Effectiveness of Cognitive Behavioral Therapy for Depression and Anxiety in Patients With Cardiovascular Disease

A Systematic Review and Meta-Analysis

Reavell, James; Hopkinson, Michael; Clarkesmith, Danielle; Lane, Deirdre A

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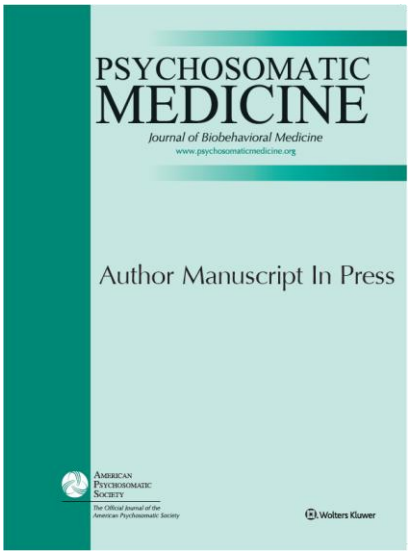

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Authors: James Reavell, Michael D. Hopkinson, Danielle Clarkesmith, and Deirdre A. Lane

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Effectiveness of cognitive behavioral therapy for depression and anxiety in patients with cardiovascular disease: a systematic review and meta-analysis

James Reavell, BMedSci[a], Michael Hopkinson, BMedSci[a],

Danielle Clarkesmith, PhD[b], Deirdre A Lane, PhD[b,c]

[a]College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom.

[b]University of Birmingham Institute of Cardiovascular Sciences, City Hospital, Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, United Kingdom.

[c]Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark.

Address for correspondence:

Dr DA Lane; University of Birmingham Institute of Cardiovascular Sciences, City Hospital, Sandwell and West Birmingham Hospitals NHS Trust, Dudley Road, Birmingham, B18 7QH, United Kingdom

Tel.: +44 (0)121 507 5080; Fax: +44 (0)121 554 4083

Email: deirdrelane@nhs.net

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ABSTRACT

Objective: Depression and anxiety are highly prevalent in patients with cardiovascular disease (CVD), and influence their mental wellbeing and CVD prognosis. The primary objective was to assess the effectiveness of cognitive behavioral therapy (CBT) for depression and anxiety in patients with CVD. Secondary objectives were to assess the impact of CBT on cardiovascular mortality, cardiovascular events, patient satisfaction and quality of life (QoL).

Methods: MEDLINE, PsycINFO, CINAHL, CENTRAL, and alternative sources, were searched for randomized controlled trials (RCTs) and observational studies with a control. Studies were required to assess CBT in coronary heart disease, acute coronary syndrome, atrial fibrillation or post-myocardial infarction patients, with anxiety and/or depression. Studies were independently screened by two reviewers and critically appraised using the Cochrane Risk of Bias tool. The random effects model was used to pool standardized mean differences.

Results: Twelve RCTs were included. At follow-up, depression (SMD -0.35, 95% CI -0.52 to -0.17, $p< 0.001$, $I^2= 59\%$) and anxiety (SMD -0.34, 95% CI -0.65 to -0.03, $p= 0.03$, $I^2= 71\%$) scores were significantly lower in CBT patients compared to controls. Change in mental health QoL (SF-12) was also significantly greater for CBT patients, compared to controls (MD 3.62, 95% CI 0.22 to 7.02, $p= 0.04$, $I^2= 0\%$). No differences in patient satisfaction or cardiovascular events were evident between CBT and control groups. Among the study reports included in this meta-analysis, data specific to cardiovascular mortality were not reported.

Conclusions: CBT appears to be an effective treatment for reducing depression and anxiety in patients with CVD and should be considered in standard clinical care.

Key words: Cognitive behavioral therapy; Depression; Anxiety; Cardiovascular disease; Systematic review; Meta-analysis

Acronyms:

ACS= acute coronary syndrome**, AF=** atrial fibrillation, **CABG=** coronary artery bypass grafting, **CBT=** cognitive behavioral therapy, **CENTRAL=** Cochrane Central Register of Controlled Trials, **CHD=** coronary heart disease, **CI**= confidence interval, **CVD=** cardiovascular disease, **DSM=** Diagnostic and Statistical Manual of Mental Disorders, **GRADE=** Grading of Recommendations Assessment, Development and Evaluation, **ICD=** implantable cardioverter defibrillator, **MI=** myocardial infarction, **NICE=** The National Institute for Health and Care Excellence, **PRISMA=** Preferred Reporting Items for Systematic Reviews and Meta-analyses, **QoL=** quality of life, **RCT=** randomized controlled trial, **RoB=** risk of bias.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of mortality worldwide and responsible for almost one third of all deaths (1). European guidelines recognize depression and anxiety as important factors that contribute to the risk of developing CVD and a worse CVD prognosis, however the relationship between mental illness and CVD has received less recognition globally (2). Mechanisms linking anxiety and depression with CVD are unconfirmed however, biological and behavioral processes have been proposed (3,4). Both anxiety and depression have been implicated in the dysfunctional activity of the autonomic nervous system and hypothalamic-pituitary-adrenal axis which affect the cardiovascular system (3,4). Poor lifestyle behaviors such as smoking, inactivity and low treatment adherence which increase the CVD risk are also common in anxious and depressed patients (4).

Prevalence of depression and anxiety among CVD patients is up to 3-fold higher than in the general population (5,6). Changes in quality of life (QoL) and the impact of a chronic disease can significantly affect mental wellbeing. Among coronary heart disease (CHD) patients, approximately 20% meet the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for major depression, and this can impact on disease outcomes (7). Depressed CVD patients experience a 2-fold increased risk of associated cardiovascular events and mortality (8). After a cardiovascular event, patients often experience anxiety which remains unresolved for 50% of patients throughout the following year (9). Anxiety and depression commonly co-occur however the prognostic implications of suffering with both conditions are worse, resulting in a 3-fold increased risk of mortality (10). Therefore, treating depression and anxiety within CVD groups is important for both their mental wellbeing and CVD outcomes.

Cognitive behavioral therapy (CBT) is currently recommended as the first-line treatment for anxiety (11) and depression (12) by the National Institute for Health and Care Excellence

(NICE) in the United Kingdom. During CBT, patients learn to monitor and improve their psychological wellbeing by recognizing and challenging unhelpful thinking patterns. Implementing different behaviors and thinking patterns, identified with the therapist, is integral to overcoming the negative emotions (13). CBT adopts a range of strategies that alter factors which maintain, trigger and exacerbate symptoms thus having the potential to increase adherence to medications and cardiac rehabilitation programmes (13,14).

Current systematic reviews investigating the effectiveness of CBT are limited to patients with implantable cardioverter defibrillators (ICD), which report 20-60% reductions in depressive and anxious symptoms after CBT (15), and heart failure patients which found that CBT improved both anxious and depressive symptoms, and cardiac event survival (16,17). These findings however, should be interpreted with caution as few studies were included, interventions were mixed (e.g. CBT +/- an additional intervention), and lengths of follow-up differed. Further systematic reviews with meta-analyses have also found significantly improved anxious and depressive symptoms in CHD patients receiving various (non-CBT specific) psychological interventions (18-20).

