (Bringager et al. 2008; Potts et al 1995; Mayou et al.94 & 99). Mean score on BSQ increased during the six months following the cardiac evaluation. Fifty-two percent of the patients had higher score at follow-up, 40% had lower, and 8 % had similar score when comparing follow-up with attendance. A normal cardiac test seems to leave the patients with anxiety about the heart, as is in accordance with the results from the study by Mc Donald et al. (1996). This anxiety reinforces the focus on the heart, which leads to increased possibility for detecting and being aware of functional symptoms and misinterpreting these, with development of increasingly problematic non-cardiac chest pain and/or benign palpitations as a consequence. The increased level of depressive symptoms from attendance to six-month follow-up may be a demoralisation reaction, due to the limitations from the somatic complaints.

Similarities and differences between patients with chest pain and palpitations

Patients with non-cardiac chest pain and patients with benign palpitations had similar prevalence of psychiatric disorders at attendance, similar level of mental distress at attendance and at follow-up. There was overlap of symptoms between the groups, and they did not differ with regard to the effects of treatment. Both in the present study as well as in the Mayou study (1994), those referred for palpitations were younger and more likely to be female. These findings of clinical characteristics support and expand the previous knowledge about the similarities of these two groups (Mayou et al. 1994). Therefore, with regard to psychological

characteristics, tendency for poor outcome, and improvement following CBT, these two groups could be considered as one group

Prediction of poor outcome

Poor outcome, defined as clinically significant complaints at six-month follow-up, was predicted by BDI score above five, which is below clinical cut-off (BDI>9, Klimes et al. 1990). The BDI score correlated more strongly with clinically significant complaints than did the BSQ score. Because non-cardiac chest pain and benign palpitations are more closely associated with anxiety disorders than with depression, these results are somewhat surprising. This is, however, in line with a recent study where depression at baseline was a predictor for somatoform disorder eleven years after (Leiknes, Finset, Moum & Sandanger 2008). The usefulness of BDI as a screening instrument should be evaluated in new studies.

Interest in psychological treatment

Among patients with clinically significant complaints at six-month follow-up, 60% agreed to participate in the trial consisting of psychological treatment for their complaints. This result is in line with what Kisely et al. (2010) reported in the Cochrane review. Furthermore, the present study is the first to state that interest in psychological treatment was associated with fear of bodily sensations and that those patients, who were interested in treatment, were more likely to attribute their symptoms to heart disease. In addition, we have confirmed the finding from Van Peski-Oosterbaan et al. (1998), who reported that interest in psychological treatment was associated with limitations in activity, but not with frequency of symptoms. It seems like fear of bodily symptom is a motivator for treatment and that changing fear of bodily symptoms is a sensible aim for the treatment.

Effect of treatment for non-cardiac chest pain and benign palpitations

The present study is the first CBT study which has included exposure to physical activity and assessed the patients 12 months after the end of the intervention.
Three sessions of CBT included exposure to physical activity, was effective treatment for non-cardiac chest pain and benign palpitations regarding BSQ, BDI, avoidance of physical activity because of worry about the heart, and for HRQOL (SF-36). Esler et al. (2003) reported that one session with CBT was effective in reducing chest pain, but had no effects on HRQOL (SF-36). Sanders et al. (1997) reported that one session with information by a nurse (CBT) affected neither symptoms nor quality of life. Three CBT studies with up to 12 individual sessions (Klimes et al. 1990; Mayou et al. 1997; van Peski-Oosterbaan et al. 1999) and one study with six group sessions (Potts et al. 1999) all reported, at least at one follow-up, significant reduction of chest pain and some reduction in functional impairment. Among the studies using non-cognitive interventions, some effect on symptoms is reported following hyperventilation control (DeGuire et al. 1996), hypnotherapy (Jones et al. 2006), functional relaxation (Lahmann et al. 2008), Johrei (Gasiorowska et al. 2008), and autogenic training (Asbury et al. 2009), and some effect on functional impairment is reported following physical training/relaxation (Tyni-Lenne et al. 2002) and hypnotherapy (Jones et al. 2006).

In general it seems like one session intervention might give some effect on symptoms (Esler et al. 2003; Sanders et al. 1997). However, to affect on more general well being, more

sessions (about ten individual sessions or 6 two-hour sessions in group) are needed (Mayou et al. 1997; Klimes et al. 1990; Potts et al. 1999). Our hypothesis was that exposure to physical activity would have such a strong impact that we could reach the aims of better general well being with only three sessions. Our results at three months follow-up, show obvious effect of the intervention on general well being (significant for 4/8 domains of SF-36) as well as on fear of bodily symptoms, avoidance of physical activity because of worry about the heart, and depressive symptoms. At 12 month follow-up the effect was still obvious for fear of bodily symptoms, avoidance of physical activity because of worry about the heart, and depressive symptoms, but the effect of HRQOL, even though a significant difference was found (1/8 domains), was reduced.

When we developed the treatment manual, we assumed that avoidance of physical activity because of worry about the heart was an essential element in sustained complaints of non-cardiac chest pain or benign palpitations. Therefore we included exposure to physical activity (waking/running on a treadmill) in the treatment. The assumption about avoidance of physical activity was later confirmed as 70% of those, who participated in the treatment trial, had at least "rare but sometimes" avoidance of physical activity because of worry about the heart. None of the previous treatment trials using CBT to treat non-cardiac chest pain or benign palpitations have included exposure to physical activity in their manuals. We suppose, based on feed back from the patients and clinical impression, that this exposure was critical for the generalized effect achieved after only three sessions.

However, regarding the obvious effect on the more generalized measures in the present study, the lack of effect on symptom frequency is surprising. The questionnaire for measuring symptom frequency is coarse grained and time dependent, and therefore not very sensitive to change during the actual follow-up period. This might be an explanation for the lack of effect on this variable. However, our results indicate that the effects of the intervention were a consequence of change in the interpretation of symptoms rather than changes in frequency of symptoms.

Effect sizes

The effect sizes (partial eta Square) for BSQ, BDI and avoidance of physical activity are given in Table 2. The partial eta square for BSQ, BDI, and avoidance of physical activity at twelve month follow-up were 0.19, 0.15,and 0.19 respectively, showing that the intervention gave a large effect one year after the treatment (partial eta square: 0.01 is categorized as small, 0.06 as moderate, and 0.14 as large effect). The stable effect indicates that permanent changes have occurred. The measuring of effect size is important, because it makes it easier to compare effects of different treatments used in different trials.

Because of differences in assessment methods and follow-up time, and lack of analyses of effect sizes, it is difficult to compare the effects of the present treatment study with the previous studies. Three of the previous CBT studies have used BDI (Mayou et al. 2002, Klimes et al. 1990, Sanders et al. 1997), and one of these (Klimes et al. 1990) reported statistically significant differences between intervention and control group. However, no standard deviation was reported and consequently, no effect size can be calculated. None of the CBT studies used BSQ as outcome measure.

Mediation of treatment effect

Mayou (1998) have made a descriptive model for development of functional symptoms: They state that physiological or minor pathological symptoms are misinterpreted as evidence of serous illness. Once established, secondary anxiety may worsen the physical

symptoms. This model fits well with the cognitive model of panic and health anxiety and clinical experience from a wide range of functional symptoms (Mayou 1998; Mayou, Bass & Sharp 1995). This has, however, not previously been evaluated for patients with non-cardiac chest pain or benign palpitations. We wanted to test this model by analysing how much of the effect size of BDI and avoidance of physical activity because of worry about the heart (frequency of symptoms did not differ between treatment and control and could therefore not be included in the analysis) that could be explained by the change in BSQ. Since about 70-75% of the effect size could be related to the change in BSQ, we consider this partly being a confirmation of the model. This indicates that BSQ is an important focus for treatment of these patients, and psychological treatment and general information to the patients during a normal cardiac evaluation should emphasize to reduce fear of bodily sensations. The role of interpretations/catastrophizing of symptoms is in line with theories about pain treatment in general (Quartana et al. 2009) and with treatment of chronic back pain (Smeets et al. 2006).

Methodological issues

5.2.0. Sample

The sample size in paper II (N=154) is larger than in the only previous study (Mayou et al. 1994), which has evaluated and compared patients with non-cardiac chest pain and benign palpitations (N=51).
The adherence among eligible patients was high at attendance 160/198(81%) as well as at follow-up 138/154 (90%). The number, who had a cardiac disorder at the cardiac evaluation (6/160), was too small to make statistical comparisons with those without a cardiac condition. Because of the small sample size, they were also excluded from the follow-up study.

Power analyses for RCT

It is a methodologically weak point that no power analysis and determination of sample size were carried out. Forty patients participated in the treatment study, 21 in the intervention group and 19 in the control group (paper 3). We considered the size of the groups to be close to the lower limit to point out significantly differences between the groups. However, since as much as about 95% participated in the follow-up assessments, the sample proved to be sufficient for statistical analyses.

5.2.1. Internal validity

Selection bias and confounding might reduce the internal validity.

Selection bias

We intended to study all patients fulfilling the inclusion criteria. The head of the cardiac outpatient clinic at Molde Hospital screened all referrals according to the inclusion criteria. A control procedure, ensuring that all eligible patients actually were traced for study participation, was not applied. Registration procedures and questions concerning the inclusion criteria were discussed with the investigator during the inclusion period. We have not been aware of any systematic bias in registration that could affect outcome. Because we did not control whether all eligible patients actually were registered for study referral, it is possible

that some eligible patients may have been missed or overlooked for study inclusion. We stated clearly to the head of the cardiac outpatient clinic that both patients with and without suspected heart disorders were eligible for study inclusion. The patients were accepted for the study before cardiac evaluations were made. Hence, the head of the cardiac outpatient clinic was blinded to the cardiac results to minimize a selection bias toward skewing of the sample in the direction of including patients without heart disorders. A bias may also occur if the phenomena of interest are associated with "unwillingness" to participate. Among the eligible patients, those who did not want to participate at attendance (about 19%) did not differ from the participants regarding prevalence of heart disorders, or other relevant variables (paper 1). We consider the response rate (81%) to be satisfactory and the participants to be fairly representative of the current target population of patients.

At follow-up it is of interest to know whether a systematic subject loss has occurred. Theoretically one might assume that patients with more somatic symptoms, more worry about the health would be more interested in the follow-up investigations. Additionally, fully employed patients who are feeling well might not be willing to spend time going through a relatively time-consuming self-reporting exercise. The finding of more symptoms of depression, higher fear of bodily symptoms, and lower score for general health (SF-36) at follow-up compared with at attendance, raises the question whether there was such a bias. To evaluate a potential systematic bias, we compared the participants to the non-participants at follow-up regarding baseline data. No significant differences were found (paper II). Therefore we consider the participants at follow-up to be representative of the sample at attendance.

