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Collaborative care for comorbid depression and coronary heart disease: a systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Objectives: To systematically review the efficacy of collaborative care for depression in adults with coronary heart disease (CHD) and depression.

Design: Systematic review and meta-analysis

Data sources: Electronic databases (Cochrane Central Register of Controlled Trials MEDLINE, EMBASE, PsycINFO and CINAHL) were searched until April 2014 exploding the topics CHD, depression and RCT.

Inclusion criteria: Population, depression comorbid with CHD; intervention, RCT of collaborative care; comparison, either usual care, wait-list control group or no further treatment; and outcome, (primary) major adverse cardiac events (MACE), (secondary) standardized measure of depression, anxiety, quality of life and cost-effectiveness.

Data extraction and analysis: Cochrane Review Manager 5.3 was used to synthesize the data as risk ratios, odds ratios (OR) and standardized mean differences (SMD) with 95% confidence intervals (CI).

Results: Sixteen papers met the inclusion criteria and reported six RCTs. The RCTs were comprised by 655 participants randomized to collaborative care and 629 participants randomized to control group (total 1,284). Collaborative depression care did not significantly reduce MACE in the first six months. Small reductions in depressive symptoms were evident in the short term (pooled SMD −0.30; 95% CI −0.41 to −0.19, p <.00001) and depression remission was more likely to be achieved with collaborative care (OR 1.79; 95% CI 1.36 to

2.35, p <.0001). Likewise a significant effect was observed for anxiety symptoms (SMD -.36) and mental quality of life (SMD .24) but not physical quality of life or cost-effectiveness.

Conclusions: Collaborative depression care did not lead to a reduction in the primary MACE endpoint. Small effects were observed for depression, depression remission, anxiety and mental quality of life. The cost-effectiveness of collaborative depression care has not been established yet and further research outside of North America is required for the population with CHD.

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Strengths

- Protocol based systematic review of randomized controlled trials with a priori defined primary and secondary outcomes
- Exhaustive literature search and additional unpublished data provided by most authors
- GRADE rating of strength of evidence as moderate

Limitations

- Substantial heterogeneity observed between studies
- Few studies performed outside of the USA

INTRODUCTION

Depression is widely reported to lead to an adverse coronary heart disease (CHD) prognosis [1, 2], poorer quality of life (QOL) [3, 4] and high healthcare costs [5]. Despite ongoing efforts to better identify and treat depression, prior psychological and pharmacological interventions designed especially for the CHD population have reported markedly lower effect sizes than has been observed among other chronic diseases such as diabetes [6, 7]. Moreover, large trials such as the landmark Enhancing Recovery in Coronary Heart Disease (ENRICHD) study [8] did not lead to a significant reduction in major adverse cardiac events (MACE), raising questions about the design [9] and acceptability [10] of depression interventions in the population with CHD.

Collaborative care is emerging as a promising model of healthcare among populations with complex mental health needs [11] and mental disorders comorbid with chronic diseases including diabetes and CHD [12, 13]. Collaborative care is defined by a multi-professional approach to patient care delivered by a primary care physician (PCP) and at least one other health professional, involving a structured patient management plan and interventions, scheduled patient follow-ups, and enhanced inter-professional communication between the multi-professional team [12]. Prior systematic reviews have not reported on the efficacy of CHD studies in particular [14, 15] although mixed CHD and diabetes samples are commonplace [12]. Several large prospective RCT's of collaborative care versus usual care have been reported recently [16-18] making it feasible to examine the efficacy and early benefits of collaborative care, that might in turn assist in the design of subsequent trials and inform clinical practice. This systematic review extends beyond previous studies by reporting the efficacy of collaborative care for depression in adults with comorbid depression and CHD [19].

METHODS

Search Strategy

This review conformed to the PRISMA guidelines [20] and a protocol has been published elsewhere [19]. Electronic databases were searched without language restrictions until April 2014: the Cochrane Central Register of Controlled Trials (CENTRAL) on The Cochrane Library, MEDLINE, EMBASE, PsycINFO and CINAHL. The search string exploded the topics CHD, depression and RCT, as reported previously [19]. Hand searching reference lists of articles selected for full-text supplemented electronic searches. The principal investigators of studies were contacted to ascertain unpublished data and their knowledge of any other collaborative care trials not included in our primary search. Additional data was provided for five trials [17, 21, 22, 16, 23] and no response was received from the TrueBlue study authors [18].

Inclusion Criteria

Population: RCT studies performed among adults (18 years and older) with comorbid depression and CHD. Depression defined as depression disorder or clinical depression assessed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) by a standardized interview (e.g. Structured Clinical Interview, Composite International Diagnostic Interview), or a validated self-reports or rating scales with specific cut-off points for depression. Mixed samples (e.g. heart failure, arrhythmia, diabetes) were eligible if ≥ 50% of the sample have a CHD diagnosis.

Intervention: collaborative care intervention defined as a coordinated model of care involving multidisciplinary healthcare providers, including: (a) at least one health professional (e.g. nurse, psychiatrist, psychologist) in addition to the PCP; (b) a structured patient management

plan that delivers either pharmacological or non-pharmacological depression intervention; (c) scheduled patient follow-up; (d) enhanced inter-professional communication between the multiprofessional team. Collaborative care may include usual CHD care or blended depression-CHD care.

Comparison: control group being either (enhanced) usual care, wait-list control group, or no further treatment for comorbid depression-CHD.

Outcomes: Primary; all-cause and CHD-related mortality as well as MACE (e.g. subsequent myocardial infarction, coronary revascularization procedure, incident heart failure, stroke). Secondary; secondary outcomes include depression, anxiety and quality of life (measured either dimensionally or categorically) following the intervention assessed by validated self-report questionnaires or standardized interview. In addition, we considered economic evaluations of health care costs or resource utilization including cost-effectiveness (incremental cost-effectiveness ratio) and cost-utility (quality-adjusted life years).

Study Selection Process, Risk of Bias and Assessment

Two reviewers (PJT, HB) independently screened abstracts and articles for eligibility. In the case of title/abstract disagreements, the study was subjected to full-text review and disagreements were resolved by discussion. Two reviewers (PJT, HB) independently assessed included studies using the Cochrane Collaboration's tool for assessing risk of bias [24]. The tool covers sequence generation, allocation concealment, selective outcome reporting and other sources of bias. Adjudication of the strength of evidence for each endpoint was made according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria with GRADE Profiler 3.6.1 [25].

Synthesis of Data and Summary Measures

Standardized mean differences (SMD) for continuous variables, risk ratios (RR) for MACE and odds ratios (OR) for dichotomous endpoints are reported with 95% CI. Data were pooled together with fixed-effects model using the inverse-variance method when heterogeneity was low to moderate ($I^2 < 60\%$), otherwise a random-effects model was used [26, 24]. To evaluate the presence of publication bias, the funnel plot was inspected. All analyses were performed with Review Manager Version 5.3.

RESULTS

The search yielded 1,755 citations from which 46 articles were reviewed in detail, 16 papers were retained which reported on 6 RCTs (Figure 1). Five collaborative care trials performed with diabetes and CHD or mixed chronic disease populations were excluded as they did not meet the threshold of more than 50% CHD patients [27, 12, 28-30]. Two trials were close to meeting the definition of collaborative care for depression comorbid with CHD but were excluded. The IDACC [31] study was excluded as the intervention did not initiate pharmacological or non-pharmacological depression treatment and did not involve structured follow-up of participants to augment treatment if necessary. The UPBEAT-UK study [32] was excluded as the intervention was a case-management intervention and did not incorporate other healthcare professionals such as the PCP.

The 6 RCTs that met the inclusion criteria comprised a total of 1,284 patients with comorbid depression and CHD: 655 participants randomized to collaborative care and 629 participants randomized to a control group. A description of the included trials' is shown in Table 1. The median proportion of participants with CHD in the trials was 78.9% suggesting high representative sampling of the chronic disease understudy. The median sample size was 179 participants per study with a median of 47.6% female participants. Four trials recruited

participants from multiple sites [33, 10, 34, 35] and two trials were performed at a single-center [36, 16]. Five trials were from the United States of America [17, 21, 22, 16, 23] and one trial was performed in Australia [18]. The comparison group was usual care or enhanced usual care in five studies consisting of informing participants' PCP [17, 21, 22, 16, 23] and one trial used a wait-list control group [35].

Depression screening questionnaires varied only minimally. Depression was assessed with the Patient Health Questionnaire (PHQ) to determine study eligibility in 4 trials [22, 16, 18, 23]. Specifically three trials used a two-step screening approach with the PHQ-2 and a PHQ-9 for participants with an initial positive depression response on the PHQ-2 [34, 36, 16]. These trials used a moderate depression threshold consisting of PHQ-9 total scores ≥ 10 [34, 36, 16]. The TrueBlue study [35] included patients with mild depression symptoms consisting of PHQ-9 scores ≥ 5. In the COPES and CODIACS trials the Beck Depression Inventory (BDI) was used for screening and trial eligibility [10, 33]. The clinical cutoff was set at ≥ 10 on at least two different screening occasion's in COPES [10]. In CODIACS [33] the clinical cutoff was set at BDI ≥ 10 on at least two different screening occasion's or BDI ≥ 15 on 1 occasion. Five of the trials utilizing either the PHQ-9 [35, 36, 16] or Beck Depression Inventory [10, 33] to determine trial eligibility also used the same measure for depression symptom response at the conclusion of the trial. The Bypassing The Blues trial employed the Hamilton Rating Scale for Depression [23] for depression symptom clinical response.

Collaborative care was managed by an allied health team in two trials [33, 10], by nurses in two studies [35, 34] and by social workers in two studies [36, 16]. The collaborative care intervention duration ranged from 3 to 12 months and the median duration was 6 months. The psychotherapy component of the collaborative care package consisted of problem-solving therapy in two studies [10, 33], telephone-delivered manualized CBT in one study [36],

referral to community mental health services in two studies [35, 34], and was mixed in another study [16]. The pharmacological component of the trials varied. In Bypassing The Blues [34] depression pharmacotherapy consisted of citalopram, serotonin norepinephrine reuptake inhibitor or bupropion. In CODIACS [33] depression pharmacotherapy consisted of sertraline, citalopram, or bupropion. In COPES [10] pharmacotherapy consisted of sertraline, escitalopram, venlafaxine, bupropion and mirtazipine. In MOSAIC [36] depression pharmacotherapy consisted of selective serotonin reuptake inhibitor (SSRI, most commonly citalopram), serotonin norepinephrine reuptake inhibitor, bupropion, mirtazapine and anxiety treatment with SSRI or benzodiazepine. In SUCCEED [16] depression pharmacotherapy consisted of SSRI. No specific depression pharmacotherapy regimen was reported in TrueBlue [35].

