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TABLE OF CONTENTS

ABSTRACT 1
PLAIN LANGUAGE SUMMARY 2
BACKGROUND 3
OBJECTIVES 4
METHODS 4
RESULTS 7
Figure 1. 7
DISCUSSION 11
AUTHORS' CONCLUSIONS 12
ACKNOWLEDGEMENTS 12
REFERENCES 13
CHARACTERISTICS OF STUDIES 18
DATA AND ANALYSES 36
Analysis 1.1. Comparison 1: Psychological intervention versus no such therapy, Outcome 1: Any chest pain up to 3 months after intervention 38
Analysis 1.2. Comparison 1: Psychological intervention versus no such therapy, Outcome 2: Any chest pain from 3 to 12 months after intervention 38
Analysis 1.3. Comparison 1: Psychological intervention versus no such therapy, Outcome 3: Chest pain free days up to 3 months after intervention 38
Analysis 1.4. Comparison 1: Psychological intervention versus no such therapy, Outcome 4: Chest pain frequency up to 3 months after intervention 39
Analysis 1.5. Comparison 1: Psychological intervention versus no such therapy, Outcome 5: Chest pain frequency 3 to 12 months after intervention 39
Analysis 1.6. Comparison 1: Psychological intervention versus no such therapy, Outcome 6: Chest pain severity up to 3 months 39
Analysis 1.7. Comparison 1: Psychological intervention versus no such therapy, Outcome 7: Quality of life - physical functioning up to 3 months after intervention 40
Analysis 1.8. Comparison 1: Psychological intervention versus no such therapy, Outcome 8: Quality of life - physical functioning 3 to 12 months after intervention 40
Analysis 1.9. Comparison 1: Psychological intervention versus no such therapy, Outcome 9: Quality of life - role problems due to emotional limitations up to 3 months after intervention 40
Analysis 1.10. Comparison 1: Psychological intervention versus no such therapy, Outcome 10: Quality of life - role problems due to emotional limitations 3 to 12 months after intervention 41
Analysis 1.11. Comparison 1: Psychological intervention versus no such therapy, Outcome 11: Quality of life - social functioning up to 3 months after intervention 41
Analysis 1.12. Comparison 1: Psychological intervention versus no such therapy, Outcome 12: Quality of life - social functioning 3 to 12 months after intervention 41
Analysis 1.13. Comparison 1: Psychological intervention versus no such therapy, Outcome 13: Psychological symptoms up to 3 months after the intervention (depression & overall) 42
Analysis 1.14. Comparison 1: Psychological intervention versus no such therapy, Outcome 14: Psychological symptoms up to 3 months after the intervention (anxiety and overall) 42
Analysis 1.15. Comparison 1: Psychological intervention versus no such therapy, Outcome 15: Psychological symptoms 3 to 12 months after the intervention 42
Analysis 1.16. Comparison 1: Psychological intervention versus no such therapy, Outcome 16: Cardiac anxiety fear up to 3 months 43
Analysis 1.17. Comparison 1: Psychological intervention versus no such therapy, Outcome 17: Cardiac anxiety fear 3 to 12 months 43
Analysis 1.18. Comparison 1: Psychological intervention versus no such therapy, Outcome 18: Cardiac anxiety avoidance up to 3 months 43
Analysis 1.19. Comparison 1: Psychological intervention versus no such therapy, Outcome 19: Cardiac anxiety avoidance 3 to 12 months 43
Analysis 1.20. Comparison 1: Psychological intervention versus no such therapy, Outcome 20: Cardiac anxiety attention up to 3 months 44
Analysis 1.21. Comparison 1: Psychological intervention versus no such therapy, Outcome 21: Cardiac anxiety attention 3 to 12 months 44

APPENDICES 44
WHAT'S NEW 57
HISTORY 57
CONTRIBUTIONS OF AUTHORS 58
DECLARATIONS OF INTEREST 58
SOURCES OF SUPPORT 58
DIFFERENCES BETWEEN PROTOCOL AND REVIEW 58
INDEX TERMS 59

[Intervention Review]

Psychological interventions for symptomatic management of non-specific chest pain in patients with normal coronary anatomy

Steve R Kisely[1], Leslie A Campbell[2], Michael J Yelland[3], Anita Paydar[4]

[1]School of Medicine, The University of Queensland, Woolloongabba, Australia. [2]Department of Community Health and Epidemiology, Dalhousie University, Halifax, Canada. [3]School of Medicine, Logan Campus, Griffith University, Meadowbrook, Australia. [4]School of Population Health, The University of Queensland, Brisbane, Australia

Contact: Steve R Kisely, s.kisely@uq.edu.au, steve.kisely@health.qld.gov.au.

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ABSTRACT

Background

Recurrent chest pain in the absence of coronary artery disease is a common problem which sometimes leads to excess use of medical care. Although many studies have examined the causes of pain in these patients, few clinical trials have evaluated treatment. This is an update of a Cochrane review originally published in 2005 and last updated in 2010. The studies reviewed in this paper provide an insight into the effectiveness of psychological interventions for this group of patients.

Objectives

To assess the effects of psychological interventions for chest pain, quality of life and psychological parameters in people with non-specific chest pain.

Search methods

We searched the Cochrane Library (CENTRAL, Issue 4 of 12, 2014 and DARE Issue 2 of 4, 2014), MEDLINE (OVID, 1966 to April week 4 2014), EMBASE (OVID, 1980 to week 18 2014), CINAHL (EBSCO, 1982 to April 2014), PsycINFO (OVID, 1887 to April week 5 2014) and BIOSIS Previews (Web of Knowledge, 1969 to 2 May 2014). We also searched citation lists and contacted study authors.

Selection criteria

Randomised controlled trials (RCTs) with standardised outcome methodology that tested any form of psychotherapy for chest pain with normal anatomy. Diagnoses included non-specific chest pain (NSCP), atypical chest pain, syndrome X or chest pain with normal coronary anatomy (as either inpatients or outpatients).

Data collection and analysis

Two review authors independently selected studies for inclusion, extracted data and assessed quality of studies. We contacted trial authors for further information about the included RCTs.

Main results

We included two new papers, one of which was an update of a previously included study. Therefore, a total of 17 RCTs with 1006 randomised participants met the inclusion criteria, with the one new study contributing an additional 113 participants. There was a significant reduction in reports of chest pain in the first three months following the intervention: random-effects relative risk = 0.70 (95% CI 0.53 to 0.92). This was maintained from three to nine months afterwards: relative risk 0.59 (95% CI 0.45 to 0.76). There was also a significant

increase in the number of chest pain-free days up to three months following the intervention: mean difference (MD) 3.00 (95% CI 0.23 to 5.77). This was associated with reduced chest pain frequency (random-effects MD -2.26, 95% CI -4.41 to -0.12) but there was no evidence of effect of treatment on chest pain frequency from three to twelve months (random-effects MD -0.81, 95% CI -2.35 to 0.74). There was no effect on severity (random-effects MD -4.64 (95% CI -12.18 to 2.89) up to three months after the intervention. Due to the nature of the main interventions of interest, it was impossible to blind the therapists as to whether the participant was in the intervention or control arm. In addition, in three studies the blinding of participants was expressly forbidden by the local ethics committee because of issues in obtaining fully informed consent. For this reason, all studies had a high risk of performance bias. In addition, three studies were thought to have a high risk of outcome bias. In general, there was a low risk of bias in the other domains. However, there was high heterogeneity and caution is required in interpreting these results. The wide variability in secondary outcome measures made it difficult to integrate findings from studies.

Authors' conclusions

This Cochrane review suggests a modest to moderate benefit for psychological interventions, particularly those using a cognitive-behavioural framework, which was largely restricted to the first three months after the intervention. Hypnotherapy is also a possible alternative. However, these conclusions are limited by high heterogeneity in many of the results and low numbers of participants in individual studies. The evidence for other brief interventions was less clear. Further RCTs of psychological interventions for NSCP with follow-up periods of at least 12 months are needed.

PLAIN LANGUAGE SUMMARY

Cognitive-behavioural treatments for non-cardiac chest pain

Recurrent chest pain in the absence of coronary artery disease is a common, difficult to treat problem that sometimes leads to excess use of medical care. A substantial number of patients are not reassured by negative medical assessment, reporting persistent pain and limitations. Psychological factors appear to be of importance for treatment. This Cochrane review included all studies of psychotherapy for non-cardiac chest pain. Seventeen trials met the inclusion criteria, and included a total of 1006 participants. The review found that cognitive-behavioural treatments are probably effective (in terms of reduced chest pain frequency) in the short term, for the treatment of non-cardiac related chest pain. No adverse effects of the psychotherapy were found. Hypnotherapy is also a possible alternative. A limitation of this review is the high variability of the studies included, reflected in a wide range of outcome measures, although there was an overall fairly low risk of bias.

BACKGROUND

Chest pain is one of the most frequent reasons for people's presentation to emergency services. Of patients admitted to the emergency department for chest pain, more than half are discharged with a diagnosis of noncardiac chest pain (NCCP) or chest pain of unknown cause (Capewell 2000; Knockaert 2002). Non-specific chest pain (NSCP) accounts for between 2% to 5% of all admissions to the emergency department (Eslick 2003; Knockaert 2002). Approximately 50% of new referrals to outpatient cardiac clinics with the presenting complaint of chest pain are found to have a non-cardiac basis for their pain (Mayou 1997). The reported prevalence of NCCP in the community ranges from 23% to 33% (Eslick 2002; Eslick 2003). While various causes have been proposed, including microvascular coronary artery disease, coronary spasm, chest wall pain, oesophageal dysmotility or reflux, hyperventilation, panic disorder and general anxiety, many patients are given a non-specific diagnosis (Mayou 1997). In all groups of patients there is some association with psychiatric disorder, although the importance of this varies according to diagnosis.

Chest pain with normal coronary anatomy and no clear physical cause has been described by a number of terms including NSCP, NCCP, atypical chest pain, syndrome X or chest pain with normal coronary anatomy. Syndrome X refers to a triad of angina pectoris, positive exercise electrocardiogram (ECG) for myocardial ischaemia and angiographically smooth coronary arteries (Asbury 2005a). In this Cochrane review we will use the term NSCP. Most NSCP studies are concerned with outpatients with normal coronary angiograms whose chest pain is chronic. In one study, 61% of patients with NSCP had psychiatric symptoms on structured interview (the Clinical Interview Schedule), compared with 23% of patients with abnormal coronary arteries (Bass 1984). The respective figures for NSCP and coronary heart disease in another study using the Diagnostic Interview Schedule were 43% and 6.5% for panic disorder, 36% and 4% for major depression, and 36% and 15% for phobias (Katon 1988). These proportions are much higher than in patients with coronary heart disease, although a possible confounding factor may have been the chronic nature of the NSCP.

There have been similar findings in inpatients. In one study of consecutive admissions to a coronary intensive care unit, 55% of patients with NSCP (n = 27) had panic disorder compared with 11% of those with coronary heart disease (Carter 1992a). There was a similar but non-significant association between major depression and NSCP (22%) as opposed to coronary heart disease (11%).

The prognosis of patients with NSCP varies with the outcome measure. In contrast to patients with coronary disease, the incidence of myocardial infarction or death in patients with chest pain and normal cardiac arteriography is very low in most long-term studies (Chambers 1990). In terms of functional disability, approximately 75% of patients continue seeing a physician, 50% remain or become unemployed, and 50% regard their lives as significantly disabled. Fewer than 50% of NSCP patients appear reassured that they do not have serious heart disease. Most continue to report residual chest pain during follow-up (Chambers 1990).

A number of possible mechanisms for NSCP have been suggested. These include hyperventilation (DeGuire 1992; DeGuire 1996) or panic disorder (Mayou 1989b) and an association with alcohol and cigarette use (Kisely 1997), possibly mediated through changes in oesophageal motility (Kahrilas 1990; Matsuguchi 1984). Other potential mechanisms are less clear. There may be an interaction in which psychological factors affect the interpretation of physiological perceptions, which in turn worsen mental state (Chambers 1990). In addition, recent life events as measured by a structured interview or personality factors, such as an excess of Type A behaviour (hard driving and competitive behaviour, a potential for hostility, pronounced impatience and vigorous speech stylistics (Hemingway 1999)), have been identified as occurring more frequently in patients with NSCP compared with physically healthy controls matched for age and sex (Roll 1987). In addition, the presence of pain is associated with increased psychiatric morbidity, including psychophysiological symptoms other than pain, thus exacerbating the problem (Von Korff 1988). Chest pain forms part of the spectrum of medically unexplained symptoms, the exact presenting features varying by specialty. For instance, the equivalent for NCCP in cardiology would be irritable bowel syndrome in gastroenterology or fibromyalgia in rheumatology (Hatcher 2008).

Treatment is known to be difficult (Klimes 1990). Some patients are reassured by negative medical assessment, but a substantial number report persistent pain and limitations. A variety of drugs have been used including anti-secretory drugs, anxiolytics, antidepressants, nitrates and calcium channel blockers (Bennett 2001). As cognitions are of aetiological importance in NSCP and with high levels of psychiatric co-morbidity, psychological approaches have been suggested as appropriate interventions (Bass 1984; Klimes 1990; Ockene 1980) as early intervention might help prevent the pain becoming chronic. Such approaches generally use a behavioural framework and include an explanation of the nature of the pain, treatment of anxiety or depression, and cognitive behavioural psychotherapy.

The exact contributions to a successful outcome are unknown. Given the wide range of behavioural treatments in use, any systematic review would have to include a sensitivity analysis. The sensitivity analysis would identify any dilution of findings in the meta-analysis.

Both cognitive-behavioural therapy (CBT) and psychodynamic therapy are effective in treating anxiety and depressive disorders (Shapiro 1994). CBT is effective in the treatment of patients with unexplained physical symptoms (Speckens 1995; Hatcher 2008) and chronic fatigue syndrome (Price 2008; Sharpe 1996). Previous versions of this review indicated modest to moderate benefit for psychological interventions, particularly those using a cognitive-behavioural framework, which was largely restricted to the first three months after the intervention (Kisely 2005; Kisely 2010). This is consistent with findings for other types of medically unexplained symptoms (Kroenke 2000; Hatcher 2008).

Given the large number of people living with chest pain and the high prevalence of psychiatric co-morbidity, it is important to identify psychological interventions that may alleviate such symptoms. This is an update of a previously published Cochrane review (Kisely 2005; Kisely 2010).

OBJECTIVES

To assess the effects of psychological interventions for chest pain, quality of life and psychological parameters in people with NSCP. We included the psychological interventions of:

1. CBT;
2. Relaxation therapy;
3. Hyperventilation control;
4. Hypnotherapy;
5. Other psychotherapy/talking/counselling therapy;
6. Standard care, 'attention' placebo, waiting list controls or no intervention as the control conditions.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

People presenting with chest pain who have normal anatomy as assessed on clinical history, cardiac enzymes, ECGs, exercise ECGs or coronary angiography. Diagnoses included NSCP, atypical chest pain, syndrome X, or chest pain with normal coronary anatomy (as either inpatients or outpatients). We included psychiatric co-morbidity, although we excluded patients who were receiving drug therapy for psychiatric disorders.

Types of interventions

Cognitive behavioural therapy

For the purposes of this Cochrane review, we based CBT on Jones 2004's definition. In order to be classified as 'well defined' the intervention must clearly demonstrate the following components:

1. The intervention involves the recipient establishing links between their thoughts, feelings and actions with respect to the target symptom;
2. The intervention involves the correction of the person's misperceptions, irrational beliefs and reasoning biases related to the target symptom;
3. The intervention should involve either or both of the following:
    - the recipient monitoring his or her own thoughts, feelings and behaviours with respect to the target symptom;
    - the promotion of alternative ways of coping with the target symptom.

All therapies that did not meet these inclusion criteria and were described as 'CBT' or 'cognitive therapy' were labelled as 'less-well defined' CBT. We established the exact nature of 'less-well defined' therapies by contacting study authors.

We conducted a sensitivity analysis on the primary outcomes (see Types of outcome measures) of this Cochrane review to determine whether there was a difference based on the 'well-defined' or 'less-well defined' classification of CBT.

Relaxation therapy

Relaxation therapy consists of alternating tension and relaxation of various muscle groups (Woolfolk 1983). Some studies have added imagery to the relaxation (Borkovec 1982).

Hyperventilation control

Hyperventilation control techniques consist of an explanation of how hyperventilation can contribute to symptoms (DeGuire 1992). Control of hyperventilation can be achieved by holding the breath for 20 seconds and then breathing on a six-second cycle (10 breaths per minute). Breathing should be as light as possible and preferably diaphragmatic. Additional relief can be obtained from either breathing into cupped hands or into a re-breathing bag for one to two minutes every five minutes until symptoms abate (QAP 1982).

Hypnotherapy

Hypnosis can be induced by eye closure, followed by progressive muscular relaxation and standard deepening techniques. Suggestions for normalisation of function and sensitivity are made using both imagery and conditioning techniques (Jones 2006).

Other psychotherapy/talking/counselling therapy

Any psychological intervention described as behavioural therapy such as psychosocial interventions such as non-directive counselling and supportive therapy and other 'talking therapies'.

Control interventions

Any of the above interventions compared with:

Standard care

The care that a person would normally receive had they not been included in the research trial. We considered standard care to include no change to normal daily activities, and no care in the context of the study, but patients were free to use any health agencies (such as their general practitioner (GP) or medical specialist) on their own initiative. The category 'standard care' also incorporates 'waiting list control groups' where participants receive drug or other interventions.

'Attention' placebo

Interventions where participants are involved in education.

No intervention

Untreated control group.

Types of outcome measures

Primary outcomes

A significant reduction in chest pain (as defined in the individual studies) following the intervention.

1. Pain intensity measured by categorical scales or visual analogue scales (VAS);
2. Pain diaries (mean difference (MD) in pain scores or recorded frequency of exacerbation of pain).

Secondary outcomes

1. Psychological symptoms as defined by standardised psychiatric instruments or criteria such as the General Health Questionnaire, Beck Depression Inventory (BDI), Zung Depression Scale, Hamilton Anxiety and Depression Scales, Hospital Anxiety and Depression Scales (HADS), Present State Examination (PSE), Clinical Global Impression Severity, and Composite International Diagnostic Interview;
2. Quality of life e.g. Short Form-36 (SF-36) scores;
3. Health service use e.g. hospital re-admission for chest pain, outpatient contacts, visits to primary care;
4. Non-fatal cardiovascular events (stroke, myocardial infarction, angina pectoris, pulmonary embolism or peripheral arterial embolism);
5. Cardiac behavioural risk factors reduction (e.g. smoking, exercise and alcohol consumption);
6. Death (cardiovascular and all-cause mortality);
7. Health beliefs.