Sample participating in the treatment trial

Recruitment to the treatment trial was done by asking all patients the following question by mail: Do you want to participate in a research project in which we aim to explore the efficacy of a treatment regimen comprising three individual sessions, which has been developed to increase your ability to cope with chest pain and/or palpitations? The letter was, in addition to the person responsible for the study (EJ), signed by the head of the cardiac outpatient clinic.

It is likely that more patients will accept treatment for non-cardiac chest pain or benign palpitations if the treatment is performed in a cardiac setting. In the present study the treatment was performed by a psychiatrist and physician with training in CBT in a psychiatric setting. However, all patients had met the first author during the psychiatric interview before the cardiac evaluation, and it was stated that the study was in cooperation with the cardiac unit. Since the proportion of participants among those with clinically significant complaints, is similar to that found in previous studies (40-60%) (Kisely et al. 2010), and that they seems to have common characteristics as the patients in the study by Van Peski-Oosterbaan et al. (1998), we consider the sample to be representative of patients who want to participate in such treatment.

Confounding (internal validity)

In paper II we used logistic regression to determine predictors of poor outcome. In this setting confounding will occur when the effect of a predictor is due to a common underlying cause which has not been identified. In this study BDI at attendance stands out as a strong predictor of poor outcome. Including sex and age as covariates in the analyses did no influence the results (these were not confounders). Potential confounders might have been 1) dispositional optimism/pessimism which is found to correlate with depression as well as with

general physical and psychological well-being (Conversano, Rotondo, Lensi et al. 2010) or 2) the degree of symptoms at attendance.

5.2.2. Internal validity of the treatment trial

Selection bias refers to the problem that at pre-test, differences between intervention and control group exist, and that these differences might affect the independent variable and thus be responsible for the observed outcome.

The present study is a RCT. The most important advantage of proper randomization is that it should both eliminate selection bias and obtain balancing both with respect to known and unknown prognostic factors (third variables) in the assignment of treatments. In the present study randomization was performed by a web module which is separate from the intervention location. In addition, the intervention and control groups were compared regarding baseline data. The groups did not differ significantly for any of the variables. However, some differences were present. The prevalence of PD was higher in the control group 36% vs 19%, however, for any psychiatric disorder the prevalence was higher in the treatment group 57% vs 42% (Paper 3). It is unclear whether these differences may have influenced our results.

In the present study the control group received treatment as usual, which in most cases involves no direct treatment of chest pain or palpitations. The patients in the intervention group, in addition to having three sessions with CBT, also received more care than patients in the control group (attention affect). The additional effect of this unspecific variable is difficult to measure. However, the lack of an effect of the intervention on the frequency of symptoms indicates that the effect of such an unspecified variable perhaps is rather negligible.

5.2.3. Psychiatric assessments

Diagnoses

Psychiatric disorders were obtained by the SCID interview for Axis I disorders which is known to yield highly reliable diagnoses (Segal, Hersen & Van Hasselt 1994). It is often considered to be the gold standard of diagnostic assessments in clinical research. All interviews were performed by an experienced psychiatrist (EJ), who was trained in the use of the instrument. The first 15 interviews were discussed in detail with the main supervisor (EWM) and consensus was obtained. Ideally a selection of the interviews should be independently assessed by another researcher, to assess interrater reliability, but this was not done. All interviews were performed before the cardiac evaluation, so that the interviewer was blind to the results of the cardiac evaluations.

Wulsin et al. (Wulsin, Arnold & Hillard 1991) found instability of specific anxiety and mood disorders when they compared attendance to 5-12 months follow up in a study conducted on patients with atypical chest pain presenting to an emergency room. It was noted that these results might be due to the difficulty in making diagnoses in medically ill patients. We think that this potential problem is less at an outpatient clinic, where the conditions are less acute, and the surroundings probably are more relaxed. However, these potential weaknesses in making psychiatric diagnoses in medical settings should not be disregarded.

Self-report questionnaires

We used questionnaires with sound psychometric properties, which are widely used clinically and in research, and with authorized translations (BDI, BSQ, MI, SF-36).

The questionnaires were filled in a relaxed atmosphere, and the interviewer was available for answering questions about the forms.
In addition we developed, for follow-up, questionnaires about symptom frequency, impact of symptoms on family life, social life or at work, and avoidance of physical activity because of fear about the heart. These questionnaires are easy to understand, but not validated. There might have been some recall problems regarding the frequency of the symptoms, but since the subject probably was of interest for the patients, we think that the recall was not too bad about this.

For the treatment trial we intended to use assessments which are sensitive to change in misinterpretations about body sensations (BSQ), impact of symptoms (scale made for the present study) avoidance of physical activity because of worry about the heart (scale made for the present study), and health related quality of life (SF-36) and depression (BDI). We found these assessments suitable for the purpose of the present study. However, the self-made questionnaire about frequency and impact of the symptoms might have been difficult to differentiate between the response categories.

5.2.4. Cardiological assessments

Diagnostic assessments

The cardiac evaluation is described in the method section. All patients referred for chest pain underwent a bicycle stress test as a part of the cardiac evaluation. When the evaluations were non-conclusive, patients were sent for addition myocardial scintigraphy and/or coronary angiography (paper 1).
For patients with chest pain the estimated sensitivity and specificity of the exercise ECG are 50% and 90% respectively (Gibbons, Balady, Beasley et al. 1997). Therefore there might have been some patients with CAD who were not detected during the cardiac evaluation (false negative).
A clinical review of exercise thallium scintigraphy reports the average sensitivity and specificity for the angiographic diagnoses of CAD to be 84% and 87%, respectively (Kotler & Diamond 1990).

In the present study, 14 of the 16 patients who were sent for additional myocardial scintigraphy and 4 of the10 who were sent for additional myocardial angiography had normal findings. The threshold for sending patients to further investigation after the bicycle stress test seems not to have been too high.

All patients except one, referred for palpitations, had a 24-hour ECG monitoring (Holter monitoring). If there was doubt about the conclusion from the Holter monitoring, the patients also underwent seven days of ECG monitoring (R-test) or a bicycle stress test. Holter monitoring and R-test have limitations regarding detection of intermittent arrhythmias, because the arrhythmias have to emerge during the recording to be detected. It is therefore likely that some arrhythmias were not detected. The one, who did not have a Holter monitoring despite referred for palpitations, had a bicycle stress test and a myocardial angiography.

5.2.5. Reliability

Inter-rater reliability is the variation in measurements when different persons use the same method or instruments. No inter-rater reliability analysis was performed in this study neither for cardiac nor psychiatric evaluations. However, the SCID-I diagnostic interviews in general tends to show adequate inter-rater reliability (Segal et al 1994), and in the present

study the 15 first interviews were discussed in detail with the main supervisor in order to obtain consensus. The other assessments where self-report, and assessments of interrater reliability is not possible.

Internal consistency reliability assesses the consistency of items within a test, and is usually measured as Cronbach´s alpha. It measures the average correlation between the items of the test. At attendance Cronbach´s alfa for BDI was 0.90, which is satisfactory.

5.2.6. Clinically significant complaints vs eligibility for RCT

Using the results collected six months following the cardiac evaluation; more patients fulfilled the criteria as eligible for RCT in paper three than were described as having clinically significant complaints in paper two. The authors had the opinion that more patients than those defined in paper two as having clinically significant complaints, could potentially benefit from the treatment used in the RCT.

5.2.7. External validity

External validity concerns the extent to which results might be generalized to the target population.

The mean scores for BDI in this study are at the same level or somewhat lower than in previous studies (Mayou et al. 1994; Ehlers et al. 2000) and BSQ scores are somewhat lower (Dammen et al. 1999; Ehlers et al. 2000). This tendency for lower BSQ scores might be explained by the lower prevalence of PD, which may be due to change in referral policy, in which today more of the acute cases are hospitalized emergently. Therefore, in the present study the samples should be considered to be fairly representative of defined target populations of the study. The results at attendance and at six-month follow-up are therefore considered to be representative of patients referred for chest pain or palpitations in general. Further, for the treatment trial, the sample is considered to be representative and we consider the results valid for generalization to other patients with non-cardiac chest pain or benign palpitations. Whether the results of the RCT can be generalized to patients with other psychosomatic disorders, is unclear.

5.2.8. Statistical analysis

The large number of comparisons we made in the RCT raises the possibility that some of the significant effects were observed by chance (Type I error). On the other hand the small sample size in the RCT demands substantial differences between the groups in order to become statistically significant (danger of type II-error).

5.2.9. Strengths and limitations

A major strength is that the study was conducted in routine clinical practice, including all patients consecutively referred to a unit receiving all referrals in a catchment area, and with the use of methods commonly used in cardiac and psychiatric clinical practice. At attendance, a large proportion agreed to participate in the study and the response rate was high at six-month follow-up. The treatment trial has a randomized controlled design with 12-month follow-up. The randomization procedure was performed at a remote site of the intervention. The treatment was manualized and easy to apply. Most of the questionnaires used for effect evaluations are well known and seem to be meaningful in this setting. All patients completed

the treatment and a high percentage participated at follow-up.

As for limitations, patients aged above 65 were excluded from the study. These comprise a rather large proportion of patients referred for cardiac evaluation and the relatively low frequency of patients with CAD/arrhythmias in our study may at least partly be a result of the exclusion of these patients. The methods used for non-invasive testing (exercise ECG, myocardial scintigraphy, and ECG monitoring) all have false negatives.
The waiting time for patients referred for chest pain was two to three months, and some patients with psychiatric disorders and symptomatic heart disease may have recovered during this delay.

Symptom attribution was assessed using two single items (mental and cardiac). Because symptom attribution is complex, this approach is simplistic, and important information might have been lost. Symptom frequency, the impact of chest pain or palpitations, and avoidance of physical activity because of worry about the heart were assessed using questionnaires developed for the present study. These instruments were not tested for psychometrical properties. There were some dropouts (10%) at follow-up. When asked about their interest in psychological treatment, patients were asked only whether they wanted to participate in the treatment trial or not, and we do not know the reasons for their decision.

Several limitations of the treatment trial are apparent. No power analyses and determination of sample size were carried out. Since only about half of eligible patients wanted to participate, there might have been a selection bias. Those who wanted to participate might have been more susceptible to psychological treatment. Patients were randomized to CBT intervention or control condition. The patients in the control condition had less time with a therapist than the patients in the CBT group. The improvements observed in the intervention group could both be specific to the content of the treatment or could be attributed to spending time with a therapist alone (e.g. the placebo-attention effect). However, the finding of no significant changes in symptom frequency, but changes in interpretations of symptoms, indicate that the results are not due to an attention effect. All assessments were done by self-report measures, and no blind rating of outcomes was included. The large number of comparisons we made raises the possibility that some of the significant effects were observed by chance. No Bonferoni correction was carried out. The small sample size, the low participation rate, and the limited selection of therapists restrict the generalizability of our findings to the general clinical setting.