Risk of Bias

Risk of bias varied in the included primary trials (eSupplement 1). Missing trial characteristics were common despite all studies having published a trial protocol. In four trials the allocation concealment was unclear. Blinding to subjective endpoints was rated as high in all studies. Selective reporting was noted in three studies because of discrepancies in the study endpoints reported in the protocol by comparison to the primary trial results.

Primary Outcome: Major Adverse Cardiac Events

Three trials reported 89 MACE in 609 participants in the short to medium term (< 12 months) [23, 17, 37]. Collaborative care was associated with a non-significant reduction in MACE during the short to medium term (RR = 0.62; 95% CI 0.30 to 1.29, p = .20) however there was evidence of substantial moderate heterogeneity (I^2 = 66%) (Fig 2). In the long-term

(> 12 months follow-up) only the COPES trial [38] reported MACE with no significant difference between collaborative care and usual care (RR 0.88; 95% CI 0.41 to 1.88, p = .75).

Secondary Outcomes

Depression Symptoms and Remission

All 6 trials reported change in self-reported depression symptoms by six months post-intervention. Collaborative care was associated with a significant reduction in depressive symptoms (pooled SMD −0.30; 95% CI −0.41 to −0.19, p <.00001: I^2 = 13%) (Fig 3). There was no depression symptom data available in the medium or long term. Four trials reported depression remission or clinically significant depression response and additional data was provided by the MOSAIC trial [22]. Collaborative care was significantly associated with depression remission in the short term (OR = 1.79; 95% CI 1.36 to 2.35, p <.0001: I^2 = 23%) (Fig 4). In the medium term only the COPES trial [38] reported depression response based on the BDI ≤ 10 (OR 2.26; 95% CI 1.14 to 4.46, p = .02).

Other Secondary Outcomes

The forest plots for each of the secondary endpoints are reported in eSupplements 2 through 5. Four trials reported anxiety symptom change. It was found that collaborative care led to a small but significant reduction in anxiety symptoms in the short term (SMD -.36; 95% CI -.54 to -.17, p = .0001: I^2 = 25%). Collaborative care was also associated with a significant improvement in mental quality of life in the short term across five trials (SMD .24; 95% CI .11 to .37, p = .0004: I^2 = 27%), while effects for physical QOL were non-significant (SMD 0.11; 95% CI -.03 to .25, p = .12: I^2 = .13). In terms of cost-effectiveness, there was no significant benefit afforded by collaborative care based on two trials in the short term (SMD -0.09; 95% CI -0.32 to 0.13, p = .42: I^2 = 0%). Medium term results were reported by

Bypassing The Blues [39] which did not indicate significantly lower costs with collaborative care (SMD 0.07; 95% CI -0.22 to 0.35, p = .65).

Ancillary Analyses

Because there was heterogeneity in the primary MACE endpoint we performed ancillary analysis restricted to acute coronary syndrome hospitalizations, coronary revascularization, heart failure and stroke. There was no significant effect for collaborative care to reduce any of these more specific cardiovascular endpoints (eSupplements 6 through 9). Also, as five trials differentiated between MACE and cardiac-cause hospital readmissions we performed an analysis according to the latter outcome which occurs more frequently. Analysis of 5 trials showed no significant reduction in cardiac-cause hospital readmissions (RR = 0.92; 95% CI 0.73 – 1.15, p = .44: I^2 = 35%) (eSupplement 10).

Sensitivity Analyses

For depression change, a sensitivity analysis was performed excluding the trials comprised by diabetes patients without CHD [18] and non-depressed CHD patients with anxiety [22]. The sensitivity analysis revealed a small increase in the effect size (pooled SMD −.39; 95% CI −.53 to −.25, p <.00001: I^2 = 0%).

The timing of depression onset [40] and intervention [10] after a cardiac hospitalization has been raised by several scholars as an important methodological consideration. Thus we stratified studies as providing collaborative care immediately upon screening or as an in-patient [36, 16, 35] versus those which considered depression chronicity with a secondary screener at a later stage and as an outpatient [10, 34, 33]. It was found that timing of depression intervention was a source of between-group heterogeneity for depression

severity in six trials (between groups p = .04, I^2 = 76.5%) (eSupplement 11), but not for depression remission (between groups p = .50, I^2 = 0% (eSupplement 12).

When analyzing the effect of collaborative care in relation to components of depression treatment, as described in our protocol [19], it was found that collaborative care was not associated with higher prescription rate of antidepressant medication (6 trials, OR = 1.38; 95% CI 0.91 to 2.10, p = .13, I^2 = 62%). There was no increase in the initiation of psychological therapy with collaborative care (6 trials, OR 2.01; 95% CI 0.85 to 4.76, p = .11, I^2 = 84%) (eSupplement 13 and 14).

Publication Bias and GRADE Strength of Recommendations

For the primary MACE and secondary endpoints we did not find any evidence of publication bias after inspection of the funnel plots (eSupplements 15 and 16). All of the primary and secondary outcomes were graded as moderate strength according to the GRADE criteria [25].

DISCUSSION

This systematic review adds to the extant literature by reporting the efficacy and healthcare costs of collaborative care interventions in comorbid depression and CHD populations. It was found that collaborative care was not associated with a significant reduction in MACE in the short term (< 6 months) comparable to other findings with pharmacological or psychological interventions [7, 41]. The results pertaining to the secondary depression endpoints indicated a small albeit significant reduction in depression symptoms with collaborative care, and depression remission was also more likely in the short term. In addition, collaborative care was associated with a significant reduction in anxiety

symptoms and an improvement in mental QOL. The findings did not suggest a significant benefit for physical QOL or healthcare costs. Taken together the findings generally support previous systematic reviews regarding more specific depression treatments such as antidepressants or psychotherapy [7, 41].

The absence of a significant reduction in MACE in the short term parallels a prior Cochrane review [7] and other systematic reviews reporting on medical outcomes [42, 43]. However the generalization of these findings is limited as findings were based on only three trials for the primary MACE endpoint in the short term. Thus it is likely that there were simply too few MACE reported resulting in low statistical power. This is further exemplified by comparing the cumulative sample in our analyses to the ENRICHD study [8] which randomized 2,481 myocardial infarction patients to cognitive behavioral therapy supplemented with selective serotonin reuptake inhibitors versus usual care. At 29-month follow-up in the ENRICHD trial there was no difference in event free survival from death or recurrent myocardial infarction (75.8% intervention vs. 75.9% usual care) [8]. The findings of our review align with the general consensus that depression treatment does not lead to a clinically meaningful impact upon cardiovascular events in CHD patients [44-46]. With regards to depression remission, short term results with collaborative care were promising indicating a higher remission rate with collaborative care. However only the COPES trial [38] reported medium term follow-up data. With regards to secondary endpoints of anxiety and mental QOL the results here appear comparable to other systematic reviews on psychological interventions [7].

The limitations of the primary studies are that the predominant collaborative care research has been performed in the United States of America [23, 22, 17, 21, 16] with only one Australian study included here [18]. Other collaborative care trials that did not meet our

CHD threshold have been performed in the United Kingdom [27] and The Netherlands [51]. Further trials with CHD populations may assist in clarifying the extent to which collaborative care can be readily applied in other healthcare settings outside the United States of America. As a consequence of low uptake of collaborative care RCTs outside the USA, the total number of RCTs retained for our meta-analysis was low. Nonetheless, Thombs and colleagues' [52] meta-analysis also included only six studies combining efficacy and effectiveness trials evaluating mirtazapine, fluoxetine, sertraline and citalopram, and CBT with adjunctive sertraline. Another limitation was that risk of bias assessment showed that some studies were characterized by methodological limitations, especially a lack of blinding regarding intervention staff and participants (which is not possible in collaborative care interventions when compared to usual care) and blinding of depression assessment (i.e. only self-report instruments used).

In favour of a more comprehensive overview of the topic we included studies with diabetes [18] and anxiety [22]. As shown in sensitivity analyses, this might have underestimated the effect sizes when compared to cardiac-depression populations only. Indeed, evidence for collaborative care appears to be more firmly established in the population with diabetes [42] highlighting discrepancies between depression intervention efficacy in CHD [7, 6]. Given that collaborative care interventions consist of scheduled follow-up it cannot be ruled out that depression efficacy was partly attributable to the attention given to participants in the treatment condition. Further RCTs using attention control groups might also explicate whether treatment effects are partly attributable to time spent with patients.

In conclusion, collaborative depression care in the CHD population did not lead to significant reductions in MACE. Small reductions in depressive symptoms were evident for collaborative care and intervention participants were more likely to achieve depression remission. Small effect sizes for anxiety symptom reduction and improvement in mental QOL were evident with collaborative care. However it remains to be shown that collaborative depression care can lead to sustained reductions in cardiovascular events and a moderate depression response in the longer term. Scant RCT data exists outside of the USA and the cost-effectiveness has not been established at this time.

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Table 1. Characteristics of included collaborative care studies in the treatment of comorbid depression and coronary heart disease

Study, Country	Design and Intervention Length	CHD population (% CHD in total sample)	Sample Size of CC vs. UC (% females in total sample)	Depression Assessment	Collaborative Care Intervention	Control Group
Bypassing The Blues, Rollman et al. 2009, USA [23, 34, 39]	Single-blind effectiveness RCT, 8 months	CABG (100%)	150 CC vs. 152 UC (41.4)	PHQ-2 positive screen as an inpatient and PHQ-9 score ≥ 10 2 weeks post-CABG, PRIME-MD for mood disorders	Structured telephone f/up, patient preferences for depression care, psychoeducation, bibliotherapy, promoting adherence, and initiation or adjustment of antidepressant pharmacotherapy provided by PCP (citalopram, SNRI or bupropion); referral to a community MHS; a combination of the above; "watchful-waiting"	Usual care, given brochure on depression and heart disease, PCP informed of depression status
CODIACS, Davidson et al. USA [33, 17]	Single-blind effectiveness RCT, 6 months	UA, MI (100%)	73 CC vs. 77 UC (42.0)	BDI-I score ≥ 10 on 2 screening occasions or ≥ 15 on 1 occasion 2 to 6 months after hospitalization	Initial patient preference for problem-solving therapy and/or pharmacotherapy (sertraline, citalopram, buproprion), or neither, then a stepped-care approach every 6-8 weeks, structured f/up initially every week with PST or 1-2 and 3 - 5 weeks to titrate doses with pharmacotherapy, study team included a site physician and fed back information to PCP	Usual care, locally administered, ad libitum depression care, PCP informed of depression status
COPES, Davidson et al. [21, 38, 10, 37, 53]	Single-blind effectiveness RCT, 6 months	UA, MI (100%)	80 CC vs. 77 UC (53.5)	BDI-I score ≥ 10 on 2 screening occasions 1 week and 3 months after hospitalization	Initial patient preference for problem-solving therapy and/or pharmacotherapy (sertraline, escitalopram, venlafaxine, bupropion, mirtazapine), then a stepped-care approach, repeated	Usual care, locally administered, ad libitum depression care, PCP informed of depression status

