The effectiveness of non-pharmacological interventions in improving psychological outcomes for heart transplant recipients: A systematic review

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**Disclosures**

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ABSTRACT

Background
Post-heart transplant psychological distress may both directly hinder physiological health as well as indirectly impact on clinical outcomes by increasing unhealthy behaviours, such as immunosuppression non-adherence. Reducing psychological distress for heart transplant recipients is therefore vitally important, in order to improve patients’ overall health and well-being but also clinical outcomes, such as morbidity and mortality. Evidence from other populations suggests that non-pharmacological interventions may be an effective strategy.

Aim
To appraise the efficacy of non-pharmacological interventions on psychological outcomes after heart transplant.

Method
A systematic review was conducted using the Joanna Briggs Institute methodology. Experimental and quasi-experimental studies that involved any non-pharmacological intervention for heart transplant recipients were included, provided that data on psychological outcomes were reported. Multiple electronic databases were searched for published and unpublished studies and reference lists of retrieved studies were scrutinized for further primary research. Data were extracted using a standardised data extraction tool. Included studies were assessed by two independent reviewers using standardised critical appraisal instruments.

Results
Three studies fulfilled the inclusion and exclusion criteria, which involved only
125 heart transplant recipients. Two studies reported on exercise programs. One study reported a web-based psychosocial intervention. While psychological outcomes significantly improved from baseline to follow-up for the recipients who received the interventions, between-group comparisons were not reported. The methodological quality of the studies was judged to be poor.

**Conclusions**

Further research is required, as we found there is insufficient evidence available to draw conclusions for or against the use of non-pharmacological interventions after heart transplant.

**Keywords**

Heart transplant, anxiety, depression, quality of life, systematic review.
Introduction

Psychological disorders, such as anxiety and depression, and high levels of psychological distress are common post-heart transplant. The largest prospective study of the cumulative rates of post-transplant psychological disorders reported that 38% of 191 recipients developed a mood or anxiety disorder within three years.\textsuperscript{1} A smaller, yet more recent study, identified that the risk for post heart transplant major depression was 41%, 12% for post traumatic stress disorder and 21% for partial post traumatic stress disorder.\textsuperscript{2} Most recently, 26.7% of heart transplant recipients reported clinically significant levels of mental distress using the Global Severity Index of the SCL-90-R.\textsuperscript{3}

Evidence also indicates that these poor psychological outcomes are harmful, because they have been associated with increased morbidity and mortality. For example, after controlling for known transplant-related predictors of morbidity and mortality, recipients who met the criteria for post-traumatic stress disorder in the first year post-transplant were over 15 times more likely to have died within three years.\textsuperscript{4} This study also reported that recipients who were depressed were nearly five times more likely to develop chronic allograft rejection and were two times more likely to die within three years.\textsuperscript{4} Another study reported that recipients with psychological disorders were significantly more likely ($p<0.01$) to contract an infection in the first 18 months after transplant.\textsuperscript{5} A statistically significant association between depression and post-transplant malignancies was uncovered in a recent study with 8 years follow-up.\textsuperscript{2}
The reasons for these associations are complex and not completely understood. It is possible that psychological distress may hinder physiological health and recovery after transplantation through biopsychological mechanisms. For example, psychological disorders have been linked with immunosuppression and increased infections post coronary artery bypass graft surgery.\textsuperscript{6} Another explanation is that psychological symptoms influence the course and development of underlying physical disease, as is the case with coronary artery disease in non-transplanted populations.\textsuperscript{7} In support of this explanation, a recent retrospective study demonstrated an increasing prevalence of traditional cardiovascular disease risk factors over the first five years post heart-transplant.\textsuperscript{8} It is also possible that psychological disorders may indirectly impact on clinical outcomes through behavioural means. For example, heart transplant recipients with anxiety or depression may be less likely to engage in healthy behaviours and rely on poor coping strategies, such as using alcohol.\textsuperscript{9-11} Finally, evidence also indicates that psychological disorders, such as depression, are associated with medication non-adherence, which, in the heart transplant population, has been linked to disastrous consequences, including acute rejection and death.\textsuperscript{12-15}