We grouped outcomes into short-term (within 12 weeks of the start of therapy), medium-term (between 13 to 24 weeks after the beginning of therapy) and long-term (> 24 weeks after the start of therapy).

Search methods for identification of studies

Electronic searches

We searched the following sources up to 6 May 2014 to identify potentially eligible studies and review articles: the Cochrane Library (CENTRAL, Issue 4 of 12, 2014 and DARE Issue 2 of 4, 2014), MEDLINE (OVID, 1966 to April week 4 2014), EMBASE (OVID, 1980 to week 18 2014), CINAHL (EBSCO, 1982 to April 2014), PsycINFO (OVID, 1887 to April week 5 2014) and BIOSIS Previews (Web of Knowledge, 1969 to 2 May 2014). We used methodological filters to identify RCTs in MEDLINE and EMBASE (Lefebvre 2011).

We have listed the search details in Appendix 1 (initial search up to 2002), Appendix 2 (from 2002 to 2008), Appendix 3 (2011 updated searches) and Appendix 4 (2014 updated searches).

Searching other resources

We checked the reference lists of all references that were retrieved as full-text articles and were potentially relevant, as well as relevant systematic reviews and literature reviews to identify other potentially relevant articles. We retrieved these articles and assessed them for possible inclusion in the review.

We wrote to the lead authors of all relevant references to ascertain if they knew of any additional published or unpublished studies that might be relevant to the review.

We scrutinised abstracts from national and international cardiology, psychiatry and psychology conferences to identify unpublished studies. These included meetings organised by national and international medical colleges, specialty societies and professional organisations.

We did not apply any language restrictions and we translated all relevant foreign language papers.

Data collection and analysis

Selection of studies for inclusion/exclusion

Two review authors (SK, LAC) independently selected suitable studies for inclusion in the original review (Kisely 2005), as detailed below. For the review updates, SK and AP performed this. Where the two review authors disagreed about the inclusion of a study, we resolved disagreements by consensus of opinion, and consulted a third review author if disagreements could not be resolved. Where resolution was not possible we contacted the trial authors to obtain more information and clarification.

We assessed titles and abstracts of studies identified by searching electronic databases to determine whether each article met the eligibility criteria. In order to prevent any bias, we printed a list of all titles and abstracts and excluded the author names, institutions and journal title. If the title and abstract contained sufficient information to determine that the article did not meet the inclusion criteria, then it was rejected. We recorded all rejected papers and the reasons for rejection. We scanned the reference lists of all relevant papers for published reports, conference abstracts and citations of unpublished research.

We retrieved the full papers of all remaining titles and abstracts deemed relevant. Also we reviewed all other potentially relevant articles identified by the various search strategies (reference checking, personal communications etc). Two review authors independently assessed all articles, who completed a form for each study and scored the quality of the research as defined below. We documented the reasons for exclusion. Where the same study had more than one article written about the outcomes, we treated all articles as one study and presented the results only once.

Risk of bias

We prepared a 'Risk of bias' table for any new articles included in this update. The 'Risk of bias' table included random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias) and selective reporting (reporting bias) using the methodology described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Losses to follow-up

Ideally, included papers should have given an adequate description of the loss of its participants in terms of the number of withdrawals, dropouts and protocol deviations. In the protocol for this review we stated that we would only include RCTs where < 20% of participants originally randomised were lost to follow-up. In view of the limited number of trials, we relaxed these criteria to include studies that combined RCT and cross-over designs, and those that had greater losses to follow-up. In each case, we performed sensitivity analyses to assess the effect of the inclusion of these studies.

Addressing publication bias

Where there were more than 10 studies in an analysis, we entered data into a funnel plot (size of study versus effect size) (Egger 1997), to detect the possibility of publication bias.

Data extraction

Two review authors (SK and LAC or AP) completed a data extraction form for each included study to elicit the following information:

- General: published/unpublished, title, authors, source, contact address, country, language of publication, year of publication, duplicate publications, sponsoring, setting (hospital inpatients or outpatients, primary care, community);
- Trial characteristics: design, duration, randomisation and method, allocation concealment and method, blinding of outcome assessors, check of blinding;
- Interventions (frequency, timing), comparison interventions, co-medications;
- Patient characteristics - sampling, exclusion criteria number of participants, age, sex, ethnicity, marital status, educational status, duration of symptoms, number of complications, mode of referral (e.g. self-referral or via psychiatrists, psychologists, or other clinicians), similarity of groups at baseline (including any co-morbidity), withdrawals/losses to follow-up (reasons/ descriptions), history of myocardial infarction (MI);
- Type of intervention - CBT, psychotherapy, 'talking/ counselling' therapy, no intervention versus psychological intervention; usual care versus psychological intervention; and 'attention' placebo versus psychological intervention; timing of intervention (early vs late);
- Type of outcomes - level of chest pain at baseline, and at subsequent follow-ups, psychiatric symptoms, quality of life, number of hospital re-admissions, non-fatal cardiovascular events, reduction of cardiovascular behavioural risk factors, death (cardiovascular and all-cause mortality), and health beliefs;
- Type of psychiatric outcome - clinical diagnosis or symptomatology assessed by questionnaire;
- Type of assessment tool used to assess psychiatric outcome - e.g. BDI, Zung Depression Scale, HADS, Structured interview, DSM-IV criteria;Cut-off used on psychiatric scale, percentage of people defined as psychiatric cases on this basis; mean (SD) symptom score;
- Duration of follow-up and point from which follow-up was calculated start or end of intervention.

We stated that we would group outcomes into short term (within 12 weeks of the start of therapy), medium term (between 13 to 24 weeks after the beginning of therapy) and long-term (more than 24 weeks after the start of therapy). As interventions varied in length from one session to treatment lasting three months, we used time from the end of intervention to ensure that comparison between treatments were appropriate (i.e. an assessment made six months after baseline assessment and a three month course of treatment is the equivalent of three months after initial assessment for an intervention lasting a few days). Using this methodology, it was only possible to divide outcomes into those within three months of the end of the intervention (or the equivalent time for controls), and those from three to 12 months after the intervention (or the equivalent time for controls). Only one study reported data on ten participants at 36 month follow-up (DeGuire 1996).

Data analysis

Data entry

Two review authors (SK and LAC or AP) independently entered data into RevMan 2014. We reported a summary of data extracted from included studies. If studies were available that were sufficiently similar and of sufficient quality we pooled those that could be grouped together and meta-analysed the data. We synthesised the data using MetaView within RevMan 2014.

Data types

We assessed outcomes using continuous (e.g. changes on depression scales), categorical (e.g. one of three categories on a quality of life scale, such as 'better', 'worse' or 'no change') or dichotomous (e.g. either depressed or not-depressed) measures.

Continuous data

Many rating scales are available to measure outcomes in psychological trials. These scales vary in the quality of their validation and reliability. Therefore, if validation of a rating scale was not published in a peer-reviewed journal, then we did not include the data in this Cochrane review. In addition, the rating scale should either be self-reported or completed by an independent observer or relative. Trials that used the same instrument to measure specific outcomes were used in direct comparisons where possible. Where continuous data were presented from different scales rating the same effect, we presented both sets of data and inspected the general direction of the effect. We reported the mean and standard deviation (SD). Where SDs were not reported in the paper, we attempted to obtain them from the trial authors or to calculate them using other reported measures of variation, such as the confidence intervals (CIs). We pooled data from different scales rating the same outcome using the standardised mean difference (SMD).

Dichotomous data

We converted continuous outcome measures to dichotomous data where it was necessary to combine these with dichotomous outcomes. If the trial authors used a designated cut-off point for determining clinical effectiveness we used this where appropriate. Otherwise, we identified cut-offs on rating scales and divided participants on the basis of whether they were 'clinically improved' or 'not clinically improved'. For dichotomous outcomes, we estimated a risk ratio with its associated 95% CIs. As a summary measure of effectiveness, where possible we calculated the number needed to treat statistic (NNT).

Initially we compared any psychological intervention to any control. Depending on the number of included studies, we compared each intervention category with any control, and also subgroup according to type of control. We investigated the effect of different approaches using sensitivity analyses (see below).

Heterogeneity

When we inspected graphical representations of the data, if the CIs of the study results did not overlap, we deemed the differences were likely to be statistically significant (Walker 1988). In addition, we checked the differences between the results of each included trial using a test of heterogeneity. As these tests usually have low statistical power, we used a type I error level of 0.10 rather than the customary 0.05 for rejecting the null hypothesis of homogeneity.

We analysed the results using both fixed-effect and random-effects methods. However, where there was significant heterogeneity (I^2 statistic > 50%), we only used a random-effects model. We attempted to explore the reasons for this heterogeneity in post hoc analyses of omitting each study in turn where there were more than two studies. However, we reported both fixed-effect and random-effects models when there was no statistical heterogeneity.

Sensitivity analyses

We investigated factors which may have led to differences between the results of individual studies by using sensitivity analyses. In this Cochrane review we investigated differences between:

- Trials which defined psychiatric symptoms operationally (e.g. clinician diagnosis or validated questionnaire and whether the questionnaire had been validated in this specific population or in other groups);
- Types of psychological interventions and types of controls;
- Route of referral for intervention (e.g. referred to psychiatrists, clinical psychologists, other mental health professionals or other clinicians for management);
- Participants with and without a family history of heart disease;
- Studies that used subject reported pain or assessments by clinicians or carers;
- Well-defined and less-well defined psychological interventions;
- Analyses involving all studies and excluding trials of low methodological quality;
- Analyses involving all studies and those that excluded comorbid psychiatric disorder;
- Participants with and without a history of myocardial infarction;
- Participants with and without coronary angiography; and
- Self referral and referral from a clinician.

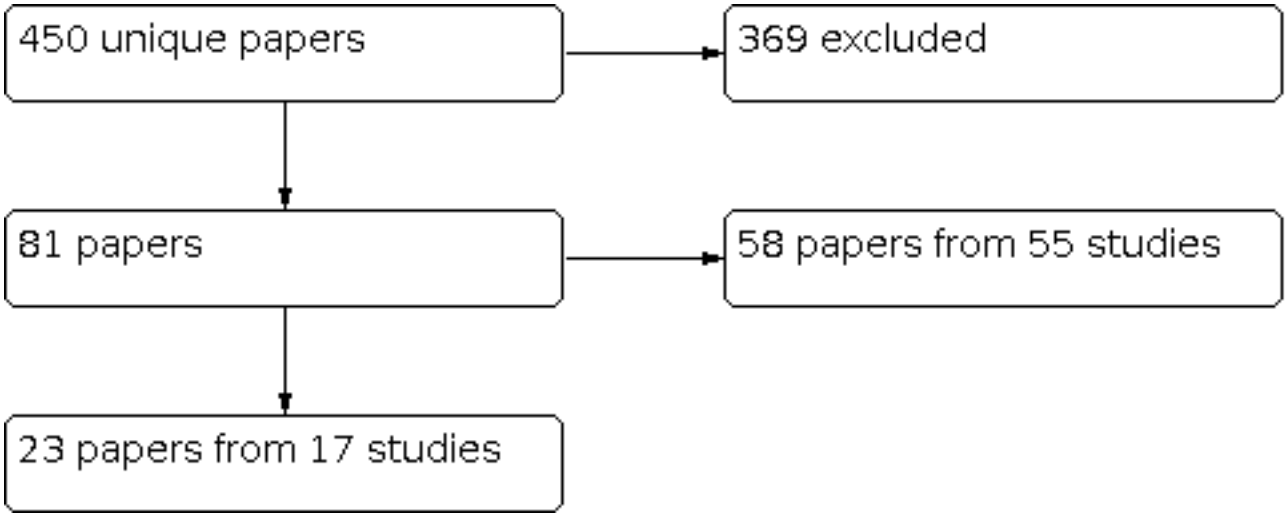
RESULTS

Description of studies

Results of the search

In the literature search in 2014 we identified 81 unique references in addition to the 369 articles we identified in 2011, 2008 and 2002. From these, and the original searches, we considered 81 papers in detail for inclusion. Of these, we excluded 58 papers from 55 studies, and included 23 papers from 17 studies (Figure 1).

Figure 1. Study flow diagram.



Included studies

We included 17 RCTs (1006 participants) (Asbury 2007; Asbury 2008; Asbury 2011; DeGuire 1996; Esler 2003; Jonsbu 2011; Keefe 2011; Klimes 1990; Lahmann 2008; Jones 2006; Mayou 1997; Potts 1999; Sanders 1997; Spinhoven 2010; Tyni-Lenne 2002; van Beek 2013; Van Peski-Oosterbaan 1999). Of these, one was new to this update (n = 113) (van Beek 2013). See Characteristics of included studies for further details of each included trial.

Data reporting

Two studies combined the results of the RCT and crossover designs (Klimes 1990; Potts 1999). Three studies did not report SDs (Klimes 1990; Potts 1999; Tyni-Lenne 2002). The authors of Potts 1999 kindly provided the missing SDs for the RCT component of their study, including pain episodes and pain-free days.

Interventions and analysis

Comparisons of psychological interventions included CBT, hypnotherapy, autogenic training, group support, brief intervention by a nurse, relaxation training and breathing re-training. Only two studies evaluated a group intervention (Asbury 2011; Potts 1999). Two studies used a combined randomised controlled and crossover design where participants in the control groups were offered the active treatment after the initial controlled trial (Klimes 1990; Potts 1999). In one trial, control participants were given an initial behavioural explanation of their symptoms before being placed on the wait-list. Although both studies reported some data of the RCT component, many of the reported outcomes combined the results of the RCT and crossover designs. Where it was not possible to find data of the RCT alone, we conducted sensitivity analyses including and excluding combined data. In the other studies, control participants were offered assessment only combined with either usual care (Tyni-Lenne 2002; Van Peski-

Oosterbaan 1999) or no care (DeGuire 1996; Mayou 1997). In the case of the former, no information was reported on details of usual care the controls received. Where studies had more than two arms (DeGuire 1996; Keefe 2011; Tyni-Lenne 2002), we used the control treatment that most readily allowed comparison with other studies. For DeGuire 1996 we used guided re-breathing training without physiological monitoring of diaphragmatic breathing or end-tidal CO_2. For Tyni-Lenne 2002, we used relaxation as opposed to physical training. It was not possible to examine differences in the timing of the interventions. In the case of Keefe 2011, there were four study arms: 1) placebo; 2) psychological treatment and placebo; 3) sertraline and placebo; and 4) sertraline plus psychological treatment. We used the results of the first two arms. Six of the 15 studies did not described timing of the intervention (early vs. late). One study examined the differences between "immediate" and "delayed" interventions, but as per the inclusion criteria, participants may have had an angiogram within the past year (Potts 1999). Similarly, Esler 2003 conducted the intervention while the patient was in the emergency room, but did not provide information regarding a history of chest pain. Therefore, it is unclear whether the patients were presenting for the first time or not. Therapist training was not noted in four of the studies. Nine studies described adherence to a treatment manual or plan. Keefe 2011 also assessed fidelity. Therapists met weekly for supervision with a senior psychologist who reviewed audiotapes of the sessions and provided feedback regarding treatment quality and adherence to the study protocol.

Participants

Four studies was restricted to females (Asbury 2007; Asbury 2008; Asbury 2011; Tyni-Lenne 2002). All studies were of outpatients who were either referred by treating physicians or GPs, or undergoing coronary angiography. One study, DeGuire 1996, included participants who responded to a newspaper advertisement. A sensitivity analysis excluding this study made no difference to the results. All included participants whose main symptom was chest pain and who had been investigated to some degree to exclude cardiac explanations for their pain. Only one study excluded participants who had other co-morbid medical conditions, such as diabetes (Tyni-Lenne 2002). Only three studies excluded participants who had comorbid psychiatric disorder, such as major depression (Klimes 1990; Mayou 1997; Van Peski-Oosterbaan 1999). We conducted sensitivity analyses of studies that used such exclusion criteria and those that did not.

Completion rates

Completion rates varied widely. Only ten studies reported the number of subjects eligible for inclusion who agreed to participate (Jones 2006; Jonsbu 2011; Keefe 2011; Klimes 1990; Lahmann 2008; Mayou 1997; Sanders 1997; Spinhoven 2010; van Beek 2013; Van Peski-Oosterbaan 1999). In most cases, only 40% to 60% agreed to participate. Lahmann 2008 and van Beek 2013 were the only exceptions, where 90% of eligible subjects participated. Completion rates following randomisation were generally acceptable (approximately 80%), although in three trials over 35% were lost to follow-up (DeGuire 1996; Mayou 1997; van Beek 2013). We conducted sensitivity analyses of studies where completion rates were less than 80%.

Outcomes

All included studies reported change in frequency and severity of chest pain except one (van Beek 2013). Some also included the number of days when participants were free of chest pain. Studies reported a wide range of other outcomes covering psychological morbidity, quality of life, health beliefs and service use. Both observer-rated and self-report measures were included.

Duration of follow-up

Follow-up periods varied from three to 36 months. Studies generally dated follow-up from baseline intervention rather than the end of the intervention. Duration of interventions varied from a single session, to a few days or several months. We calculated duration from follow-up from the end of the intervention. For example, we classified a trial in which participants were followed up for six months dated from baseline intervention, with an intervention duration of three months as followed up for three months.

Excluded studies

We excluded 58 papers from 55 studies (see Characteristics of excluded studies). Most were reviews that did not contain primary data or were not intervention studies. Eight intervention studies were excluded; three were trials of antidepressant medication (Cox 1998; Handa 1999; Wulsin 2002) and another was an uncontrolled trial of behavioural therapy (Hegel 1989). The fifth trial pooled data from 90 patients with mitral valve prolapse with 14 participants with NSCP (Cott 1992). We tried to contact the study authors to determine whether there were any data restricted to patients with NSCP. The sixth trial was an evaluation of a chest pain unit where patients received up to six hours of observation and biochemical testing followed by an exercise treadmill test (Goodacre 2004). The seventh was a quasi-experimental evaluation of brief CBT in an emergency department (Lessard 2012). We excluded a final study, (Mayou 1999), because it reported on a consecutive sample of 133 outpatients referred to cardiac outpatient clinics, and was not a RCT.