					assessments and augmentation if required at 8 week intervals, structured f/up initially every week with PST or 1-2 and 3 – 5 weeks to titrate doses with pharmacotherapy, study team included a site physician and fed back information to PCP	
MOSAIC, Huff man et al., USA [36, 22]	Single-blind effectiveness RCT, 6 months	UA, MI, HF, arrhythmia (51%)	92 CC vs. 91 EUC (53.0)	Two-step screening process; PHQ-2, GAD-2 and item about panic attacks as an inpatient and PRIME-MD for depression, GAD and PD	Social worker and psychiatrist developed individualized treatment recommendations; patient preference for pharmacotherapy (SSRI most commonly citalopram, SNRI, bupropion, mirtazapine and anxiety treatment with SSRI or benzodiazepine) or CBT (min. six session CBT when allocated); stepped-care; PCP informed of patient preference; structured telephone call and f/up to monitor symptoms, promote adherence and engagement;	Enhanced usual care, PCP informed of psychiatric status at baseline and subsequent screening
SUCCEED Huffman et al 2011, USA [16, 54]	Single-blind effectiveness RCT, 3 months	UA, MI, HF, arrhythmia (52.6%)	90 CC vs. 85 UC (48.6)	Two-step screening process; PHQ-2 positive screen and PHQ-9 score ≥ 10 as an inpatient	Social worker and psychiatrist individualized depression treatment recommendations based on history and patient preference (SSRI or psychotherapy); study team provided the PCP or cardiologist with treatment recommendations; verbal and written recommendations to the inpatient treatment team; depression education for pleasant activities scheduling; monitored for	Usual care, PCP informed of depression status

					adequate depression response;	
TrueBlue, Morgan et al., AUS [35, 18]	Cluster randomized RCT, 12 months	CHD and diabetes (57.8)	170 CC vs. 147 WLC (46.7)	PHQ-9 score ≥ 5 as a primary care patient	Scheduled visits to PN and PCP every 3 months over 12-months; referrals to MHS; development and recording of patient goals;	Usual care, PN monitor depression by screening at scheduled intervals

BDI-I; Beck Depression Inventory-I; CABG, coronary artery bypass graft; CC, collaborative care; CHD, coronary heart disease; COPES, Coronary Psychosocial Evaluation Studies; CODIACS, Centralized, Stepped, Patient Preference–Based Treatment for Patients With Post–Acute Coronary Syndrome Depression; GAD, generalized anxiety disorder; HF, heart failure; MHS, mental health services; MI, myocardial infarction; MOSAIC, Management of Sadness and Anxiety in Cardiology; PCP, primary care physician; PD, panic disorder; PHQ, Patient Health Questionnaire; PN, practice nurse; PRIME-MD, Primary Care Evaluation of Mental Disorders; PST, problem-solving therapy; RCT, randomized controlled trial; SSRI, selectoive serotonin reuptake inhibitors; SNRI, serotonin norepinephrine reuptake inhibitor; SUCCEED, Screening Utilization and Collaborative Care for More Effective and Efficient Treatment of Depression; UA, unstable angina; WLC, wait-list control;

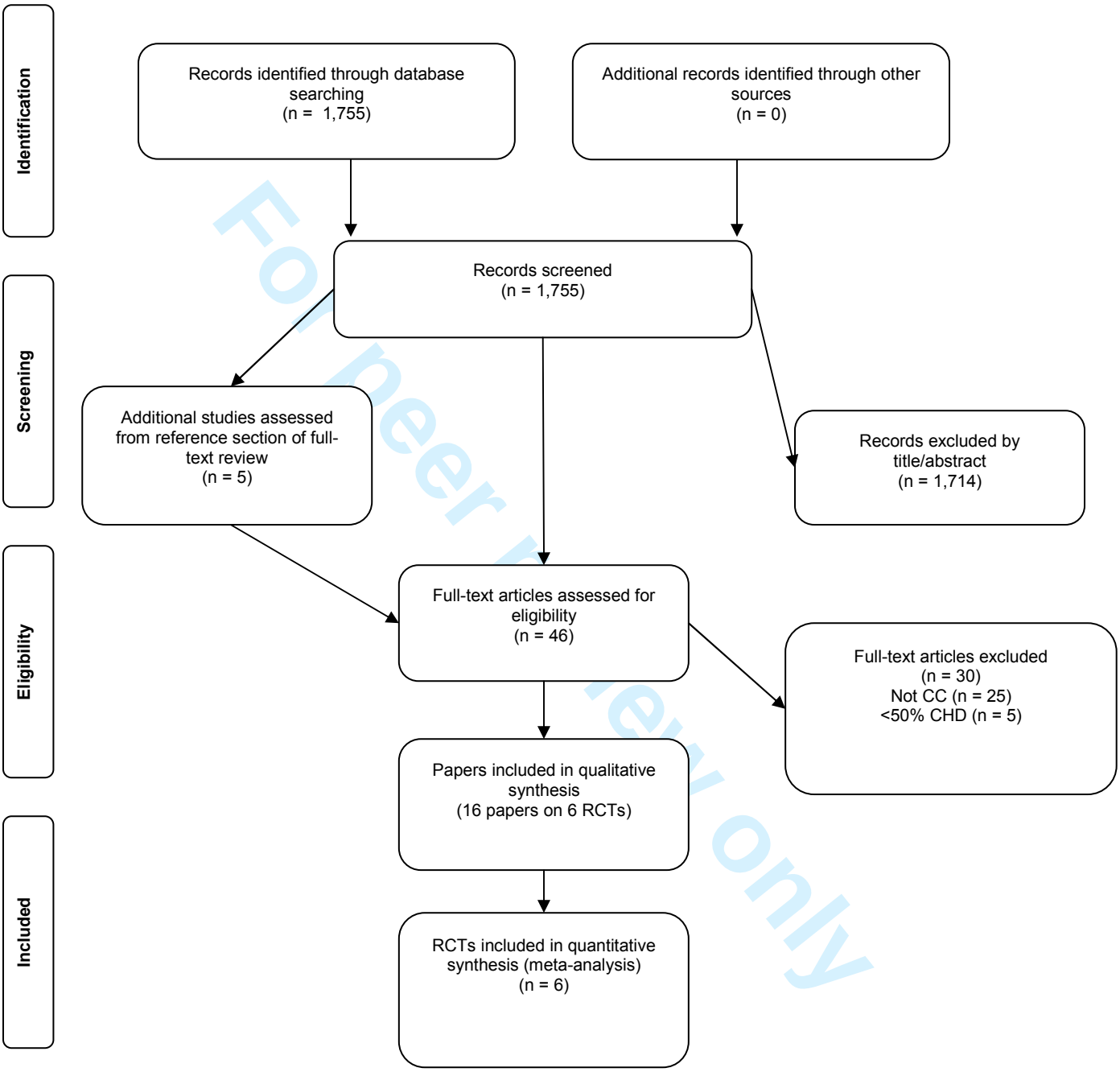


Figure 1. Flow chart of article selection

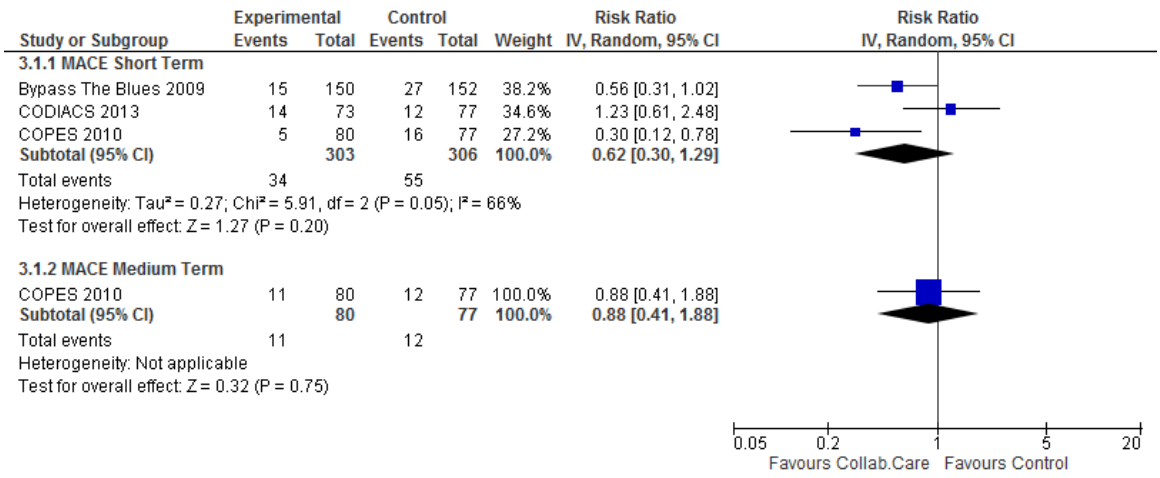


Fig 2. Forest plot showing the risk ratio for MACE post intervention in collaborative care studies versus usual care or waiting list control (short and medium term)

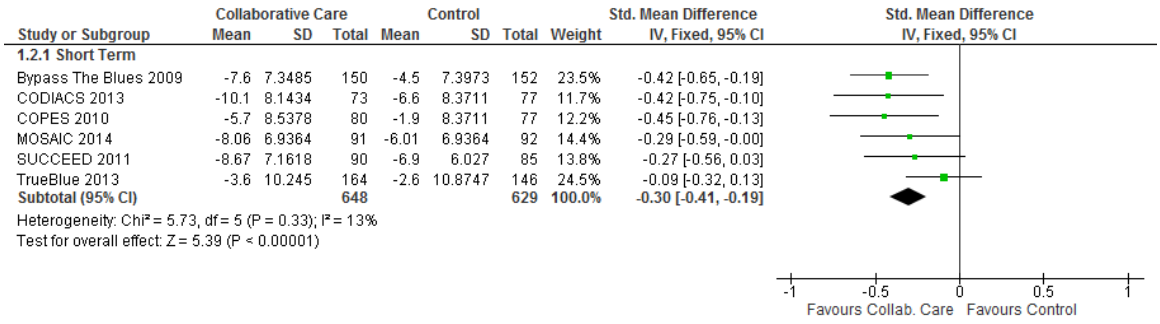


Fig 3. Forest plot showing depressive symptoms in collaborative care studies versus usual care or waiting list control (short term)