Developing and evaluating strategies to improve psychological outcomes for heart transplant recipients is vitally important, because such interventions have the potential to not only improve patients’ overall health and well-being but also clinical outcomes, such as morbidity and mortality. In this regard, non-pharmacological interventions have been shown to be particularly effective in reducing depression and anxiety in patients with other forms of chronic disease, most notably, coronary heart disease.\textsuperscript{16} For example, in the
largest randomised controlled trial of a non-pharmacological intervention for depression in patients with cardiovascular disease (ENRICHD), which randomised 2481 patients post-myocardial infarction, reported that the improvement in psychosocial outcomes at 6 months favoured the group that received counselling (mean [SD] change -10.1[7.8] vs. -8.4[7.7]; p<0.01). It is also important to note the relevance of non-pharmacological interventions for people with mental health problems to nursing practice. Nurse-led psychological interventions have been demonstrated to decrease psychological symptoms in people with chronic disease, such as heart failure and people post coronary artery bypass surgery.18, 19

However, a review published in 2006 identified that, unlike the large body of literature examining the prevalence and consequences of poor psychological outcomes after heart transplant, intervention research focused on improving psychological outcomes was sparse.20 The lack of research also lead a workgroup of the Nursing and Social Sciences Council of the International Society for Heart and Lung Transplantation (ISHLT) to recommend that intervention studies, which evaluate the efficacy of strategies to maximise psychological outcomes, should be conducted.21

Potentially then, since the ISHLT report21 and the previous review in 200620, studies reporting on the efficacy of non-pharmacological interventions in improving psychological outcomes for heart transplant recipients may have been published. Thus, further evidence may currently be available to inform policy and practice decision-making regarding the implementation of such interventions. Accordingly, an evaluation of the existing evidence is required. This review sought to appraise and synthesise the evidence that is currently
available regarding the efficacy of non-pharmacological interventions on psychological outcomes after heart transplantation.

**Methods**

**Design**

As per our protocol, we conducted a systematic review using the Joanna Briggs Institute methodology.\(^{22, 23}\)

**Search Strategy**

The literature was searched to identify experimental and quasi-experimental studies that involved the application of any non-pharmacological intervention for heart transplant recipients, provided that data on psychological outcomes were reported. Explanation of the inclusion and exclusion criteria for the review, including operating definitions of the terms that were used, is presented in Box 1. A comprehensive three step search strategy was used to find published and unpublished studies. The databases searched included Medline, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Excerpta Medica Database (EMBASE), Cochrane Database of Controlled Clinical Trials and PsycINFO. The search for unpublished studies included ProQuest Dissertation & Theses and Virginia Henderson International Nursing Library. The search for conference proceedings included Web of Science-ISI proceedings. Initial keywords used were ‘heart transplant’, ‘anxiety’, ‘depression’, ‘quality of life’ and ‘distress’.

The reference lists of retrieved papers, conference proceedings and unpublished literature (e.g. theses) were scrutinised for further primary research using the Google Scholar search engine, including its forward
citation search capacity. An example of the terms used for the database searches is in the Supplementary file 1. Also, the World Health Organisation’s International Clinical Trials Registry was searched to identify trials in-progress or being planned. No time limits were applied. Only articles written in English were included.

**Study Selection**

Titles and abstracts were initially screened. Then, all potentially relevant publications were retrieved in full-text. The full text version of all articles identified as being potentially relevant to the inclusion criteria was read by two reviewers for a final determination of study inclusion. Difference of opinion regarding study inclusion between the two reviewers was resolved through discussion and consultation with a content expert if required.

**Data Extraction and Risk of Bias Assessment**

Data was extracted from studies included in the review using the standardised data extraction tool from JBI-MAStARI. Included studies were assessed by two independent reviewers using standardised critical appraisal instruments from the Joanna Briggs Institute Meta Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI – Supplementary File 2).²²

**Data synthesis**

Due to sample size, heterogeneity of interventions and lack of comparisons between the control and intervention groups, meta-analysis was not performed. Instead, results from the included studies are summarised in a table and in narrative form.
**Results**

Seven articles were identified as being potentially relevant *Figure 1*. Three studies fulfilled the inclusion and exclusion criteria. There were no in-progress or planned trials identified in the search of conference abstracts and the World Health Organisation’s International Clinical Trial Registry Platform.