The effectiveness of CBT has not been assessed in CHD, acute coronary syndrome (ACS), atrial fibrillation (AF) and post-myocardial infarction (MI) patients, and the management of anxiety in CVD patients has also received less research focus (3). Therefore, this systematic review will assess the effectiveness of CBT for depression and/or anxiety in patients with CVD (CHD, ACS, AF or post-MI) and investigate the effects of CBT on cardiovascular events, cardiovascular mortality, patient satisfaction and QoL.

METHODS

This systematic review and meta-analysis was prospectively registered with the PROSPERO database of systematic reviews (CRD42017057723) (21), and conducted in accordance with

the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (22).

Criteria for considering studies for the review

Randomized controlled trials (RCTs) and observational studies with a concurrent control group were eligible for inclusion. Studies were required to have a baseline and at least one follow-up measure for depression and/or anxiety. Access to the full-text publication was a requirement. There were no date or language restrictions.

Participants

Eligible participants were those with CVD (CHD, ACS, AF or post-MI) and depression or anxiety. Anxiety or depression was defined as either a clinical diagnosis (International Classification of Diseases (23), DSM (24), or similar) or the presence of anxious and/or depressive symptoms (≥ a pre-defined cut-off on a validated questionnaire). Studies of ICD and heart failure patients were excluded as recent previous systematic reviews have assessed the effectiveness of CBT for depression and/or anxiety in these patients (15,17).

Interventions

Interventions described as CBT or based on CBT principles were eligible for inclusion, where patients were taught to monitor their mood by identifying and challenging the thoughts and behaviors at the source of their depressive or anxious state. This could have been referred to as CBT, cognitive therapy or behavioral therapy. However, interventions that solely used the principles of cognitive therapy or behavioral therapy alone were excluded. 'Third wave' CBT was also excluded because some forms only focus on one traditional CBT principle. Other psychotherapies (e.g. cognitive analytical therapy, psychodynamic psychotherapy and interpersonal psychotherapy) were excluded. Studies that investigated CBT as one element

within a mixed intervention package were not included, although CBT with an adjunctive antidepressant as recommended by NICE was accepted (12).

Comparators

Eligible comparators were medications, usual care (including other psychological therapies), waiting list control or no treatment.

Outcomes

The primary outcome was a reduction in anxiety and/or depression in CVD patients following CBT. Patients still classified as depressed and/or anxious according to a validated questionnaire and those no longer meeting the clinical diagnosis at follow-up were also reported. Secondary outcomes included: cardiovascular events, cardiovascular mortality, patient satisfaction and QoL.

Search Strategy

The search strategy was developed by the research team and checked by an information specialist prior to execution (see Supplementary Figure S1, Supplemental Digital Content, http://links.lww.com/PSYMED/A498). Key words such as 'CBT', 'Heart diseases', 'Anxiety' and 'Depression' were used. MEDLINE, PsycINFO, CINAHL and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched from inception to 10th February 2017 for relevant studies. No language restrictions were applied.

Reference lists of included studies were manually searched and citation searches were completed to identify other relevant articles. Grey literature was addressed by contacting the leading authors of included papers and key opinion leaders for unpublished data. Clinicaltrials.gov was searched for unpublished protocols of RCTs from 2007-2017. Conference proceedings of the European Society of Cardiology, American Heart Association and American College of Cardiology 2015-2017 were also searched.

Study Selection

Study selection was undertaken by two independent reviewers (JR, MH). Papers with irrelevant titles and abstracts were excluded and those deemed eligible or unclear were further assessed in their full-texts. Original authors were contacted for additional information when necessary for eligibility assessments. Disagreements over study eligibility were resolved by discussion and adjudication by a third reviewer (DL).

Data Extraction

Using a standardized, pre-piloted data extraction form, data were extracted by one reviewer (JR), with 25% checked by another reviewer (MH). Information regarding the study characteristics (study design, and sample size), participants (age, sex, psychiatric assessment, and CVD diagnosis), intervention (mode of delivery, duration, frequency, providers, and follow-up points) and comparator were gathered. For the primary outcome, mean differences and standard deviations for anxiety and depression scores between baseline and follow-up and the proportion still classified as depressed and/or anxious at follow-up were extracted. The proportion no longer meeting the clinical diagnosis for anxiety and/or depression at follow-up was noted. For the secondary outcomes, the proportions of patients experiencing cardiovascular events and death were collected in addition to mean differences and standard deviations for patient satisfaction (on a Likert scale) and QoL (on a validated questionnaire) between baseline and follow-up.

Original authors were contacted when information was unclear or missing. If changes in scores between baseline and follow-up were unavailable and could not be imputed, follow-up scores were used as an alternative outcome. Only findings reported post-CBT were extracted.

Four authors (25-28) were contacted for missing standard deviations, however only one author provided this data (27). Six authors provided data on an eligible study subgroup of their population (29-34).

Risk of Bias Assessment

Two reviewers independently assessed the risk of bias (RoB) using the Cochrane RoB tool (35) for RCTs (all included studies were RCTs), consisting of six domains: random sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; selective reporting; and other sources of bias. RoB was assigned as 'high', 'low' or 'unclear' for each domain.

Data Synthesis

For anxiety, depression, patient satisfaction and QoL outcomes, attempts were made to report change from baseline scores. If this data were not reported and could not be provided by study authors, imputation was attempted. However, the correlation coefficients calculated for anxiety, depression, and QoL were ≤0.5 or were too different to average and therefore, follow-up scores were used as an alternative outcome, as recommended by Cochrane (36). Standardized mean differences and 95% confidence intervals (CIs) were calculated for continuous outcomes when data were measured using different scales. When outcomes were measured using the same scales, mean differences and 95% CIs were calculated. The proportions experiencing continued depression and/or anxiety (according to a validated questionnaire), cardiovascular death, cardiovascular event(s), and those no longer meeting a clinical diagnosis of depression and/or anxiety at follow-up were each summarized with odds ratios and 95% CIs.

Effect estimates were pooled using RevMan 5.3. DerSimonian and Laird random-effects method (36) was employed when outcome scales differed between studies and standardized mean differences were used; when outcomes used the same scales in analyses, the fixed effects model was employed when pooling mean differences. Heterogeneity was assessed by observing the overlap of confidence intervals on the forest plots and the I^2 value, with meta-analysis deemed inappropriate if there was considerable heterogeneity ($I^2 \geq 75\%$) (36).

When studies had multiple trial arms, the CBT intervention was compared to usual care. If outcomes were measured at different time-points, the first outcome measure reported post-CBT was used in the meta-analysis. If studies reported multiple depression scores from different scales, the most common scale used by other eligible studies was chosen when pooling effect estimates to minimize heterogeneity.

Publication Bias

Publication bias was assessed using a funnel plot and Egger's test when outcomes included ≥10 studies.

Risk of Bias across Studies (Quality Assessment)

Quality of the outcomes was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) considerations (37).

Subgroup Analyses

Pre-specified subgroup analyses were conducted for each CVD (e.g., CHD, AF, etc.) where data were available, the mode of CBT delivery, and different lengths of follow-up. Study data on post-coronary artery bypass grafting (CABG) participants were included within the CHD subgroup analysis (a CHD history was assumed). Subgroup analyses for the mode of delivery (face-to-face, telephone and mixed-method sessions), length of CBT course (short: 0-300 minutes, medium: 301-600 minutes, and long: >600 minutes), and length of follow-up (short-term: baseline to ≤3 months, medium-term: >3 months but ≤6 months, and long-term: >6 months) were completed.