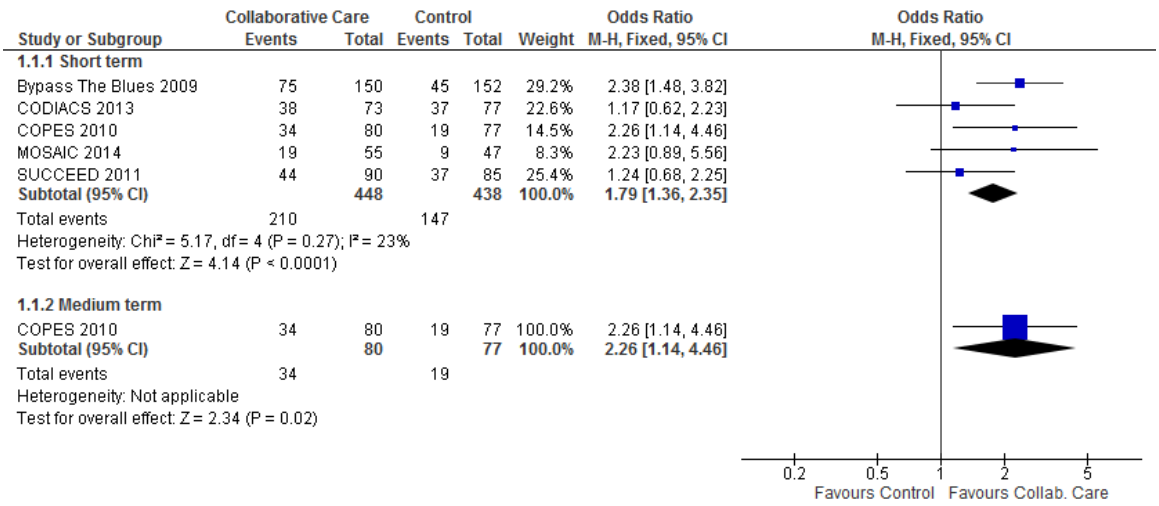


Fig 4. Forest plot showing depression remission in collaborative care studies versus usual care or waiting list control (short and medium term)

eSupplement 1. Risk of Bias Adjudication for Included Trials

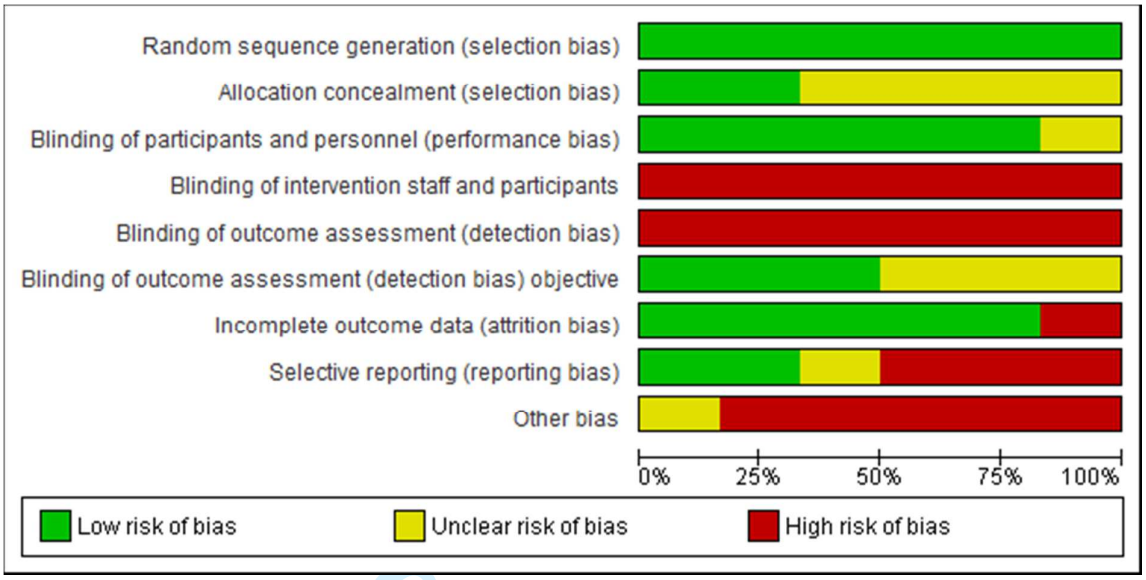
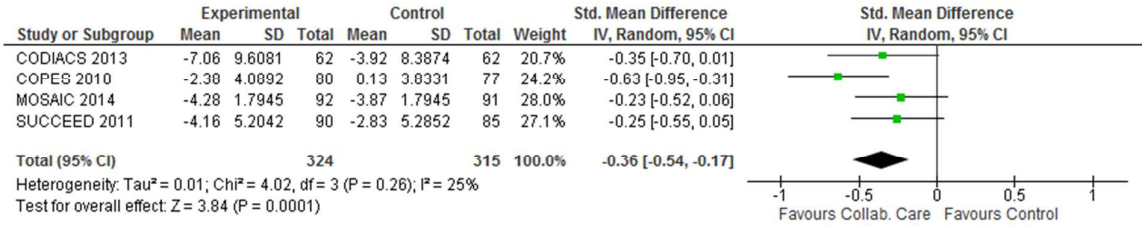


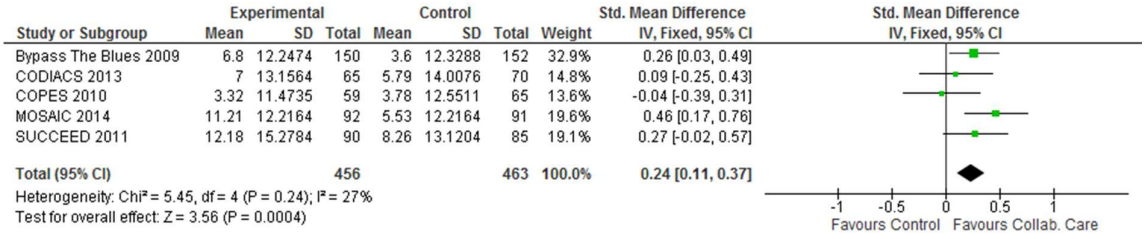
Figure showing the adjudication of risk of bias in included trials. Risk of bias independently adjudicated by PJT and HB using Cochrane Review Manager 5.3. Final risk of bias determined by consensus between the two raters.

eSupplement 2. Forest plot showing anxiety symptoms in collaborative care studies versus usual care or waiting list control (short term)



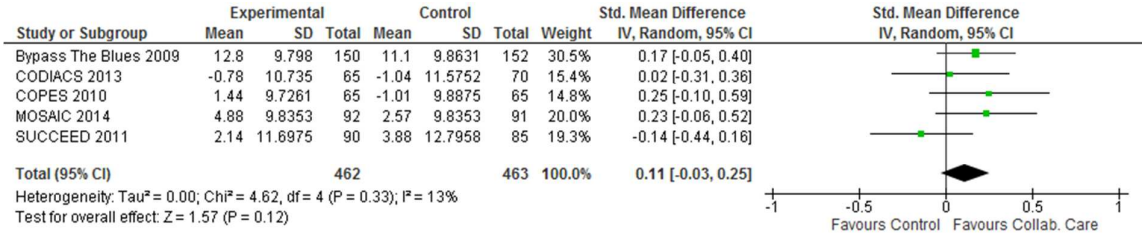
CI, confidence interval; IV, inverse variance;

eSupplement 3. Forest plot showing mental quality of life symptoms in collaborative care studies versus usual care or waiting list control (short term)



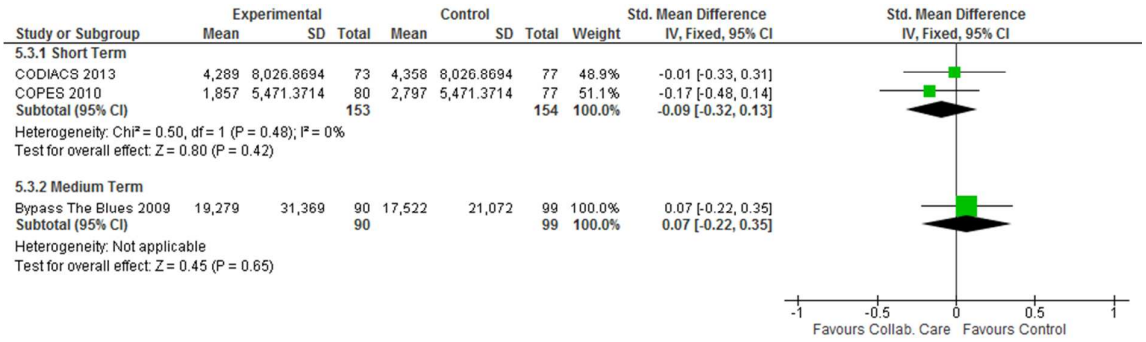
CI, confidence interval; IV, inverse variance;

eSupplement 4. Forest plot showing physical quality of life symptoms in collaborative care studies versus usual care or waiting list control (short term)



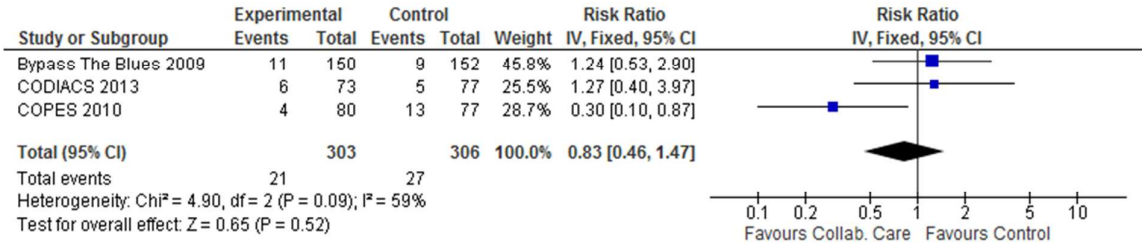
CI, confidence interval; IV, inverse variance;

eSupplement 5. Forest plot showing healthcare costs in collaborative care studies versus usual care or waiting list control (short term and medium term)



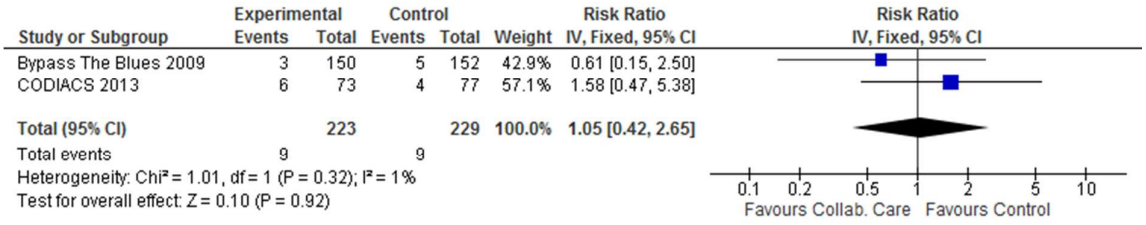
CI, confidence interval; IV, inverse variance;

eSupplement 6. Forest plot showing the risk ratio for acute coronary syndrome post intervention in collaborative care studies versus usual care or waiting list control (short term)