Risk of bias in included studies

We created a 'Risk of bias' table for the new trial identified in this update, as well as those added in previous revisions. In ten studies there was a low risk of random sequence generation and/or selection bias (Asbury 2007; Asbury 2008; Asbury 2011; Esler 2003; Jones 2006; Jonsbu 2011; Keefe 2011; Mayou 1997; Spinhoven 2010; van Beek 2013). In seven, there was unclear risk for both of these biases (DeGuire 1996; Klimes 1990; Potts 1999; Sanders 1997; Tyni-Lenne 2002; Lahmann 2008; Van Peski-Oosterbaan 1999). In studies where there was a medical aspect to the intervention, the patients were blinded to medication or placebo (Keefe 2011; Spinhoven 2010). However, due to the nature of the main interventions of interest (normally counselling or CBT), it was impossible to blind the people delivering the treatment as to whether the participant was in the intervention or control arm. In addition, in three studies the blinding of participants was expressly forbidden by the local ethics committee because of issues in obtaining fully informed consent (Asbury 2007; Asbury 2008; Asbury 2011). For this reason, we considered all studies to be at high risk of performance bias. As outcomes were largely assessed by self-reports, and the patients were at least in part not blinded to the intervention, we judged most studies at high risk of outcome assessment bias. One exception was

van Beek 2013, which assessed disease severity with the Clinical Global Inventory (CGI) rated by a blinded independent rater. Most studies did not discuss intention-to-treat (ITT) analysis, but most studies appeared to have analysed data based on ITT analysis. We considered three studies to be at high risk of outcome bias because of a high loss or differential loss from baseline to follow-up (Asbury 2011; Spinhoven 2010; van Beek 2013). The other trials were at low risk of bias for this domain. Two studies had unclear risk of selective reporting because they did not clearly state the outcomes of interest (Lahmann 2008; Spinhoven 2010).

We did not include funnel plots as all the outcomes had fewer than 10 studies.

Effects of interventions

The 17 included studies used very different ways of assessing outcomes. For this reason, we analysed some separately without attempting a quantitative integration of data (meta-analysis).

Primary outcome measures

Absence of chest pain

Studies reported either the absence of chest pain over a week (Klimes 1990; Van Peski-Oosterbaan 1999) or a month (Sanders 1997), or the number of chest-pain free days over a week (Mayou 1997). All showed significant improvements following intervention, apart from brief CBT where the improvement failed to reach statistical significance. For Klimes 1990, the results were of the combined RCT and crossover trial. Klimes 1990 also reported the number of chest-pain free days over a week at the end of the RCT stage before the crossover trial, but did not include SDs. Therefore we were only able to combine the studies of CBT that reported the absence of chest pain over a certain period of time (Klimes 1990; Van Peski-Oosterbaan 1999) or that included SDs when reporting the number of chest-pain free days (Mayou 1997; Potts 1999). In the case of absence of chest pain (Klimes 1990; Van Peski-Oosterbaan 1999), there was a significant reduction in reports of chest pain in the first three months following the intervention. The random-effects model gave a relative risk of 0.70 (95% CI 0.53 to 0.92; three studies, 172 participants; I^2 statistic = 59%; Analysis 1.1). This was maintained from three to 12 months afterwards, the relative risk being 0.59 (95% CI 0.45 to 0.76; two studies; 111 participants; I^2 statistic = 0%; Analysis 1.2) for both fixed or random-effects models. Exclusion of Sanders 1997, which reported the absence of chest pain over a month following brief CBT, made no significant difference to the results. Exclusion of the combined RCT and crossover trial (Klimes 1990) also made no significant difference to the results. There was also a significant increase in the number of chest pain free days up to three months following intervention; the MD was 3.00 (95% CI 0.23 to 5.77; two studies, 81 participants; I^2 statistic = 69%; Analysis 1.3). However, this was largely attributable to Potts 1999, which reported the results of a group intervention.

Chest pain frequency and severity

Where stated, studies reported the frequency of chest pain episodes over a week (Van Peski-Oosterbaan 1999), two weeks (DeGuire 1996; Potts 1999) or a month (Esler 2003; Mayou 1997). All studies reported reduced chest pain frequency, except Esler 2003. However, in Esler 2003 the baseline scores in the treatment group were much higher than in the controls. At one month follow-up, chest pain frequency had fallen by 7.9 per month in the treatment group as opposed to 4.8 in the controls, with a significant Group × Time interaction effect. Jonsbu 2011 reported frequency of symptoms of chest pain or palpitations on a scale rated as 1 ("daily"), 2 ("weekly or more often"), 3 ("rare but sometimes") and 4 ("no symptoms for the last 6 months"). Therefore we could not include this in the meta-analysis. There was a reduction in participants receiving either CBT or guided re-breathing compared with controls within the first three months of follow-up on the random-effects model; the MD was -2.26 (-4.41 to -0.12; seven studies, 294 participants; I^2 statistic = 94%; Analysis 1.4). However, this was not maintained at three to nine months follow-up (MD -0.81 (95% CI -2.35, 0.74; four studies, 164 participants; I^2 statistic = 75%; Analysis 1.5). Restricting the analyses to only those studies that reported the results of CBT made little difference to any of these results.

Jones 2006, a study of hypnotherapy, reported rates of overall improvement in chest pain; 80% of the hypnotherapy group improved compared with only 23% of controls (P = 0.008) at 17 weeks follow-up. This improvement was maintained approximately two years later with 14 of the 15 patients (93%) who received hypnotherapy now classified as responders compared with only 3/13 (23%) controls (P = 0.001).

Four studies reported chest pain severity (Asbury 2007; Jones 2006; Keefe 2011; Spinhoven 2010). Spinhoven 2010 calculated a daily chest pain index (PI) score in which duration of chest pain activity was weighed by the intensity of the chest pain. At three months follow-up, there was no significant difference between intervention and control groups in the random-effects model (MD = -4.64 (95% CI -12.18 to 2.89; four studies, 180 participants; I^2 statistic = 65%; Analysis 1.6). It is important to note that Spinhoven 2010 reported outcomes at two intervals; mid-treatment and post-treatment. The scores included in Analysis 1.6, are post-treatment outcomes.One study reported frequency of GP visits over 12 months (Asbury 2011): 29% of support patients made one or more GP visits over the duration of the study, compared with 54% of the control group (P = 0.06).

Secondary outcome measures

Quality of life

Studies reported very different measures of quality of life, making quantitative integration of data difficult. Two trials showed significant improvements in global quality of life following intervention using a standardised and validated instrument (the Sickness Impact Profile (SIP)) compared to controls, but reported medians and ranges instead of means and SDs (Potts 1999; Tyni-Lenne 2002). Another study, Jones 2006, gave the percentage of subjects reporting an improvement in global quality of life: 73% of the hypnotherapy group improved compared with only 23% of controls (P = 0.02) at 17 weeks follow-up. This improvement was maintained approximately two years later with 11 of the 15 patients (73%) who received hypnotherapy now classified as responders compared to only 3/13 (23%) controls (P = 0.02). Five studies reported results using some or all of the scales of the SF-36 including physical functioning, work problems, social functioning, and problems with role due to emotional limitations (Asbury 2008; Esler 2003; Jonsbu 2011; Sanders 1997; Van Peski-Oosterbaan 1999), but Sanders 1997 did not report SDs. In addition to reporting the overall percentage of patients reporting improvement in global Quality of Life (QoL), Jones 2006 gave MacNew scores for QoL

derived from emotional, physical and social domains (Jones 2006). As with the SF-36, an increase in scores indicates improvement. However, the trial authors did not report the subscores. Asbury 2007 reported QoL using the Ferrans and Powers Quality of Life Index. This covers four domains (health and functioning, psychological/spiritual domain, social and economic domain, and family). Again, an increase in scores indicates improvement. We were, therefore, only able to combine data from Esler 2003, Van Peski-Oosterbaan 1999 and Asbury 2007 for the following three areas: physical functioning, social functioning, and problems with role due to emotional limitations. In each case we combined these results with the global MacNew scores that incorporated emotional, physical and social domains. In the case of social functioning, we also attempted to integrate measures of social functioning and social disability by inverting the social impairment scale used by Mayou 1997. There were significant differences between intervention and control groups in some of the domains at short or long term follow-up (Analysis 1.8; Analysis 1.9; Analysis 1.12) except in the cases of physical or social functioning up to three months after the intervention (Analysis 1.7; Analysis 1.11) and role problems due to emotional limitations three to 12 months after the intervention (Analysis 1.10). Using the random-effects or fixed-effect model made no difference to any of these results.

Psychological measures

Again, a wide variety of measures were used that measured global outcome or the presence of depression or anxiety. Klimes 1990, a combined RCT and crossover trial, reported a significant reduction in psychiatric cases compared with controls as determined by a standardised psychiatric interview following intervention; the relative risk was 0.42 (95% CI 0.22 to 0.8). We quantitatively analysed seven studies of self-reported depression using standardised instruments (Asbury 2007; Asbury 2008; Jonsbu 2011; Keefe 2011; Lahmann 2008; Potts 1999; Van Peski-Oosterbaan 1999), combined with a further study that reported overall morbidity including depression (Mayou 1997). There was no significant difference between intervention and control groups up to three months after the intervention (Analysis 1.13). Notably, Asbury 2008 reported outcomes at two intervals within the three month time-frame. Using one or the other made no difference in the results of Analysis 1.13. We also quantitatively analysed seven studies of self-reported anxiety using standardised instruments (Asbury 2007; Asbury 2008; Keefe 2011; Lahmann 2008; Potts 1999; Spinhoven 2010; Van Peski-Oosterbaan 1999), combined with a further study that reported overall morbidity including anxiety (Mayou 1997). A ninth study reported medians and ranges rather than means and SDs (Jones 2006). This precluded inclusion in quantitative analyses. Asbury 2011 reported P values but no actual scores. For the eight studies that we were able to combine data from, there was a significant difference between intervention and controls up to three months after the intervention; the SMD was -0.24 (95% CI -0.47 to -0.01; eight studies, 383 participants; Analysis 1.14). Again, Asbury 2008 reported outcomes at two intervals within the three month time-frame. Using one or the other made no difference in the results of this analysis. There was no significant difference between intervention and control groups in overall psychological symptoms measured by either the Brief Symptom Inventory (BSI) or HADS from three to 12 months afterwards, with the SMD being -0.14 (95% CI -0.39 to 0.11; four studies, 246 participants; Analysis 1.15). One study, van Beek 2013, only gave the results of the anxiety and depression subscales of the HADS but using either made no difference to these results. Four studies reported three subscores of a scale specific to cardiac anxiety including fear, avoidance and attention to symptoms rather than generalised anxiety (Asbury 2007; Asbury 2008; Esler 2003; Spinhoven 2010). There were no significant differences in any of the domains at any time period (Analysis 1.16; Analysis 1.17; Analysis 1.18; Analysis 1.19; Analysis 1.20; Analysis 1.21). Using the random-effects model or fixed-effect model made no difference to any of these results. Spinhoven 2010 reported outcomes at two intervals; mid-treatment and post-treatment. The scores included in Analysis 1.14 and Analysis 1.16 are post-treatment outcomes. One study, van Beek 2013, assessed disease severity with the CGI by a blinded independent rater. An analysis of covariance (ANCOVA) in the ITT and completer sample showed that CBT was superior to treatment as usual (TAU) after 24 weeks in reducing disease severity as measured by the CGI ($P < 0.001$).

Health beliefs

Studies used very different measures of changes in health beliefs, making quantitative integration of data difficult. Of the seven studies examining CBT, two did not report change in health beliefs as an outcome (Esler 2003; Van Peski-Oosterbaan 1999). Klimes 1990 reported that prior to the intervention, all study patients believed their chest pain was due to a physical cause, while afterwards 69% attributed their pain to stress. They did not report the difference between intervention and control groups. A further study reported that Illness perceptions mediated the short and long term treatment effects of a three-session CBT programme for patients with NCCP (Jonsbu 2011). Asbury 2011, a study of support groups, reported that patients randomised to support showed a trend towards improved health beliefs total score ($P = 0.068$) and threat perception ($P = 0.062$) compared with the controls. Two studies reported non significant differences in health beliefs after the intervention (Mayou 1997; Sanders 1997). Only Potts 1999 reported that participants were significantly less likely to believe they had heart disease after the intervention (11/56, 20%) than before (25/56, 45%, $P < 0.05$).

Heterogeneity

Many of our analyses had a high level of statistical heterogeneity. We explored possible reasons for this heterogeneity in post hoc analyses, omitting each study in turn where there were more than two studies. This did not alter heterogeneity apart from the following two comparisons: Analysis 1.1: Any chest pain up to three months after intervention, and Analysis 1.5: Chest pain frequency three to 12 months after intervention. In each case, exclusion of Van Peski-Oosterbaan 1999 reduced heterogeneity to non-significant levels. The reasons for this heterogeneity are unclear and as a consequence, we have presented the results of random effects models in all the tables to take heterogeneity into account. We did this even where there was no evidence of statistical heterogeneity as we could not definitely exclude other sources of between-study variation, such as clinical heterogeneity, given the increase in studies since the first version of this review (Kisely 2005). However, when there was no evidence of statistical heterogeneity, we reported the results of both the fixed-effect and random-effects models in the text.

Sensitivity analyses

Due to the small number of included trials in each analysis, these results are limited and should be interpreted with caution. Issues concerning the proposed sensitivity analyses are as follows:

- Differences between studies that define psychiatric symptoms operationally (clinician diagnosis or validated questionnaire (and whether validated in this specific population or in other groups): all studies included in the meta-analysis used standardised instruments;
- Differences between types of psychological interventions and types of controls: there was little change to the results when analyses were restricted to CBT or hypnotherapy only. All but two studies used individual therapy;
- Differences between routes of referral for intervention (referred to psychiatrists, clinical psychologists, other mental health professionals, or other clinicians for management): most studies did not report route of referral. There was no difference to the results when studies were excluded by route of referral;
- Differences between participants with and without a family history of heart disease: there were no studies in which this information was included;
- Differences between studies that use subject reported pain or assessments by clinicians or carers: there were no studies that used assessments by clinicians or carers;
- Differences between well defined and less-well defined psychological interventions: there was little change to the results when analyses were restricted to CBT or hypnotherapy only;
- Differences between analyses involving all studies and excluding trials of lower methodological quality: two studies combined the results of the RCT and crossover designs (Klimes 1990; Potts 1999). There was no difference in the results when we excluded studies that combined results of a RCT and crossover trial;
- Differences between analyses involving all studies and those that excluded co-morbid psychiatric disorder: all but two studies included in the meta-analysis excluded co-morbid psychiatric disorder (DeGuire 1996; Jones 2006). There was no difference to the results when we excluded these studies from the analysis;
- Differences between participants with and without a history of myocardial infarction: a history of myocardial infarction was excluded from three studies, and not captured in the remainder. This made little change to the results;
- Differences between participants with and without coronary angiography: there was no difference to the results with this analysis;
- Differences between self referrals and referral from a clinician: one study, DeGuire 1996, included participants who responded to a newspaper advertisement. Exclusion of this study made no difference to the results.

DISCUSSION

Recurrent chest pain in the absence of coronary artery disease is a common problem that sometimes leads to excess use of medical care. Although many studies have examined the causes of pain in these patients, few clinical trials have evaluated treatment. The studies included in this updated Cochrane review provide an insight into the effectiveness of psychological interventions for this group of patients. We have attempted to draw modest conclusions based on available evidence, and to highlight areas requiring further study, rather than draw conclusions that may not be based on evidence of high quality.

This Cochrane review revealed limited evidence for the effective psychological treatment of NSCP. We identified only a small number of RCTs, and two combined data from RCTs and crossover trials. The identified studies were heterogeneous in terms of design, types of and implementation of interventions, outcome measurement and follow-up periods. All had small numbers of participants and questions concerning methodological quality. For example, where participants were waiting-list controls, especially in combined RCT and crossover designs, it is not possible for the subject to be unaware of which group they are in, and many studies relied on participants' self-report assessments of outcome. In addition, due to the nature of the main interventions of interest, it was impossible to blind the therapists as to whether the participant was in the intervention or control arm. Furthermore, in three studies the blinding of participants was expressly forbidden by the local ethics committee because of issues in obtaining fully informed consent (Asbury 2007; Asbury 2008; Asbury 2011). For this reason, all studies had a high risk of performance bias. Finally, three studies were thought to have a high risk of outcome bias. Although there was a low risk of bias in other domains, the results showed heterogeneity and caution is therefore required in their interpretation. Given the clinical and statistical heterogeneity, we have stressed the random effects results.

Despite these problems, it was possible to aggregate some data for short and long-term outcomes and the aggregated data support a modest to moderate benefit for psychological interventions, especially those using a cognitive-behavioural framework or hypnotherapy. These results are consistent with findings for other types of medically unexplained symptoms (Hatcher 2008; Kroenke 2000). The evidence for other interventions, such as brief nurse-led counselling, is less clear.

There are several practical difficulties concerning the delivery of psychological interventions for NSCP. One is that participation rates in many studies were low (40% to 60%). It has been suggested that this is because many studies of approaches such as CBT use the Attribution Model (Esler 2004). This requires patients to complete a cardiological work up, such as stress testing, to definitely establish that the pain is noncardiac in origin before therapy can begin, thus marking one obstacle to treatment. Furthermore the Attribution Model may be incompatible with the patient's view of their symptoms. Even if patients can be convinced, this psychological attribution may still be controversial with their family and friends, and many physicians. If patients are accustomed to thinking of chest pain as a medical illness they may not be ready to attribute their symptoms to having a psychological cause. By contrast, the Biopsychosocial Model accepts that most illness, whether physical or psychiatric, is influenced and determined by biological, psychological and social phenomena. This model assumes that better patient outcomes are achieved when therapeutic interventions are based on evaluation of the relationship between biological, psychological and social variables. This approach may be more in tune with the patient's perception of their problems and does not require physical investigations to be completed before therapy can begin (Esler 2004).

Another difficulty is access to psychotherapists, as cardiologists or gastroenterologists have neither the time nor training necessary to provide the treatment. Furthermore, there is considerable variation in presenting physical symptomatology, concerns, needs, beliefs and outcomes among patients. A 'stepped' approach to the implementation of psychological interventions has therefore been suggested (Mayou 1997; Sanders 1997). Such an approach would include a fuller explanation of the possibility and meaning of a negative outcome of angiography as preparation for the procedure and more opportunity for discussion with cardiologists prior to discharge. There should also be follow-up for review of the findings, reinforcement of the plan for symptomatic treatment and encouragement for a return to fuller activities.

One of our objectives was to compare different psychological treatments. However, due to the small number of included studies, we can only draw conclusions about CBT and possibly hypnotherapy. We also wished to assess the association between treatment effect sizes and methodological features. We were unable to do so because of the small number of included participants and methodological characteristics.

Only 17 studies met the inclusion criteria. The lack of research in this area and standardisation of outcomes may mean this is a relatively new field. Alternatively, researchers may be uncomfortable with randomisation and the use of controls. A further possibility is that participants with NSCP are reluctant to accept psychological explanations and interventions for their symptoms, making this a difficult group with which to conduct such studies. The high rates of attrition in many of the studies lends support for this final explanation.