Sensitivity Analyses

Sensitivity analyses were undertaken for studies with clinically diagnosed anxiety and/or depression versus no clinical diagnosis, and for the primary outcomes excluding studies with a high RoB. A sensitivity analysis comparing RCTs versus observational studies was planned

but all included studies were RCTs. Further sensitivity analyses were completed for all studies vs no US trials, and all studies vs no ENRICHD trial.

RESULTS

Study Selection

Searches identified 2115 articles (Figure 1). After the removal of duplicates (n=141), the titles and abstracts of 1974 papers were independently assessed for eligibility by two reviewers. Of these, 117 papers were deemed potentially relevant and assessed for eligibility in their full-texts; 107 articles were excluded and 2 studies were ongoing (CBT-AF (ISRCTN33129243) (38) and U-CARE Heart trial (NCT01504191) (39)). Reviewers' agreement was 96.7%. Twelve papers were included, of which 2 were identified from reference lists of included studies (28,31) and 2 through citation searches (26,32).

Characteristics of the Included Studies

All included studies were RCTs and in English, conducted in the US (n=7) (26-32), Germany (n=2) (25,40), Australia (n=2) (33,41), and the UK (n=1) (34), (Table 1).

Participants

Participants were CHD (6 studies) (25-27,32,34,40), ACS (4 studies) (28,30,31,41) or post-MI (1 study) (29) patients, and 1 study was a mixed CVD group (33). Studies recruited participants based on anxiety and/or depression (3 studies) (26,28,34), depression alone (8 studies) (25,27,29-33,41), or anxiety alone (1 study) (40). Eight studies recruited participants using a validated questionnaire (26, 28,30,31,33,34,40,41), 1 used a formal clinical diagnosis (29) and 3 used a combination (25,27,32). Participants tended to be male (38.5-87.5%), over 60 years (mean= 55.6-64.2 years), and of white ethnicity. Study sample sizes ranged from 43 to 1332 participants.

Interventions

CBT was the named intervention in 8 studies (25-29,32,33,41), and 4 studies described interventions based on CBT principles (30,31,34,40). Adjunctive antidepressants were offered in 3 studies (29-31). CBT was delivered through face-to-face (7 studies) (25-27,29,32,33,40), mixed-method (3 studies) (30,31,34) or telephone (2 studies) (28,41) sessions; all studies delivered ≥4 sessions. CBT was provided by psychologists (5 studies) (26,28,33,40,41), psychotherapists (3 studies) (25,29,31), mixed groups of healthcare professionals (2 studies) (27,30), and trained nurses (2 studies) (32,34).

Comparator

All comparators were usual/standard care, except in 2 studies which either provided a brief intervention of information and feedback on baseline assessments (also received by the intervention group) or no intervention (33,40). Studies described usual care as dependent on the patient's primary care physician (30-32,41) and standard care involved identification of risk factors and advice on risk reduction (34), or booklets on coping with CVD (28).

Outcomes

Baseline and follow-up scores for anxiety were available in 9 studies (25-28,31-34,40) and depression in 12 studies (25-34,40,41). Four depression scales and 5 anxiety scales were used at various time-points (1-12 months) to measure depression and anxiety (Table 2). Four studies reported the proportion of participants achieving remission of depression at follow-up; the proportion still depressed at follow-up was calculated (27,31-33). One study reported the proportion of participants no longer meeting a clinical diagnosis of depression at follow-up (32). No studies published cardiovascular mortality data for participants eligible for inclusion in this review; however, 2 studies recorded cardiovascular events (nonfatal MI or hospitalization for unstable angina) (30,31). Two studies reported changes in patient satisfaction between baseline and follow-up (30,34). Participant QoL was available in 5

studies (26,27,31,34,41) and was assessed as physical or mental QoL (SF-12) separately, or the sum of the QoL.

Risk of Bias within Studies

Due to the nature of CBT all studies had a high RoB for personnel and participant blinding. Of the 12 included studies, a high RoB was assigned to 3 for incomplete outcome data (25,28,40), 2 for other biases (28,29) and 1 for selective reporting (29) (Figure 2). An unclear RoB was assigned to 4 studies for allocation concealment (26,28,32,40), and to 6 studies (25,26,28,32-34) for selective reporting as protocols were unavailable.

Sensitivity analyses of the primary outcomes were conducted for studies without a high RoB for the following domains: blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. The domains listed were those with studies rated at a high RoB. Sensitivity analyses demonstrated the inclusion of studies with a high RoB did not significantly influence the primary outcomes (data not shown).

Effectiveness of CBT for Depression and Anxiety

The pooled depression follow-up scores from all 12 studies included 2254 participants (25-34,40,41). Depression follow-up scores were significantly lower in CBT patients than in controls (SMD -0.35, 95% CI -0.52 to -0.17, $p< 0.001$, $I^2= 59\%$) (Figure 3A). Compared to controls, fewer CBT participants remained depressed after the intervention (OR 0.29, 95% CI 0.12 to 0.69, $p= 0.005$, $I^2= 62\%$) (Figure 3B). One study reporting the proportion of participants no longer meeting a clinical diagnosis of depression found the CBT group had significantly fewer participants (31%) no longer meeting the diagnosis for depression compared to the controls (83%) (OR 0.10, 95% CI 0.03 to 0.36, $p< 0.001$) (32).

The pooled anxiety follow-up scores from 9 studies included 605 participants (25-28,31-34,41). Anxiety was significantly lower in CBT patients than in controls however, substantial heterogeneity was present (SMD -0.34, 95% CI -0.65 to -0.03, $p= 0.03$, $I^2= 71\%$) (Figure 4).

Cardiovascular mortality

No studies published cardiovascular mortality data for depressed or anxious CVD patients. One trial had subgroup data for depressed only CVD patients, but this was not accessible to the authors for inclusion in this review (29).

Cardiovascular events

Two studies including 260 participants reported cardiovascular events (30,31). The pooled scores showed fewer cardiovascular events in CBT patients compared to the controls however, this was not statistically significant (OR 0.80, 95% CI 0.33 to 1.93, p= 0.62, I^2= 0%).

Patient satisfaction

Two studies (130 participants) provided a change in patient satisfaction between baseline and follow-up (30,34). Pooled scores demonstrated greater patient satisfaction in favor of CBT compared to controls however, this was not statistically significant (SMD 0.11, 95% CI -0.29 to 0.51, p= 0.28, I^2= 16%).

Quality of Life

A non-significant difference between the CBT and control groups was observed for the change in physical health QoL (SF-12) (MD 2.59, 95% CI -0.41 to 5.60, p= 0.09, I^2= 0%) however, the change in mental health QoL (SF-12) was significantly better in CBT patients compared to controls (MD 3.62, 95% CI 0.22 to 7.02, p= 0.04, I^2= 0%). Overall QoL at follow-up was greater in CBT patients compared to controls but this was not significant (SMD -0.10, 95% CI -0.47 to 0.26, p= 0.58, I^2= 47%).

Publication Bias

A visual assessment of the funnel plot for depression follow-up highlighted little asymmetry (see Supplementary Figure S2, Supplemental Digital Content,

http://links.lww.com/PSYMED/A498). The Egger's test for publication bias was not significant (0.034, 95% CI -1.82 to 1.89, p= 0.97).