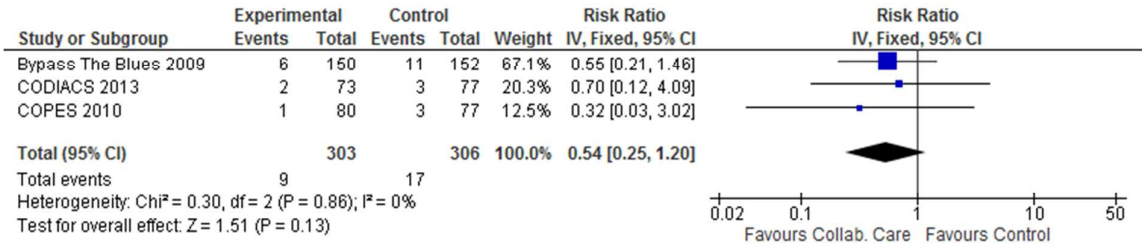
CI, confidence interval; IV, inverse variance;

eSupplement 7. Forest plot showing the risk ratio for coronary revascularization post intervention in collaborative care studies versus usual care or waiting list control (short term)



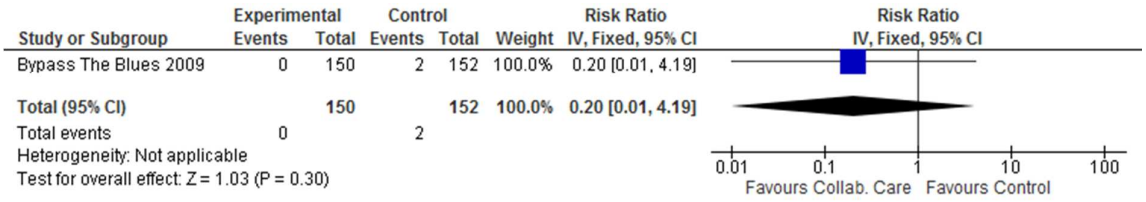
CI, confidence interval; IV, inverse variance;

eSupplement 8. Forest plot showing the risk ratio for heart failure post intervention in collaborative care studies versus usual care or waiting list control (short term)



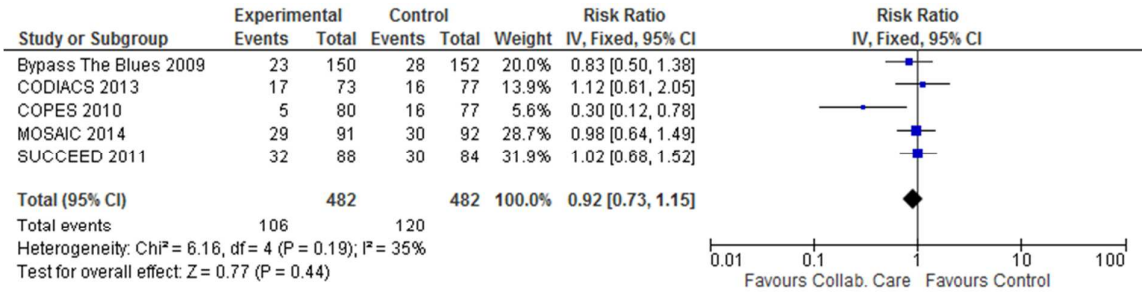
CI, confidence interval; IV, inverse variance;

eSupplement 9. Forest plot showing the risk ratio for stroke post intervention in collaborative care studies versus usual care or waiting list control (short term)



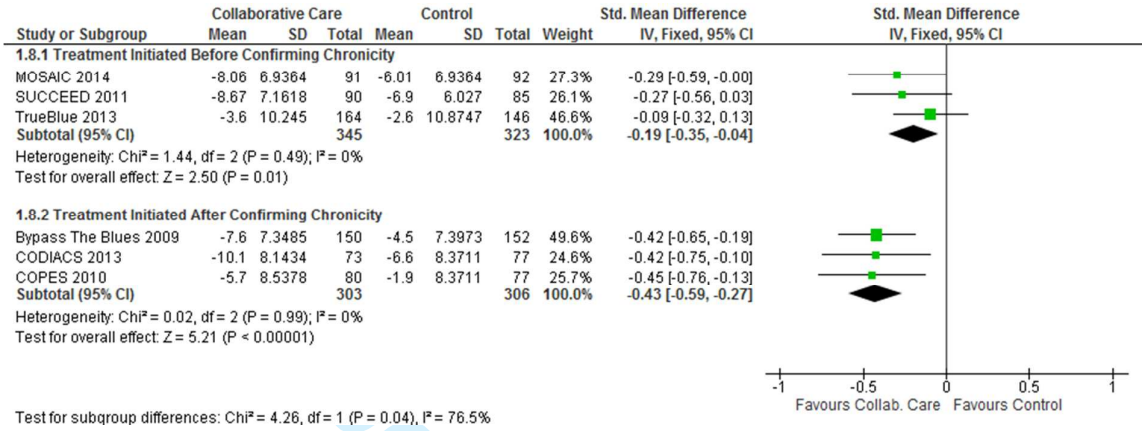
CI, confidence interval; IV, inverse variance;

eSupplement 10. Forest plot showing the risk ratio for cardiac-cause hospital admission post intervention in collaborative care studies versus usual care or waiting list control (short term)

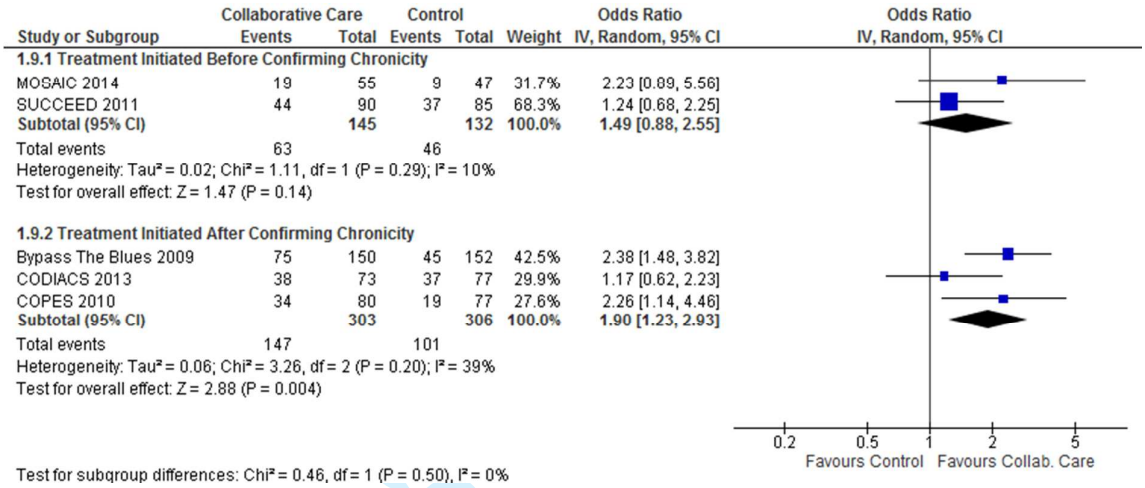


CI, confidence interval; IV, inverse variance;

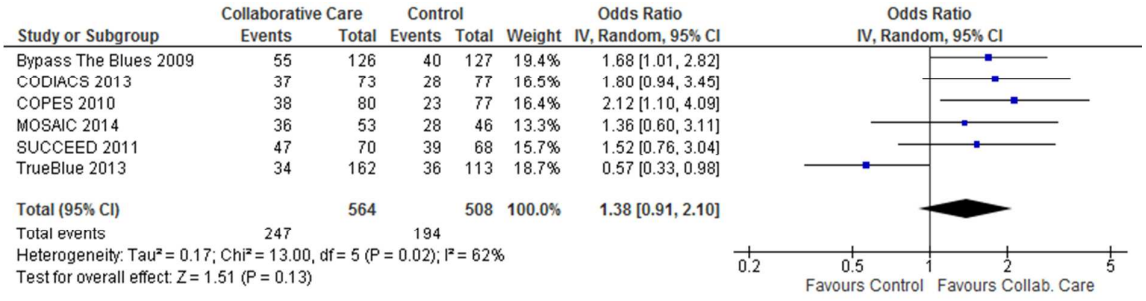
eSupplement 11. Forest plot of sensitivity analysis showing depression symptoms post intervention in collaborative care studies versus usual care or waiting list control (short term)



eSupplement 12. Forest plot of sensitivity analysis showing depression remission post intervention in collaborative care studies versus usual care or waiting list control (short term)

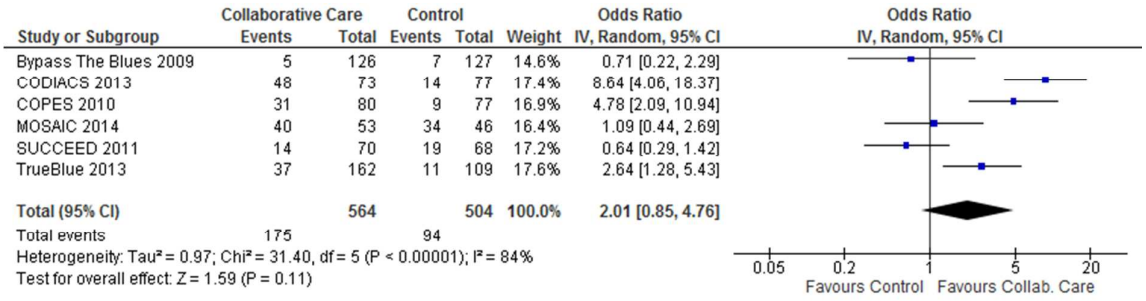


eSupplement 13. Forest plot showing the odds ratio for anti-depressant therapy post intervention in collaborative care studies versus usual care or waiting list control (short term)