The characteristics and outcomes of the included studies are summarized in Table 1. In total, the studies involved only 125 heart transplant recipients. The methodological quality of the studies was low. Results of the quality appraisal for each of the included studies is presented in Supplementary File 3. Two of the studies investigated the efficacy of exercise on psychological outcomes. The other study was stated to test the efficacy of a psychosocial intervention.

**Exercise interventions**

The Christensen et al.\(^2\)\(^4\) study was a subanalysis of a randomized controlled trial of high intensity exercise. Anxiety and depression were measured with the Hospital Anxiety and Depression Scale (HADS) and mental health was measured with the Short Form (36) Health Survey (SF-36) at baseline and at 8 weeks follow-up. Of note, the baseline measurement was taken at study enrolment, which ranged in this sample around a mean of 6.7 years post-transplant for the intervention group and 7 years post-transplant for the control group. As measured by the HADS, a statistically significant (*p*=0.001) reduction in the mean anxiety score for the intervention group was observed (Baseline=4.7 (SD=1.8) to 1.8 (SD=1.2). Similarly, a statistically significant (*p*=0.001) reduction in the mean depression score for the intervention group...
was also observed (Baseline=1.9 (SD=1.8) to 0.7 (SD=0.8). There were no statistically significant changes in depression or anxiety scores in the usual care group. The mean score for the mental health domain of the SF-36 significantly improved (p=0.03) from 81.7 (SD=15.1) at baseline to 90 (SD=8.1) at the 8-week follow-up for the intervention group. There were no statistically significant changes in mental health, as measured by the SF-36, in the usual care group. Between-group comparisons were not reported for SF-36 or HADS scores.

Karapolat et al25 conducted a randomised controlled trial of hospital-supervised versus home-based exercise. Participants who conducted exercise at home were14.5 months (mean) post-transplant and participants who conducted exercise in the hospital were 16.7 months (mean) post-transplant. Quality of life was measured with the SF-36, depression was measured with the Beck Depression Inventory (BDI) and anxiety was measured with the State-Trait Anxiety Inventory (STAI). In the hospital-based exercise group, a significant increase (p<.05) from 74.13(SD=13.34) at baseline (study enrolment) to 80.93(SD=13.98) at 8 weeks follow-up was observed in the mental health domain of the SF-36. Changes observed in the BDI and STAI were not statistically significant (p>.05). Of note, no between-group comparisons were reported.

Psychosocial interventions

Dew et al.26 reported a non-randomised trial of an internet-based psychosocial intervention that enrolled a group of historical controls matched according to age, education, income and relationship to the caregiver. The web-based intervention incorporated stress and medical regimen workshops,
monitored discussion groups, access to communication with the transplant-team and information on transplant-related issues. Symptoms of anxiety and depression were measured with the Symptom Checklist-90 and quality of life was measured with the SF-36. In this study, while at baseline (study enrolment) the intervention group had significantly greater levels of anxiety and depressive symptoms compared with the control group, at 4 months follow-up there were no statistically significant differences (p>.05). Significantly greater reductions in depression and anxiety were observed among participants who used the website at least weekly (Depression r=0.29; p=0.036; Anxiety r=0.31; p=0.021). Mental health, as measured by the mental health domain of the SF-36, did not improve from pre (Mean=69; SD=5.2) to post (Mean=69.4; SD=4.2) intervention.

Discussion

We identified that only three studies have reported on the impact of non-pharmacologic interventions on psychological outcomes for heart transplant recipients. No ‘in-progress’ or ‘planned’ trials were identified in our search of the International Clinical Trial Registry Platform. This was a somewhat surprising finding, given that it has been more than six years since the call for more research in this field.