Risk of Bias across Studies (Quality Assessment)

Using the GRADE considerations, the quality of the primary and secondary outcomes was reported as either 'low' or 'very low' within a Summary of Findings table (see Supplementary Table S3, Supplemental Digital Content, http://links.lww.com/PSYMED/A498).

Subgroup Analyses

A subgroup analysis conducted for CHD participants found a smaller proportion of those receiving CBT were still classified as depressed at follow-up, compared to controls (OR 0.14, 95% CI 0.06 to 0.30, p< 0.001, I^2= 0%), however, anxiety and depression follow-up scores demonstrated considerable heterogeneity (I^2 ≥75%) so pooling was deemed inappropriate. There was insufficient data for subgroup analyses of the secondary outcomes.

A significant difference in depression at follow-up (SMD -0.29, 95% CI -0.48 to -0.09, p= 0.003, I^2= 4%) was observed in ACS patients receiving CBT but not for anxiety (SMD -0.16, 95% CI -0.48 to 0.16, p=0.34, I^2= 0%).

There was a significant reduction in depression at follow-up between CBT and control patients after face-to-face sessions (SMD -0.48, 95% CI -0.73 to -0.23, p< 0.001, I^2= 60%) but not following telephone (SMD -0.17, 95% CI -0.57 to 0.23, p= 0.40, I^2= 49%) or mixed-method (SMD -0.19, 95% CI -0.56 to 0.18, p= 0.32, I^2= 66%) sessions. Anxiety was only significantly reduced following face-to-face CBT (SMD -0.48, 95% CI -0.90 to -0.07, p= 0.02, I^2= 73%).

Depression and anxiety were significantly reduced in patients receiving CBT at short-term (SMD -0.47, 95% CI -0.84 to -0.10, p= 0.01, I^2= 69% for depression; SMD -0.44, 95% CI -0.88 to 0.01, p= 0.05, I^2= 77% for anxiety) and medium-term follow-up (SMD -0.26, 95% CI

-0.39 to -0.12, p< 0.001, I^2= 28% for depression; SMD -0.26, 95% CI -0.46 to -0.06, p= 0.01, I^2= 3% for anxiety), but not at long-term follow-up (SMD -0.37, 95% CI -1.12 to 0.38, p= 0.34, I^2= 72% for depression; SMD -0.46, 95% CI -0.83 to -0.10, p= 0.01, I^2= 0% for anxiety) compared to controls.

A significant reduction in anxiety was seen in long CBT courses (SMD -0.42, 9%% CI -0.77 to -0.08, p= 0.02, I^2= 0%) but not in short or medium courses (SMD -0.33, 95% CI -1.01 to 0.35, p= 0.34, I^2= 88%; SMD -0.30, 95% CI -0.63 to 0.02, p=0.07, I^2= 0%), compared to controls. A significant reduction in depression was seen in medium CBT courses (SMD -0.35, 95% CI -0.45 to -0.26, p<0.001, I^2= 0%) but not for short or long courses (SMD -0.23, 95% CI -0.72 to 0.26, p=0.36, I^2= 79%; SMD -0.55, 95% CI -1.40 to 0.30, p=0.20, I^2= 82%), compared to controls.

Sensitivity Analysis

Removal of participants with clinically diagnosed depression (29) did not significantly alter the primary outcomes (depression: SMD -0.34, 95% CI -0.56 to -0.12, p= 0.002; anxiety: SMD -0.34, 95% CI -0.65 to -0.03, p= 0.03; proportion remaining depressed: OR 0.29, 95% CI 0.12 to 0.69, p= 0.005).

Depression and anxiety at follow-up were attenuated and became non-significant when the US trials were excluded from the analyses (SMD -0.12, 95% CI -0.36 to 0.13, p= 0.36, I^2= 25%; SMD -0.12, 95% CI -0.38 to 0.15, p= 0.38, I^2= 0%). Removal of the ENRICHD trial (29), resulted in a marginal change in depression at follow-up and it remained significant (SMD -0.34, 95% CI -0.56 to -0.12, p= 0.002, I^2= 63%).

DISCUSSION

This is the first systematic review and meta-analysis to specifically investigate the effectiveness of CBT for anxiety and depression in CHD, ACS, AF and post-MI patients. CBT significantly reduced both depression and anxiety, and improved QoL compared to

controls. However, substantial heterogeneity was present in the pooled anxiety follow-up scores so these results should be interpreted with caution. CBT also significantly reduced the proportion of patients still depressed at follow-up, when compared to controls. However, there were no significant differences between CBT and control patients regarding cardiovascular events or patient satisfaction. This may be partly attributable to the lack of available data for these outcomes. Compared to controls, face-to-face CBT was the only mode of delivery to demonstrate statistically significant differences in anxiety and depression. Depression and anxiety were significantly reduced at all follow-up points.

With the known association between poor mental health and worse CVD outcomes (2), future studies should investigate the impact of CBT on cardiovascular mortality and events. A previous systematic review in CHD patients found a small but non-significant effect of psychological interventions in reducing cardiac mortality (RR 0.80, 95% CI 0.64 to 1.00, p= 0.56, I^2= 0%) (20). Previous reviews have also demonstrated beneficial effects of mixed psychological interventions in depressed CHD patients (18-20). Greater reductions in depression have been demonstrated in this review, and may indicate the superiority of CBT to other psychological interventions. Unfortunately, other CVDs such as AF have received less research focus and only one included study recruited AF patients (33). An on-going trial is currently investigating the effectiveness of CBT in AF patients with depression and/or anxiety (38).

The benefit of face-to-face CBT over other methods may indicate the importance of personal and interactive sessions, and this should be considered in future CBT trials. Internet-based CBT alone was not investigated by any included study so the individual effect could not be deduced. This method may provide a widely accessible and cheaper form of CBT although may not be suitable for moderate-to-severe depression or anxiety. No study has investigated the effectiveness of internet-based CBT in CVD patients (post-MI, CHD, ACS or AF) with

depression and/or anxiety. However, an on-going trial, examining the effectiveness of internet-based CBT in post-MI patients with depression and/or anxiety (39), may indicate any potential benefit of internet-based CBT in CVD patients. Interestingly, depression and anxiety at follow-up were attenuated and non-significant after the removal of the US trials. When interpreting this finding, it is important to remember that 7/12 trials included within this review were conducted in the US and therefore, US patients represent the largest proportion (84%). The sensitivity analysis suggests that the US trials are driving the positive findings of CBT on a reduction in depression and anxiety. There may be country-specific differences in the experiences of patients and/or delivery of CBT which influenced the results of these trials.

Reductions in depression were greatest at short-term follow-up, thus suggesting longer CBT courses may be required to maintain psychological wellbeing post-intervention. Anxiety symptoms however, were most improved at long-term follow-up. This could be explained by heightened anxiety regarding therapy completion, and concerns of less therapist contact (14).

This review has numerous strengths. A range of databases were searched without restrictions on language or timescales, authors supplied subgroup data, and the study selection process and RoB assessments were conducted independently by two reviewers. However, there was considerable heterogeneity between study participants, outcome scales, CBT content and delivery, which may influence the findings.