5.3.0. Suggestions for future research

Cardiac and psychiatric diagnosis

The prevalence of cardiac diagnoses was surprisingly low, and new studies should evaluate these findings. Our results might be a result of lowering of the threshold for referral for cardiac evaluation. Anyhow, many patients at a cardiac unit have normal test result. Little is known about the consequences of referring patients with few symptoms and no heart disease to a cardiac evaluation. It is of interest to know whether this procedure develops anxiety among the patients and how the normal test influence on the potential anxiety. Studies, which aim to find the best way to inform the patients about a normal cardiac test, are recommended.

Psychiatric disorders are common among patients with non-cardiac chest pain and benign palpitations. Most focus has been directed to PD, since the physical symptoms are common during a panic attack. However, in the present study the prevalence of PD was lower than in previous studies. Since more acute cases today are urgently hospitalized, it is likely that more cases with PD are hospitalized rather than referred for outpatient evaluation. We

therefore suggest new studies which evaluate the prevalence of PD among patients with chest pain or palpitations in emergency units.

Screening for poor outcome among patients with non-cardiac chest pain or benign palpitations

Screening might be a proper way to detect patients with poor outcome. In the present study BDI seemed to be suitable for this purpose, and this should be evaluated in future studies. Further studies should also try to find/develop even simpler assessment for this purpose.

Interest in psychological treatment

Even though it seems like those who are most disabled from their symptoms are interested in psychological treatment, still there are patients who of unknown reasons choose not to participate. This should be further evaluated.

Illness perception

We have evaluated the association between fear of body sensations and outcome. It is likely that other interpretations of the symptoms might be important for outcome among patients with non-cardiac chest pain or benign palpitations. Identification of these interpretations is important because it might be important elements in newer and more effective treatments.

Treatment

Still few randomized controlled trials among patients with non-cardiac chest pain or benign palpitations are published. This is the first RCT with three sessions or less, which had an effect on generalized measures like health related quality of life and avoidance of physical activity. This is also the first CBT based RCT with twelve months follow- up. Replication of the present study with larger samples and further research about short term and easily applied treatments for these patients is recommended.

5.4.0. Implications for clinical practice

Most patients referred for chest pain or palpitations have no heart disease. Among patients with non-cardiac chest pain and benign palpitations, a significant proportion have poor outcome. A cardiac evaluation is necessary, but a negative cardiac evaluation is not sufficient to solve the problems. Since psychiatric disorders are common among these patients, they easily fall between two chairs. It is therefore essential that general practitioners and cardiologists are aware of them, make an effort to detect them and cooperate about giving adequate treatment. This thesis has shown that a simple self report questionnaire for depression at the cardiac evaluation might be a simple way of reaching the patients who are vulnerable to develop sustained complaints. For those with sustained complaints six months after the cardiac evaluation, a standard intervention of three sessions of CBT including exposure to physical activity is an acceptable and effective treatment.

General conclusions

Among patients referred to cardiac out patient clinic for chest pain or palpitations, only a minority have cardiac disorders.

Psychiatric disorders are common, and especially the prevalence of panic disorder and somatisation disorder are high.

Among patients with no heart disease, symptoms of depression and anxiety increased and general health (domain of SF-36) deteriorated during a six-month observation period following a normal cardiac investigation. After six months 43% had clinically significant complaints.

Depression score at admission predicted clinically significant complaints at six-month follow-up. BDI score of five or above had rather good screening properties for clinically significant complaints at follow-up, sensitivity of 64% and specificity of 74%.

Patients with benign palpitations were more likely to be female and younger, and less likely to attribute their symptoms to cardiac disorder, otherwise they had similar characteristics regarding prevalence of psychiatric disorders, psychological distress, and tendency to develop sustained complaints compared to those with non-cardiac chest pain.

Among patients with clinically significant complaints at follow-up, 60 % were interested in participating in a treatment trial for evaluating short term psychological treatment (cognitive behavioural therapy). Those who were interested in psychological treatment to a higher degree attributed their symptoms to heart disorder at attendance and had more fear of bodily sensations and limitations in activity at follow-up.

Three sessions of cognitive behavioural therapy, including exposure to physical activity, reduced the impact of symptoms, fear of bodily symptoms, depression, and increased health related quality of life. The effect lasted at least12 months after the end of treatment.

Changes in interpretations of bodily sensations mediated most of the effects on depression and avoidance of physical activity.

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Tables

Table 1 DSM-IV criteria for panic attack and panic disorder

Panic attack
A discrete period of intense fear or discomfort, in four (or more) of the following symptoms develop abruptly and reached a peak within 10 minutes.

(1) palpitations, pounding heart, or accelerated heart rate
(2) sweating
(3) trembling or shaking
(4) sensations of shortness of breath or smothering
(5) feeling of choking
(6) chest pain or discomfort
(7) nausea or abdominal distress
(8) feeling dizzy unsteady lightheaded, or faint
(9) derealization (feeling of unreality) or depersonalization (being detached from oneself)
(10) fear of loosing control or going crazy
(11) fear of dying
(12) paresthesias (numbness or tingling sensation)
(13) chills or hot flushes

Panic Disorder
A. Both (1) and (2):

(1) Recurrent unexpected panic attacks
(2) At least one of the attacks has been followed by one months (or more) of one (or more) of the following:
    (a) persistent concern about having additional attacks
    (b) worry about the implications of the attacks or its consequences (e.g. losing control, having heart attack, going crazy)
    (c) a significant change in behavior related to the attacks

B. Absence of agoraphobia
C. The panic attacks are not due to the direct physiological effect of a substance (e.g. drug abuse, medication) or a general medical condition (e.g. hyperthyroidism)
D. The panic attacks are not better accounted for by another mental disorder.

Table 2 Effect size (partial eta square) following three sessions of CBT (ANCOVA)

Variables	End of treatment	Three-month follow-up	Twelve-month follow-up
Body sensation questionnaire	0.53	0.30	0.19
Beck Depression Inventory	0.19	0.18	0.15
Avoidance of physical activity	0.15	0.21	0.19

Paper I

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Patients with noncardiac chest pain and benign palpitations referred for cardiac outpatient investigation: a 6-month follow-up☆

Egil Jonsbu, M.D.[a,b,*], Toril Dammen, M.D., Ph.D.[c,d], Gunnar Morken, M.D., Ph.D.[b,e], Egil W. Martinsen, M.D., Ph.D.[f,g]

[a]*Department of Psychiatry, Molde Hospital, 6407 Molde, Norway*
[b]*Department of Neuroscience, Norwegian University of Science and Technology, 7491 Trondheim, Norway*
[c]*Institute of Basic Medical Sciences, Department of Behavioural Sciences in Medicine, Faculty of Medicine, University of Oslo, 0317 Oslo, Norway*
[d]*Oslo University Hospital Ullevaal, Department of Psychiatry, 0407 Oslo, Norway*
[e]*Østmarka Department of Psychiatry, St Olavs University Hospital, Trondheim Norway*
[f]*Institute of Psychiatry, University of Oslo, 0318 Oslo, Norway*
[g]*Oslo University Hospital, Aker, 0514 Oslo, Norway*

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Abstract

Objectives: The aims were to (a) study the characteristics and outcome in patients with noncardiac chest pain or benign palpitations referred for cardiac evaluation, (b) compare psychological characteristics in the two groups, (c) identify predictors of outcome (d) and explore characteristics of patients who wanted psychological treatment.
Methods: The patients (*N*=154) were first evaluated by a psychiatrist and than by a cardiologist at the initial attendance and by self report after 6 months.
Results: Thirty nine percent had at least one *DSM-IV* psychiatric disorder at attendance. At the 6-month follow-up, 43% still had clinically significant complaints and/or impaired function. Patients with palpitations were more likely to be female, younger and less likely to attribute cardiac symptoms to heart disease, but had otherwise similar psychological features to noncardiac chest pain patients. Depression score at attendance predicted significant complaints at follow-up. Interest in psychological treatment was associated with more fear of bodily sensations, more impaired function, and greater tendency to attribute symptoms to heart disease.
Conclusion: Psychiatric disorders were common. The 6-month outcome was poor and was associated with the depression score at attendance. Patients with fear of bodily symptoms and impaired function were most interested in psychological treatment.

Keywords: Chest pain; Palpitations; Follow-up; Interest in treatment

1. Background

Chest pain and palpitations are common in the general population, with prevalence rates of 20–40% and 11%, respectively [1–3], and are the two most common reasons for referral to a cardiologist [4]. In cardiac settings, a considerable proportion of these patients have no heart disease or other medical disorder that can account for their symptoms [5–7]. Previous studies in cardiac settings have found a high frequency of psychiatric disorders (25–50%), especially panic disorder (PD) [6,8,9] and reduced quality of life [10–13] among these patients. Follow-up studies have reported poor outcomes in terms of maintenance of symptoms that affect daily life, worry about the heart, and increased use of health care services. This is especially true for patients with psychiatric disorders [14–16], who are rarely offered any specific treatment besides the cardiac evaluation [17,18].

During the past decade, there has been a change in referral policy for patients with acute coronary syndrome. Most of

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* Corresponding author. Department of Psychiatry, Molde Hospital, 6407 Molde, Norway. Tel.: +47 71122900; fax: +47 71122902.
E-mail address: egil.jonsbu@helsenr.no (E. Jonsbu).

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these patients are now hospitalized urgently and not referred for outpatient evaluation. Whether this new referral policy has led to fewer cases with acute symptomatology (e.g., PD) has not been investigated thoroughly [19]. On the other hand, continual provision of information about the importance of early detection of cardiac disorders might have lowered the threshold for referrals.

Most research has focused on chest pain patients, whereas less attention has been given to those with palpitations. The importance of improving health care for patients with noncardiac chest pain is well documented [15,16]. Whether patients with palpitations have the same needs has not been investigated thoroughly.

In both patients with noncardiac chest pain and benign palpitations, there is some evidence of an association between psychiatric disorders and subsequent poor outcome [14,15]. However, there is a need to identify the predictors of poor outcomes and to explore their value for screening patients.

Cognitive behavioural therapy has been documented to be effective in treating patients with noncardiac chest pain and benign palpitations [20,21], but a low percentage of eligible patients (40–60%) elect to seek such treatment. It is of interest to enhance the understanding about the characteristics of the patients who want to participate in psychological treatment, in order to target them for psychological treatment.

The aims of the present study were to:

(1) describe the clinical status prior to cardiac evaluation and at 6-month follow-up for patients with noncardiac chest pain and benign palpitations;
(2) compare the psychological characteristics of patients with noncardiac chest pain and benign palpitations;
(3) identify factors that predict poor outcome and evaluate theirs suitability for screening and
(4) identify factors associated with the patients' interest in psychological treatment.