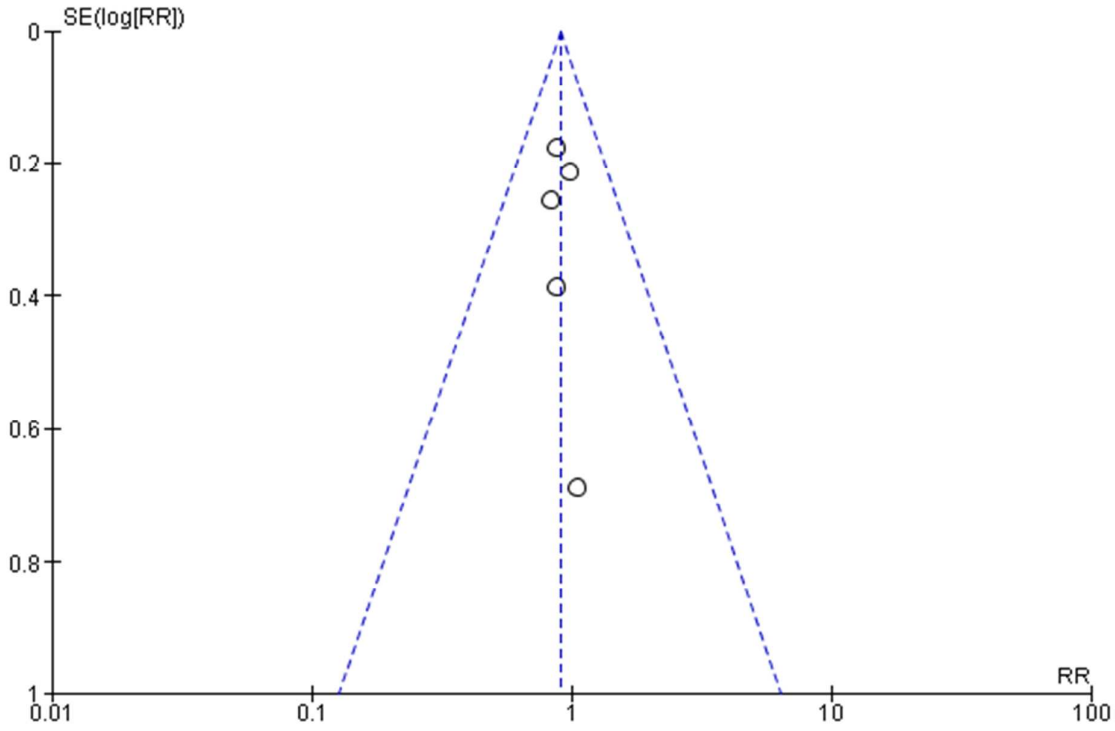
CI, confidence interval; IV, inverse variance;

eSupplement 14. Forest plot showing the odds ratio for psychotherapy post intervention in collaborative care studies versus usual care or waiting list control (short term)



CI, confidence interval; IV, inverse variance;

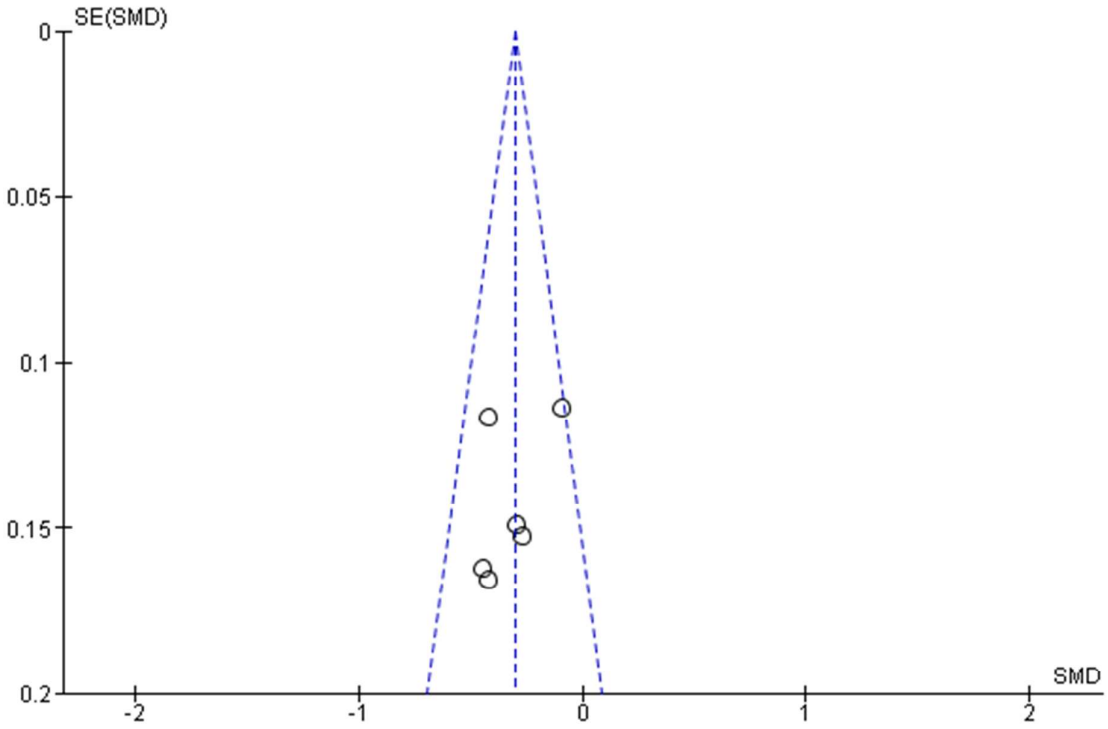
eSupplement 15. Publication bias in the MACE endpoint



Funnel showing the publication bias in the MACE endpoint. Primary study results are plotted as RR on the x axis by SE of the logRR on the y-axis.

MACE, major adverse cardiac events; RR, risk ratio; SE, standard error;

eSupplement 16. Publication bias in depression change (SMD) endpoint



Funnel showing the publication bias in depression symptom change endpoint. Primary study results are plotted as SMD on the x axis by SE of the SMD on the y-axis.

SE, standard error; SMD, standardized mean difference

eSupplement 17. GRADE assessment of each endpoint

GRADE Item	MACE Endpoint	Depression	Anxiety	Mental QOL	Physical QOL	Cost Effectiveness
Risk of bias	Serious (-1)	Serious (-1)	Serious (-1)	Serious (-1)	Serious (-1)	Serious (-1)
Inconsistency	No	No	No	No	No	No
Indirectness	No	No	No	No	No	No
Imprecision	No	No	No	No	No	No
Publication bias	Undetected	Undetected	Undetected	Undetected	Undetected	Undetected
Large effect	No	No	No	No	No	No
Plausible confounding would change the effect	No	No	No	No	No	No
Dose response gradient	No	No	No	No	No	No
Quality of evidence	**Moderate**	**Moderate**	**Moderate**	**Moderate**	**Moderate**	**Moderate**

GRADE assessment made using GRADE profiler 3.6.1 [27]

MACE included myocardial infarction, coronary revascularization procedure, incident heart failure, stroke

MACE, major adverse cardiac events; QOL, quality of life

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6 and abstract
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6 - 7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	eSupplement 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8, Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8-10, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10, eSupplement 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Fig 2 - 4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10 - 13 Fig 2 – 4;
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10, eSupplement 1
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11-13, eSupplements 2-14
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14-16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13-16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

PRISMA 2009 Checklist

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

BMJ Open

Collaborative care for comorbid depression and coronary heart disease: a systematic review and meta-analysis of randomized controlled trials

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Collaborative care for comorbid depression and coronary heart disease: a systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Objectives: To systematically review the efficacy of collaborative care for depression in adults with coronary heart disease (CHD) and depression.

Design: Systematic review and meta-analysis

Data sources: Electronic databases (Cochrane Central Register of Controlled Trials MEDLINE, EMBASE, PsycINFO and CINAHL) were searched until April 2014.

Inclusion criteria: Population, depression comorbid with CHD; intervention, RCT of collaborative care; comparison, either usual care, wait-list control group or no further treatment; and outcome, (primary) major adverse cardiac events (MACE), (secondary) standardized measure of depression, anxiety, quality of life and cost-effectiveness.

Data extraction and analysis: RevMan 5.3 was used to synthesize the data as risk ratios (RR), odds ratios (OR) and standardized mean differences (SMD) with 95% confidence intervals (CI) in random effect models.

Results: Six RCTS met the inclusion criteria and were comprised by 655 participants randomized to collaborative care and 629 participants randomized to control group (total 1,284). Collaborative depression care led to a significant reduction in MACE in the short-term (3 trials, RR 0.54; 95% CI 0.31 to 0.95, p = 0.03) that was not sustained in the longer term. Small reductions in depressive symptoms were evident in the short term (6 trials, pooled SMD −0.31; 95% CI −0.43 to −0.19, p <0.00001) and depression remission was more likely to be achieved with collaborative care (5 trials, OR 1.77; 95% CI 1.28 to 2.44, p = 0.0005).

Likewise a significant effect was observed for anxiety symptoms (SMD -.36) and mental quality of life (SMD .24). The timing of intervention was a source of between-group heterogeneity for depression symptoms (between groups p = .04, I^2 = 76.5%).

Conclusions: Collaborative depression care did not lead to a sustained reduction in the primary MACE endpoint. Small effects were observed for depression, depression remission, anxiety and mental quality of life.

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Strengths

- Systematic review of randomized controlled trials and a priori defined primary and secondary outcomes
- Exhaustive literature search and additional unpublished data provided by 5/6 authors
- GRADE rating of strength of evidence as moderate

Limitations

- Heterogeneity observed between studies
- Few studies performed outside of the USA
- Insufficient healthcare cost data

INTRODUCTION

Depression is widely reported to lead to an adverse coronary heart disease (CHD) prognosis [1 2], poorer quality of life (QOL) [3 4] and high healthcare costs [5]. Despite ongoing efforts to better identify and treat depression [6], prior psychological and pharmacological interventions designed especially for the CHD population have reported markedly lower effect sizes than has been observed among other chronic diseases such as diabetes [7 8]. Moreover, large trials such as the landmark Enhancing Recovery in Coronary Heart Disease (ENRICHD) study [9] did not lead to a significant reduction in major adverse cardiac events (MACE), raising questions about the design [10] and acceptability [11] of depression interventions in the population with CHD.

Collaborative care is emerging as a promising model of healthcare among populations with complex mental health needs [12] and mental disorders comorbid with chronic diseases including diabetes and CHD [13 14]. Collaborative care is defined by a multi-professional approach to patient care delivered by a primary care physician (PCP) and at least one other health professional, involving a structured patient management plan and interventions, scheduled patient follow-ups, and enhanced inter-professional communication between the multi-professional team [13]. Prior systematic reviews have not reported on the efficacy of CHD studies in particular [15 16] although mixed CHD and diabetes samples are commonplace [13]. Several large prospective RCT's of collaborative care versus usual care have been reported recently [17-19] making it feasible to examine the efficacy and early benefits of collaborative care, that might in turn assist in the design of subsequent trials and inform clinical practice. This systematic review extends beyond previous studies by reporting the efficacy of collaborative care for depression in adults with comorbid depression and CHD [20].

METHODS

Search Strategy

This review conformed to the PRISMA guidelines [21] and a protocol has been published elsewhere [20]. Electronic databases were searched without language restrictions until April 2014: the Cochrane Central Register of Controlled Trials (CENTRAL) on The Cochrane Library, MEDLINE, EMBASE, PsycINFO and CINAHL. The search string exploded the topics CHD, depression and RCT, as reported previously [20]. Hand searching reference lists of articles selected for full-text supplemented electronic searches. The principal investigators of studies were contacted to ascertain unpublished data and their knowledge of any other collaborative care trials not included in our primary search. Additional data was provided for five trials [17 18 22-24] and no response was received from the TrueBlue study authors [19].

Inclusion Criteria

Population: RCT studies performed among adults (18 years and older) with comorbid depression and CHD. Depression defined as depression disorder or clinical depression assessed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) by a standardized interview (e.g. Structured Clinical Interview, Composite International Diagnostic Interview), or a validated self-reports or rating scales with specific cut-off points for depression. Mixed samples (e.g. heart failure, arrhythmia, diabetes) were eligible if ≥ 50% of the sample have a CHD diagnosis.