There are some limitations to this review. Within studies, blinding participants to CBT is challenging and can be problematic when outcomes are self-reported. The participant's knowledge of their allocation could influence their responses and introduce social desirability bias. Four studies (25,28,29,40) also had a high RoB for ≥1 of the remaining RoB tool domains. However, when assessed in a sensitivity analysis, removal of studies with a high RoB did not significantly affect the review's primary results. The review outcomes were

assessed by GRADE as low or very low quality which is partly attributable to the fact that the participants and personnel could not be blinded. However, other factors affecting outcome quality such as heterogeneity and differences in intervention delivery between studies could be overcome in future RCT trials by using similar outcome measures, methodology and intervention delivery. As this review has suggested, at least 5 hours of CBT is necessary to reduce anxiety and depression in CVD patients. Furthermore, long-term follow-up may be more valuable for identifying the effects of CBT on anxiety and depression. For some studies only a specific sample of their participants were relevant to this review, which consequently created smaller sample sizes. Furthermore, subgroup analysis data were not available from all the studies (29). Future RCTs should increase their sample sizes of CHD, ACS, AF and post-MI patients in order to improve the quality of review outcomes.

This review supports the use of CBT as a first-line treatment for anxiety and depression in CVD patients, as recommended by NICE (11,12). To maximize the benefit of this therapy, clinicians should prioritize face-to-face sessions and increase CBT duration. However, CBT is time-consuming and expensive, therefore other methods may be required. On-going research may demonstrate the benefits of internet-based sessions with the potential to lower CBT costs (39). Previous research suggests men and women with CHD respond differently to depression treatment (29). However, no review within this field has assessed the effects of CBT on depression or cardiovascular outcomes by gender. Due to lack of access to data separately for men and women in half of the studies included in this review, an analysis by gender was not possible however, future research should assess the gender differences in the effects of CBT and report findings by gender.

In conclusion, this review and meta-analysis supports the effectiveness of CBT in reducing anxiety and depression and improving QoL in CVD patients, and indicates this therapy should be considered by clinicians. However, considerable heterogeneity was present

between studies and AF patients were poorly represented. Face-to-face CBT sessions appear to achieve the greatest patient benefit and this should be considered when designing future studies. Furthermore, it is essential that cardiovascular outcomes are recorded to develop our understanding of the impact of CBT on CVD prognoses.