We have been able to elicit some insights from this review for researchers to consider in future intervention studies. First of all, two studies that reported on the efficacy of hospital-based exercise interventions identified significant improvements in anxiety and depression; albeit over a relatively short period of follow-up. Other research is consistent with these findings. A Cochrane review and meta-analysis identified that exercise improves mood in people
who have been diagnosed with a depressive disorder.\textsuperscript{27} The mechanism by which exercise improves mood has not been clearly identified though. It is possible that mood is improved as a direct result of increased physical fitness. As poor functional status has been linked with increased risk of psychological disorders post-transplant, this seems to be one plausible explanation for the improvements observed in psychological symptoms of those heart transplant recipients who participated in exercise.\textsuperscript{4} However, it is also possible that the social contact associated with a supervised exercise program rather than the actual exercise itself is the mechanism by which mood becomes improved. In the study by Karapolat et al.\textsuperscript{25}, which randomised heart transplant recipients to hospital-based or home-based exercise, improvements in the mental health domain of the SF-36 were only observed in the hospital-based group. Therefore, this seems to support the hypothesis that it might be social contact and not exercise that promotes psychological well-being for heart transplant recipients. It is important to note, though, that between group comparisons were not reported in either of the studies focused on exercise. As such, it is possible that the improvement in anxiety and depression in the intervention group from baseline to follow-up could have been caused by some other unmeasured factor. Therefore, while results from the studies included in our review support the conduct of further research to determine the efficacy of exercise in improving psychological symptoms post-heart transplant, careful attention should be paid to designing a study that can provide more valid and generalisable results.

The other study included in this review examined the efficacy of an internet-delivered psychosocial intervention.\textsuperscript{26} While levels of psychological symptoms
in the intervention group of this trial were higher than controls at baseline, symptoms decreased at follow up to a level that was comparable to the control group. Also of note, mental health and QOL benefits were greater among more frequent users of the website. These preliminary results suggest that internet-based psychosocial intervention could be an effective strategy. Also of note, this web-based psychosocial intervention addressed a number of the risk factors for psychological disorders post-heart transplant. For example, both insufficient social support and low perceived control have been associated with poor psychological outcomes.28, 29 It is possible that the transplant-related information provided and access to online peer and healthcare provider support improved perceived control and social support for heart transplant recipients. It is important to note that data on these specific variables were not reported though. As such, these potential mechanisms for the improvements in psychological outcomes observed in this study cannot be confirmed. Further studies that examine the efficacy of similar psychosocial interventions for heart transplant recipients should consider collecting this data in order to explain potential mechanisms for observed changes in psychological symptoms between intervention and control groups.

Absent from the literature were studies that investigated the impact of non-pharmacological interventions on psychological outcomes in heart transplant recipients fitting the criteria for psychopathology. All three studies recruited convenience samples of heart transplant recipients.24-26 Moreover, it is possible that heart transplant recipients with elevated depression or anxiety symptoms declined participation in the exercise and internet-based psychosocial intervention, due to a lack of motivation, as is common in this
Due to the high prevalence of psychological symptoms in heart transplant recipients, liberal application of non-pharmacological interventions to reduce or prevent the occurrence of anxiety and depression does seem reasonable. However, evidence from studies focused on non-pharmacological interventions, such as cognitive behavioural therapy, conducted with people who have other forms of cardiovascular disease that is complicated by comorbid depression or anxiety suggest that these interventions are effective in reducing psychological symptoms. As such, it seems reasonable that studies should also be conducted to determine efficacy in the heart transplant population.

A further important finding from this review is that the methodological quality of the studies that have reported on the impact of non-pharmacological interventions on psychological outcomes after heart transplantation was poor. Future studies should be conducted using more rigorous research designs, such as randomised controlled trials with sufficiently powered sample sizes.

It should also be noted that while this study focused on heart transplant recipients specifically, there have been similarly few studies that have reported on the efficacy of non-pharmacological interventions to improve psychological outcomes in the broader transplant population. For example, in a randomised controlled trial that enrolled 150 transplant recipients, eight 2.5 hour sessions of mindfulness meditation reduced anxiety symptoms more than active control participants who received health education. While promising, due to the small number of heart transplant recipients enrolled in this study, the effectiveness of this intervention in these patients cannot be confidently ascertained. Therefore, further study into improving psychological
outcomes for heart transplant recipients should consider meditation-based interventions. Only one further trial, the ‘Empowering Lung and Heart-Lung Transplant Patient’ trial, which has yet to be reported in the literature, was identified in the WHO clinical trials registry.

As the ISHLT report called for intervention studies for all cardiothoracic transplant recipients, a limitation of our review is that we focused on non-pharmacologic interventions to improve psychological outcomes for heart transplant recipients specifically. Therefore, it is possible that more studies have been undertaken that investigated pharmacological interventions, or interventions for lung transplant recipients. In addition, only articles written in English were included.