Intervention: collaborative care intervention defined as a coordinated model of care involving multidisciplinary healthcare providers, including: (a) at least one health professional (e.g. nurse, psychiatrist, psychologist) in addition to the PCP; (b) a structured patient management

plan that delivers either pharmacological or non-pharmacological depression intervention; (c) scheduled patient follow-up; (d) enhanced inter-professional communication between the multiprofessional team. Collaborative care may include usual CHD care or blended depression-CHD care.

Comparison: control group being either (enhanced) usual care, wait-list control group, or no further treatment for comorbid depression-CHD.

Outcomes: Primary; all-cause and CHD-related mortality as well as MACE (e.g. subsequent myocardial infarction, coronary revascularization procedure, incident heart failure, stroke). Secondary; secondary outcomes include depression, anxiety and quality of life (measured either dimensionally or categorically) following the intervention assessed by validated self-report questionnaires or standardized interview. In addition, we considered economic evaluations of health care costs or resource utilization including cost-effectiveness (incremental cost-effectiveness ratio) and cost-utility (quality-adjusted life years).

Study Selection Process, Risk of Bias and Assessment

Two reviewers (PJT, HB) independently screened abstracts and articles for eligibility. In the case of title/abstract disagreements, the study was subjected to full-text review and disagreements were resolved by discussion. Two reviewers (PJT, HB) independently assessed included studies using the Cochrane Collaboration's tool for assessing risk of bias [25]. The tool covers sequence generation, allocation concealment, selective outcome reporting and other sources of bias. Adjudication of the strength of evidence for each endpoint was made according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria with GRADE Profiler 3.6.1 [26].

Synthesis of Data and Summary Measures

Standardized mean differences (SMD) for continuous variables, risk ratios (RR) for MACE and odds ratios (OR) for dichotomous endpoints are reported with 95% CI. Data were pooled together with random effect models using the inverse-variance method [25 27]. To evaluate the presence of publication bias, the funnel plot was inspected. All analyses were performed with RevMan Version 5.3.

RESULTS

The search yielded 1,755 citations from which 46 articles were reviewed in detail, 16 papers were retained which reported on 6 RCTs (Figure 1). Five collaborative care trials performed with diabetes and CHD or mixed chronic disease populations were excluded as they did not meet the threshold of more than 50% CHD patients [13 28-31]. Two trials were close to meeting the definition of collaborative care for depression comorbid with CHD but were excluded. The IDACC [32] study was excluded as the intervention did not initiate pharmacological or non-pharmacological depression treatment and did not involve structured follow-up of participants to augment treatment if necessary. The UPBEAT-UK study [33] was excluded as the intervention was a case-management intervention and did not incorporate other healthcare professionals such as the PCP.

The 6 RCTs that met the inclusion criteria comprised a total of 1,284 patients with comorbid depression and CHD: 655 participants randomized to collaborative care and 629 participants randomized to a control group. A description of the included trials' is shown in Table 1. The median proportion of participants with CHD in the trials was 78.9% suggesting high representative sampling of the chronic disease understudy. The median sample size was 179 participants per study with a median of 47.6% female participants. Four trials recruited participants from multiple sites [11 34-36] and two trials were performed at a single-center

[17 37]. Five trials were from the United States of America [17 18 22-24] and one trial was performed in Australia [19]. The comparison group was usual care or enhanced usual care in five studies consisting of informing participants' PCP [17 18 22-24] and one trial used a wait-list control group [36].

Depression screening questionnaires varied only minimally. Depression was assessed with the Patient Health Questionnaire (PHQ) to determine study eligibility in 4 trials [17 19 23 24]. Specifically three trials used a two-step screening approach with the PHQ-2 and a PHQ-9 for participants with an initial positive depression response on the PHQ-2 [17 35 37]. These trials used a moderate depression threshold consisting of PHQ-9 total scores ≥ 10 [17 35 37]. The TrueBlue study [36] included patients with mild depression symptoms consisting of PHQ-9 scores ≥ 5. In the COPES and CODIACS trials the Beck Depression Inventory (BDI) was used for screening and trial eligibility [11 34]. The clinical cutoff was set at ≥ 10 on at least two different screening occasion's in COPES [11]. In CODIACS [34] the clinical cutoff was set at BDI ≥ 10 on at least two different screening occasion's or BDI ≥ 15 on 1 occasion. Five of the trials utilizing either the PHQ-9 [17 36 37] or Beck Depression Inventory [11 34] to determine trial eligibility also used the same measure for depression symptom response at the conclusion of the trial. The Bypassing The Blues trial employed the Hamilton Rating Scale for Depression [24] for depression symptom clinical response.

Collaborative care was managed by an allied health team in two trials [11 34], by nurses in two studies [35 36] and by social workers in two studies [17 37]. The collaborative care intervention duration ranged from 3 to 12 months and the median duration was 6 months. The psychotherapy component of the collaborative care package consisted of problem-solving therapy in two studies [11 34], telephone-delivered manualized CBT in one study [37], referral to community mental health services in two studies [35 36], and was mixed in another

study [17]. The pharmacological component of the trials varied. In Bypassing The Blues [35] depression pharmacotherapy consisted of citalopram, serotonin norepinephrine reuptake inhibitor or bupropion. In CODIACS [34] depression pharmacotherapy consisted of sertraline, citalopram, or bupropion. In COPES [11] pharmacotherapy consisted of sertraline, escitalopram, venlafaxine, bupropion and mirtazipine. In MOSAIC [37] depression pharmacotherapy consisted of selective serotonin reuptake inhibitor (SSRI, most commonly citalopram), serotonin norepinephrine reuptake inhibitor, bupropion, mirtazapine and anxiety treatment with SSRI or benzodiazepine. In SUCCEED [17] depression pharmacotherapy consisted of SSRI. No specific depression pharmacotherapy regimen was reported in TrueBlue [36].

Risk of Bias

Risk of bias varied in the included primary trials (eSupplement 1). Missing trial characteristics were common despite all studies having published a trial protocol. In four trials the allocation concealment was unclear. Blinding to subjective endpoints was rated as high in all studies. Selective reporting was noted in three studies because of discrepancies in the study endpoints reported in the protocol by comparison to the primary trial results.

Primary Outcome: Major Adverse Cardiac Events

Three trials reported MACE [18 24 38] and pooling all data irrespective of follow-up showed that collaborative care did not reduce MACE (RR = 0.87; 95% CI 0.53 to 1.42, p = .20, I^2 = 39%). Collaborative care was associated with significant reduction in MACE during the short to medium term (RR = 0.54; 95% CI 0.31 to 0.95, p = 0.03) that was not sustained in the long-term (> 12 months follow-up) where only the COPES trial [39] reported MACE (RR

1.04; 95% CI 0.51 to 2.14, p = 0.91) (Fig 2). There was no association with mortality (5 trials, RR 1.38; 95% CI 0.53 to 3.58, p = 0.51).

Secondary Outcomes

Depression Symptoms and Remission

All 6 trials reported change in self-reported depression symptoms by six months post-intervention. Collaborative care was associated with a significant reduction in depressive symptoms (pooled SMD −0.31; 95% CI −0.43 to −0.19, p <.00001: $I^2 = 13\%$) (Fig 3). There was no depression symptom data available in the medium or long term. Four trials reported depression remission or clinically significant depression response and additional data was provided by the MOSAIC trial [23]. Collaborative care was significantly associated with depression remission (OR = 1.77; 95% CI 1.28 to 2.44, p = .0005: $I^2 = 23\%$) (Fig 4). In the medium term only the COPES trial [39] reported depression response based on the BDI ≤ 10 (OR 2.26; 95% CI 1.14 to 4.46, p = .02). As the COPES trial [39] reported similar depression remission results in the short to medium term pooling all depression remission data in the 5 trials, irrespective of timeframe, indicated similar results.

Other Secondary Outcomes

The forest plots for each of the secondary endpoints are reported in eSupplements 2 through 5. Four trials reported anxiety symptom change. It was found that collaborative care led to a small but significant reduction in anxiety symptoms in the short term (SMD -0.36; 95% CI -0.54 to -0.17, p = 0.0001: $I^2 = 25\%$). Collaborative care was also associated with a significant improvement in mental quality of life in the short term across five trials (SMD 0.23; 95% CI 0.08 to 0.38, p = 0.003: $I^2 = 27\%$), while effects for physical QOL were non-significant (SMD 0.11; 95% CI -0.03 to 0.25, p = 0.12: $I^2 = 13\%$). In terms of cost-effectiveness, there was no significant benefit afforded by collaborative care based on two

trials in the short term (SMD -0.09; 95% CI -0.32 to 0.13, p = 0.42: I^2 = 0%). Medium term results were reported by Bypassing The Blues [40] which did not indicate significantly lower costs with collaborative care (SMD 0.07; 95% CI -0.22 to 0.35, p = 0.65).

Ancillary Analyses

We performed ancillary analysis with each constituent of the MACE endpoint encompassing acute coronary syndrome hospitalizations, coronary revascularization, heart failure and stroke. There was no significant effect for collaborative care to reduce any of these more specific cardiovascular endpoints (eSupplements 6 through 9). Also, as five trials differentiated between MACE and cardiac-cause hospital readmissions we performed an analysis according to the latter outcome which occurs more frequently. Analysis of 5 trials showed no significant reduction in cardiac-cause hospital readmissions (RR = 0.89; 95% CI 0.66 – 1.19, p = 0.43: I^2 = 35%) (eSupplement 10).

Sensitivity Analyses

For depression change, a sensitivity analysis was performed excluding the trials comprised by diabetes patients without CHD [19] and non-depressed CHD patients with anxiety [23]. The sensitivity analysis revealed a small increase in the effect size (pooled SMD −.39; 95% CI −.53 to −.25, p <.00001: I^2 = 0%). We also evaluated the trials comprised by patients with only CHD (excluding other cardiac disorders) and assessed depression response. The trials were associated with depression remission (OR = 1.94; 95% CI 1.40 – 2.70, p = <0.0001: I^2 = 39%) and depression symptom reduction (pooled SMD −0.43; 95% CI −0.59 to −0.27, p <.00001: I^2 = 0%).

The timing of depression onset [41] and intervention [11] after a cardiac hospitalization has been raised by several scholars as an important methodological

consideration. Thus we stratified studies as providing collaborative care immediately upon screening or as an in-patient [17 36 37] versus those which considered depression chronicity with a secondary screener at a later stage and as an outpatient [11 34 35]. It was found that timing of depression intervention was a source of between-group heterogeneity for depression severity in six trials (between groups p = .04, I^2 = 76.5%) (eSupplement 11), but not for depression remission (between groups p = .50, I^2 = 0% (eSupplement 12).