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Figure captions

Figure 1: PRISMA flow diagram for the study selection process

Figure 2: Risk of Bias Assessment for the Included Studies

Figure 3A: Forest plot of depression follow-up scores

Figure 3B: Forest plot of participants remaining depressed at follow-up

Figure 4: Forest plot of anxiety follow-up scores

Figure 1: PRISMA flow diagram for the study selection process

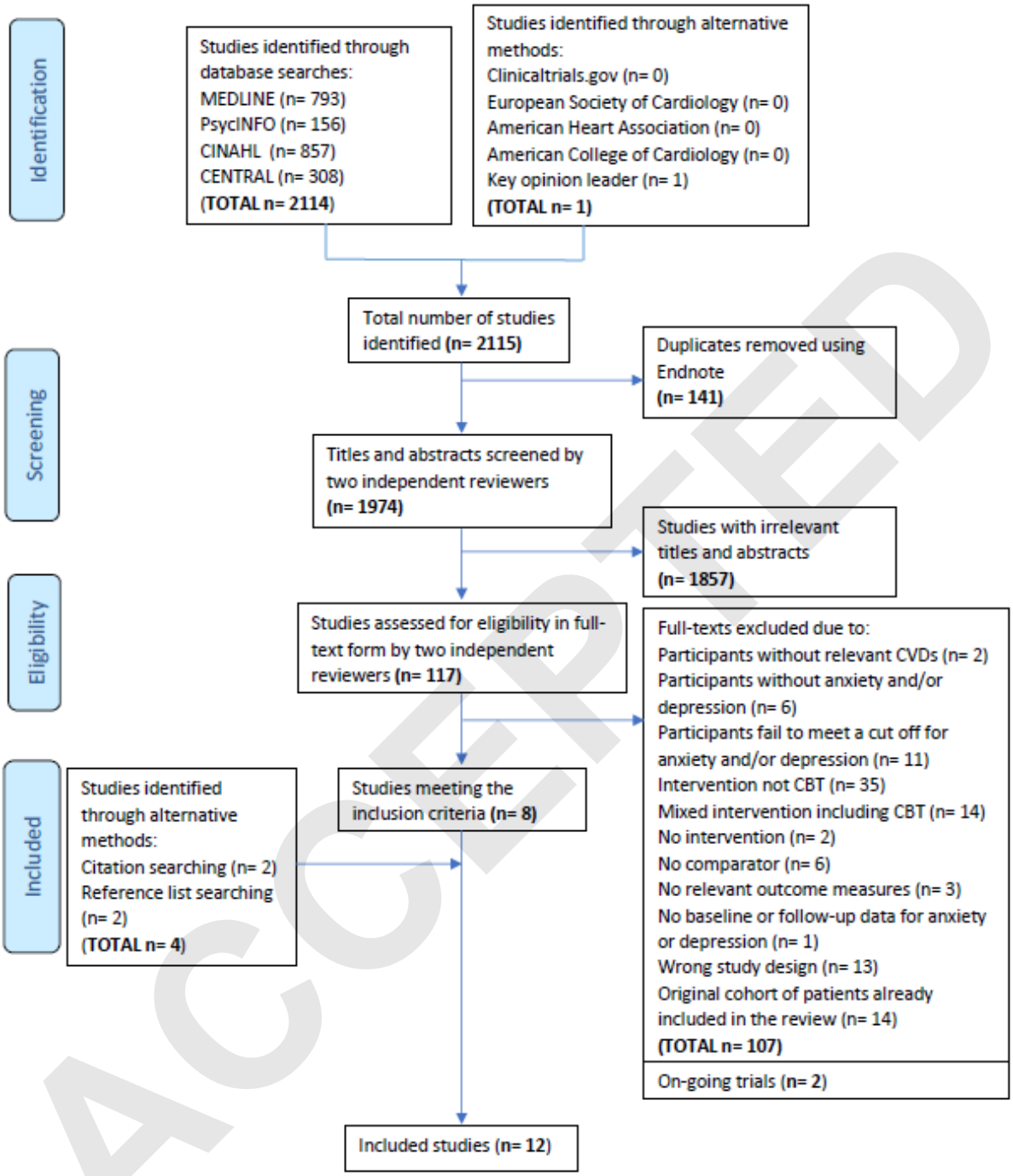

Figure 2

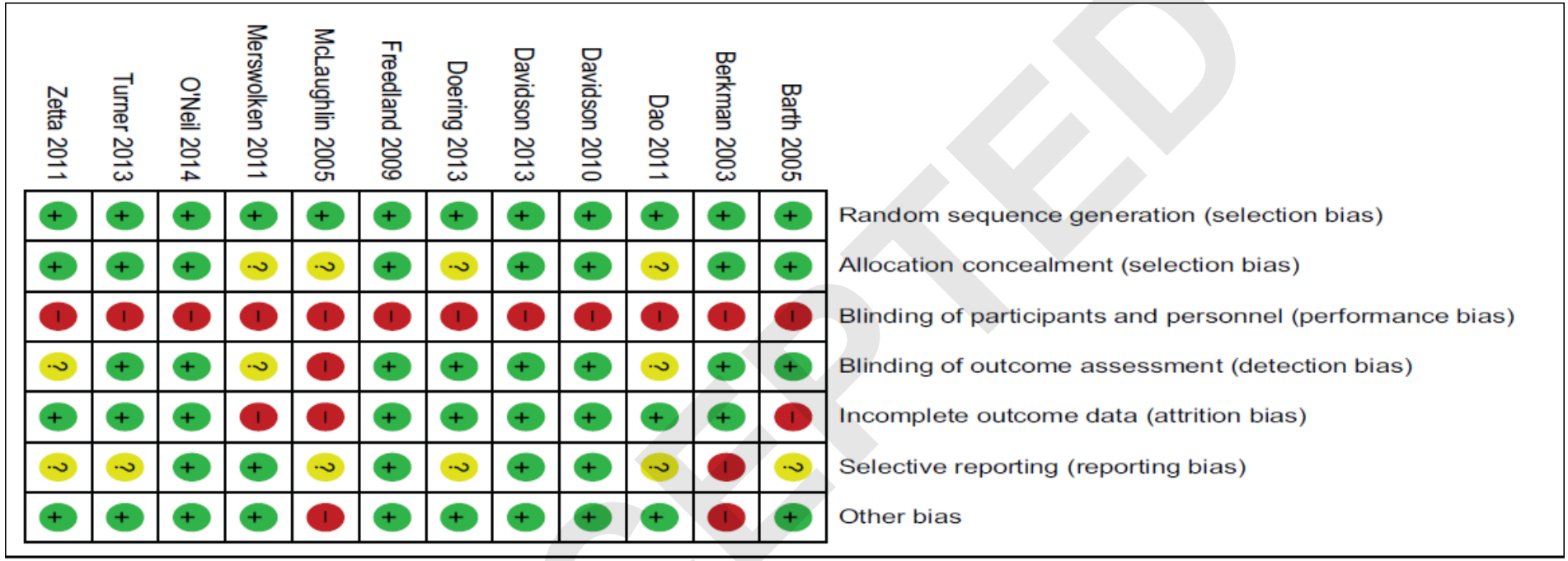

Figure 3a

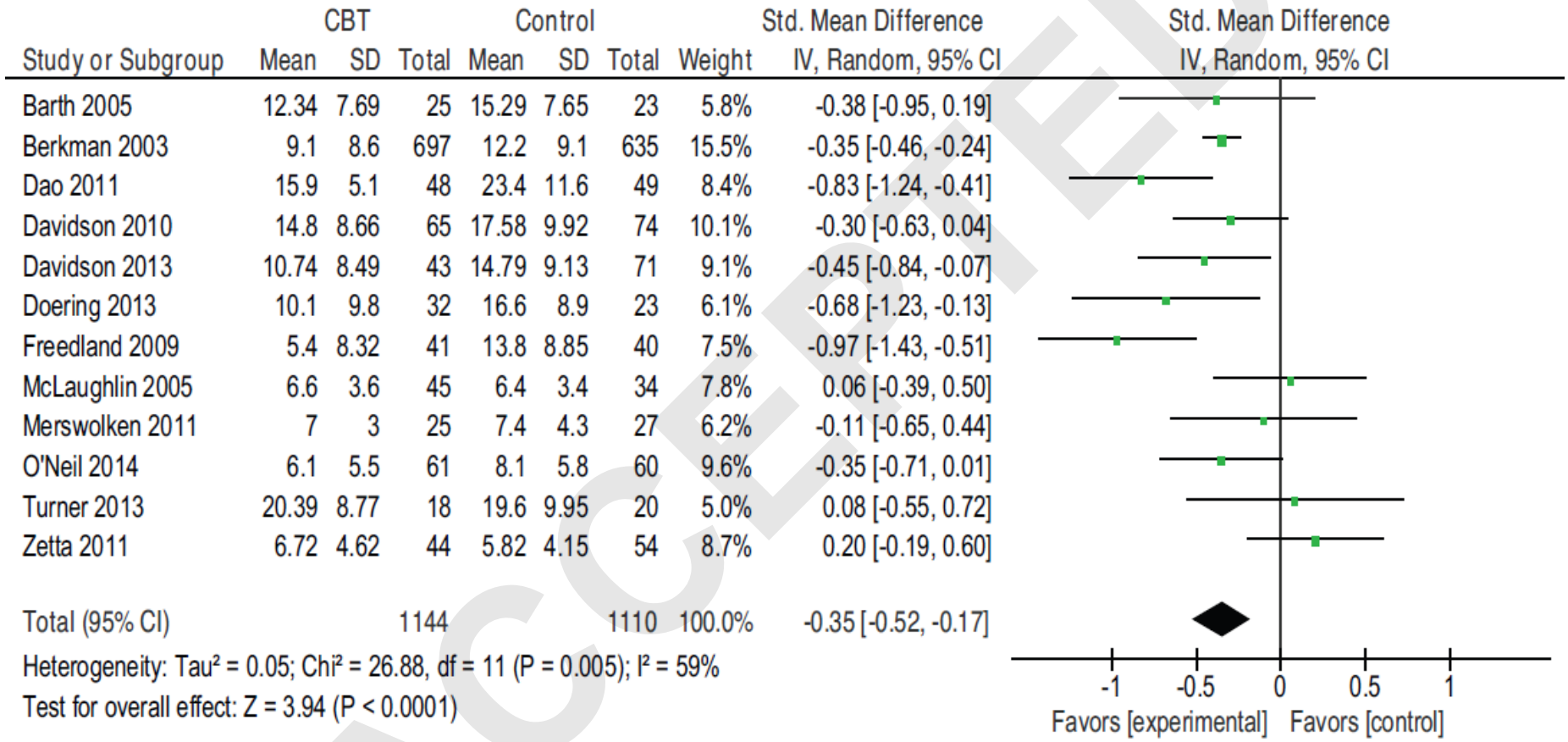

Figure 3b

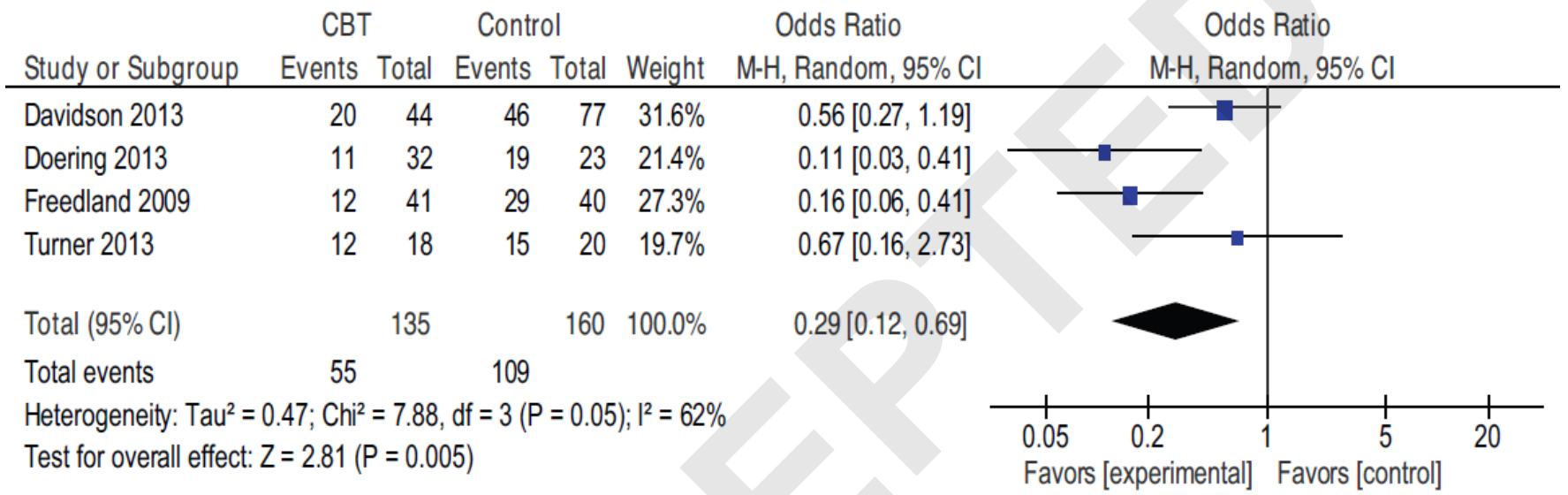

Figure 4

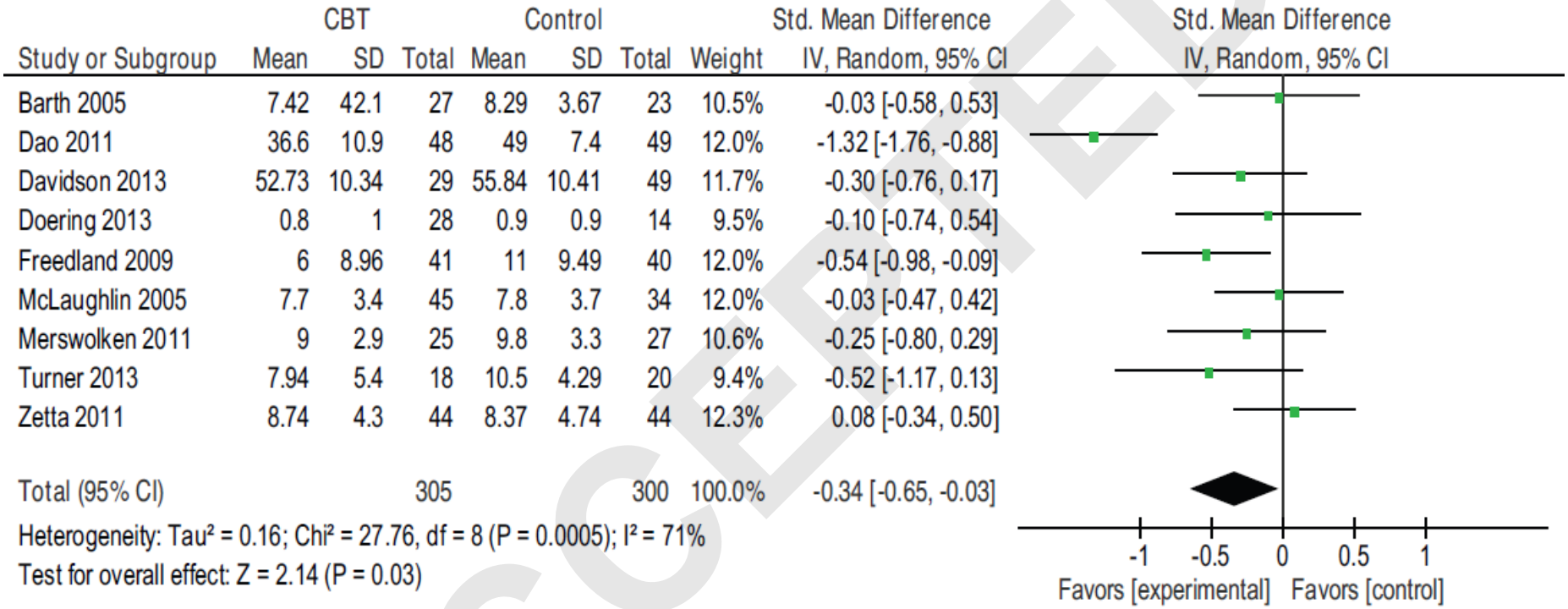

Table 1: Characteristics of Included Studies

First Author; Year; Country; Study Design	Total number of participants randomized (n); Mean (SD) Age, years; % Male; % White Ethnicity	CVD Diagnosis	Anxiety and/or Depression	Method of anxiety and/or depression diagnosis	CBT intervention	Comparator	Outcomes (Modality used)
Barth 2005 (25) **Germany** **RCT**	n=59 **Intervention:** 60.8 (11.1); 81.5%; † **Comparator:** 55.6 (10.1); 71.9%; †	CHD	Depression	HADS total ≥17 and met DSM-IV depression criteria	Four to six, 50-minute, face-to-face sessions, delivered by a psychotherapist.	Usual Care	Depression (BDI) Anxiety (HADS-A)
Berkman 2003* (29) **USA** **RCT**	n=1332 **Intervention:** †; †; † **Comparator:** †; †; †	Post-MI	Depression	Met DSM-IV depression criteria	Six, 60-minute, face-to-face sessions, delivered by trained therapists.	Usual Care	Depression (BDI)