2. Methods

2.1. Patients

Consecutive patients referred to the cardiac outpatient unit at the Molde Hospital in Norway between May 2006 and May 2007 for evaluation of chest pain or palpitations were asked to participate. This outpatient clinic receives all referrals in a catchment area of about 75,000 inhabitants.

The head of the cardiac unit screened all referrals. The inclusion criteria were: (1) referral for a main complaint of chest pain or palpitations; (2) age 18–65 years and (3) ability to understand and write the Norwegian language. The exclusion criteria were: (1) mental retardation; (2) psychosis; or (3) organic heart disease confirmed by a cardiologist. Among 219 consecutive patients, 21 cancelled both the cardiac and psychiatric evaluation, and 36 did not want to participate in the study. A total of 162 patients participated in the psychiatric and cardiac evaluations at admission (Fig. 1). Of these, eight were excluded, six because of coronary heart disease confirmed by the cardiac evaluation (five in the chest pain group and one in the palpitation group), one because of lack of Norwegian language competency, and one because of mental retardation. No arrhythmias in need of treatment were detected.

In the final sample, which comprised 154 patients, 107 were referred because of chest pain and 47 because of palpitations. The 36 patients who did not want to participate in the study did not differ significantly from the participants on age, sex, prevalence of heart disease (as assessed by the cardiac evaluation), or chest pain/palpitations ratio.

2.1.1. Sample at the 6-month follow-up

Of the total sample of 154 patients, 138 (90%) responded to mailed questionnaires at the 6-month follow-up: 95 (89%) in the chest pain group and 43 (91%) in the palpitations group (Fig. 1). The participants who did not participate at follow-up did not differ from the participants who responded on sex, age, prevalence of psychiatric disorders, or scores on any variable with importance for the outcome (i.e., depression, anxiety symptoms, and avoidance).

2.1.2. Cardiac evaluation

The patients referred for chest pain underwent a standard bicycle stress test. If the cardiologist found the results consistent with coronary heart disease or if there was doubt about the diagnosis, the patients were referred for myocardial scintigraphy or coronary angiography. The patients referred for palpitations were monitored with Holter monitoring. If there was doubt about the conclusion from the Holter monitoring, the patients also underwent 7 days of electrocardiography monitoring (R-test) or a bicycle stress test.

2.2. Assessments at attendance

Sex, age, marital status, education, work status, duration of symptoms and days on sick leave during the three months before the consultation were registered at attendance.

Psychiatric disorders were assessed using the Structured Clinical Interview for *DSM-IV* Axis I disorders [22]. The interviews were performed by the first author, an experienced psychiatrist, who was trained in the use of the instrument. For current diagnoses, the criteria had to be met within one month before the interview; for lifetime diagnoses, the criteria had to be met previously or currently. All patients were informed about the results of the psychiatric evaluation.

2.2.1. Depression, anxiety, and health-related quality of life (HRQOL)

The Beck Depression Inventory (BDI) [23] measures the level of depression. The BDI comprises 21 items that are rated on a 0–3 scale.

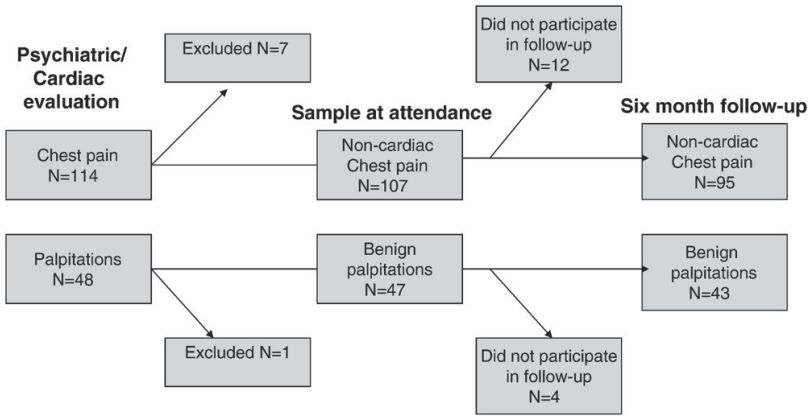

Fig. 1. Flow diagram of study participation.

The Body Sensations Questionnaire (BSQ) [24] measures fear of body sensations. The BSQ comprises 17 different bodily symptoms that are rated on a 1–5 scale.

The Mobility Inventory (MI) [25] measures avoidance in 24 different places or situations and is rated on a 1–5 scale. For each place or situation, the patients indicated when they were alone or accompanied by others.

The 36-item SF-36 [26] measures the patient's perceptions of HRQOL and function across eight areas of life (domains): physical functioning, physical role limitations (i.e., role limitations because of physical health problems), bodily pain, general health perception, vitality, social function, emotional role limitations (i.e., role limitations because of emotional problems), and mental health. Domain scores range from 0 to 100; higher scores indicate better health. A validated Norwegian translation of the SF-36 was used in the present study [27,28].

These self-rating questionnaires are used widely in clinical practice and research, and cover central aspects of depression, anxiety, and HRQOL.

2.2.2. Symptom attribution

Patients were asked the following questions: (1) To what degree do you find it likely that your symptoms are caused by a heart disease? (2) To what degree do you find it likely that your symptoms are caused by mental stress or anxiety? The responses were categorized as: 1, not likely; 2, less likely; 3, most likely and 4, for sure.

2.2.3. Treatment of psychiatric disorders

Psychotherapy was defined as at least one session with psychological treatment/counselling for mental problems during the patient's lifetime. The following current medications were registered: use of antidepressants, anxiolytics, hypnotics, or other medications for mental disorders.

2.3. Assessment at follow-up

2.3.1. Frequency of symptoms

Symptoms of chest pain or palpitations were recorded on a registration form developed for the present study. The frequency of symptoms was rated as: 1, daily; 2, weekly or more often; 3, rarely but sometimes; or 4, no symptoms in the last 6 months. For patients who reported both chest pain and palpitations, the highest frequency score was entered in the statistical analyses.

2.3.2. Consequences of chest pain and palpitations

The impact of cardiac symptoms on the domains of family, social, and work life were recorded separately as: 1, high impact; 2, moderate impact; 3, some impact and 4, no impact. The highest score (the domain most affected) among the three was used.

Avoidance of physical activity was assessed using the following question: "Do you avoid physical activity because of worries about the heart?" The response categories were: 1, often; 2, now and then; 3, rarely but sometimes and 4, never.

2.3.3. Clinically significant complaints at follow-up

Clinically significant complaints at follow-up were defined as reports of at least one of the following: At least weekly symptoms; moderate impact on family life, social life, or work; or avoiding physical activity now and then because of worries about the heart. Clinically significant complaints were categorized as present or not present. The purpose of the generation of this variable was to identify individuals who were considered to be in need of treatment. All patients with clinically significant complaints were evaluated as being in need of treatment.

2.3.4. Interest in psychological treatment at follow-up

At the 6-month follow-up, all patients were asked the following question: "Do you want to participate in a research

project in which we aim to explore the efficacy of a treatment regimen comprising three individual sessions, which has been developed to increase your ability to cope with chest pain and/or palpitations?" Response categories were: 1, yes; 2, I want more information on the phone and 3, no.

2.4. Procedure

The inquiry about participation in the study was mailed together with information about the appointment at the cardiac outpatient clinic. The patients were informed that the purpose of the study was to evaluate psychological distress and prevalence of psychiatric disorders among patients referred for chest pain or palpitations. The psychiatric evaluation and assessments at attendance were performed before the cardiac evaluation; thus, the interviewer and the patients were blind to the results of the cardiac evaluation. All information about the patients at the 6-month follow-up was collected by mail (except for interest in treatment, for which some patients were phoned).

2.5. Ethics

The research protocol was approved by the Regional Committee for Medical Research Ethics in May 2006 and by the Norwegian Social Science Data Service in June 2006. All participating patients signed an informed consent form.

2.6. Statistical analysis

Data were compared between groups using a chi-squared or Fisher's Exact test for dichotomous data, the Mann–Whitney for ordinal variables, and Student's *t*-test for continuous variables. Multiple linear regression analysis was used to control for age and sex when comparing patients with chest pain and those with palpitations. The paired-samples *t*-test was used to compare results at attendance and at follow-up. Correlations were calculated as Pearson's r (for pairs of continuous variables), point-biserial (for one dichotomous and one continuous variable), and phi (for two dichotomous variables). Prediction of poor outcome (clinical significant complaints) was analysed using logistic regression. All tests were two-tailed. $P<.05$ was considered significant. The SPSS version 16 software was used in all analyses.

3. Results

3.1. Clinical status at attendance

3.1.1. Demographic and clinical data

The demographic and clinical are shown in Table 1. Those referred for palpitations were younger and included more women; otherwise the groups did not differ significantly.

3.1.2. Prevalence of psychiatric disorders

The prevalence of current psychiatric disorders and level of mental distress are shown in Table 2. In addition to the current diagnoses, 31 (20%) had lifetime major depression, and 57 (31%) had any lifetime anxiety disorder. There were no significant differences between patients with chest pain and palpitations regarding the prevalence of psychiatric disorders, level of depression and anxiety, or avoidance (Table 2). Adjusting for age and sex did not change the results (data not shown).

3.1.3. Symptom attribution

In both groups combined, 26% of patients reported "most likely" or "for sure" that their complaints were caused by heart disease. Most patients (64%) attributed their symptoms ("most likely" or "for sure") to mental distress or anxiety.

Patients with palpitations were less likely to attribute their symptoms to heart disease. The scores for palpitations and chest pain were "not likely," 17% vs. 5%; "less likely," 69% vs. 62%; "most likely," 12% vs. 29% and "for sure," 2% vs. 3% ($P=.014$, Mann–Whitney *U* test). The groups did not differ regarding the attribution of symptoms to mental stress or anxiety.

Table 1
Demographic and clinical data at attendance

	Total $N=154$	Chest pain $N=107$	Palpitations $N=47$	*P*
Women	85 (55%)	51 (48%)	34 (72%)	.005[a]
Age, median (range)	52 (18–65)	54 (18–65)	44 (21–62)	<.001[b]
Married/cohabiting	119 (77%)	85 (79%)	34 (72%)	ns
Vocational school/university	108 (70%)	75 (71%)	33 (70%)	ns
Main source of income past 6 months:				
Work	101 (66%)	70 (65%)	31 (66%)	ns
Sickness benefit	41 (26%)	29 (27%)	12 (26%)	ns
Other	12 (8%)	8 (8%)	4 (8%)	ns
Duration of symptoms in months before evaluation, median (range)	9.5 (1–420)	12 (1–420)	6 (2–360)	ns
Days on sick leave past 3 months median (range)	6 (0–90)	6.5 (0–90)	2.5 (0–90)	ns

ns, not significant.
[a] chi-squared test.
[b] Mann–Whitney *U* test.