AUTHORS' CONCLUSIONS

Implications for practice

Psychological treatments, especially CBT therapy and hypnotherapy, may be effective in the short-term for the treatment of patients with NSCP. However, the evidence is limited to small trials of questionable quality.

Evidence suggests that if untreated, patients with NSCP have levels of health service use comparable to patients with chest pain of organic causes (Kisely 1997). It may be useful to detect NCCP early, identify individual treatment needs and intervene before it becomes chronic. Patients in emergency departments or with recent onset of chest pain should be prepared for the possibility and meaning of negative findings. Those patients with chronic NSCP may benefit from specialist psychological intervention.

Implications for research

Further RCTs of psychological interventions for NSCP are needed. These should:

- Include a larger number of participants and be informed by explicit sample size and power analysis;
- Have follow-up periods of at least 12 months and preferably longer;
- Have adequate concealment of allocation, ITT analyses and at least single blind assessments of outcome;
- Use meaningful standardised outcome measurements;
- Use interventions that are explicitly described, manualised and monitored for treatment fidelity.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Asbury 2007

Study characteristics	
Methods	RCT
Participants	Fifty three female Syndrome X patients (mean ± SD; 57.4 ± 8.0 yrs).
Interventions	2 groups. Weekly group autogenic training (AT) sessions were supported by an individual home program and symptom diary Symptom diary only control.
Outcomes	The HADS Spielberger State-Trait Anxiety Inventory (STAI) Cardiac Anxiety Questionnaire (CAQ) and the Ferrans & Powers Quality of Life Index (QLI) were completed pre- and post-intervention and at 8-week follow-up.
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Low risk	Randomization was performed using identical opaque, sealed brown envelopes containing an equal number of paper strips marked 'autogenic training' or 'monitoring'.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Due to the nature of the psychological intervention, it was impossible to blind the people delivering the treatment to whether the participant was in the intervention or control arm. In addition, the use of group blinding was expressly forbidden by the local ethics committee because of issues relating to obtaining fully informed consent.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Patients knew what group they were in, and assessment by self reports
Incomplete outcome data (attrition bias) All outcomes	Low risk	23 out of 27 AT participants and 25 out of 26 symptom monitoring controls successfully completed the study with a full compliment of psychological and physiological measures.

Asbury 2007 *(Continued)*

Selective reporting (reporting bias)	Low risk	Appears that all outcomes were reported on.

Asbury 2008

Study characteristics	
Methods	RCT
Participants	Sixty-four women aged 57.3 ± 8.6 years (mean ± SD) with cardiac syndrome X.
Interventions	8-week phase III CR exercise program or symptom monitoring control.
Outcomes	HADS, Health Anxiety Questionnaire, and SF-36, energy, general health, Shuttle Walk Test, diastolic blood pressure and body mass index.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomly assigned using envelopes. Not described, but sounds plausible.
Allocation concealment (selection bias)	Low risk	Patients given identical envelopes with either rehabilitation or monitoring written on them.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Due to the nature of the psychological intervention, it was impossible to blind the people delivering the treatment to whether the participant was in the intervention or control arm. In addition, the use of group blinding was expressly forbidden by the local ethics committee because of issues relating to obtaining fully informed consent.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Patients knew what group they were in, and assessment by self reports.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysed as ITT. One additional patient dropped out of CR arm.
Selective reporting (reporting bias)	Low risk	All outcomes appear to have been reported.

Asbury 2011

Study characteristics	
Methods	RCT
Participants	Forty-nine women with cardiac syndrome X (mean + SD 61.8 + 8 years).

Asbury 2011 *(Continued)*

Interventions	12 monthly support group meetings or usual care control.
Outcomes	The Health Anxiety Questionnaire (HAQ), HADS, SF-36, York Angina Beliefs scale, ENRICHD Social Support Instrument (ESSI) and a demographic information scale, along with hospital admissions, GP or cardiologist appointments were measured at baseline, 6 months and 12 months.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned using envelopes. Not described, but sounds plausible.
Allocation concealment (selection bias)	Low risk	Patients given identical envelopes with either support group or usual care written on them.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Due to the nature of the psychological intervention, it was impossible to blind the people delivering the treatment to whether the participant was in the intervention or control arm. In addition, the use of group blinding was expressly forbidden by the local ethics committee due to issues relating to obtaining fully informed consent.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Patients knew what group they were in, and assessment by self reports.
Incomplete outcome data (attrition bias) All outcomes	High risk	Analysed as ITT. One patient from intervention group (4%) and three (12%) from control group dropped out.
Selective reporting (reporting bias)	Low risk	Appears that all outcomes reported on.

DeGuire 1996

Study characteristics

Methods	RCT Ratings of respiratory physiology and self-reports of cardiac symptoms. 66 subjects referred/responded of whom 41 (63%) completed follow-up.
Participants	Referred from physicians or responded to newspaper advertisement Inclusion criteria: Seen by physician ≤ 1 year before recruitment who had excluded organic causes for symptoms. Symptoms occurred at least once/week and include chest pain, palpitations, tachycardia and arrhythmias.
Interventions	4 groups: 3 active treatment groups with 6 individual sessions over 3 weeks. • Guided breathing retraining and physiological monitoring of diaphragmatic breathing and end-tidal CO_2; • Guided breathing retraining and physiological monitoring of diaphragmatic breathing; • Guided breathing retraining;

DeGuire 1996 *(Continued)*

	• No treatment (controls).
Outcomes	Chest pain: frequency & severity over 2/52 Respiratory rate and mean end-tidal CO2 using an Ohmeda 5200 CO_2 monitor
Notes	High attrition rate leading to potential follow-up bias.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Due to the nature of the psychological intervention, it was impossible to blind the people delivering the treatment to whether the participant was in the intervention or control arm.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	66 subjects referred/responded of whom 41 (63%) completed follow-up.
Selective reporting (reporting bias)	Low risk	All outcomes appear to be reported on.

Esler 2003

Study characteristics

Methods	RCT Self-report ratings of cardiac symptoms. 94 subjects referred of whom 59 (63%) were randomised. 36 of the 59 subjects (56%) completed all follow-up assessments.
Participants	Referred by Accident & Emergency or observation ward physician. Inclusion criteria: • Chest pain as main presenting feature; • Adequate medical work up and ready for discharge; • Low suspicion of cardiac disease; • Over 18 years old. Exclusion criteria: • Known/documented hx of MI, CABG, PTCA, prior angiography or stress testing indicating CAD; • Other significant medical illness (e.g. CCF, PE, lung Discase) or cause of chest pain (e.g. pneumonia, bronchitis, trauma).

Esler 2003 *(Continued)*

Interventions	One brief CBT intervention lasting 1 hr including psychoeducation, cognitive restructuring and breathing exercises. Controls received treatment as usual including information, instructions and medications typically given by treating physicians to patients with negative cardiac findings.
Outcomes	Chest pain episodes over 1/12. Severity of episodes over 1/52 & 1/12 (chest pain visual analogue scale) QoL: SF-36 PM: Cardiac Anxiety Questionnaire, Anxiety Sensitivity Index, BSI At 1/12 and 3/12 follow-up
Notes	High attrition rate leading to potential follow-up bias.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Low risk	Participants were randomly assigned using sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Due to the nature of the psychological intervention, it was impossible to blind the people delivering the treatment to whether the participant was in the intervention or control arm.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Participants were contacted by mail 1 and 3 months after enrolment & asked to complete self-reported measures.However they would have been aware of their allocation status
Incomplete outcome data (attrition bias) All outcomes	High risk	36 of the 59 subjects (56%) completed all follow-up.
Selective reporting (reporting bias)	Low risk	All outcomes appear to have been reported on.

Jones 2006

Study characteristics

Methods	RCT
Participants	28 patients with angina-like chest pain in whom coronary angiography was normal and oesophageal reflux was not contributory.
Interventions	12 sessions of hypnotherapy or supportive therapy plus placebo medication over a 17 week period. A further paper reported results of a 2 year follow-up.
Outcomes	The primary outcome measure was global assessment of chest pain improvement. Secondary variables were a change in scores for quality of life, pain severity, pain frequency, anxiety, and depression, as well as any alteration in the use of medication.
Notes	Of 81 eligible patients, only 28 entered the RCT.

Jones 2006 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was by a computer generated randomisation list.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Due to the nature of the psychological intervention, it was impossible to blind the people delivering the treatment to whether the participant was in the intervention or control arm. Blinding of participants was not explicitly discussed but the two treatments were designed to mimic each other except for the use of hypnotherapy.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All outcome data comparing status at baseline and the end of the treatment period were collected and subsequently analysed by an independent researcher who was not involved in any of the treatments and was kept completely blind to the treatment allocation of all patients throughout the course of the study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All 28 randomised patients completed the study.
Selective reporting (reporting bias)	Low risk	All outcomes appear to be reported on although study reported medians and ranges for secondary outcomes rather than means and SDs.

Jonsbu 2011

Study characteristics	
Methods	RCT
Participants	Patients with persistent complaints six months after a negative evaluation at a cardiological outpatient clinic were invited to participate. Of the 94 eligible patients, 40 agreed to participate and were randomly assigned to either an intervention or control group.
Interventions	Three manualised sessions with CBT, including one physical activity exposure session. The control group received usual care from their general practitioner.
Outcomes	Health-related quality of life (HRQOL) - the Body Sensations Questionnaire (BSQ), SF-36, frequency of symptoms of chest pain or palpitations, impact of cardiac symptoms on domains of family life, social life and work, and avoidance of physical activity at up to 3-month follow-up. A subsequent paper evaluated changes and impact of illness perceptions at up to 12-month follow-up.
Notes	Only a half of the eligible subjects entered the study.

Risk of bias

Bias	Authors' judgement	Support for judgement

Jonsbu 2011 *(Continued)*

Random sequence generation (selection bias)	Low risk	The participants were assigned to groups by a web module that offers block randomisation. This was performed by a clinical research unit that is separate from the intervention location.
Allocation concealment (selection bias)	Low risk	Allocation conducted at an institution unrelated to study.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Assessment by self-reporting and patient not blinded to treatment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Same number of patients dropped out in both groups.
Selective reporting (reporting bias)	Low risk	All outcomes appear to be reported on.

Keefe 2011

Study characteristics	
Methods	A randomised clinical trial of the separate and combined effects of coping skills training (CST) and antidepressant medication (sertraline) in participants with NCCP.
Participants	Eligibility criteria for study entry were: 1. Presented for medical care with complaints of chest pain in the previous six months; 2. Received a negative stress test within the past 2 years, normal coronary angiogram within the past 2 years, or had a survival probability P 98% at 2 years (calculated from a prognostogram developed by statistical modelling from the Duke Cardiovascular Database); 3. A low likelihood of significant coronary artery disease (< 25%) on the National Cholesterol Education Program's (NCEP) modification of the Framingham Risk Calculator (FRC); 4. Able to swallow oral medication; 5. Age 18 to 85 years.38 (33%) men and 77 (67%) women.
Interventions	Random assignment to one of four treatments: 1. CST plus sertraline(CST + sertraline); 2. CST plus placebo (CST + placebo); 3. Sertraline alone; or 4. Placebo alone.
Outcomes	Chest pain intensity and unpleasantness from pain diaries, State-Trait Anxiety Inventory (STAI), the 13-item Pain Catastrophizing Scale (PCS), the BDI, the physical disability scale of the Sickness Impact Profile (SIP), two items from Stone and Neale's Daily Coping Inventory, two items from the Coping Strategies Questionnaire were used to assess daily perceived pain control over pain.
Notes	

Keefe 2011 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A statistician who was not involved with the rest of the study created a randomisation table to randomly assign participants.
Allocation concealment (selection bias)	Low risk	Allocation concealment is described although treatment components were blinded only for the medication and not for the CST component.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Patients were blinded to the medication and not to the CST component (which is training). Medication and placebo were given in identical capsules that both investigators and participants were blind to.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Patient's outcomes were self assessed through pain scores, and pain diaries, but internal consistency was high for all tests.
Incomplete outcome data (attrition bias) All outcomes	Low risk	While there were many patients who did not complete therapy, there was no difference in attrition among the four treatment groups.
Selective reporting (reporting bias)	Low risk	All stated outcomes reported on.

Klimes 1990

Study characteristics	
Methods	RCCT Self-report and blind ratings. 35 out of 56 assessed were recruited (63%) of whom 29(83%) completed follow-up. Undetermined if treatment manual was used.
Participants	Referred by cardiologist or GP Inclusion criteria: • Chest pain as main presenting feature ≥ one episode weekly; • Normal CVS (cardiology or equivalent opinion and investigation) ≥ 3/12 duration. Exclusion criteria: • Depression on treatment; • Multiple somatic symptoms; • Investigations not completed.
Interventions	Individual CBT: Maximum 11 sessions over 3/12 cognitive restructuring, problem solving, relaxation, breathing exercises. Controls: Behavioural explanation of symptoms and offered CBT after 3/12 follow-up.
Outcomes	Chest pain free days and pain episodes over 1/52 QoL: 5-point activity avoidance scale, 8-point distress scale 8-point disruption of everyday life scale PM: PSE, STAI-T, BDI, SRT

Klimes 1990 *(Continued)*

	Autonomic symptoms
Notes	High drop-out rate at recruitment stage.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	No description of randomisation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Due to the nature of the psychological intervention, it was impossible to blind the people delivering the treatment to whether the participant was in the intervention or control arm.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All subjects were independently assessed by a research assistant.
Incomplete outcome data (attrition bias) All outcomes	Low risk	29 (83%) completed follow-up
Selective reporting (reporting bias)	Low risk	All outcomes appear to be reported on.

Lahmann 2008

Study characteristics

Methods	RCT
Participants	Patients included in the study were over the age of 18 years who presented with NSCP. 22 patients (10 men, 12 women) were eligible to take part in the study.
Interventions	Functional Relaxation and Patient Education. The study period in the functional relaxation (FR) group began with a 60-minute psychosomatic-education session, in which the development of NSCP was presented, as well as basic information relating to structure and function of the cardiovascular and autonomic nervous system. Throughout the course of the study, a total of 10 group-therapy sessions, 90 minutes each, were held during the 6-week treatment period. Controls assigned to "enhanced medical care" were informed of their diagnosis and were encouraged to pass this information on without restrictions to their general-practitioner in order to initiate primary-care or specialty treatment.
Outcomes	The Symptom Checklist of Derogatis (SCL–90) and the Giessen Inventory of Complaints (GBB), which are both self-administered tests.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Lahmann 2008 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	"randomization was carried out confidentially". Likely ok, but not described.
Allocation concealment (selection bias)	Unclear risk	"allocation concealment implemented by the hospital's administration department". Likely ok, but not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No discussion of blinding. However, due to the nature of the psychological intervention, it was impossible to blind the people delivering the treatment to whether the participant was in the intervention or control arm.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Patients not blinded, and outcome assessment by self reports.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients (22) appear to have completed the trial.
Selective reporting (reporting bias)	Unclear risk	Study did not clearly outline outcomes of interest.

Mayou 1997

Study characteristics	
Methods	RCT Self-report measures and observer ratings (?blinded) Of 133 referrals, 90 (67%) reached baseline assessment, of whom 56 met inclusion criteria. Of these, 37 (66%) entered the study of whom 19 (64%) completed follow-up. Undetermined if treatment manual was used. CBT group rated chest pain as more severe than control group.
Participants	Recruited from general hospital cardiology outpatient clinic Inclusion criteria: • Persisting NCCP ≥ one episode weekly for 1/12. Exclusion criteria: • Subsequent cardiac diagnosis; • Current major depression; • Living outside country; • Unable to speak English.
Interventions	Individual CBT: Maximum 12 sessions including cognitive restructuring, problem solving, relaxation, breathing exercises. Controls: Assessment only.
Outcomes	Chest pain: frequency, severity, distress over 1/12, and number of pain-free days over 1/52. QoL: 4-point scales of avoidance, limitation and impairment (leisure, work, family, overall). PM: BSI. Health beliefs: Whitely score.
Notes	High attrition rate leading to potential follow-up bias.

Mayou 1997 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly allocated to cognitive behavioural treatment (CBT) or assessment only control (AOC) using a system of sealed envelopes prepared by random number generation
Allocation concealment (selection bias)	Low risk	Patients were randomly allocated to cognitive behavioural treatment (CBT) or assessment only control (AOC) using a system of sealed envelopes prepared by random number generation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Due to the nature of the psychological intervention, it was impossible to blind the people delivering the treatment to whether the participant was in the intervention or control arm.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	Of 56 who met inclusion criteria, 37 (66%) entered the study of whom 19 (64%) completed follow-up.
Selective reporting (reporting bias)	Low risk	All outcomes appear to be reported on.

Potts 1999

Study characteristics	
Methods	RCCT No information on number of subjects asked to participate. 60 subjects randomised of whom 56 (93%) completed follow-up.
Participants	Patients undergoing coronary angiography.
Interventions	Group CBT: 6 sessions including education, cognitive restructuring, relaxation, breathing exercises, graded exposure and light physical exercise. Waiting-list controls.
Outcomes	Chest pain free days and pain episodes over 1/52 HV score GTN dose/week Exercise duration (minutes) QoL: NHP, SIP PM: HADS
Notes	Impossible to assess attrition rate as no information on number of subjects asked to participate.

Risk of bias

Bias	Authors' judgement	Support for judgement

Potts 1999 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Due to the nature of the psychological intervention, it was impossible to blind the people delivering the treatment to whether the participant was in the intervention or control arm.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Impossible to assess attrition rate as no information on number of subjects asked to participate.
Selective reporting (reporting bias)	Low risk	All outcomes appear to be reported on.

Sanders 1997

Study characteristics	
Methods	RCT Self-report measures & observer ratings (blinded). Of 142 referrals who met inclusion criteria, 57 (40%) entered the study of whom 50 (88%) completed follow-up, although only 41 (72%) completed psychological assessments.
Participants	Patients undergoing coronary angiography.
Interventions	Brief CBT intervention by nurse consisting of a single hour-long session including education, relaxation, breathing exercises, and graded exposure supplemented by a booklet and cassette tape of breathing and relaxation exercises.
Outcomes	Chest pain: frequency, severity, distress, and number of pain-free days over 1/12. Associated sx i.e. palpitations and breathlessness. QoL: SF-36. PM: SCL, STAI-T, BDI. Health beliefs: Whitely score.
Notes	High attrition rate leading to potential follow-up bias.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

Sanders 1997 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Due to the nature of the psychological intervention, it was impossible to blind the people delivering the treatment to whether the participant was in the intervention or control arm.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Outcomes were assessed blind to treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	High risk	Of 142 referrals who met inclusion criteria, 57 (40%) entered the study of whom 50 (88%) completed follow-up, although only 41 (72%) completed psychological assessments
Selective reporting (reporting bias)	Low risk	All outcomes appear to be reported on.