In summary, we found there is insufficient high-quality evidence available to draw conclusions for or against the use of non-pharmacologic interventions to improve psychological outcomes for heart transplant recipients. As such, further research is indicated.
<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Design</th>
<th>Number of Participants</th>
<th>Population characteristics</th>
<th>Interventions</th>
<th>Comparison</th>
<th>Results</th>
<th>JBI-MAStARI</th>
<th>Risk of bias</th>
</tr>
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<tbody>
<tr>
<td>Christiansen et al. (2012)²⁴</td>
<td>Randomised controlled trial</td>
<td>27 participants (14 received intervention)</td>
<td>• Participants were 6.8 years (mean intervention group) and 7 years (mean control group) post transplant</td>
<td>An 8 week program consisting of high-intensity aerobic interval training (&gt;80% of VO₂ max) for 60 minutes 3 days per week.</td>
<td>Standard care (no formalised exercise program)</td>
<td>At 8 weeks the intervention group had significantly improved levels of anxiety and depressive symptoms and mental health subscale scores of the SF-36.</td>
<td>5/10</td>
<td>High</td>
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<tr>
<td>Karopolat et al. (2007)²⁵</td>
<td>Randomised controlled trial</td>
<td>28 participants (15 hospital-based; 13 home-based)</td>
<td>• Participants were 14.5 months (hospital-based) and 16.7 months (home-based) post-transplant</td>
<td>Three home-based exercise sessions per week for 8 weeks, lasting approximately 1.5 hours, which included: • Flexibility • Aerobics (30 minutes duration on stationary bike or treadmill at</td>
<td>Three hospital-based exercise sessions per week for 8 weeks, lasting approximately 1.5 hours, which included: • Flexibility • Aerobics (30 minutes duration on stationary bike or treadmill at</td>
<td>• Mental health domain of SF-36 improved at follow-up in the hospital-based group • No significant difference in symptoms of anxiety (STAI) or depression (BDI) from baseline to follow-up in</td>
<td>5/10</td>
<td>High</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Sample</td>
<td>Intervention Details</td>
<td>Control Group Details</td>
<td>Notes</td>
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<tr>
<td>Dew et al. (2004)</td>
<td>Quasi-experimental trial with matched controls</td>
<td>60 participants (20 received intervention)</td>
<td>6-36 months post-transplant&lt;br&gt;75% male&lt;br&gt;Proportion of Orthotopic/heterotopic transplant recipients not reported</td>
<td>Internet-based psychosocial intervention that incorporated:&lt;br&gt;- Stress and medical regimen workshops&lt;br&gt;- Monitored discussion&lt;br&gt;- Electronic communication with healthcare providers&lt;br&gt;- Information on transplant-related health issues</td>
<td>Follow up at 4 months&lt;br&gt;Depressive and anxiety symptoms improved compared with control group&lt;br&gt;QOL in social functioning significantly improved&lt;br&gt;Mental health and QOL benefits were greater among more frequent users of the website</td>
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</tbody>
</table>

- 89% male
- 60-70% VO² max
- Strength training using progressively greater resistance
- Progressive muscle relaxation to conclude session
- 60-70% VO² max
- Strength training using progressively greater resistance
- Progressive muscle relaxation to conclude session
- Either hospital-based or home-based groups
- Dew et al. (2004) |

- Non-randomised
- Short follow-up
- No power analysis performed
- Intervention only offered to patients with access to the internet
- Psychiatric symptom levels higher at baseline (study enrolment) in intervention group
Box 1 Inclusion criteria & Exclusion criteria

**Inclusion criteria**

**Study type:** Experimental or quasi-experimental design

**Population:** Adult patients who had received a heart transplant

**Intervention:** Any non-pharmacological intervention. These may have been psychological interventions including, but not limited to, cognitive behaviour therapy, stress management and psychotherapy as well as other non-psychological interventions including, but not limited to, exercise and relaxation techniques.