Table 2
Prevalence of current psychiatric disorders and intensity of psychiatric symptoms at attendance

Diagnoses	Total N (%)	Chest pain N (%)	Palpitations N (%)	P
Total	154 (100%)	107 (69%)	47 (31%)	
Panic disorder	22 (14%)	16 (15%)	6 (13%)	ns
Any anxiety disorder	48 (31%)	34 (32%)	14 (30%)	ns
Major depression	7 (5%)	5 (5%)	2 (4%)	ns
Any somatoform disorder	21 (14%)	14 (13%)	7 (15%)	ns
Any current substance abuse	4 (3%)	4 (4%)	0	ns
Any current psychiatric disorder	60 (39%)	41 (38%)	19 (40%)	ns
BDI, mean (S.D.)	4.9 (5.4)	5.1 (5.5)	4.5 (5.1)	ns
BSQ, mean (S.D.)	1.6 (0.5)	1.6 (0.6)	1.6 (0.5)	ns
MI, mean (S.D.)	1.2 (0.4)	1.2 (0.5)	1.2 (0.3)	ns

3.1.4. Psychiatric treatment

In the combined group, 13 patients (8%) used selective serotonin reuptake inhibitors, eight (5%) anxiolytics, 26 (17%) hypnotics and 41 (27%) had received psychotherapy during their lifetime. Of the 22 patients with current PD, three received antidepressants; two of these attended psychotherapy and one was on the waiting list at a psychiatric outpatient clinic, meaning that only 3 of 22 (14%) patients with PD received adequate treatment. Of the seven patients with current major depression, two received antidepressants. There were no differences between the chest pain and palpitations groups regarding the use of psychotropic medication or attendance for psychological treatment.

3.2. Status at follow-up

In both groups combined, 43% (60/138) had clinically significant complaints, 39% (54/138) reported at least "rare but sometimes" avoidance of physical activity because of worry about the heart. Patients with clinically significant complaints did not differ significantly from the remaining regarding sex, age, reason for referral (chest pain or palpitations), days on sick leave before attendance, or whether they attributed their symptoms to mental or cardiac conditions. However, they had a higher frequency of panic disorder, depression, and any psychiatric disorder, and longer duration of actual symptoms (median, 6 vs. 12 months; P=.03) before attendance. Patients with clinically significant complaints also at follow-up had significantly higher scores for BDI, BSQ, and MI, and lower quality of life on all eight domains of HRQOL.

There was a non-significant tendency for patients referred for palpitations to have had more frequent symptoms than those referred for chest pain (P=.053); otherwise, the groups did not differ significantly at follow-up.

There was some overlap of symptoms between the groups. Among patients referred for chest pain, 20% reported at least weekly palpitations, and among those referred for palpitations, 14% reported at least weekly chest pain.

3.3. Course from attendance to the 6-month follow-up

For the whole sample there was a significant increase from attendance to follow-up in BDI (mean±S.D., 5.0±5.5 vs. 5.8±6.3; P=.04)and BSQ score (mean, 1.61±0.54 vs. 1.71±0.63; P=.04), whereas this was not the case for MI scores. The analysis of SF-36 results revealed that, at follow-up, the score for bodily pain was higher (better health) (mean, 62.4±24.8 vs. 68.0±25.4; P=.007) and general health was lower (poorer health) (72.6±18.6 vs. 68.1±20.5; P=.002).

Table 3
Patients with sustained complaints (N=60) at the 6-month follow-up

	Total (N=60)	Interested in treatment (N=36)	Not interested in treatment (N=24)	P
Frequency of symptoms, mean (S.D.)	2.1 (0.6)	2.0 (0.6)	2.1 (0.7)	ns
Impact on family life, social life, or work, mean (S.D.)	2.8 (0.7)	2.6 (0.6)	3.2 (0.7)	.001
Avoidance of physical activity because of worry about the heart, mean (S.D.)	3.0 (1.0)	2.8 (0.9)	3.4 (0.9)	.008
BDI, mean (S.D.)	8.5 (7.5)	10.0 (8.2)	6.2 (5,7)	.06
BSQ, mean (S.D.)	1.8 (0.7)	2.0 (0.7)	1.5 (0.5)	.005
MI, mean (S.D.)	1.4 (0.5)	1.5 (0.6)	1.3 (0.3)	ns
SF-36				
Physical functioning, mean (S.D.)	82.7 (16.1)	80.0 (16.4)	84.3 (17.6)	ns
Role limitations; physical, mean (S.D.)	51.3 (42.1)	44.4 (42.7)	57.6 (41.6)	ns
Bodily pain, mean (S.D.)	57.2 (22.9)	51.6 (19.9)	64.7 (26.1)	.05
General health perception, mean (S.D.)	61.2 (20.1)	56.4 (20.5)	65.1 (22.2)	ns
Vitality	44.2 (20.6)	39.7 (20.2)	52.3 (19.1)	.02
Social functioning, mean (S.D.)	79.6 (23.6)	75.3 (26.6)	83.7 (23.4)	ns
Role limitations; emotional, mean (S.D.)	69.0 (41.2)	63.9 (44.6)	75.4 (36.5)	ns
Mental health, mean (S.D.)	72.5 (17.9)	69.9 (19.4)	77.3 (14.0)	ns

Comparison of patients interested/not interested in psychological treatment.
SF-36, 36-Item Short Form Health Survey.
All were analyzed using the Mann–Whitney U test.

3.4. Predictors of poor outcome

There were significant correlations between presence of clinically significant complaints at follow-up and the baseline variables BDI (r=0.37, P<.001); BSQ (r=0.21, P=.02); diagnosis of depression [r(phi)=0.27, P=.002]; PD [r(phi)=0.29, P=.002]; and any psychiatric disorder [r(phi)=0.20, P=.02]. To determine whether BDI could serve as a screening tool for clinically significant complaints at follow-up, the BDI score was collapsed into the dichotomous variable with cutoff at five or greater. This cutoff gave the strongest correlation with clinically significant complaints. The correlation was r(phi)=0.39 (P<.001, OR=5.2), corresponding to a sensitivity of 64% (38/59) and specificity of 74% (58/78), or a positive predictive value of 66% (38/58).

3.5. Interest in psychological treatment

At follow-up, 44/138 (32%) were interested in psychological treatment. Of these, 11 received information by telephone before making a decision.

Among the 60 patients with clinically significant complaints at follow-up, 36 (60%) were interested in psychological treatment. The differences between those interested in psychological treatment and those not interested, are shown in Table 3. Those interested in psychological treatment to a higher degree attributed their symptoms to heart disease, mean (S.D.) 2.3 (0.7) vs. 1.9 (0.6), P=.02. When collapsing the variable, "To what degree do you find it likely that your symptoms are caused by a heart disease?" into two groups — (1) not likely/less likely and (2) most likely/for sure — those in the latter group (most likely/for sure) had a higher BSQ score at attendance and follow-up [mean (S.D.), 1.52 (0.47) vs. 1.78 (0.63), P=.006 and 1.63 (0.54) vs. 1.93 (0.78) P=.04, respectively].

4. Discussion

At attendance 39% had any psychiatric disorder and 14% had PD. The majority believed that it was more likely that their symptoms were caused by distress or anxiety than by a cardiac condition. At 6-month follow-up 43% had clinically significant complaints, and this was associated with depression scores at attendance. Patients with benign palpitations had similar psychological characteristics as those with noncardiac chest pain. Those who were interested in psychological treatment, had reduced vitality, more fear of bodily sensations and were more likely to attribute their symptoms to heart disease.

The incidence of PD among patients with noncardiac chest pain was lower than that in studies performed some years ago, where the incidence was >25% [29]. The mean BSQ score in our sample is lower than in other clinical samples [6,8] but is higher than the scores in the general population [24]. Because PD often presents with acute symptoms, the lower prevalence might be explained by the change in referral procedure over the past decade, where more acute cases are urgently hospitalized.

Most patients attributed their symptoms to mental distress. This indicates that many patients are aware of the connection between physical symptoms and mental distress.

Several other studies have reported poor long-term outcome for patients with noncardiac chest pain and benign palpitations [14–16], and our study confirms these findings. Almost half (43%) had clinically significant complaints at follow-up.

Clinically significant complaints at follow-up was predicted by BDI scores, and BDI score above five seems to be a good predictor of poor outcome. The usefulness of BDI as a screening instrument should be evaluated in new studies.

The present study indicates that patients with benign palpitations have the same need for treatment as those with noncardiac chest pain. The similar fear of bodily symptoms, as assessed by the BSQ, is of special interest. Catastrophic interpretation of bodily symptoms is the key element in the cognitive model explaining how the symptoms are maintained [4]. Our results suggest that psychological treatment aiming to reduce fear of bodily symptoms is appropriate for both groups.

To our knowledge, no previous studies have explicitly investigated avoidance of physical activity because of worries about the heart, which was frequently reported in both groups. Avoidance of physical activity due to catastrophic beliefs about heart disease may contribute to the maintenance of symptoms.

Sixty percent of the patients with clinically significant complaints at the 6-month follow-up wanted psychological treatment, and this fits well with a previous review [20]. One previous study [30] reported that interest in psychological treatment was associated with limitations in activity, but not with frequency of symptoms. In addition to confirm these findings, the present study shows an obvious association between interest in psychological treatment and fear of bodily sensations. Patients who were interested in treatment were also more likely to attribute their symptoms to heart disease. This might be explained by the increased fear of bodily symptoms among those who attributed their symptoms to heart disease.

4.1. Study strengths and limitations

A major strength is that the study was performed in a general cardiac setting and included consecutive patients in a catchment area. A limitation is that patients older than 65 years were excluded. The waiting time for patients referred for chest pain was two to three months, and some patients with psychiatric disorder may have recovered during this delay. No non-clinical control group was included, and it is therefore difficult to evaluate to what extent the studied sample differs from the general population. Symptom attribution was assessed using two single items (mental and cardiac). Because

symptom attribution is complex, this approach is simplistic, and important information might have been lost. The impact of chest pain or palpitations and avoidance of physical activity because of worry about the heart were assessed using questionnaires developed for the present study. These instruments were not tested for psychometrical properties. There were some dropouts (10%) at follow-up. It is likely that those, who were worried about their health and/or experienced sustained complaints, were more interested in participation in the follow-up investigation, and this might have led to systematic subject loss. When asked about their interest in psychological treatment, patients were asked only whether they want treatment or not, and we do not know the reasons for their decision.

5. Conclusions

Psychiatric disorders were common among patients with noncardiac chest pain or benign palpitations. Symptoms and psychological distress tended to persist despite the negative cardiac evaluation, and depression score was a predictor of outcome. Patients with noncardiac chest pain and benign palpitations have similar psychological features. Interest in psychological therapy was significantly associated with fear of bodily symptoms and limitations in activity.

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123. Geir Smedslund: A THEORETICAL AND EMPIRICAL INVESTIGATION OF SMOKING, STRESS AND DISEASE: RESULTS FROM A POPULATION SURVEY.