Dao 2011 (26) **USA** **RCT**	n=100 **Intervention:** 62.8 (11.8); 77.1%; 81.2% **Comparator:** 64.2 (11.9); 79.6%; 77.6%	CHD	Anxiety and/or Depression	STAI ≥40 on the State or Trait Scale. BDI-II ≥14	Four, 60-minute, face-to-face sessions, delivered by clinical psychologists.	Usual Care	Depression (BDI-II) Anxiety (STAI-Trait) QoL (SF-12)
Davidson 2010* (30) **USA** **RCT**	n=150 **Intervention:** 61.5 (10.7); 38.5%; 52.0% **Comparator:** 61.1 (10.6); 46.8%: 52.0%	ACS	Depression	BDI ≥ 10 on 2 occasions	30-45 minute, face-to-face or telephone sessions, delivered by a specialist nurse, social worker or psychologist. Mean number of sessions= 8.2	Usual Care	Depression (BDI) Patient satisfaction (Likert scale) MACE
Davidson 2013* (31) **USA** **RCT**	n=121 **Intervention:** 60.3 (10.3); 56.8%; 47.7% **Comparator:** 60.0 (11.1); 57.1%; 54.5%	ACS	Depression	BDI ≥10 on 2 occasions or BDI >15 on 1 occasion	30-45 minute, internet and telephone sessions, delivered by problem-solving therapy specialists. Mean number of sessions= 7.7	Usual Care	Depression (BDI) Anxiety (PROMIS) Remission (BDI) QoL (SF-12) Cardiovascular events
Doering 2013* (32) **USA** **RCT**	n=55 **Intervention:** 62.3 (7.7); 87.5%; 56.3% **Comparator:** 63.0 (12.4); 60.9%; 69.6%	Post-CABG	Depression	BDI >10 and met DSM-IV depression criteria	Eight, 50-60 minute, face-to-face sessions, delivered by nurses.	Usual Care	Depression (BDI) Anxiety (BSI) Remission (BDI, SCID)
Freedland 2009 (27) **USA** **RCT**	n=123 **Intervention:** 62.0 (11.0); 44.0%; 88.0% **Comparator:** 61.0 (9.0); 57.0%; 90.0%	Post-CABG	Depression	BDI ≥10 and met DSM-IV depression criteria	Twelve, 50-60 minute, face-to-face sessions, delivered by clinical psychologists and social workers.	Usual Care	Depression (BDI) Anxiety (BAI) Remission (BDI) QoL (SF-36)