Spinhoven 2010

Study characteristics	
Methods	RCT of CBT, paroxetine and placebo in the treatment of NCCP.
Participants	Eligible participants were cardiology outpatients of two academic and two nonacademic hospitals who had been discharged with a diagnosis of NCCP. Inclusion criteria were NCCP as main presenting complaint; NCCP occurring at least once a week, or at least once per month if accompanied by severe psychological distress; age between 18 and 75 years. An initial charts review identified 3270 patients diagnosed with NCCP. Between January 1997 and January 2002. Of these, 2367 patients (72.4%) returned a questionnaire about current symptoms, of whom 583 (24.6%) had no interest in the study, and 1310 (55.3%) did not fulfil the inclusion criteria regarding chest pain frequency. The remaining 474 potential participants received detailed information about the study and were invited for a screening and information session. After the screening session, 95 patients (20.0%) agreed to be randomised. After the intake, 26 patients had to be excluded, leaving 69 patients (37 males) who started the trial.
Interventions	CBT, paroxetine and placebo.
Outcomes	Frequency, duration, and intensity of chest pain, The HADS, heart-focused anxiety by the Cardiac Anxiety Questionnaire (CAQ), the M.I.N.I.-Plus.
Notes	High attrition rate.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Patients were randomised using random permuted blocks with a length of six.
Allocation concealment (selection bias)	Low risk	Randomisation carried out by the hospital pharmacist and the details were unknown to any of the researchers.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Medical treatment blinded, but CBT not.

Spinhoven 2010 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessment by self report.
Incomplete outcome data (attrition bias) All outcomes	High risk	Analyses conducted on ITT, but differences in drop outs between arms. No patients dropped out of CBT, but four (17%) dropped out of placebo group and seven (30%) dropped out of paroxetine group, mostly because of adverse effects.
Selective reporting (reporting bias)	Unclear risk	Did not clearly state outcomes of interest.

Tyni-Lenne 2002

Study characteristics	
Methods	Single-blind RCT with three groups: physical training, relaxation and control groups. No information on number of subjects asked to participate. 24 subjects entered study of whom 21 (88%) were followed-up. Measurement of exercise capacity, peak heart rate & distance walked during 6 minutes. Self-report measures of exertion & Quality of Life.
Participants	Inclusion criteria: females only, limited by chest pain (Canadian Cardiovascular Society functional class II). Exclusion criteria: History of musculoskeletal impairment, hypertension, DM or other systemic illness.
Interventions	Physical training: endurance training on a cycle ergometer three times/week for 8/52. Relaxation training twice/week for 8/52. Controls: normal daily activities.
Outcomes	Peak oxygen uptake, peak work rate and distance walked during 6 minutes. Rating of perceived exertion. QoL: SOC, SCI-93, SIP.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single-blinded only.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement

Tyni-Lenne 2002 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information on number of subjects asked to participate. 24 subjects entered study of whom 21 (88%) were followed-up.
Selective reporting (reporting bias)	Low risk	All outcomes appear to be reported on.

van Beek 2013

Study characteristics	
Methods	RCT Of 137 referrals who met inclusion criteria, 113 (82%) subjects entered study of whom 75 (54%) were followed-up up to six months.
Participants	Subjects aged 18 years or older who presented with chest pain and were convinced they were experiencing a heart attack. Eligible patients were subjects in whom full medical examination revealed no cardiopulmonary, gastrointestinal or endocrinal explanation for their complaints (and thus were diagnosed with "noncardiac chest pain") and who scored eight or higher on either or both subscales of the HADS.
Interventions	CBT consisted of six individual sessions with a duration of 45 min. TAU consisted of reassurance by a cardiologist that patients' complaints were not caused by cardiac disease. TAU was tailored to the individual needs of the patients but did not include psychotherapy, including CBT, or antidepressants.
Outcomes	The main outcome was disease severity assessed with the CGI by a blinded independent rater. Secondary outcomes were anxiety as measured by the HADS-anxiety and state trait anxiety inventory (STAI)-trait), as well as depressive symptoms on the Hamilton depression rating scale.
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Simple randomization, with an equal allocation ratio, with reference to a table of random numbers (to which all researchers and physicians were blinded).
Allocation concealment (selection bias)	Low risk	See above.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Due to the nature of the psychological intervention, it was impossible to blind the people delivering the treatment to whether the participant was in the intervention or control arm.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Patients were assessed by an independent rater, who was blinded to the condition to which they were allocated.
Incomplete outcome data (attrition bias)	High risk	Only 75 (54%) were followed-up at six months but bias was reduced through the use of ITT analyses.

van Beek 2013 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	All outcomes appear to be reported on.

Van Peski-Oosterbaan 1999

Study characteristics	
Methods	RCT Self-report measures some confirmed with treating doctor. Of 143 referrals who met inclusion criteria, 65 (44%) subjects entered study of whom 63 (43%) were followed-up at 12/12.
Participants	Inclusion criteria: 18 to 75 yrs old. Normal CVS according to a cardiologist. Exclusion criteria: Proven CAD of MI on coronary angiography, exercise test, laboratory results, ECG of CXR, a history of typical angina, insufficient fluency in Dutch, current psychiatric treatment for NCCP, current diagnosis of major depression, bipolar disorder, psychoactive substance use (except nicotine) in previous 3/12.
Interventions	Individual CBT: maximum 12 sessions including cognitive restructuring, problem solving, relaxation, breathing exercises. Controls: assessment only and usual care.
Outcomes	Chest pain free days and pain episodes including severity over 1/52 PM: HADS QoL: SF-36 Health service use
Notes	High attrition rate leading to potential follow-up bias.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Due to the nature of the psychological intervention, it was impossible to blind the people delivering the treatment to whether the participant was in the intervention or control arm.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	Of 143 referrals who met inclusion criteria, 65 (44%) subjects entered study of whom 63 (43%) were followed-up at 12/12.

Van Peski-Oosterbaan 1999 *(Continued)*

Selective reporting (reporting bias)	Low risk	All outcomes appear to be reported on.

Abbreviations: RCCT = randomised controlled cross-over trial; RCT = randomised controlled trial; QoL = quality of life; PM = psychological morbidity; PSE = Present State Examination; STAI-T = State-trait Anxiety Inventory; BDI = Beck Depression Inventory; SRT = symptom rating test; AS = autonomic symptoms; BSI = brief symptom inventory; CGI = Clinical Global Inventory.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Achem 2008	Review article - no primary data.
Adler 2001	Review article - no primary data. Psychological interventions not covered.
Asbury 2005a	Review article - no primary data.
Asbury 2005b	Review article - no primary data.
Barker 2013	Review article on hyperventillation in children - no primary data.
Carter 1992a	Not an intervention study.
Carter 1992b	Not an intervention study.
Chambers 1998	Review article - no primary data. Suggests that cognitive-behavioural therapy is effective for non-cardiac chest pain.
Chen 2010	An RCT of treatments for gastroesophageal reflux disease (GERD).
Coss-Adame 2014	Review article - no primary data. Systematic review of treatments for esophageal (noncardiac) chest pain.
Cott 1992	An RCT that pooled data from 90 patients with mitral valve prolapse with only 14 subjects with NSCP.
Cox 1998	RCT of antidepressant medication.
Elkins 2012	Review article on cognitive hypnotherapy for pain management - no primary data.
Esler 2004	Review article - no primary data. Suggests that biopsychosocial rather than attribution models may be more effective for noncardiac chest pain.
Eslick 2004	Not an intervention study.
Eslick 2005	Review article - no primary data.
Faybush 2004	Not an intervention study.
Fleet 1998	Not an intervention study.
Goodacre 2001	Not an intervention study of a psychological treatment.
Goodacre 2004	Not an intervention study of a psychological treatment.

Study	Reason for exclusion
Handa 1999	Non-RCT of antidepressant medication.
Hegel 1989	Uncontrolled trial of behavioural therapy.
Hershcovici 2012	Review article - no primary data. Suggests that patients with GERD-related noncardiac chest pain should be treated with at least double dose PPI.
Jackson 2006	Review article - no primary data. Suggests that cognitive-behavioural therapy is effective for non-cardiac chest pain.
Jeejeebhoy 2000	Review article - no primary data. Suggests that cognitive-behavioural therapy is effective for non-cardiac chest pain.
Kaski 2001	Review article - no primary data. Suggests that cognitive-behavioural therapy is effective for non-cardiac chest pain.
Katz 2000	Review article - no primary data. Suggests that cognitive-behavioural therapy is effective for non-cardiac chest pain.
Kroenke 2000	Review article - no primary data.
Lahmann 2010	No primary data.
Lessard 2012	Quasi-experimental study.
Looper 2002	Review article - no primary data. Suggests that cognitive-behavioural therapy is effective for non-cardiac chest pain.
Masanga 2011	A study of a pulmonary rehabilitation programme.
Mayou 1989	Conference abstract - insufficient information on intervention and control groups.
Mayou 1994	Not an intervention study.
Mayou 1999	A consecutive sample of 133 outpatients referred to cardiac outpatient clinics, not an RCT
Nanke 2004	Review article - no primary data. Suggests that biofeedback, relaxation and cognitive-behavioural therapy are effective for somatoform symptoms including noncardiac chest pain.
Nezu 2001	Review article - no primary data. Suggests that cognitive-behavioural therapy is effective for non-cardiac chest pain.
Olden 2004	Not an intervention study.
Olden 2006	Review article - no primary data.
Otte 2011	Review article - no primary data. Suggests that CBT is both efficacious and effective in the treatment of anxiety disorders.
Palsson 2006	Commentary - no primary data.
Petrie 2007	Not a study of non-specific chest pain.
Ringel 1999	Review article - no primary data. Suggests that cognitive-behavioural therapy is effective for non-cardiac chest pain.

Study	Reason for exclusion
Romeo 1993	Not an intervention study.
Ryan 2004	Of the 70 subjects, only 11 had functional cardiac pain and data for these were not presented separately.
Schey 2007	Review article - no primary data. Suggests that hypnotherapy is effective for noncardiac chest pain.
Schmulson 2004	Review article - no primary data. Suggests that cognitive-behavioural therapy is effective for non-cardiac chest pain.
Serlie 1995	Review article - no primary data. Suggests that cognitive-behavioural therapy is effective for non-cardiac chest pain.
Sert 2013	Not an RCT but a descriptive study of the clinical characteristics and causes of chest pain in children referred to a paediatric cardiology unit.
Van Peski-Oosterbaan 1997	Uncontrolled trial of cognitive-behavioural therapy.
Wang 2012	Review article - no primary data. Suggests that antidepressant medications are associated with improvements in pain and psychological symptoms in non-cardiac chest pain.
Wertli 2013	A systematic review and meta-analysis of diagnostic indicators of non-cardiovascular chest pain.
Wu 2002	Review article - no primary data. Suggests that cognitive-behavioural therapy is effective for non-cardiac chest pain.
Wulsin 2002	Pharmacotherapy only.
Zachariae 2001	Not an intervention study.
Zaubler 1998	Review article - no primary data. Suggests that cognitive-behavioural therapy is effective for non-cardiac chest pain.

DATA AND ANALYSES

Comparison 1. Psychological intervention versus no such therapy

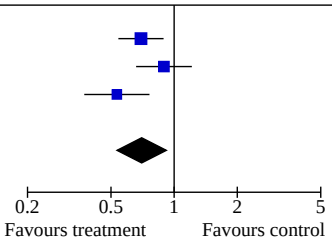
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Any chest pain up to 3 months after intervention	3	172	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.53, 0.92]
1.2 Any chest pain from 3 to 12 months after intervention	2	111	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.45, 0.76]
1.3 Chest pain free days up to 3 months after intervention	2	81	Mean Difference (IV, Random, 95% CI)	3.00 [0.23, 5.77]
1.4 Chest pain frequency up to 3 months after intervention	7	294	Mean Difference (IV, Random, 95% CI)	-2.26 [-4.41, -0.12]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.5 Chest pain frequency 3 to 12 months after intervention	4	164	Mean Difference (IV, Random, 95% CI)	-0.81 [-2.35, 0.74]
1.6 Chest pain severity up to 3 months	4	180	Mean Difference (IV, Random, 95% CI)	-4.64 [-12.18, 2.89]
1.7 Quality of life - physical functioning up to 3 months after intervention	5	221	Std. Mean Difference (IV, Random, 95% CI)	0.24 [-0.03, 0.50]
1.8 Quality of life - physical functioning 3 to 12 months after intervention	4	192	Std. Mean Difference (IV, Random, 95% CI)	0.29 [0.01, 0.58]
1.9 Quality of life - role problems due to emotional limitations up to 3 months after intervention	6	284	Std. Mean Difference (IV, Random, 95% CI)	0.35 [0.11, 0.58]
1.10 Quality of life - role problems due to emotional limitations 3 to 12 months after intervention	4	192	Std. Mean Difference (IV, Random, 95% CI)	0.18 [-0.22, 0.57]
1.11 Quality of life - social functioning up to 3 months after intervention	7	310	Std. Mean Difference (IV, Random, 95% CI)	0.19 [-0.04, 0.41]
1.12 Quality of life - social functioning 3 to 12 months after intervention	4	173	Std. Mean Difference (IV, Random, 95% CI)	0.43 [0.12, 0.73]
1.13 Psychological symptoms up to 3 months after the intervention (depression & overall)	8	377	Std. Mean Difference (IV, Random, 95% CI)	-0.18 [-0.46, 0.10]
1.14 Psychological symptoms up to 3 months after the intervention (anxiety and overall)	8	383	Std. Mean Difference (IV, Random, 95% CI)	-0.24 [-0.47, -0.01]
1.15 Psychological symptoms 3 to 12 months after the intervention	4	246	Std. Mean Difference (IV, Random, 95% CI)	-0.14 [-0.39, 0.11]
1.16 Cardiac anxiety fear up to 3 months	4	199	Std. Mean Difference (IV, Random, 95% CI)	-0.08 [-0.36, 0.20]
1.17 Cardiac anxiety fear 3 to 12 months	2	89	Mean Difference (IV, Random, 95% CI)	0.05 [-0.24, 0.33]
1.18 Cardiac anxiety avoidance up to 3 months	3	153	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.32, 0.25]
1.19 Cardiac anxiety avoidance 3 to 12 months	2	89	Mean Difference (IV, Random, 95% CI)	0.08 [-0.47, 0.64]
1.20 Cardiac anxiety attention up to 3 months	3	153	Mean Difference (IV, Random, 95% CI)	0.17 [-0.04, 0.37]
1.21 Cardiac anxiety attention 3 to 12 months	2	89	Mean Difference (IV, Random, 95% CI)	0.03 [-0.21, 0.27]

Analysis 1.1. Comparison 1: Psychological intervention versus no such therapy, Outcome 1: Any chest pain up to 3 months after intervention

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Klimes 1990	20	29	29	29	38.5%	0.69 [0.54 , 0.89]
Sanders 1997	21	29	17	21	33.0%	0.89 [0.66 , 1.21]
Van Peski-Oosterbaan 1999	16	32	30	32	28.5%	0.53 [0.37 , 0.76]
Total (95% CI)		**90**		**82**	**100.0%**	**0.70 [0.53 , 0.92]**
Total events:	57		76			

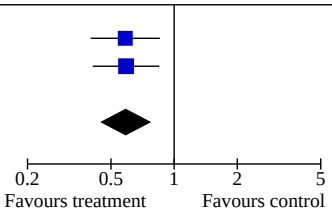
Heterogeneity: Tau² = 0.03; Chi² = 4.84, df = 2 (P = 0.09); I² = 59%
Test for overall effect: Z = 2.58 (P = 0.010)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Psychological intervention versus no such therapy, Outcome 2: Any chest pain from 3 to 12 months after intervention

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Klimes 1990	11	19	29	29	48.1%	0.58 [0.40 , 0.85]
Van Peski-Oosterbaan 1999	16	31	28	32	51.9%	0.59 [0.41 , 0.85]
Total (95% CI)		**50**		**61**	**100.0%**	**0.59 [0.45 , 0.76]**
Total events:	27		57			

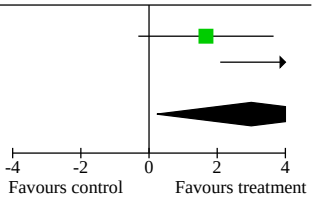
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.97); I² = 0%
Test for overall effect: Z = 3.96 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: Psychological intervention versus no such therapy, Outcome 3: Chest pain free days up to 3 months after intervention

Study or Subgroup	Treatment Mean	Treatment SD	Treatment Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Mayou 1997	3.85	2.62	15	2.18	2.38	10	53.1%	1.67 [-0.31 , 3.65]
Potts 1999	9.1	5.1	32	4.6	4.1	24	46.9%	4.50 [2.09 , 6.91]
Total (95% CI)			**47**			**34**	**100.0%**	**3.00 [0.23 , 5.77]**

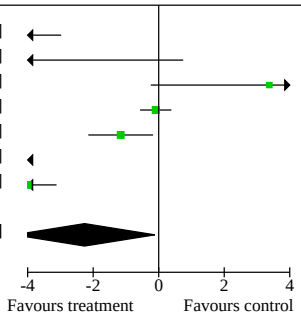
Heterogeneity: Tau² = 2.74; Chi² = 3.16, df = 1 (P = 0.08); I² = 68%
Test for overall effect: Z = 2.12 (P = 0.03)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: Psychological intervention versus no such therapy, Outcome 4: Chest pain frequency up to 3 months after intervention

Study or Subgroup	Treatment Mean	Treatment SD	Treatment Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Asbury 2007	1.66	2.19	27	6.11	3.17	26	19.6%	-4.45 [-5.92 , -2.98]
DeGuire 1996	9	12	10	26	26	10	1.4%	-17.00 [-34.75 , 0.75]
Esler 2003	4.59	7.43	17	1.21	1.78	19	13.4%	3.38 [-0.24 , 7.00]
Jonsbu 2011	2.5	0.83	21	2.59	0.71	19	21.4%	-0.09 [-0.57 , 0.39]
Mayou 1997	2.55	1.53	15	3.71	0.99	10	20.6%	-1.16 [-2.15 , -0.17]
Potts 1999	7	9.1	32	25.3	28.7	24	2.8%	-18.30 [-30.21 , -6.39]
Van Peski-Oosterbaan 1999	1.16	1.8	32	5.16	1.8	32	20.8%	-4.00 [-4.88 , -3.12]
Total (95% CI)			**154**			**140**	**100.0%**	**-2.26 [-4.41 , -0.12]**