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124. Torstein Vik: GROWTH, MORBIDITY, AND PSYCHOMOTOR DEVELOPMENT IN INFANTS WHO WERE GROWTH RETARDED *IN UTERO*.
125. Siri Forsmo: ASPECTS AND CONSEQUENCES OF OPPORTUNISTIC SCREENING FOR CERVICAL CANCER. Results based on data from three Norwegian counties.
126. Jon S. Skranes: CEREBRAL MRI AND NEURODEVELOPMENTAL OUTCOME IN VERY LOW BIRTH WEIGHT (VLBW) CHILDREN. A follow-up study of a geographically based year cohort of VLBW children at ages one and six years.
127. Knut Bjørnstad: COMPUTERIZED ECHOCARDIOGRAPHY FOR EVALUTION OF CORONARY ARTERY DISEASE.
128. Grethe Elisabeth Borchgrevink: DIAGNOSIS AND TREATMENT OF WHIPLASH/NECK SPRAIN INJURIES CAUSED BY CAR ACCIDENTS.
129. Tor Elsås: NEUROPEPTIDES AND NITRIC OXIDE SYNTHASE IN OCULAR AUTONOMIC AND SENSORY NERVES.
130. Rolf W. Gråwe: EPIDEMIOLOGICAL AND NEUROPSYCHOLOGICAL PERSPECTIVES ON SCHIZOPHRENIA.
131. Tonje Strømholm: CEREBRAL HAEMODYNAMICS DURING THORACIC AORTIC CROSSCLAMPING. An experimental study in pigs.

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132. Martinus Bråten: STUDIES ON SOME PROBLEMS REALTED TO INTRAMEDULLARY NAILING OF FEMORAL FRACTURES.
133. Ståle Nordgård: PROLIFERATIVE ACTIVITY AND DNA CONTENT AS PROGNOSTIC INDICATORS IN ADENOID CYSTIC CARCINOMA OF THE HEAD AND NECK.
134. Egil Lien: SOLUBLE RECEPTORS FOR **TNF** AND **LPS**: RELEASE PATTERN AND POSSIBLE SIGNIFICANCE IN DISEASE.
135. Marit Bjørgaas: HYPOGLYCAEMIA IN CHILDREN WITH DIABETES MELLITUS

136. Frank Skorpen: GENETIC AND FUNCTIONAL ANALYSES OF DNA REPAIR IN HUMAN CELLS.
137. Juan A. Pareja: SUNCT SYNDROME. ON THE CLINICAL PICTURE. ITS DISTINCTION FROM OTHER, SIMILAR HEADACHES.
138. Anders Angelsen: NEUROENDOCRINE CELLS IN HUMAN PROSTATIC CARCINOMAS AND THE PROSTATIC COMPLEX OF RAT, GUINEA PIG, CAT AND DOG.
139. Fabio Antonaci: CHRONIC PAROXYSMAL HEMICRANIA AND HEMICRANIA CONTINUA: TWO DIFFERENT ENTITIES?
140. Sven M. Carlsen: ENDOCRINE AND METABOLIC EFFECTS OF METFORMIN WITH SPECIAL EMPHASIS ON CARDIOVASCULAR RISK FACTORES.

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141. Terje A. Murberg: DEPRESSIVE SYMPTOMS AND COPING AMONG PATIENTS WITH CONGESTIVE HEART FAILURE.
142. Harm-Gerd Karl Blaas: THE EMBRYONIC EXAMINATION. Ultrasound studies on the development of the human embryo.
143. Noèmi Becser Andersen:THE CEPHALIC SENSORY NERVES IN UNILATERAL HEADACHES. Anatomical background and neurophysiological evaluation.
144. Eli-Janne Fiskerstrand: LASER TREATMENT OF PORT WINE STAINS. A study of the efficacy and limitations of the pulsed dye laser. Clinical and morfological analyses aimed at improving the therapeutic outcome.
145. Bård Kulseng: A STUDY OF ALGINATE CAPSULE PROPERTIES AND CYTOKINES IN RELATION TO INSULIN DEPENDENT DIABETES MELLITUS.
146. Terje Haug: STRUCTURE AND REGULATION OF THE HUMAN UNG GENE ENCODING URACIL-DNA GLYCOSYLASE.
147. Heidi Brurok: MANGANESE AND THE HEART. A Magic Metal with Diagnostic and Therapeutic Possibilites.
148. Agnes Kathrine Lie: DIAGNOSIS AND PREVALENCE OF HUMAN PAPILLOMAVIRUS INFECTION IN CERVICAL INTRAEPITELIAL NEOPLASIA. Relationship to Cell Cycle Regulatory Proteins and HLA DQBI Genes.
149. Ronald Mårvik: PHARMACOLOGICAL, PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL STUDIES ON ISOLATED STOMACS.
150. Ketil Jarl Holen: THE ROLE OF ULTRASONOGRAPHY IN THE DIAGNOSIS AND TREATMENT OF HIP DYSPLASIA IN NEWBORNS.
151. Irene Hetlevik: THE ROLE OF CLINICAL GUIDELINES IN CARDIOVASCULAR RISK INTERVENTION IN GENERAL PRACTICE.
152. Katarina Tunòn: ULTRASOUND AND PREDICTION OF GESTATIONAL AGE.
153. Johannes Soma: INTERACTION BETWEEN THE LEFT VENTRICLE AND THE SYSTEMIC ARTERIES.
154. Arild Aamodt: DEVELOPMENT AND PRE-CLINICAL EVALUATION OF A CUSTOM-MADE FEMORAL STEM.
155. Agnar Tegnander: DIAGNOSIS AND FOLLOW-UP OF CHILDREN WITH SUSPECTED OR KNOWN HIP DYSPLASIA.
156. Bent Indredavik: STROKE UNIT TREATMENT: SHORT AND LONG-TERM EFFECTS
157. Jolanta Vanagaite Vingen: PHOTOPHOBIA AND PHONOPHOBIA IN PRIMARY HEADACHES

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158. Ola Dalsegg Sæther: PATHOPHYSIOLOGY DURING PROXIMAL AORTIC CROSS-CLAMPING CLINICAL AND EXPERIMENTAL STUDIES
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160. Christina Vogt Isaksen: PRENATAL ULTRASOUND AND POSTMORTEM FINDINGS – A TEN YEAR CORRELATIVE STUDY OF FETUSES AND INFANTS WITH DEVELOPMENTAL ANOMALIES.
161. Holger Seidel: HIGH-DOSE METHOTREXATE THERAPY IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA: DOSE, CONCENTRATION, AND EFFECT CONSIDERATIONS.
162. Stein Hallan: IMPLEMENTATION OF MODERN MEDICAL DECISION ANALYSIS INTO CLINICAL DIAGNOSIS AND TREATMENT.
163. Malcolm Sue-Chu: INVASIVE AND NON-INVASIVE STUDIES IN CROSS-COUNTRY SKIERS WITH ASTHMA-LIKE SYMPTOMS.
164. Ole-Lars Brekke: EFFECTS OF ANTIOXIDANTS AND FATTY ACIDS ON TUMOR NECROSIS FACTOR-INDUCED CYTOTOXICITY.

165. Jan Lundbom: AORTOCORONARY BYPASS SURGERY: CLINICAL ASPECTS, COST CONSIDERATIONS AND WORKING ABILITY.
166. John-Anker Zwart: LUMBAR NERVE ROOT COMPRESSION, BIOCHEMICAL AND NEUROPHYSIOLOGICAL ASPECTS.
167. Geir Falck: HYPEROSMOLALITY AND THE HEART.
168. Eirik Skogvoll: CARDIAC ARREST Incidence, Intervention and Outcome.
169. Dalius Bansevicius: SHOULDER-NECK REGION IN CERTAIN HEADACHES AND CHRONIC PAIN SYNDROMES.
170. Bettina Kinge: REFRACTIVE ERRORS AND BIOMETRIC CHANGES AMONG UNIVERSITY STUDENTS IN NORWAY.
171. Gunnar Qvigstad: CONSEQUENCES OF HYPERGASTRINEMIA IN MAN
172. Hanne Ellekjær: EPIDEMIOLOGICAL STUDIES OF STROKE IN A NORWEGIAN POPULATION. INCIDENCE, RISK FACTORS AND PROGNOSIS
173. Hilde Grimstad: VIOLENCE AGAINST WOMEN AND PREGNANCY OUTCOME.
174. Astrid Hjelde: SURFACE TENSION AND COMPLEMENT ACTIVATION: Factors influencing bubble formation and bubble effects after decompression.
175. Kjell A. Kvistad: MR IN BREAST CANCER – A CLINICAL STUDY.
176. Ivar Rossvoll: ELECTIVE ORTHOPAEDIC SURGERY IN A DEFINED POPULATION. Studies on demand, waiting time for treatment and incapacity for work.
177. Carina Seidel: PROGNOSTIC VALUE AND BIOLOGICAL EFFECTS OF HEPATOCYTE GROWTH FACTOR AND SYNDECAN-1 IN MULTIPLE MYELOMA.

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178. Alexander Wahba: THE INFLUENCE OF CARDIOPULMONARY BYPASS ON PLATELET FUNCTION AND BLOOD COAGULATION – DETERMINANTS AND CLINICAL CONSEQUENSES
179. Marcus Schmitt-Egenolf: THE RELEVANCE OF THE MAJOR hISTOCOMPATIBILITY COMPLEX FOR THE GENETICS OF PSORIASIS
180. Odrun Arna Gederaas: BIOLOGICAL MECHANISMS INVOLVED IN 5-AMINOLEVULINIC ACID BASED PHOTODYNAMIC THERAPY
181. Pål Richard Romundstad: CANCER INCIDENCE AMONG NORWEGIAN ALUMINIUM WORKERS
182. Henrik Hjorth-Hansen: NOVEL CYTOKINES IN GROWTH CONTROL AND BONE DISEASE OF MULTIPLE MYELOMA
183. Gunnar Morken: SEASONAL VARIATION OF HUMAN MOOD AND BEHAVIOUR
184. Bjørn Olav Haugen: MEASUREMENT OF CARDIAC OUTPUT AND STUDIES OF VELOCITY PROFILES IN AORTIC AND MITRAL FLOW USING TWO- AND THREE-DIMENSIONAL COLOUR FLOW IMAGING
185. Geir Bråthen: THE CLASSIFICATION AND CLINICAL DIAGNOSIS OF ALCOHOL-RELATED SEIZURES
186. Knut Ivar Aasarød: RENAL INVOLVEMENT IN INFLAMMATORY RHEUMATIC DISEASE. A Study of Renal Disease in Wegener's Granulomatosis and in Primary Sjögren's Syndrome
187. Trude Helen Flo: RESEPTORS INVOLVED IN CELL ACTIVATION BY DEFINED URONIC ACID POLYMERS AND BACTERIAL COMPONENTS
188. Bodil Kavli: HUMAN URACIL-DNA GLYCOSYLASES FROM THE UNG GENE: STRUCTRUAL BASIS FOR SUBSTRATE SPECIFICITY AND REPAIR
189. Liv Thommesen: MOLECULAR MECHANISMS INVOLVED IN TNF- AND GASTRIN-MEDIATED GENE REGULATION
190. Turid Lingaas Holmen: SMOKING AND HEALTH IN ADOLESCENCE; THE NORD-TRØNDELAG HEALTH STUDY, 1995-97
191. Øyvind Hjertner: MULTIPLE MYELOMA: INTERACTIONS BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MICROENVIRONMENT
192. Asbjørn Støylen: STRAIN RATE IMAGING OF THE LEFT VENTRICLE BY ULTRASOUND. FEASIBILITY, CLINICAL VALIDATION AND PHYSIOLOGICAL ASPECTS
193. Kristian Midthjell: DIABETES IN ADULTS IN NORD-TRØNDELAG. PUBLIC HEALTH ASPECTS OF DIABETES MELLITUS IN A LARGE, NON-SELECTED NORWEGIAN POPULATION.
194. Guanglin Cui: FUNCTIONAL ASPECTS OF THE ECL CELL IN RODENTS
195. Ulrik Wisløff: CARDIAC EFFECTS OF AEROBIC ENDURANCE TRAINING: HYPERTROPHY, CONTRACTILITY AND CALCUIM HANDLING IN NORMAL AND FAILING HEART