**Comparison:** Consisted of standard care, pharmacological intervention or a variation of another non-pharmacological intervention

**Outcomes:** Diagnosis of a psychological disorder; Anxiety and/or depressive symptoms, as measured by a validated instrument; or mental health subscale of a validated quality of life instrument

**Exclusion Criteria**

Studies with mixed interventions (pharmacological and non-pharmacological) were excluded
Figure 1 Results of search strategy

Records identified through database searching
Medline, PsychInfo and CINAHL
n = 1323

Duplicates removed
n =  71

Records screened
n =  1252

Records excluded
n =   1246

Full-text articles assessed for eligibility
n =  7

Studies included in synthesis
n =  3

Additional records identified through other sources
Forward citation search using Google Scholar n=0
Bibliography search n=1
Conference abstracts n=1 (full report identified in database search)
WHO International Clinical Trials Registry n=0

Full-text articles excluded, with reasons
Report of program implementation with no psychological outcomes reported n=2
Reported on the use of psychological support services n=1
No pre to post intervention data reported n=1
REFERENCES


Supplementary File I: Search strategy

Identifiers (combined with 'OR')
heart transplant*
cardi* transplan*
heart allo*
cardi* allo*

Outcomes (combined with 'OR')
depress*
dysthyrm*
anxi*
stres*
mood dis*
mood dys*
adjustment dys*
adjustment dis*

Adjustment
Design (combined with 'OR')
clin* trial*
random* trial*
exp*
random* contro* trial*

Trial*
RCT

Controlled trial
Clinical controlled trial
Case control study
Cohort study
Case series
Case study
Supplementary File II: Appraisal instruments

this is a test message

JBI Critical Appraisal Checklist for Randomised Control / Pseudo-randomised Trial

Reviewer ___________________________ Date ___________________________

Author ___________________________ Year __________ Record Number __________

1. Was the assignment to treatment groups truly random? □ □ □ □ □
2. Were participants blinded to treatment allocation? □ □ □ □ □
3. Was allocation to treatment groups concealed from the allocator? □ □ □ □ □
4. Were the outcomes of people who withdrew described and included in the analysis? □ □ □ □ □
5. Were those assessing outcomes blind to the treatment allocation? □ □ □ □ □
6. Were the control and treatment groups comparable at entry? □ □ □ □ □
7. Were groups treated identically other than for the named interventions □ □ □ □ □
8. Were outcomes measured in the same way for all groups? □ □ □ □ □
9. Were outcomes measured in a reliable way? □ □ □ □ □
10. Was appropriate statistical analysis used? □ □ □ □ □

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## JBI Critical Appraisal Checklist for Comparable Cohort/Case Control

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<th>No</th>
<th>Unclear</th>
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<tr>
<td>1. Is sample representative of patients in the population as a whole?</td>
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<tr>
<td>2. Are the patients at a similar point in the course of their condition/illness?</td>
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<tr>
<td>3. Has bias been minimised in relation to selection of cases and of controls?</td>
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<tr>
<td>4. Are confounding factors identified and strategies to deal with them stated?</td>
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<tr>
<td>5. Are outcomes assessed using objective criteria?</td>
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<tr>
<td>6. Was follow up carried out over a sufficient time period?</td>
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<tr>
<td>7. Were the outcomes of people who withdrew described and included in the analysis?</td>
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<tr>
<td>8. Were outcomes measured in a reliable way?</td>
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<tr>
<td>9. Was appropriate statistical analysis used?</td>
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Overall appraisal: Include □ Exclude □ Seek further info. □

Comments (Including reason for exclusion)

____________________________________________________________________

____________________________________________________________________
### Supplementary File III

#### Table 1: Results of critical appraisal of included randomised controlled trials

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<th>Q8</th>
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<th>Q10</th>
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<tr>
<td>Christiansen et al. (2012)²⁴</td>
<td>Y</td>
<td>N</td>
<td>U</td>
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<td>U</td>
<td>N</td>
<td>U</td>
<td>N</td>
<td>U</td>
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Legend: Y=Yes; N=No; U=Unclear; N/A=Not applicable

#### Table 2: Results of critical appraisal of included cohort/case control studies

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<th>Citation</th>
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<th>Q3</th>
<th>Q4</th>
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<th>Q7</th>
<th>Q8</th>
<th>Q9</th>
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<td>Dew et al. (2004)</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>N/A</td>
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</table>

Legend: Y=Yes; N=No; U=Unclear; N/A=Not applicable