First Author; Year; Country; Study Design	Total number of participants randomized (n); Mean (SD) Age, years; % Male; % White Ethnicity	CVD Diagnosis	Anxiety and/or Depression	Method of anxiety and/or depression diagnosis	CBT intervention	Comparator	Outcomes (Modality used)
McLaughlin 2005 (28) **USA** **RCT**	n=100 **Intervention:** 59.9 (10.2); 68.9%; 88.9% **Comparator:** 60.7 (9.8); 64.7%; 88.2%	ACS	Anxiety and/or Depression	HADS-A ≥7 or HADS-D ≥7	Six, 30-minute, telephone sessions, delivered by doctoral level clinicians.	Standard Care	Depression (HADS-D) Anxiety (HADS-A)
Merswolken 2011 (40) **Germany** **RCT**	n=62 **Intervention:** 62.5 (8.3); 76.0%; † **Comparator:** 59.8 (7.5); 70.0%; †	CHD	Anxiety	HADS-A ≥8	Twelve, 2-hour, face-to-face sessions, plus 3 additional booster sessions, delivered by clinical psychologists.	No intervention	Depression (HADS-D) Anxiety (HADS-A)
O'Neil 2014 (41) **Australia** **RCT**	n=121 **Intervention:** 61.0 (10.2); 73.8%; † **Comparator:** 58.9 (10.7); 76.7%; †	ACS	Depression	PHQ-9= 5-19	Ten, 30-40 minute, telephone sessions, delivered by master level qualified psychologists.	Usual Care	Depression (PHQ-9) QoL (SF-12)
Turner 2013* (33) **Australia** **RCT**	n=43 **Intervention:** 61.6 (11.0); 81.8%; † **Comparator:** 62.0 (9.0); 71.4%; †	AF, ACS, Post-CABG, Post-PCI	Depression	BDI-II ≥14	Six, 90-minute, face-to-face sessions (plus additional 120 minutes), delivered by clinical psychologists.	Brief intervention of information	Depression (BDI-II) Anxiety (HADS-A) Remission (BDI-II)
Zetta 2011* (34) **Scotland** **RCT**	n=98 **Intervention:** 62.4 (10.2); 68.2%; 97.7% **Comparator:** 61.8 (11.1); 63.0%; 100%	CHD	Anxiety and/or Depression	HADS-A ≥8 and/or HADS-D ≥8	One, 45-minute, face-to-face session and three, 5-minute, telephone sessions delivered by nurses.	Standard Care	Depression (HADS-D) Anxiety (HADS-A) Patient satisfaction (SAQ) QoL (SEIQoL-DW)

ACS, acute coronary syndrome; AF, atrial fibrillation; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; BDI-II, Beck Depression Inventory-II; BSI, Brief Symptom Inventory; CABG, coronary artery bypass grafting; CHD, coronary heart disease; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders-IV; HADS, Hospital Anxiety and Depression Scale; HADS-A, Hospital Anxiety and Depression Scale-Anxiety Subscale; HADS-D, Hospital Anxiety and Depression Scale-Depression Subscale; MACE, nonfatal myocardial infarction or hospitalisation for unstable angina; MI, myocardial infarction; PCI, percutaneous coronary intervention; PHQ-9, Patient Health Questionnaire-9; PROMIS, Patient-Reported Outcomes Measurement Information System; QoL, quality of life; SAQ, Seattle Angina Questionnaire; SCID, Structured Clinical Interview for DSM-5; SD, standard deviation; SEIQoL-DW, Schedule for the Evaluation of Individual Quality of life: a Direct Weighting Procedure; SF-12, 12-Item Short Form Survey; SF-36, 36-Item Short Form Survey; STAI, State-Trait Anxiety Inventory; *, subgroup; †, not reported.

Table 2: Anxiety and Depression Outcomes for Included Studies

First author; Year	Anxiety Measure (Time-points)	Intervention Mean (SD) at Study Time-points	Comparator Mean (SD) at Study Time-points	Depression Measure (Time-points)	Intervention Mean (SD) at Study Time-points	Comparator Mean (SD) at Study Time-points
Barth 2005 (25)	HADS-A (1 month)	7.4 (4.2)	8.3 (3.7)	BDI (1 month)	12.3 (7.7)	15.3 (7.7)
Berkman 2003* (29)	-			BDI (6 months)	9.1 (8.6)	12.2 (9.1)
Dao 2011 (26)	STAI-Trait (Post treatment; 3-4 weeks follow-up)	36.6 (10.9); 40.6 (12.1)	49.0 (7.4); 45.6 (7.7)	BDI-II (Post treatment; 3-4 weeks follow- up)	15.9 (5.1); 19.2 (6.7)	23.4 (11.6); 22.5 (10.7)
Davidson 2010* (30)	-			BDI (6 months)	14.8 (8.7)	17.6 (9.9)
Davidson 2013* (31)	PROMIS (6 months)	52.7 (10.3)	55.8 (10.4)	BDI (6 months)	10.7 (8.5)	14.8 (9.1)
Doering 2013* (32)	BSI (2 months)	0.8 (1.0)	0.9 (0.9)	BDI (2 months)	10.1 (9.8)	16.6 (8.9)
Freedland 2009 (27)	BAI (3 months; 6 months; 9 months)	6.0 (9.0); 8.1 (9.0); 9.1 (9.0)	11.0 (9.5); 12.7 (9.5); 14.2 (9.5)	BDI (3 months; 6 months; 9 months)	5.4 (8.3); 7.8 (8.3); 6.7 (8.3)	13.8 (8.9); 10.7 (8.9); 12.9 (8.9)
McLaughlin 2005 (28)	HADS-A (2 months; 3 months; 6 months)	7.7 (3.4); 6.6 (3.6); 6.3 (3.5)	7.8 (3.7); 8.0 (3.8); 7.0 (3.8)	HADS-D (2 months; 3 months; 6 months)	6.6 (3.6); 6.1 (3.7); 5.7 (3.6)	6.4 (3.4); 6.6 (3.5); 6.6 (3.9)
Merswolken 2011 (40)	HADS-A (6 months)	9.0 (2.9)	9.8 (3.3)	HADS-D (6 months)	7.0 (3.0)	7.4 (4.3)
O'Neil 2014 (41)	-			PHQ-9 (6 months)	6.1 (5.5)	8.1 (5.8)
Turner 2013* (33)	HADS-A (7 weeks; 6 months; 12 months)	7.9 (5.4); 9.6 (4.9); 8.6 (5.1)	10.5 (4.3); 9.79 (4.7); 10.1 (5.0)	BDI-II (7 weeks; 6 months; 12 months)	20.4 (8.8); 20.2 (10.8); 17.4 (9.6)	19.6 (10.0); 17.5 (9.9); 16.9 (10.4)
Zetta 2011* (34)	HADS-A (6 months)	8.7 (4.3)	8.4 (4.7)	HADS-D (6 months)	6.7 (4.6)	5.8 (4.2)

BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; BDI-II, Beck Depression Inventory-II; BSI, Brief Symptom Inventory; HADS-A, Hospital Anxiety and Depression Scale-Anxiety Subscale; HADS-D, Hospital Anxiety and Depression Scale-Depression Subscale; PHQ-9, Patient Health Questionnaire-9; PROMIS, Patient-Reported Outcomes Measurement Information System; SD, standard deviation; STAI-Trait, State-Trait Anxiety Inventory-Trait Scale; *, subgroup.