196. Øyvind Halaas: MECHANISMS OF IMMUNOMODULATION AND CELL-MEDIATED CYTOTOXICITY INDUCED BY BACTERIAL PRODUCTS
197. Tore Amundsen: PERFUSION MR IMAGING IN THE DIAGNOSIS OF PULMONARY EMBOLISM
198. Nanna Kurtze: THE SIGNIFICANCE OF ANXIETY AND DEPRESSION IN FATIQUE AND PATTERNS OF PAIN AMONG INDIVIDUALS DIAGNOSED WITH FIBROMYALGIA: RELATIONS WITH QUALITY OF LIFE, FUNCTIONAL DISABILITY, LIFESTYLE, EMPLOYMENT STATUS, CO-MORBIDITY AND GENDER
199. Tom Ivar Lund Nilsen: PROSPECTIVE STUDIES OF CANCER RISK IN NORD-TRØNDELAG: THE HUNT STUDY. Associations with anthropometric, socioeconomic, and lifestyle risk factors
200. Asta Kristine Håberg: A NEW APPROACH TO THE STUDY OF MIDDLE CEREBRAL ARTERY OCCLUSION IN THE RAT USING MAGNETIC RESONANCE TECHNIQUES

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201. Knut Jørgen Arntzen: PREGNANCY AND CYTOKINES
202. Henrik Døllner: INFLAMMATORY MEDIATORS IN PERINATAL INFECTIONS
203. Asta Bye: LOW FAT, LOW LACTOSE DIET USED AS PROPHYLACTIC TREATMENT OF ACUTE INTESTINAL REACTIONS DURING PELVIC RADIOTHERAPY. A PROSPECTIVE RANDOMISED STUDY.
204. Sylvester Moyo: STUDIES ON STREPTOCOCCUS AGALACTIAE (GROUP B STREPTOCOCCUS) SURFACE-ANCHORED MARKERS WITH EMPHASIS ON STRAINS AND HUMAN SERA FROM ZIMBABWE.
205. Knut Hagen: HEAD-HUNT: THE EPIDEMIOLOGY OF HEADACHE IN NORD-TRØNDELAG
206. Li Lixin: ON THE REGULATION AND ROLE OF UNCOUPLING PROTEIN-2 IN INSULIN PRODUCING ß-CELLS
207. Anne Hildur Henriksen: SYMPTOMS OF ALLERGY AND ASTHMA VERSUS MARKERS OF LOWER AIRWAY INFLAMMATION AMONG ADOLESCENTS
208. Egil Andreas Fors: NON-MALIGNANT PAIN IN RELATION TO PSYCHOLOGICAL AND ENVIRONTENTAL FACTORS. EXPERIENTAL AND CLINICAL STUDES OF PAIN WITH FOCUS ON FIBROMYALGIA
209. Pål Klepstad: MORPHINE FOR CANCER PAIN
210. Ingunn Bakke: MECHANISMS AND CONSEQUENCES OF PEROXISOME PROLIFERATOR-INDUCED HYPERFUNCTION OF THE RAT GASTRIN PRODUCING CELL
211. Ingrid Susann Gribbestad: MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY OF BREAST CANCER
212. Rønnaug Astri Ødegård: PREECLAMPSIA – MATERNAL RISK FACTORS AND FETAL GROWTH
213. Johan Haux: STUDIES ON CYTOTOXICITY INDUCED BY HUMAN NATURAL KILLER CELLS AND DIGITOXIN
214. Turid Suzanne Berg-Nielsen: PARENTING PRACTICES AND MENTALLY DISORDERED ADOLESCENTS
215. Astrid Rydning: BLOOD FLOW AS A PROTECTIVE FACTOR FOR THE STOMACH MUCOSA. AN EXPERIMENTAL STUDY ON THE ROLE OF MAST CELLS AND SENSORY AFFERENT NEURONS

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216. Jan Pål Loennechen: HEART FAILURE AFTER MYOCARDIAL INFARCTION. Regional Differences, Myocyte Function, Gene Expression, and Response to Cariporide, Losartan, and Exercise Training.
217. Elisabeth Qvigstad: EFFECTS OF FATTY ACIDS AND OVER-STIMULATION ON INSULIN SECRETION IN MAN
218. Arne Åsberg: EPIDEMIOLOGICAL STUDIES IN HEREDITARY HEMOCHROMATOSIS: PREVALENCE, MORBIDITY AND BENEFIT OF SCREENING.
219. Johan Fredrik Skomsvoll: REPRODUCTIVE OUTCOME IN WOMEN WITH RHEUMATIC DISEASE. A population registry based study of the effects of inflammatory rheumatic disease and connective tissue disease on reproductive outcome in Norwegian women in 1967-1995.
220. Siv Mørkved: URINARY INCONTINENCE DURING PREGNANCY AND AFTER DELIVERY: EFFECT OF PELVIC FLOOR MUSCLE TRAINING IN PREVENTION AND TREATMENT

221. Marit S. Jordhøy: THE IMPACT OF COMPREHENSIVE PALLIATIVE CARE
222. Tom Christian Martinsen: HYPERGASTRINEMIA AND HYPOACIDITY IN RODENTS – CAUSES AND CONSEQUENCES
223. Solveig Tingulstad: CENTRALIZATION OF PRIMARY SURGERY FOR OVARAIN CANCER. FEASIBILITY AND IMPACT ON SURVIVAL
224. Haytham Eloqayli: METABOLIC CHANGES IN THE BRAIN CAUSED BY EPILEPTIC SEIZURES
225. Torunn Bruland: STUDIES OF EARLY RETROVIRUS-HOST INTERACTIONS – VIRAL DETERMINANTS FOR PATHOGENESIS AND THE INFLUENCE OF SEX ON THE SUSCEPTIBILITY TO FRIEND MURINE LEUKAEMIA VIRUS INFECTION
226. Torstein Hole: DOPPLER ECHOCARDIOGRAPHIC EVALUATION OF LEFT VENTRICULAR FUNCTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION
227. Vibeke Nossum: THE EFFECT OF VASCULAR BUBBLES ON ENDOTHELIAL FUNCTION
228. Sigurd Fasting: ROUTINE BASED RECORDING OF ADVERSE EVENTS DURING ANAESTHESIA – APPLICATION IN QUALITY IMPROVEMENT AND SAFETY
229. Solfrid Romundstad: EPIDEMIOLOGICAL STUDIES OF MICROALBUMINURIA. THE NORD-TRØNDELAG HEALTH STUDY 1995-97 (HUNT 2)
230. Geir Torheim: PROCESSING OF DYNAMIC DATA SETS IN MAGNETIC RESONANCE IMAGING
231. Catrine Ahlén: SKIN INFECTIONS IN OCCUPATIONAL SATURATION DIVERS IN THE NORTH SEA AND THE IMPACT OF THE ENVIRONMENT
232. Arnulf Langhammer: RESPIRATORY SYMPTOMS, LUNG FUNCTION AND BONE MINERAL DENSITY IN A COMPREHENSIVE POPULATION SURVEY. THE NORD-TRØNDELAG HEALTH STUDY 1995-97. THE BRONCHIAL OBSTRUCTION IN NORD-TRØNDELAG STUDY
233. Einar Kjelsås: EATING DISORDERS AND PHYSICAL ACTIVITY IN NON-CLINICAL SAMPLES
234. Arne Wibe: RECTAL CANCER TREATMENT IN NORWAY – STANDARDISATION OF SURGERY AND QUALITY ASSURANCE

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235. Eivind Witsø: BONE GRAFT AS AN ANTIBIOTIC CARRIER
236. Anne Mari Sund: DEVELOPMENT OF DEPRESSIVE SYMPTOMS IN EARLY ADOLESCENCE
237. Hallvard Lærum: EVALUATION OF ELECTRONIC MEDICAL RECORDS – A CLINICAL TASK PERSPECTIVE
238. Gustav Mikkelsen: ACCESSIBILITY OF INFORMATION IN ELECTRONIC PATIENT RECORDS; AN EVALUATION OF THE ROLE OF DATA QUALITY
239. Steinar Krokstad: SOCIOECONOMIC INEQUALITIES IN HEALTH AND DISABILITY. SOCIAL EPIDEMIOLOGY IN THE NORD-TRØNDELAG HEALTH STUDY (HUNT), NORWAY
240. Arne Kristian Myhre: NORMAL VARIATION IN ANOGENITAL ANATOMY AND MICROBIOLOGY IN NON-ABUSED PRESCHOOL CHILDREN
241. Ingunn Dybedal: NEGATIVE REGULATORS OF HEMATOPOIETEC STEM AND PROGENITOR CELLS
242. Beate Sitter: TISSUE CHARACTERIZATION BY HIGH RESOLUTION MAGIC ANGLE SPINNING MR SPECTROSCOPY
243. Per Arne Aas: MACROMOLECULAR MAINTENANCE IN HUMAN CELLS – REPAIR OF URACIL IN DNA AND METHYLATIONS IN DNA AND RNA
244. Anna Bofin: FINE NEEDLE ASPIRATION CYTOLOGY IN THE PRIMARY INVESTIGATION OF BREAST TUMOURS AND IN THE DETERMINATION OF TREATMENT STRATEGIES
245. Jim Aage Nøttestad: DEINSTITUTIONALIZATION AND MENTAL HEALTH CHANGES AMONG PEOPLE WITH MENTAL RETARDATION
246. Reidar Fossmark: GASTRIC CANCER IN JAPANESE COTTON RATS
247. Wibeke Nordhøy: MANGANESE AND THE HEART, INTRACELLULAR MR RELAXATION AND WATER EXCHANGE ACROSS THE CARDIAC CELL MEMBRANE