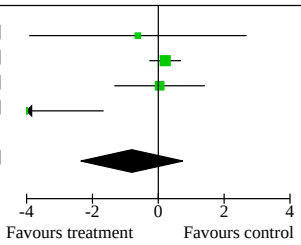
Heterogeneity: Tau² = 5.56; Chi² = 95.32, df = 6 (P < 0.00001); I² = 94%
Test for overall effect: Z = 2.07 (P = 0.04)
Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1: Psychological intervention versus no such therapy, Outcome 5: Chest pain frequency 3 to 12 months after intervention

Study or Subgroup	Treatment Mean	Treatment SD	Treatment Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Esler 2003	2.06	4.6	17	2.68	5.5	19	14.0%	-0.62 [-3.92 , 2.68]
Jonsbu 2011	2.65	0.67	21	2.44	0.86	19	36.9%	0.21 [-0.27 , 0.69]
Mayou 1997	2.75	1.59	15	2.71	1.8	10	29.4%	0.04 [-1.34 , 1.42]
Van Peski-Oosterbaan 1999	1.46	2.5	31	5.54	6.5	32	19.8%	-4.08 [-6.50 , -1.66]
Total (95% CI)			**84**			**80**	**100.0%**	**-0.81 [-2.35 , 0.74]**

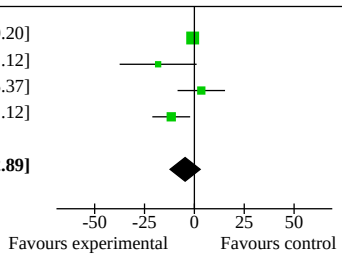
Heterogeneity: Tau² = 1.64; Chi² = 11.79, df = 3 (P = 0.008); I² = 75%
Test for overall effect: Z = 1.02 (P = 0.31)
Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1: Psychological intervention versus no such therapy, Outcome 6: Chest pain severity up to 3 months

Study or Subgroup	Treatment Mean	Treatment SD	Treatment Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Asbury 2007	1.23	1.36	27	2.08	1.03	26	42.6%	-0.85 [-1.50 , -0.20]
Jones 2006	29.13	25.31	15	47.31	26.55	13	11.2%	-18.18 [-37.48 , 1.12]
Keefe 2011	15.13	23.61	29	11.66	20.58	24	20.7%	3.47 [-8.43 , 15.37]
Spinhoven 2010	11.9	14	23	23.5	18.5	23	25.5%	-11.60 [-21.08 , -2.12]
Total (95% CI)			**94**			**86**	**100.0%**	**-4.64 [-12.18 , 2.89]**

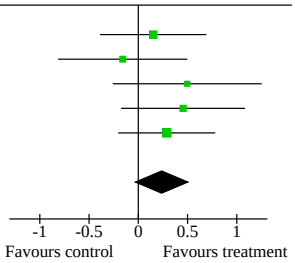
Heterogeneity: Tau² = 34.60; Chi² = 8.51, df = 3 (P = 0.04); I² = 65%
Test for overall effect: Z = 1.21 (P = 0.23)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: Psychological intervention versus no such therapy, Outcome 7: Quality of life - physical functioning up to 3 months after intervention

Study or Subgroup	Treatment Mean	Treatment SD	Treatment Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Asbury 2007	19.41	5.19	27	18.44	7.31	26	24.3%	0.15 [-0.39 , 0.69]
Esler 2003	84.4	20.1	17	87.6	19.4	19	16.4%	-0.16 [-0.81 , 0.50]
Jones 2006	5.16	0.81	15	4.68	1.07	13	12.4%	0.50 [-0.26 , 1.25]
Jonsbu 2011	89.8	10.8	21	83.5	16.1	19	17.8%	0.46 [-0.17 , 1.08]
Van Peski-Oosterbaan 1999	82	24	32	75	24	32	29.1%	0.29 [-0.20 , 0.78]
Total (95% CI)			**112**			**109**	**100.0%**	**0.24 [-0.03 , 0.50]**

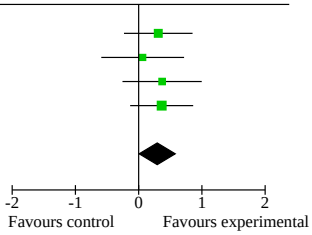
Heterogeneity: Tau² = 0.00; Chi² = 2.45, df = 4 (P = 0.65); I² = 0%
Test for overall effect: Z = 1.75 (P = 0.08)
Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1: Psychological intervention versus no such therapy, Outcome 8: Quality of life - physical functioning 3 to 12 months after intervention

Study or Subgroup	Treatment Mean	Treatment SD	Treatment Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Asbury 2007	20.09	5.47	27	18.08	7.22	26	27.6%	0.31 [-0.23 , 0.85]
Esler 2003	87.4	18.8	17	86.1	21	19	19.0%	0.06 [-0.59 , 0.72]
Jonsbu 2011	88.4	13.8	21	81.9	20.3	19	20.7%	0.37 [-0.26 , 1.00]
Van Peski-Oosterbaan 1999	87	19	31	80	19	32	32.7%	0.36 [-0.13 , 0.86]
Total (95% CI)			**96**			**96**	**100.0%**	**0.29 [0.01 , 0.58]**

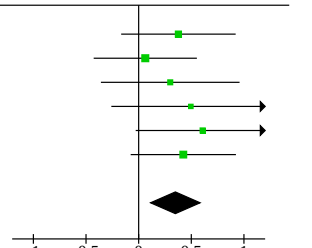
Heterogeneity: Tau² = 0.00; Chi² = 0.61, df = 3 (P = 0.89); I² = 0%
Test for overall effect: Z = 2.02 (P = 0.04)
Test for subgroup differences: Not applicable



Analysis 1.9. Comparison 1: Psychological intervention versus no such therapy, Outcome 9: Quality of life - role problems due to emotional limitations up to 3 months after intervention

Study or Subgroup	Treatment Mean	Treatment SD	Treatment Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Asbury 2007	22.01	4.81	27	19.92	6.05	26	18.7%	0.38 [-0.17 , 0.92]
Asbury 2008	72.6	38.5	32	70.1	40.1	32	23.0%	0.06 [-0.43 , 0.55]
Esler 2003	88.3	26	17	79	33.7	19	12.8%	0.30 [-0.36 , 0.96]
Jones 2006	5.16	0.81	15	4.68	1.07	13	9.7%	0.50 [-0.26 , 1.25]
Jonsbu 2011	87.3	26.8	21	66.7	39.1	19	13.7%	0.61 [-0.03 , 1.24]
Van Peski-Oosterbaan 1999	80	36	32	63	43	31	22.1%	0.42 [-0.08 , 0.92]
Total (95% CI)			**144**			**140**	**100.0%**	**0.35 [0.11 , 0.58]**

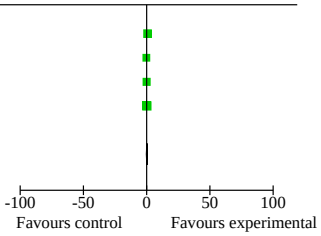
Heterogeneity: Tau² = 0.00; Chi² = 2.21, df = 5 (P = 0.82); I² = 0%
Test for overall effect: Z = 2.90 (P = 0.004)
Test for subgroup differences: Not applicable



Analysis 1.10. Comparison 1: Psychological intervention versus no such therapy, Outcome 10: Quality of life - role problems due to emotional limitations 3 to 12 months after intervention

Study or Subgroup	Treatment Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Asbury 2007	22.54	5.76	27	18.04	6.64	26	26.0%	0.71 [0.16 , 1.27]
Esler 2003	84.3	35.6	17	91.3	18.7	19	21.6%	-0.24 [-0.90 , 0.41]
Jonsbu 2011	76.7	36	21	77.8	32.3	19	23.1%	-0.03 [-0.65 , 0.59]
Van Peski-Oosterbaan 1999	79	38	31	72	42	32	29.2%	0.17 [-0.32 , 0.67]
Total (95% CI)			**96**			**96**	**100.0%**	**0.18 [-0.22 , 0.57]**

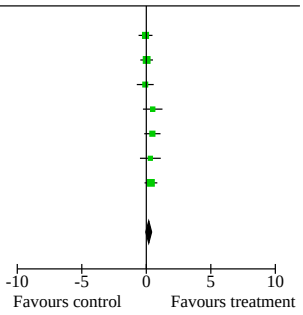
Heterogeneity: Tau² = 0.07; Chi² = 5.58, df = 3 (P = 0.13); I² = 46%
Test for overall effect: Z = 0.88 (P = 0.38)
Test for subgroup differences: Not applicable



Analysis 1.11. Comparison 1: Psychological intervention versus no such therapy, Outcome 11: Quality of life - social functioning up to 3 months after intervention

Study or Subgroup	Favours control Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Asbury 2007	22.8	4.31	27	23.08	4.8	26	17.4%	-0.06 [-0.60 , 0.48]
Asbury 2008	70.5	26.8	32	69.8	23.7	32	21.0%	0.03 [-0.46 , 0.52]
Esler 2003	80.9	28.2	17	83.1	24.2	19	11.8%	-0.08 [-0.74 , 0.57]
Jones 2006	5.16	0.81	15	4.68	1.07	13	8.8%	0.50 [-0.26 , 1.25]
Jonsbu 2011	86.3	19.7	21	75	27.2	19	12.7%	0.47 [-0.16 , 1.10]
Mayou 1997	1.45	0.95	15	1.12	1.11	10	7.8%	0.31 [-0.49 , 1.12]
Van Peski-Oosterbaan 1999	85.6	16	32	78.6	22	32	20.6%	0.36 [-0.13 , 0.85]
Total (95% CI)			**159**			**151**	**100.0%**	**0.19 [-0.04 , 0.41]**

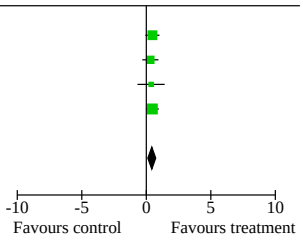
Heterogeneity: Tau² = 0.00; Chi² = 3.85, df = 6 (P = 0.70); I² = 0%
Test for overall effect: Z = 1.64 (P = 0.10)
Test for subgroup differences: Not applicable



Analysis 1.12. Comparison 1: Psychological intervention versus no such therapy, Outcome 12: Quality of life - social functioning 3 to 12 months after intervention

Study or Subgroup	Treatment Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Asbury 2007	24.18	4.53	27	21.81	5.32	26	31.0%	0.47 [-0.07 , 1.02]
Jonsbu 2011	81.3	25.8	21	72.2	30.8	19	23.7%	0.32 [-0.31 , 0.94]
Mayou 1997	1.55	1.1	12	1.12	1.11	5	8.4%	0.37 [-0.68 , 1.42]
Van Peski-Oosterbaan 1999	87.6	19	31	77.6	23	32	36.9%	0.47 [-0.03 , 0.97]
Total (95% CI)			**91**			**82**	**100.0%**	**0.43 [0.12 , 0.73]**

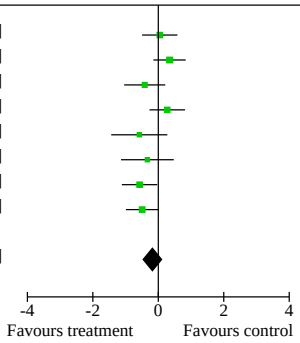
Heterogeneity: Tau² = 0.00; Chi² = 0.19, df = 3 (P = 0.98); I² = 0%
Test for overall effect: Z = 2.74 (P = 0.006)
Test for subgroup differences: Not applicable



Analysis 1.13. Comparison 1: Psychological intervention versus no such therapy, Outcome 13: Psychological symptoms up to 3 months after the intervention (depression & overall)

Study or Subgroup	Treatment Mean	Treatment SD	Treatment Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Asbury 2007	4.36	3.48	27	4.21	3.26	26	13.9%	0.04 [-0.49 , 0.58]
Asbury 2008	4.8	3.3	32	3.8	2.4	32	15.2%	0.34 [-0.15 , 0.84]
Jonsbu 2011	5.9	6.5	21	8.8	7.2	19	11.8%	-0.42 [-1.04 , 0.21]
Keefe 2011	7.26	8.6	29	5.16	6.03	24	13.8%	0.27 [-0.27 , 0.82]
Lahmann 2008	51.6	6.6	11	56.1	8.2	11	7.8%	-0.58 [-1.44 , 0.28]
Mayou 1997	0.35	0.37	15	0.47	0.31	10	8.5%	-0.33 [-1.14 , 0.47]
Potts 1999	4.3	3.2	32	6.4	4.1	24	13.9%	-0.57 [-1.11 , -0.03]
Van Peski-Oosterbaan 1999	4.26	3.2	32	5.96	3.6	32	15.1%	-0.49 [-0.99 , 0.00]
Total (95% CI)			**199**			**178**	**100.0%**	**-0.18 [-0.46 , 0.10]**

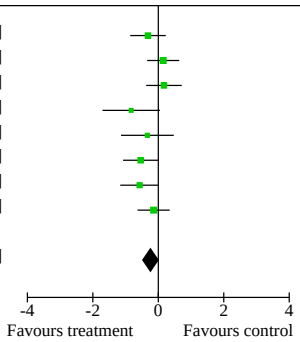
Heterogeneity: Tau² = 0.07; Chi² = 12.69, df = 7 (P = 0.08); I² = 45%
Test for overall effect: Z = 1.26 (P = 0.21)
Test for subgroup differences: Not applicable



Analysis 1.14. Comparison 1: Psychological intervention versus no such therapy, Outcome 14: Psychological symptoms up to 3 months after the intervention (anxiety and overall)

Study or Subgroup	Treatment Mean	Treatment SD	Treatment Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Asbury 2007	6.78	4.15	27	8	3.42	26	13.9%	-0.32 [-0.86 , 0.23]
Asbury 2008	6.7	3.3	32	6.2	3.3	32	16.1%	0.15 [-0.34 , 0.64]
Keefe 2011	33.96	13.19	29	31.89	9.89	24	13.9%	0.17 [-0.37 , 0.71]
Lahmann 2008	53.5	5.5	11	60.5	10.1	11	6.3%	-0.83 [-1.71 , 0.05]
Mayou 1997	0.35	0.37	15	0.47	0.31	10	7.3%	-0.33 [-1.14 , 0.47]
Potts 1999	6.2	3	32	8.4	5.1	24	14.1%	-0.54 [-1.08 , 0.00]
Spinhoven 2010	4.9	3.9	23	7	3.3	23	12.2%	-0.57 [-1.16 , 0.02]
Van Peski-Oosterbaan 1999	6.66	3.3	32	7.16	3.6	32	16.1%	-0.14 [-0.63 , 0.35]
Total (95% CI)			**201**			**182**	**100.0%**	**-0.24 [-0.47 , -0.01]**

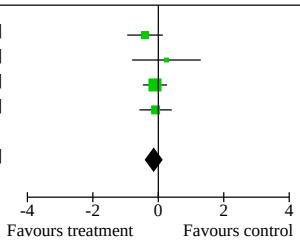
Heterogeneity: Tau² = 0.03; Chi² = 9.02, df = 7 (P = 0.25); I² = 22%
Test for overall effect: Z = 2.02 (P = 0.04)
Test for subgroup differences: Not applicable



Analysis 1.15. Comparison 1: Psychological intervention versus no such therapy, Outcome 15: Psychological symptoms 3 to 12 months after the intervention

Study or Subgroup	Treatment Mean	Treatment SD	Treatment Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Asbury 2007	11.05	7.41	27	14	6.89	26	21.5%	-0.41 [-0.95 , 0.14]
Mayou 1997	0.37	0.33	12	0.29	0.22	5	5.8%	0.25 [-0.80 , 1.30]
van Beek 2013	16.7	5.3	60	17.2	4.4	53	46.6%	-0.10 [-0.47 , 0.27]
Van Peski-Oosterbaan 1999	6.96	3.1	31	7.26	4	32	26.1%	-0.08 [-0.58 , 0.41]
Total (95% CI)			**130**			**116**	**100.0%**	**-0.14 [-0.39 , 0.11]**

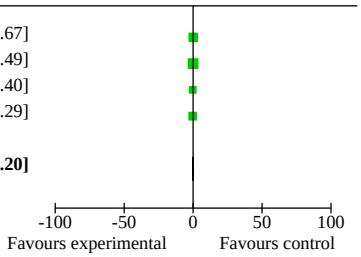
Heterogeneity: Tau² = 0.00; Chi² = 1.54, df = 3 (P = 0.67); I² = 0%
Test for overall effect: Z = 1.10 (P = 0.27)
Test for subgroup differences: Not applicable



Analysis 1.16. Comparison 1: Psychological intervention versus no such therapy, Outcome 16: Cardiac anxiety fear up to 3 months

Study or Subgroup	Treatment Mean	Treatment SD	Treatment Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Asbury 2007	1.35	0.56	27	1.27	0.63	26	26.7%	0.13 [-0.41 , 0.67]
Asbury 2008	1.2	0.5	32	1.2	0.5	32	32.3%	0.00 [-0.49 , 0.49]
Esler 2003	1.4	0.42	17	1.49	0.25	19	18.0%	-0.26 [-0.92 , 0.40]
Spinhoven 2010	12.8	7.8	23	15.1	7.5	23	23.0%	-0.30 [-0.88 , 0.29]
Total (95% CI)			**99**			**100**	**100.0%**	**-0.08 [-0.36 , 0.20]**

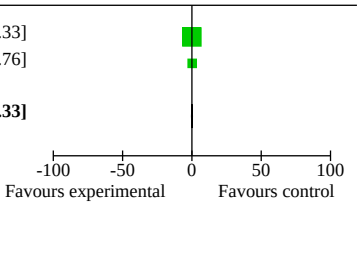
Heterogeneity: Tau² = 0.00; Chi² = 1.51, df = 3 (P = 0.68); I² = 0%
Test for overall effect: Z = 0.56 (P = 0.58)
Test for subgroup differences: Not applicable



Analysis 1.17. Comparison 1: Psychological intervention versus no such therapy, Outcome 17: Cardiac anxiety fear 3 to 12 months

Study or Subgroup	Treatment Mean	Treatment SD	Treatment Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Asbury 2007	1.3	0.67	27	1.31	0.58	26	73.4%	-0.01 [-0.35 , 0.33]
Esler 2003	1.46	0.87	17	1.26	0.84	19	26.6%	0.20 [-0.36 , 0.76]
Total (95% CI)			**44**			**45**	**100.0%**	**0.05 [-0.24 , 0.33]**

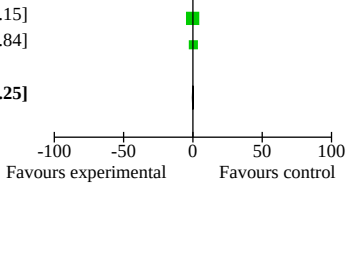
Heterogeneity: Tau² = 0.00; Chi² = 0.40, df = 1 (P = 0.53); I² = 0%
Test for overall effect: Z = 0.31 (P = 0.76)
Test for subgroup differences: Not applicable