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248. Sturla Molden: QUANTITATIVE ANALYSES OF SINGLE UNITS RECORDED FROM THE HIPPOCAMPUS AND ENTORHINAL CORTEX OF BEHAVING RATS
249. Wenche Brenne Drøyvold: EPIDEMIOLOGICAL STUDIES ON WEIGHT CHANGE AND HEALTH IN A LARGE POPULATION. THE NORD-TRØNDELAG HEALTH STUDY (HUNT)

250. Ragnhild Støen: ENDOTHELIUM-DEPENDENT VASODILATION IN THE FEMORAL ARTERY OF DEVELOPING PIGLETS
251. Aslak Steinsbekk: HOMEOPATHY IN THE PREVENTION OF UPPER RESPIRATORY TRACT INFECTIONS IN CHILDREN
252. Hill-Aina Steffenach: MEMORY IN HIPPOCAMPAL AND CORTICO-HIPPOCAMPAL CIRCUITS
253. Eystein Stordal: ASPECTS OF THE EPIDEMIOLOGY OF DEPRESSIONS BASED ON SELF-RATING IN A LARGE GENERAL HEALTH STUDY (THE HUNT-2 STUDY)
254. Viggo Pettersen: FROM MUSCLES TO SINGING: THE ACTIVITY OF ACCESSORY BREATHING MUSCLES AND THORAX MOVEMENT IN CLASSICAL SINGING
255. Marianne Fyhn: SPATIAL MAPS IN THE HIPPOCAMPUS AND ENTORHINAL CORTEX
256. Robert Valderhaug: OBSESSIVE-COMPULSIVE DISORDER AMONG CHILDREN AND ADOLESCENTS: CHARACTERISTICS AND PSYCHOLOGICAL MANAGEMENT OF PATIENTS IN OUTPATIENT PSYCHIATRIC CLINICS
257. Erik Skaaheim Haug: INFRARENAL ABDOMINAL AORTIC ANEURYSMS – COMORBIDITY AND RESULTS FOLLOWING OPEN SURGERY
258. Daniel Kondziella: GLIAL-NEURONAL INTERACTIONS IN EXPERIMENTAL BRAIN DISORDERS
259. Vegard Heimly Brun: ROUTES TO SPATIAL MEMORY IN HIPPOCAMPAL PLACE CELLS
260. Kenneth McMillan: PHYSIOLOGICAL ASSESSMENT AND TRAINING OF ENDURANCE AND STRENGTH IN PROFESSIONAL YOUTH SOCCER PLAYERS
261. Marit Sæbø Indredavik: MENTAL HEALTH AND CEREBRAL MAGNETIC RESONANCE IMAGING IN ADOLESCENTS WITH LOW BIRTH WEIGHT
262. Ole Johan Kemi: ON THE CELLULAR BASIS OF AEROBIC FITNESS, INTENSITY-DEPENDENCE AND TIME-COURSE OF CARDIOMYOCYTE AND ENDOTHELIAL ADAPTATIONS TO EXERCISE TRAINING
263. Eszter Vanky: POLYCYSTIC OVARY SYNDROME – METFORMIN TREATMENT IN PREGNANCY
264. Hild Fjærtoft: EXTENDED STROKE UNIT SERVICE AND EARLY SUPPORTED DISCHARGE. SHORT AND LONG-TERM EFFECTS
265. Grete Dyb: POSTTRAUMATIC STRESS REACTIONS IN CHILDREN AND ADOLESCENTS
266. Vidar Fykse: SOMATOSTATIN AND THE STOMACH
267. Kirsti Berg: OXIDATIVE STRESS AND THE ISCHEMIC HEART: A STUDY IN PATIENTS UNDERGOING CORONARY REVASCULARIZATION
268. Björn Inge Gustafsson: THE SEROTONIN PRODUCING ENTEROCHROMAFFIN CELL, AND EFFECTS OF HYPERSEROTONINEMIA ON HEART AND BONE

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269. Torstein Baade Rø: EFFECTS OF BONE MORPHOGENETIC PROTEINS, HEPATOCYTE GROWTH FACTOR AND INTERLEUKIN-21 IN MULTIPLE MYELOMA
270. May-Britt Tessem: METABOLIC EFFECTS OF ULTRAVIOLET RADIATION ON THE ANTERIOR PART OF THE EYE
271. Anne-Sofie Helvik: COPING AND EVERYDAY LIFE IN A POPULATION OF ADULTS WITH HEARING IMPAIRMENT
272. Therese Standal: MULTIPLE MYELOMA: THE INTERPLAY BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MARROW MICROENVIRONMENT
273. Ingvild Saltvedt: TREATMENT OF ACUTELY SICK, FRAIL ELDERLY PATIENTS IN A GERIATRIC EVALUATION AND MANAGEMENT UNIT – RESULTS FROM A PROSPECTIVE RANDOMISED TRIAL
274. Birger Henning Endreseth: STRATEGIES IN RECTAL CANCER TREATMENT – FOCUS ON EARLY RECTAL CANCER AND THE INFLUENCE OF AGE ON PROGNOSIS
275. Anne Mari Aukan Rokstad: ALGINATE CAPSULES AS BIOREACTORS FOR CELL THERAPY
276. Mansour Akbari: HUMAN BASE EXCISION REPAIR FOR PRESERVATION OF GENOMIC STABILITY
277. Stein Sundstrøm: IMPROVING TREATMENT IN PATIENTS WITH LUNG CANCER – RESULTS FROM TWO MULITCENTRE RANDOMISED STUDIES
278. Hilde Pleym: BLEEDING AFTER CORONARY ARTERY BYPASS SURGERY - STUDIES ON HEMOSTATIC MECHANISMS, PROPHYLACTIC DRUG TREATMENT AND EFFECTS OF AUTOTRANSFUSION

279. Line Merethe Oldervoll: PHYSICAL ACTIVITY AND EXERCISE INTERVENTIONS IN CANCER PATIENTS
280. Boye Welde: THE SIGNIFICANCE OF ENDURANCE TRAINING, RESISTANCE TRAINING AND MOTIVATIONAL STYLES IN ATHLETIC PERFORMANCE AMONG ELITE JUNIOR CROSS-COUNTRY SKIERS
281. Per Olav Vandvik: IRRITABLE BOWEL SYNDROME IN NORWAY, STUDIES OF PREVALENCE, DIAGNOSIS AND CHARACTERISTICS IN GENERAL PRACTICE AND IN THE POPULATION
282. Idar Kirkeby-Garstad: CLINICAL PHYSIOLOGY OF EARLY MOBILIZATION AFTER CARDIAC SURGERY
283. Linn Getz: SUSTAINABLE AND RESPONSIBLE PREVENTIVE MEDICINE. CONCEPTUALISING ETHICAL DILEMMAS ARISING FROM CLINICAL IMPLEMENTATION OF ADVANCING MEDICAL TECHNOLOGY
284. Eva Tegnander: DETECTION OF CONGENITAL HEART DEFECTS IN A NON-SELECTED POPULATION OF 42,381 FETUSES
285. Kristin Gabestad Nørsett: GENE EXPRESSION STUDIES IN GASTROINTESTINAL PATHOPHYSIOLOGY AND NEOPLASIA
286. Per Magnus Haram: GENETIC VS. AQUIRED FITNESS: METABOLIC, VASCULAR AND CARDIOMYOCYTE ADAPTATIONS
287. Agneta Johansson: GENERAL RISK FACTORS FOR GAMBLING PROBLEMS AND THE PREVALENCE OF PATHOLOGICAL GAMBLING IN NORWAY
288. Svein Artur Jensen: THE PREVALENCE OF SYMPTOMATIC ARTERIAL DISEASE OF THE LOWER LIMB
289. Charlotte Björk Ingul: QUANITIFICATION OF REGIONAL MYOCARDIAL FUNCTION BY STRAIN RATE AND STRAIN FOR EVALUATION OF CORONARY ARTERY DISEASE. AUTOMATED VERSUS MANUAL ANALYSIS DURING ACUTE MYOCARDIAL INFARCTION AND DOBUTAMINE STRESS ECHOCARDIOGRAPHY
290. Jakob Nakling: RESULTS AND CONSEQUENCES OF ROUTINE ULTRASOUND SCREENING IN PREGNANCY – A GEOGRAPHIC BASED POPULATION STUDY
291. Anne Engum: DEPRESSION AND ANXIETY – THEIR RELATIONS TO THYROID DYSFUNCTION AND DIABETES IN A LARGE EPIDEMIOLOGICAL STUDY
292. Ottar Bjerkeset: ANXIETY AND DEPRESSION IN THE GENERAL POPULATION: RISK FACTORS, INTERVENTION AND OUTCOME – THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
293. Jon Olav Drogset: RESULTS AFTER SURGICAL TREATMENT OF ANTERIOR CRUCIATE LIGAMENT INJURIES – A CLINICAL STUDY
294. Lars Fosse: MECHANICAL BEHAVIOUR OF COMPACTED MORSELLISED BONE – AN EXPERIMENTAL IN VITRO STUDY
295. Gunilla Klensmeden Fosse: MENTAL HEALTH OF PSYCHIATRIC OUTPATIENTS BULLIED IN CHILDHOOD
296. Paul Jarle Mork: MUSCLE ACTIVITY IN WORK AND LEISURE AND ITS ASSOCIATION TO MUSCULOSKELETAL PAIN
297. Björn Stenström: LESSONS FROM RODENTS: I: MECHANISMS OF OBESITY SURGERY – ROLE OF STOMACH. II: CARCINOGENIC EFFECTS OF *HELICOBACTER PYLORI* AND SNUS IN THE STOMACH

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298. Haakon R. Skogseth: INVASIVE PROPERTIES OF CANCER – A TREATMENT TARGET ? IN VITRO STUDIES IN HUMAN PROSTATE CANCER CELL LINES
299. Janniche Hammer: GLUTAMATE METABOLISM AND CYCLING IN MESIAL TEMPORAL LOBE EPILEPSY
300. May Britt Drugli: YOUNG CHILDREN TREATED BECAUSE OF ODD/CD: CONDUCT PROBLEMS AND SOCIAL COMPETENCIES IN DAY-CARE AND SCHOOL SETTINGS
301. Arne Skjold: MAGNETIC RESONANCE KINETICS OF MANGANESE DIPYRIDOXYL DIPHOSPHATE (MnDPDP) IN HUMAN MYOCARDIUM. STUDIES IN HEALTHY VOLUNTEERS AND IN PATIENTS WITH RECENT MYOCARDIAL INFARCTION
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