Analysis 1.18. Comparison 1: Psychological intervention versus no such therapy, Outcome 18: Cardiac anxiety avoidance up to 3 months

Study or Subgroup	Treatment Mean	Treatment SD	Treatment Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Asbury 2007	1.16	0.74	27	1.24	0.89	26	31.4%	-0.08 [-0.52 , 0.36]
Asbury 2008	1.3	0.6	32	1.5	0.8	32	44.2%	-0.20 [-0.55 , 0.15]
Esler 2003	0.94	0.86	17	0.62	0.71	19	24.4%	0.32 [-0.20 , 0.84]
Total (95% CI)			**76**			**77**	**100.0%**	**-0.04 [-0.32 , 0.25]**

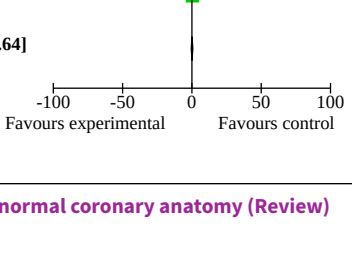
Heterogeneity: Tau² = 0.02; Chi² = 2.69, df = 2 (P = 0.26); I² = 26%
Test for overall effect: Z = 0.24 (P = 0.81)
Test for subgroup differences: Not applicable



Analysis 1.19. Comparison 1: Psychological intervention versus no such therapy, Outcome 19: Cardiac anxiety avoidance 3 to 12 months

Study or Subgroup	Treatment Mean	Treatment SD	Treatment Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Asbury 2007	1.29	0.66	27	1.46	0.95	26	55.3%	-0.17 [-0.61 , 0.27]
Esler 2003	0.93	1.01	17	0.53	0.69	19	44.7%	0.40 [-0.17 , 0.97]
Total (95% CI)			**44**			**45**	**100.0%**	**0.08 [-0.47 , 0.64]**

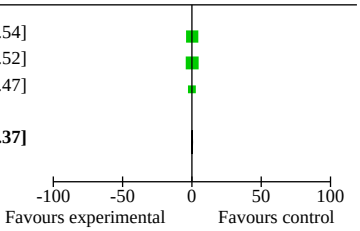
Heterogeneity: Tau² = 0.09; Chi² = 2.39, df = 1 (P = 0.12); I² = 58%
Test for overall effect: Z = 0.30 (P = 0.76)
Test for subgroup differences: Not applicable



Analysis 1.20. Comparison 1: Psychological intervention versus no such therapy, Outcome 20: Cardiac anxiety attention up to 3 months

Study or Subgroup	Treatment Mean	Treatment SD	Treatment Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Asbury 2007	1.37	0.66	27	1.16	0.57	26	39.3%	0.21 [-0.12 , 0.54]
Asbury 2008	1.4	0.6	32	1.2	0.7	32	42.3%	0.20 [-0.12 , 0.52]
Esler 2003	1.06	0.74	17	1.07	0.74	19	18.4%	-0.01 [-0.49 , 0.47]
Total (95% CI)			**76**			**77**	**100.0%**	**0.17 [-0.04 , 0.37]**

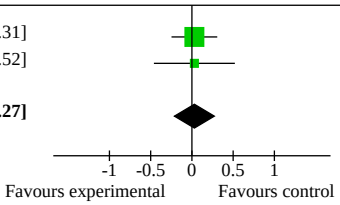
Heterogeneity: Tau² = 0.00; Chi² = 0.62, df = 2 (P = 0.73); I² = 0%
Test for overall effect: Z = 1.56 (P = 0.12)
Test for subgroup differences: Not applicable



Analysis 1.21. Comparison 1: Psychological intervention versus no such therapy, Outcome 21: Cardiac anxiety attention 3 to 12 months

Study or Subgroup	Treatment Mean	Treatment SD	Treatment Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Asbury 2007	1.28	0.13	27	1.25	0.71	26	75.8%	0.03 [-0.25 , 0.31]
Esler 2003	1.01	0.75	17	0.98	0.75	19	24.2%	0.03 [-0.46 , 0.52]
Total (95% CI)			**44**			**45**	**100.0%**	**0.03 [-0.21 , 0.27]**

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.24 (P = 0.81)
Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. 2002 search strategies

MEDLINE

1 Chest Pain/
2 Syndrome X/
3 "syndrome x".tw.
4 microvascular angina.tw.
5 cardiac syndrome$.tw.
6 chest pain$.tw.
7 ((thorax or thoracic) adj1 pain$).tw.
8 or/1-7
9 Angina Pectoris/
10 angina.tw.
11 (normal adj5 coronary).tw.
12 (normal adj5 angiogram$).tw.
13 (normal adj5 anatomy).tw.
14 or/11-13
15 9 or 10
16 14 and 15
17 8 or 16
18 exp Psychotherapy/
19 exp Counseling/
20 psychotherap$.tw.
21 counsel$.tw.
22 psychodynamic$.tw.
23 (behavio$ adj3 therap$).tw.

24 (cognitiv$ adj3 therap$).tw.
25 psychologic$.tw.
26 exp "Mind-Body and Relaxation Techniques"/
27 (relaxation adj5 (treat$ or therap$ or technique$)).tw.
28 or/18-27
29 17 and 28

EMBASE

1 Thorax Pain/
2 Syndrome X/
3 "syndrome x".tw.
4 microvascular angina.tw.
5 cardiac syndrome$.tw.
6 chest pain$.tw.
7 ((thorax or thoracic) adj1 pain$).tw.
8 or/1-7
9 Angina Pectoris/
10 angina.tw.
11 (normal adj5 coronary).tw.
12 (normal adj5 angiogram$).tw.
13 (normal adj5 anatomy).tw.
14 or/11-13
15 9 or 10
16 14 and 15
17 8 or 16
18 exp Psychiatric treatment/
19 exp Counseling/
20 psychotherap$.tw.
21 counsel$.tw.
22 psychodynamic$.tw.
23 (behavio$ adj3 therap$).tw.
24 (cognitiv$ adj3 therap$).tw.
25 psychologic$.tw.
26 (relaxation adj5 (treat$ or therap$ or technique$)).tw.
27 or/18-26
28 17 and 27

CINAHL on Ovid

1 Chest Pain/
2 "syndrome x".tw.
3 microvascular angina.tw.
4 cardiac syndrome$.tw.
5 chest pain$.tw.
6 ((thorax or thoracic) adj1 pain$).tw.
7 Angina Pectoris/
8 angina.tw.
9 (normal adj5 coronary).tw.
10 (normal adj5 angiogram$).tw.
11 (normal adj5 anatomy).tw.
12 or/9-11
13 7 or 8
14 12 and 13
15 exp Psychotherapy/
16 exp Counseling/
17 psychotherap$.tw.
18 counsel$.tw.
19 psychodynamic$.tw.
20 (behavio$ adj3 therap$).tw.
21 (cognitiv$ adj3 therap$).tw.
22 psychologic$.tw.
23 (relaxation adj5 (treat$ or therap$ or technique$)).tw.

24 or/1-6,14
25 or/15-23
26 24 and 25

PsycLIT

#23 ((((thorax or thoracic) next pain) or (cardiac syndrome*) or (microvascular angina) or (chest pain)) or (((angina) or (explode "Angina-Pectoris" in DE)) and ((normal near anatomy) or (normal near angiogram*) or (normal near coronary)))) and ((relaxation) or (psychodynamic*) or (behavio?r* therap*) or (counsel*) or (psychotherap*) or (explode "Counseling-" in DE) or (explode "Psychotherapy-" in DE))
#22 (relaxation) or (psychodynamic*) or (behavio?r* therap*) or (counsel*) or (psychotherap*) or (explode "Counseling-" in DE) or (explode "Psychotherapy-" in DE)
#21 behavio?r* therap*
#20 relaxation
#19 psychodynamic*
#18 counsel*
#17 psychotherap*
#16 explode "Counseling-" in DE
#15 explode "Psychotherapy-" in DE
#14 (((thorax or thoracic) next pain) or (cardiac syndrome*) or (microvascular angina) or (chest pain)) or (((angina) or (explode "Angina-Pectoris" in DE)) and ((normal near anatomy) or (normal near angiogram*) or (normal near coronary)))
#13 ((angina) or (explode "Angina-Pectoris" in DE)) and ((normal near anatomy) or (normal near angiogram*) or (normal near coronary))
#12 (normal near anatomy) or (normal near angiogram*) or (normal near coronary)
#11 normal near anatomy
#10 normal near angiogram*
#9 normal near coronary
#8 (angina) or (explode "Angina-Pectoris" in DE)
#7 angina
#6 explode "Angina-Pectoris" in DE
#5 ((thorax or thoracic) next pain) or (cardiac syndrome*) or (microvascular angina) or (chest pain)
#4 (thorax or thoracic) next pain
#3 cardiac syndrome*
#2 microvascular angina
#1 chest pain

BIOSIS (EDINA)

((al: (relaxation)) or (al: ((behavio* w therap*) or (cognitiv* w therap*) or psychotherap* or counsel* or psychologic* or psychodynamic*))) and ((((al: ((normal w angiogram*) or (normal with coronary) or (normal w anatomy))) and al: (angina)) or (al: ((chest w pain) or (microvascula* w angina) or (cardiac w syndrome)))) and (al: ((clin* n3 trial*) or random* or singl* or doubl* or blind* or mask* or placebo* or (clin* n3 study) or controlled)))

Appendix 2. 2008 search strategies

CENTRAL on the Cochrane LIbrary

#1 MeSH descriptor chest pain this term only
#2 chest next pain in All Text
#3 thorax next pain in All Text
#4 thoracic next pain in All Text
#5 MeSH descriptor Microvascular Angina explode all trees
#6 cardiac next syndrome* in All Text
#7 microvascular next angina in All Text
#8 ((((((#1 or #2) or #3) or #4) or #5) or #6) or #7)
#9 angina in All Text
#10 (normal in All Text near/6 coronary in All Text)
#11 (normal in All Text near/6 angiogram* in All Text)
#12 (normal in All Text near/6 anatomy in All Text)
#13 ((#10 or #11) or #12)
#14 (#13 and #9)
#15 (#14 or #8)
#16 MeSH descriptor PSYCHOTHERAPY explode all trees
#17 psychotherap* in All Text
#18 (cognitive in All Text near/6 therap* in All Text)

#19 (behaviour* in All Text near/6 therap* in All Text)
#20 (behavior* in All Text near/6 therap* in All Text) 7551
#21 MeSH descriptor COUNSELING explode all trees
#22 counsel* in All Text
#23 psychodynamic* in All Text
#24 (relax* in All Text near/6 therap* in All Text)
#25 psychologic* in All Text
#26 hyperventilation in All Text
#27 (breath* in All Text near/6 control* in All Text)
#28 (#16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27)
#29 (#15 and #28) 148

MEDLINE on Ovid

1 Chest Pain/ (6468)
2 exp Microvascular Angina/ (727)
3 "syndrome x".tw. (1275)
4 microvascular angina.tw. (150)
5 cardiac syndrome$.tw. (339)
6 chest pain$.tw. (16817)
7 ((thorax or thoracic) adj1 pain$).tw. (731)
8 cardiac syndrome$.tw. (339)
9 or/1-8 (21108)
10 Angina Pectoris/ (28905)
11 angina.tw. (37131)
12 (normal adj5 coronary).tw. (6979)
13 (normal adj5 angiogram$).tw. (1260)
14 (normal adj5 anatomy).tw. (4111)
15 or/12-14 (11535)
16 10 or 11 (49340)
17 15 and 16 (1725)
18 9 or 17 (22123)
19 exp Psychotherapy/ (122234)
20 exp Counseling/ (26136)
21 psychotherap$.tw. (24990)
22 counsel$.tw. (44851)
23 psychodynamic$.tw. (4079)
24 (behavio$ adj3 therap$).tw. (9026)
25 (cognitiv$ adj3 therap$).tw. (5666)
26 psychologic$.tw. (93626)
27 exp "Mind-Body and Relaxation Techniques"/ (33980)
28 (relaxation adj5 (treat$ or therap$ or technique$)).tw. (3240)
29 cbt.tw. (2105)
30 guided imagery.tw. (330)
31 (hyperventilat$ adj3 control$).tw. (235)
32 (hyperventilat$ adj5 (treat$ or therap$ or technique$)).tw. (404)
33 (talk$ adj3 (therap$ or treat$)).tw. (180)
34 or/19-33 (282622)
35 34 and 18 (414)
36 randomized controlled trial.pt. (269477)
37 controlled clinical trial.pt. (80776)
38 Randomized controlled trials/ (58509)
39 random allocation/ (63710)
40 double blind method/ (101566)
41 single-blind method/ (12762)
42 or/36-41 (454816)
43 exp animal/ not humans/ (3412892)
44 42 not 43 (425364)
45 clinical trial.pt. (460981)
46 exp Clinical Trials as Topic/ (215116)
47 (clin$ adj25 trial$).ti,ab. (155757)
48 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).ti,ab. (98377)

49 placebos/ (28390)
50 placebo$.ti,ab. (115404)
51 random$.ti,ab. (435396)
52 research design/ (55352)
53 or/45-52 (961765)
54 53 not 43 (892832)
55 44 or 54 (919159)
56 35 and 55 (70)
57 limit 56 to yr="2002 - 2008" (30)

EMBASE on Ovid <to 2008 Week 49>

1 Thorax Pain/ (19589)
2 Syndrome X/ (1145)
3 "syndrome x".tw. (1187)
4 microvascular angina.tw. (151)
5 cardiac syndrome$.tw. (245)
6 chest pain$.tw. (14796)
7 ((thorax or thoracic) adj1 pain$).tw. (611)
8 cardiac syndrome$.tw. (245)
9 or/1-8 (27777)
10 Angina Pectoris/ (25627)
11 angina.tw. (29619)
12 (normal adj5 coronary).tw. (6060)
13 (normal adj5 angiogram$).tw. (1075)
14 (normal adj5 anatomy).tw. (3182)
15 or/12-14 (9561)
16 10 or 11 (40997)
17 15 and 16 (1485)
18 9 or 17 (28598)
19 exp Psychiatric treatment/ (115676)
20 exp Counseling/ (46367)
21 psychotherap$.tw. (22346)
22 counsel$.tw. (36138)
23 psychodynamic$.tw. (4102)
24 (behavio$ adj3 therap$).tw. (9850)
25 (cognitiv$ adj3 therap$).tw. (7174)
26 psychologic$.tw. (79410)
27 (relaxation adj5 (treat$ or therap$ or technique$)).tw. (2922)
28 cbt.tw. (2504)
29 guided imagery.tw. (233)
30 (hyperventilat$ adj3 control$).tw. (175)
31 (hyperventilat$ adj5 (treat$ or therap$ or technique$)).tw. (317)
32 (talk$ adj3 (therap$ or treat$)).tw. (143)
33 or/19-32 (242638)
34 33 and 18 (717)
35 controlled clinical trial/ (54279)
36 random$.tw. (384980)
37 randomized controlled trial/ (163469)
38 follow-up.tw. (346476)
39 double blind procedure/ (70681)
40 placebo$.tw. (108133)
41 placebo/ (120719)
42 factorial$.ti,ab. (8024)
43 (crossover$ or cross-over$).ti,ab. (38882)
44 (double$ adj blind$).ti,ab. (83559)
45 (singl$ adj blind$).ti,ab. (7337)
46 assign$.ti,ab. (106482)
47 allocat$.ti,ab. (33672)
48 volunteer$.ti,ab. (97667)
49 Crossover Procedure/ (20766)
50 Single Blind Procedure/ (7842)

51 or/35-50 (1002039)
52 34 and 51 (218)

PsycINFO on Ovid < to December Week 1 2008

1 Thorax/ (220)
2 Pain/ (10982)
3 1 and 2 (124)
4 "syndrome x".tw. (34)
5 microvascular angina.tw. (1)
6 cardiac syndrome$.tw. (7)
7 chest pain$.tw. (588)
8 ((thorax or thoracic) adj1 pain$).tw. (18)
9 or/3-8 (644)
10 Angina Pectoris/ (228)
11 angina.tw. (614)
12 (normal adj5 coronary).tw. (58)
13 (normal adj5 angiogram$).tw. (9)
14 (normal adj5 anatomy).tw. (58)
15 or/12-14 (121)
16 10 or 11 (632)
17 15 and 16 (8)
18 9 or 17 (644)
19 exp Psychotherapy/ (134584)
20 exp Counseling/ (54251)
21 psychotherap$.tw. (79096)
22 counsel$.tw. (69295)
23 psychodynamic$.tw. (15557)
24 (behavio$ adj3 therap$).tw. (20467)
25 (cognitiv$ adj3 therap$).tw. (13689)
26 psychologic$.tw. (208058)
27 (relaxation adj5 (treat$ or therap$ or technique$)).tw. (3337)
28 cbt.tw. (3295)
29 guided imagery.tw. (795)
30 (hyperventilat$ adj3 control$).tw. (29)
31 (hyperventilat$ adj5 (treat$ or therap$ or technique$)).tw. (91)
32 (talk$ adj3 (therap$ or treat$)).tw. (562)
33 or/19-32 (428634)
34 33 and 18 (171)
35 clinical trials/ (2481)
36 "Empirical Study".md. (1109008)
37 random$.tw. (77684)
38 groups.tw. (261176)
39 (double adj3 blind).tw. (12272)
40 (single adj3 blind).tw. (818)
41 experimental design/ (7154)
42 controlled.tw. (49420)
43 (clinical adj3 study).tw. (5165)
44 trial.tw. (41661)
45 or/35-44 (1267552)
46 34 and 45 (109)
47 limit 46 to yr="2002 - 2008" (40)

CINAHL on EBSCO

((MH "Clinical Trials+") or (random* or rct or groups or trial or "clinical study")) and ((MH "Syndrome X") or (MH "Chest Pain") or ("chest pain" or "microvascular angina")) and ((MH "Psychology, Applied+") or (MH "Psychotherapy+") or (psychol* or counsel* or talk* or relaxation or hyperventilat* or CBT or cognitive or behavio*))

BIOSIS on ISI Web of Knowledge

# 3 52 #1 and #2 AND Taxa Notes=(Humans)
Databases=PREVIEWS Timespan=2002-2008

# 2 715 (ts=(angina and ((normal same angiogram*) or (normal same coronary) or (normal same anatomy))) or ts= ("microvascular angina" or "chest pain")) and TS=(random* or trial or RCT or groups or controlled or (double same blind) or (single same blind)) AND Taxa Notes=(Humans)
Databases=PREVIEWS Timespan=2002-2008
# 1 989 ts=(psychotherap* or counsel* or psychologic* or psychodynamic* or talk or talking or (behavio* same therap*) or (cognitive same therap*) or CBT or hyperventilat*) and ts=(chest or angina or thora*)
Databases=PREVIEWS Timespan=2002-2008

Appendix 3. 2011 search strategies

CENTRAL AND DARE (the Cochrane Library)

#1 MeSH descriptor Chest Pain, this term only
#2 chest next pain
#3 thorax next pain
#4 thoracic next pain
#5 MeSH descriptor Microvascular Angina, this term only
#6 cardiac next syndrome*
#7 microvascular next angina
#8 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)
#9 angina
#10 normal near/6 coronary
#11 normal near/6 coronary
#12 normal near/6 anatomy
#13 (#10 OR #11 OR #12)
#14 (#9 AND #13)
#15 (#8 OR #14)
#16 MeSH descriptor Psychotherapy explode all trees
#17 psychotherap*
#18 cognitive near/6 therap*
#19 behaviour* near/6 therap*
#20 behavior* near/6 therap*
#21 MeSH descriptor Counseling explode all trees
#22 counsel*
#23 psychodynamic*
#24 relax* near/6 therap*
#25 psychologic*
#26 hyperventilation
#27 breath* near/6 control*
#28 (#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27)
#29 (#15 AND #28)

MEDLINE (OVID)

1. Chest Pain/
2. exp Microvascular Angina/
3. "syndrome x".tw.
4. microvascular angina.tw.
5. cardiac syndrome*.tw.
6. chest pain*.tw.
7. ((thorax or thoracic) adj1 pain*).tw.
8. cardiac syndrome*.tw.
9. or/1-8
10. Angina Pectoris/
11. angina.tw.
12. (normal adj5 coronary).tw.
13. (normal adj5 angiogram*).tw.
14. (normal adj5 anatomy).tw.
15. or/12-14
16. 10 or 11
17. 15 and 16
18. 9 or 17
19. exp Psychotherapy/

20. exp Counseling/
21. psychotherap*.tw.
22. counsel*.tw.
23. psychodynamic*.tw.
24. (behavio* adj3 therap*).tw.
25. (cognitiv* adj3 therap*).tw.
26. psychologic*.tw.
27. exp Mind-Body Therapies/
28. (relaxation adj5 (treat* or therap* or technique*)).tw.
29. cbt.tw.
30. guided imagery.tw.
31. (hyperventilate* adj3 control*).tw.
32. (hyperventilate* adj5 (treat* or therap* or technique*)).tw.
33. (talk* adj3 (therap* or treat*)).tw.
34. or/19-33
35. 34 and 18
36. randomized controlled trial.pt.
37. controlled clinical trial.pt.
38. randomized.ab.
39. placebo.ab.
40. drug therapy.fs.
41. randomly.ab.
42. trial.ab.
43. groups.ab.
44. 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43
45. exp animals/ not humans.sh.
46. 44 not 45
47. 35 and 46
48. (2008121* or 2008122* or 2008123* or 2009* or 2010* or 2011*).ed.
49. 47 and 48

EMBASE (OVID)

1. thorax pain/
2. Syndrome X/
3. "syndrome x".tw.
4. microvascular angina.tw.
5. cardiac syndrome*.tw.
6. chest pain*.tw.
7. ((thorax or thoracic) adj1 pain*).tw.
8. cardiac syndrome*.tw.
9. or/1-8
10. angina pectoris/
11. angina.tw.
12. (normal adj5 coronary).tw.
13. (normal adj5 angiogram*).tw.
14. (normal adj5 anatomy).tw.
15. or/12-14
16. 10 or 11
17. 15 and 16
18. 9 or 17
19. exp psychiatric treatment/
20. exp counseling/
21. psychotherap*.tw.
22. counsel*.tw.
23. psychodynamic*.tw.
24. (behavio* adj3 therap*).tw.
25. (cognitiv* adj3 therap*).tw.
26. psychologic*.tw.
27. (relaxation adj5 (treat* or therap* or technique*)).tw.
28. cbt.tw.
29. guided imagery.tw.

30. (hyperventilat* adj3 control*).tw.
31. (hyperventilat* adj5 (treat* or therap* or technique*)).tw.
32. (talk* adj3 (therap* or treat*)).tw.
33. or/19-32
34. 33 and 18
35. random$.tw.
36. factorial$.tw.
37. crossover$.tw.
38. cross over$.tw.
39. cross-over$.tw.
40. placebo$.tw.
41. (doubl$ adj blind$).tw.
42. (singl$ adj blind$).tw.
43. assign$.tw.
44. allocat$.tw.
45. volunteer$.tw.
46. crossover procedure/
47. double blind procedure/
48. randomized controlled trial/
49. single blind procedure/
50. 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49
51. (animal/ or nonhuman/) not human/
52. 50 not 51
53. 34 and 52
54. limit 53 to embase
55. (2008121* or 2008122* or 2008123* or 2009* or 2010* or 2011*).dd.
56. 54 and 55

PsycINFO (OVID)

The RCT filter has been amended as an adaption of the Cochrane RCT filters used for MEDLINE and EMBASE.

1. Thorax/
2. Pain/
3. 1 and 2
4. "syndrome x".tw.
5. microvascular angina.tw.
6. cardiac syndrome*.tw.
7. chest pain*.tw.
8. ((thorax or thoracic) adj1 pain*).tw.
9. or/3-8
10. Angina Pectoris/
11. angina.tw.
12. (normal adj5 coronary).tw.
13. (normal adj5 angiogram*).tw.
14. (normal adj5 anatomy).tw.
15. or/12-14
16. 10 or 11
17. 15 and 16
18. 9 or 17
19. exp Psychotherapy/
20. exp Counseling/
21. psychotherap*.tw.
22. counsel*.tw.
23. psychodynamic*.tw.
24. (behavio* adj3 therap*).tw.
25. (cognitiv* adj3 therap*).tw.
26. psychologic*.tw.
27. (relaxation adj5 (treat* or therap* or technique*)).tw.
28. cbt.tw.
29. guided imagery.tw.
30. (hyperventilat* adj3 control*).tw.
31. (hyperventilat* adj5 (treat* or therap* or technique*)).tw.

32. (talk* adj3 (therap* or treat*)).tw.
33. or/19-32
34. 33 and 18
35. random$.tw.
36. factorial$.tw.
37. crossover$.tw.
38. cross-over$.tw.
39. placebo$.tw.
40. (doubl$ adj blind$).tw.
41. (singl$ adj blind$).tw.
42. assign$.tw.
43. allocat$.tw.
44. volunteer$.tw.
45. control*.tw.
46. "2000".md.
47. or/35-46
48. 34 and 47
49. (2008121* or 2008122* or 2008123* or 2009* or 2010* or 2011*).up.
50. 48 and 49

CINAHL Plus (EBSCO)

cS17 S15 and S16
S16 EM 20081210-20110909
S15 S11 and S14
S14 S12 or S13
S13 (random* or rct or groups or trial or "clinical study")
S12 (MH "Clinical Trials+")
S11 S5 and S10
S10 S6 or S7 or S8 or S9
S9 AB (psychol* or counsel* or talk* or relaxation or hyperventilat* or CBT or cognitive or behavio*)
S8 TI (psychol* or counsel* or talk* or relaxation or hyperventilat* or CBT or cognitive or behavio*)
S7 (MH "Psychotherapy+")
S6 (MH "Psychology, Applied+")
S5 S1 or S2 or S3 or S4
S4 (TI "microvascular angina") or (AB "microvascular angina")
S3 (TI "chest pain") or (AB "chest pain")
S2 (MH "Chest Pain")
S1 (MH "Syndrome X")

BIOSIS (ISI Web of Knowledge)

#6 #5 AND #4 AND #3
#5 TS=(random* or trial or RCT or groups or controlled or (double same blind) or (single same blind))
#4 TS=(angina and ((normal same angiogram*) or (normal same coronary) or (normal same anatomy)))
#3 #2 AND #1
#2 TS=(psychotherap* or counsel* or psychologic* or psychodynamic* or talk or talking or (behavio* same therap*) or (cognitive same therap*) or CBT or hyperventilat*)
#1 TS=(chest or angina or thora*)

Appendix 4. 2014 search strategies

CENTRAL and DARE

#1MeSH descriptor Chest Pain, this term only
#2chest next pain
#3thorax next pain
#4thoracic next pain
#5MeSH descriptor Microvascular Angina, this term only
#6cardiac next syndrome*
#7microvascular next angina
#8(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)
#9angina
#10normal near/6 coronary

#11normal near/6 coronary
#12normal near/6 anatomy
#13(#10 OR #11 OR #12)
#14(#9 AND #13)
#15(#8 OR #14)
#16MeSH descriptor Psychotherapy explode all trees
#17psychotherap*
#18cognitive near/6 therap*
#19behaviour* near/6 therap*
#20behavior* near/6 therap*
#21MeSH descriptor Counseling explode all trees
#22counsel*
#23psychodynamic*
#24relax* near/6 therap*
#25psychologic*
#26hyperventilation
#27breath* near/6 control*
#28(#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27)
#29(#15 AND #28)

MEDLINE OVID

1. Chest Pain/
2. exp Microvascular Angina/
3. "syndrome x".tw.
4. microvascular angina.tw.
5. cardiac syndrome*.tw.
6. chest pain*.tw.
7. ((thorax or thoracic) adj1 pain*).tw.
8. cardiac syndrome*.tw.
9. or/1-8
10. Angina Pectoris/
11. angina.tw.
12. (normal adj5 coronary).tw.
13. (normal adj5 angiogram*).tw.
14. (normal adj5 anatomy).tw.
15. or/12-14
16. 10 or 11
17. 15 and 16
18. 9 or 17
19. exp Psychotherapy/
20. exp Counseling/
21. psychotherap*.tw.
22. counsel*.tw.
23. psychodynamic*.tw.
24. (behavio* adj3 therap*).tw.
25. (cognitiv* adj3 therap*).tw.
26. psychologic*.tw.
27. exp Mind-Body Therapies/
28. (relaxation adj5 (treat* or therap* or technique*)).tw.
29. cbt.tw.
30. guided imagery.tw.
31. (hyperventilate* adj3 control*).tw.
32. (hyperventilate* adj5 (treat* or therap* or technique*)).tw.
33. (talk* adj3 (therap* or treat*)).tw.
34. or/19-33
35. 34 and 18
36. randomized controlled trial.pt.
37. controlled clinical trial.pt.
38. randomized.ab.
39. placebo.ab.
40. drug therapy.fs.

41. randomly.ab.
42. trial.ab.
43. groups.ab.
44. 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43
45. exp animals/ not humans.sh.
46. 44 not 45
47. 35 and 46
48. (201108* or 201109* or 201110* or 201111* or 201112* or 2012* or 2013* or 2014*).ed.
49. 47 and 48

EMBASE OVID

1. thorax pain/
2. Syndrome X/
3. "syndrome x".tw.
4. microvascular angina.tw.
5. cardiac syndrome*.tw.
6. chest pain*.tw.
7. ((thorax or thoracic) adj1 pain*).tw.
8. cardiac syndrome*.tw.
9. or/1-8
10. angina pectoris/
11. angina.tw.
12. (normal adj5 coronary).tw.
13. (normal adj5 angiogram*).tw.
14. (normal adj5 anatomy).tw.
15. or/12-14
16. 10 or 11
17. 15 and 16
18. 9 or 17
19. exp psychiatric treatment/
20. exp counseling/
21. psychotherap*.tw.
22. counsel*.tw.
23. psychodynamic*.tw.
24. (behavio* adj3 therap*).tw.
25. (cognitiv* adj3 therap*).tw.
26. psychologic*.tw.
27. (relaxation adj5 (treat* or therap* or technique*)).tw.
28. cbt.tw.
29. guided imagery.tw.
30. (hyperventilat* adj3 control*).tw.
31. (hyperventilat* adj5 (treat* or therap* or technique*)).tw.
32. (talk* adj3 (therap* or treat*)).tw.
33. or/19-32
34. 33 and 18
35. random$.tw.
36. factorial$.tw.
37. crossover$.tw.
38. cross over$.tw.
39. cross-over$.tw.
40. placebo$.tw.
41. (doubl$ adj blind$).tw.
42. (singl$ adj blind$).tw.
43. assign$.tw.
44. allocat$.tw.
45. volunteer$.tw.
46. crossover procedure/
47. double blind procedure/
48. randomized controlled trial/
49. single blind procedure/
50. 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49

51. (animal/ or nonhuman/) not human/
52. 50 not 51
53. 34 and 52
54. limit 53 to embase
55. (201108* or 201109* or 201110* or 201111* or 201112* or 2012* or 2013* or 2014*).dd.
56. 54 and 55

PsycINFO OVID

1. Thorax/
2. Pain/
3. 1 and 2
4. "syndrome x".tw.
5. microvascular angina.tw.
6. cardiac syndrome*.tw.
7. chest pain*.tw.
8. ((thorax or thoracic) adj1 pain*).tw.
9. or/3-8
10. Angina Pectoris/
11. angina.tw.
12. (normal adj5 coronary).tw.
13. (normal adj5 angiogram*).tw.
14. (normal adj5 anatomy).tw.
15. or/12-14
16. 10 or 11
17. 15 and 16
18. 9 or 17
19. exp Psychotherapy/
20. exp Counseling/
21. psychotherap*.tw.
22. counsel*.tw.
23. psychodynamic*.tw.
24. (behavio* adj3 therap*).tw.
25. (cognitiv* adj3 therap*).tw.
26. psychologic*.tw.
27. (relaxation adj5 (treat* or therap* or technique*)).tw.
28. cbt.tw.
29. guided imagery.tw.
30. (hyperventilat* adj3 control*).tw.
31. (hyperventilat* adj5 (treat* or therap* or technique*)).tw.
32. (talk* adj3 (therap* or treat*)).tw.
33. or/19-32
34. 33 and 18
35. random$.tw.
36. factorial$.tw.
37. crossover$.tw.
38. cross-over$.tw.
39. placebo$.tw.
40. (doubl$ adj blind$).tw.
41. (singl$ adj blind$).tw.
42. assign$.tw.
43. allocat$.tw.
44. volunteer$.tw.
45. control*.tw.
46. "2000".md.
47. or/35-46
48. 34 and 47
49. (201108* or 201109* or 201110* or 201111* or 201112* or 2012* or 2013* or 2014*).up.
50. 48 and 49

CINAHL Plus EBSCO

S17 S15 and S16

S16 EM 20110901-20140506
S15 S11 and S14
S14 S12 or S13
S13 (random* or rct or groups or trial or "clinical study")
S12 (MH "Clinical Trials+")
S11 S5 and S10
S10 S6 or S7 or S8 or S9
S9 AB (psychol* or counsel* or talk* or relaxation or hyperventilat* or CBT or cognitive or behavio*)
S8 TI (psychol* or counsel* or talk* or relaxation or hyperventilat* or CBT or cognitive or behavio*)
S7 (MH "Psychotherapy+")
S6 (MH "Psychology, Applied+")
S5 S1 or S2 or S3 or S4
S4 (TI "microvascular angina") or (AB "microvascular angina")
S3 (TI "chest pain") or (AB "chest pain")
S2 (MH "Chest Pain")
S1 (MH "Syndrome X")

BIOSIS

#6 #5 AND #4 AND #3 Timespan=2011-2014
#5 TS=(random* or trial or RCT or groups or controlled or (double same blind) or (single same blind))
#4 TS=(angina and ((normal same angiogram*) or (normal same coronary) or (normal same anatomy)))
#3 #2 AND #1
#2 TS=(psychotherap* or counsel* or psychologic* or psychodynamic* or talk or talking or (behavio* same therap*) or (cognitive same therap*) or CBT or hyperventilat*)
#1 TS=(chest or angina or thora*)

WHAT'S NEW

Date	Event	Description
26 March 2021	Review declared as stable	The evidence is current to 6 May 2014. Conclusions have not changed since publication in 2005 despite adding nine more studies.

HISTORY

Protocol first published: Issue 1, 2003
Review first published: Issue 1, 2005

Date	Event	Description
9 July 2014	New citation required but conclusions have not changed	The review conclusions have not changed.
21 May 2014	New search has been performed	We updated search strategies and performed literature searches up to 06 May 2014. We included one new study and an additional paper to an already included study.
30 November 2011	New search has been performed	We updated search strategies and performed literature searches up to September 2011. We included five new studies and an additional paper to an already included study. The conclusions were essentially unchanged.
21 September 2009	New search has been performed	We updated search strategies and reran searches up to December 2008. We included two new studies and an additional paper to an already included study. We assessed 21 new studies in de-

Date	Event	Description
		tail and excluded them. The review conclusions were essentially unchanged.
21 September 2009	New citation required but conclusions have not changed	We added a new review author.
9 September 2008	Amended	We converted to a new review format.
1 November 2004	New citation required and conclusions have changed	First version of the review was published.

CONTRIBUTIONS OF AUTHORS

Two review authors (SK, LAC) independently selected suitable studies for inclusion in the original review (Kisely 2005).

SK and AP independently selected suitable studies for subsequent updates. Where the two review authors disagreed about inclusion of a study, we resolved disagreements by consensus of opinion, or we consulted a third and fourth review author (PS, MY) if necessary.

SK, LAC or AP extracted data from the included studies. Two review authors (SK and LAC or AP) independently entered data into RevMan 2014.

DECLARATIONS OF INTEREST

SK: None known.

LAC: This review was supported by a Nova Scotia Health Research Foundation Knowledge Programs Grant.

MY: None known.

AP: None known.

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Internal sources

- Health Outcomes Unit, Capital District Health Authority, Halifax, Canada
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- Fremantle Hospital, Australia
- University of Queensland, School of Population Health, Australia

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol we stated that we would only include RCTs where < 20% of participants originally randomised were lost to follow-up. In view of the limited number of included trials, we relaxed these criteria to include studies that combined RCT and cross-over designs, and trials that had greater losses to follow-up. In each case, we performed sensitivity analyses to assess the effect of inclusion of these studies. Given the increase in the number of studies since publication of Kisely 2005, we have presented the results of random effects models in all the tables even where there was no evidence of statistical heterogeneity. This is because we could not definitely exclude other sources of between-study variation, such as clinical heterogeneity.

INDEX TERMS

Medical Subject Headings (MeSH)

Behavior Therapy; Chest Pain [*psychology] [therapy]; Cognitive Behavioral Therapy [*methods]; Coronary Vessels [*anatomy & histology]; Hypnosis; Microvascular Angina [psychology] [therapy]; Psychotherapy [methods]; Randomized Controlled Trials as Topic; Recurrence; Treatment Outcome

MeSH check words

Humans