When analyzing the effect of collaborative care in relation to components of depression treatment, as described in our protocol [20], it was found that collaborative care was not associated with higher prescription rate of antidepressant medication (6 trials, OR = 1.38; 95% CI 0.91 to 2.10, p = .13, I^2 = 62%). There was no increase in the initiation of psychological therapy with collaborative care (6 trials, OR 2.01; 95% CI 0.85 to 4.76, p = .11, I^2 = 84%) (eSupplement 13 and 14).

Publication Bias and GRADE Strength of Recommendations

Testing for publication bias was inappropriate as fewer than 10 RCTs were eligible. All of the primary and secondary outcomes were graded as moderate strength according to the GRADE [26] criteria (eSupplement 15).

DISCUSSION

This systematic review adds to the extant literature by reporting the efficacy and healthcare costs of collaborative care interventions in comorbid depression and CHD populations. It was found that collaborative care was associated with a significant reduction in MACE in the short term (< 6 months) that was not sustained in the longer term. The absence of significant reduction in MACE in the longer term is comparable to other findings with

pharmacological or psychological interventions [8 42]. The results pertaining to the secondary depression endpoints indicated a small albeit significant reduction in depression symptoms with collaborative care, and depression remission was also more likely in the short term. In addition, collaborative care was associated with a significant reduction in anxiety symptoms and an improvement in mental QOL. The findings did not suggest a significant benefit for physical QOL or healthcare costs. Taken together the findings generally support previous systematic reviews regarding more specific depression treatments such as antidepressants or psychotherapy in the population with CHD [8 42].

The significant reduction in MACE in the short term contrasts a prior Cochrane review [8] and other systematic reviews reporting on medical outcomes [43 44]. However the generalization of our findings are limited as only three trials reported the primary MACE endpoint in the short term. Thus it is likely that there were simply too few MACE reported resulting in low statistical power. This is further exemplified by comparing the cumulative sample in our analyses to the ENRICHD study [9] which randomized 2,481 myocardial infarction patients to cognitive behavioral therapy supplemented with selective serotonin reuptake inhibitors versus usual care. At 29-month follow-up in the ENRICHD trial there was no difference in event free survival from death or recurrent myocardial infarction (75.8% intervention vs. 75.9% usual care) [9]. The longer-term MACE findings of our review align with the general consensus that depression treatment does not lead to a clinically meaningful impact upon cardiovascular events in CHD patients [45-47]. With regards to depression remission, short term results with collaborative care were promising indicating a higher remission rate with collaborative care. However only the COPES trial [39] reported medium term follow-up data. With regards to secondary endpoints of anxiety and mental QOL the results here appear comparable to other systematic reviews on psychological interventions [8].

The limitations of the primary studies are that the predominant collaborative care research has been performed in the United States of America [17 18 22-24] with only one Australian study included here [19]. Other collaborative care trials that did not meet our CHD threshold have been performed in the United Kingdom [28] and The Netherlands [48]. Further trials with CHD populations may assist in clarifying the extent to which collaborative care can be readily applied in other healthcare settings outside the United States of America. As a consequence of low uptake of collaborative care RCTs outside the USA, the total number of RCTs retained for our meta-analysis was low. Moreover, the infrequent reporting of MACE and mortality data in the original studies limited our analyses to 3 trials. Another limitation was that risk of bias assessment showed that some studies were characterized by methodological limitations, especially a lack of blinding regarding intervention staff and participants (which is not possible in collaborative care interventions when compared to usual care) and blinding of depression assessment (i.e. only self-report instruments used).

Diversity in the design of collaborative care and control group may have also led to heterogeneity between the studies. In favour of a more comprehensive overview of the topic we included studies with diabetes [19] and anxiety [23]. As shown in sensitivity analyses, this might have underestimated the effect sizes when compared to cardiac-depression populations only. Indeed, evidence for collaborative care appears to be more firmly established in the population with diabetes [43] highlighting discrepancies between depression intervention efficacy in CHD [7 8]. Given that collaborative care interventions consist of scheduled follow-up it cannot be ruled out that depression efficacy was partly attributable to the attention given to participants in the treatment condition. Further RCTs using attention control groups might also explicate whether treatment effects are partly attributable to time spent with patients.

In conclusion, collaborative depression care in the CHD population did not lead to a sustained reduction in MACE. Small reductions in depressive symptoms were evident for collaborative care and intervention participants were more likely to achieve depression remission. Small effect sizes for anxiety symptom reduction and improvement in mental QOL were evident with collaborative care. However it remains to be shown that collaborative depression care can lead to sustained reductions in cardiovascular events and a moderate depression response in the longer term. Scant RCT data exists outside of the USA and the cost-effectiveness has not been established at this time.

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Figure Captions.

Fig 1. Flow chart of article selection

Fig 2. Forest plot showing the risk ratio for MACE post intervention in collaborative care studies versus usual care or waiting list control (short and medium term)

CI, confidence interval; MACE, major adverse cardiac event; IV, inverse variance;

Fig 3. Forest plot showing depressive symptoms in collaborative care studies versus usual care or waiting list control (short term)

CI, confidence interval; IV, inverse variance; SD, standard deviation

Fig 4. Forest plot showing depression remission in collaborative care studies versus usual care or waiting list control (short and medium term)

CI, confidence interval; IV, inverse variance;

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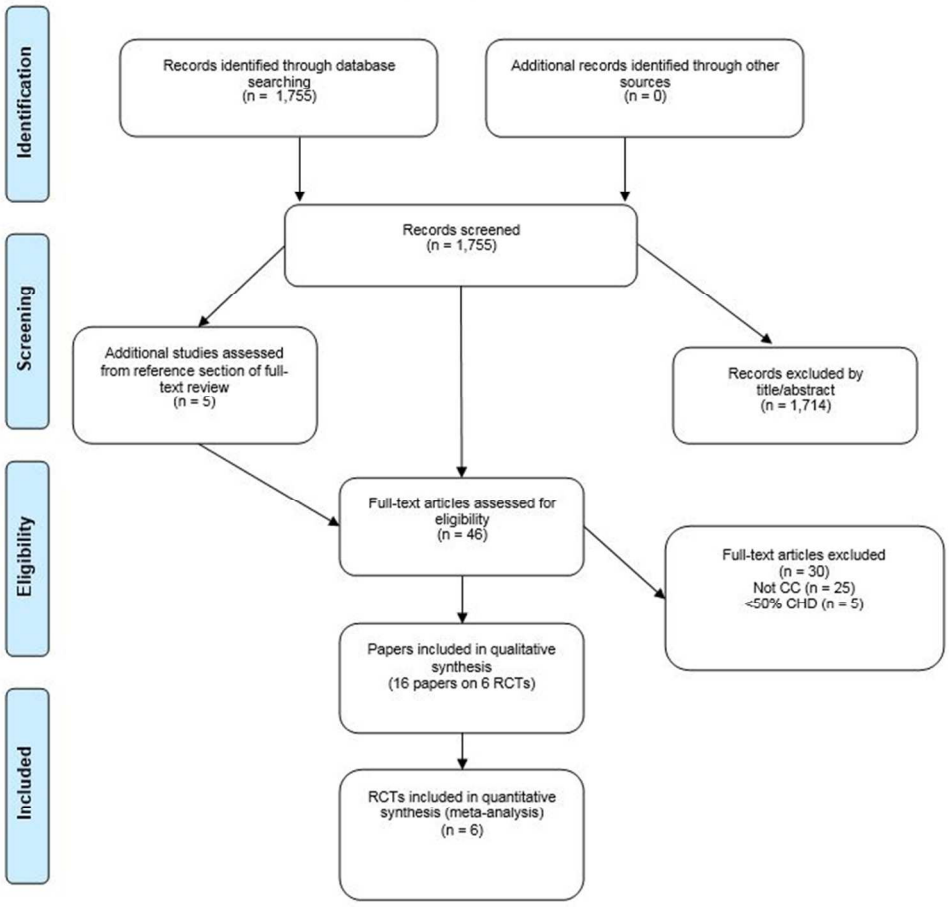
Table 1. Characteristics of included collaborative care studies in the treatment of comorbid depression and coronary heart disease

Study, Country	Design and Intervention Length	CHD population (% CHD in total sample)	Sample Size of CC vs. UC (% females in total sample)	Depression Assessment	Collaborative Care Intervention	Control Group
Bypassing The Blues, Rollman et al. 2009, USA [24 35 40]	Single-blind effectiveness RCT, 8 months	CABG (100%)	150 CC vs. 152 UC (41.4)	PHQ-2 positive screen as an inpatient and PHQ-9 score ≥ 10 2 weeks post-CABG, PRIME-MD for mood disorders	Structured telephone f/up, patient preferences for depression care, psychoeducation, bibliotherapy, promoting adherence, and initiation or adjustment of antidepressant pharmacotherapy provided by PCP (citalopram, SNRI or bupropion); referral to a community MHS; a combination of the above; "watchful-waiting"	Usual care, given brochure on depression and heart disease, PCP informed of depression status
CODIACS, Davidson et al. USA **[18 34]**	Single-blind effectiveness RCT, 6 months	UA, MI (100%)	73 CC vs. 77 UC (42.0)	BDI-I score ≥ 10 on 2 screening occasions or ≥ 15 on 1 occasion 2 to 6 months after hospitalization	Initial patient preference for problem-solving therapy and/or pharmacotherapy (sertraline, citalopram, buproprion), or neither, then a stepped-care approach every 6-8 weeks, structured f/up initially every week with PST or 1-2 and 3 - 5 weeks to titrate doses with pharmacotherapy, study team included a site physician and fed back information to PCP	Usual care, locally administered, ad libitum depression care, PCP informed of depression status
COPES, Davidson et al. [11 22 38 39 49]	Single-blind effectiveness RCT, 6 months	UA, MI (100%)	80 CC vs. 77 UC (53.5)	BDI-I score ≥ 10 on 2 screening occasions 1 week and 3 months after hospitalization	Initial patient preference for problem-solving therapy and/or pharmacotherapy (sertraline, escitalopram, venlafaxine, bupropion, mirtazapine), then a stepped-care approach, repeated	Usual care, locally administered, ad libitum depression care, PCP informed of depression status

					assessments and augmentation if required at 8 week intervals, structured f/up initially every week with PST or 1-2 and 3 – 5 weeks to titrate doses with pharmacotherapy, study team included a site physician and fed back information to PCP	
MOSAIC, Huffman et al., USA [23 37]	Single-blind effectiveness RCT, 6 months	UA, MI, HF, arrhythmia (51%)	92 CC vs. 91 EUC (53.0)	Two-step screening process; PHQ-2, GAD-2 and item about panic attacks as an inpatient and PRIME-MD for depression, GAD and PD	Social worker and psychiatrist developed individualized treatment recommendations; patient preference for pharmacotherapy (SSRI most commonly citalopram, SNRI, bupropion, mirtazapine and anxiety treatment with SSRI or benzodiazepine) or CBT (min. six session CBT when allocated); stepped-care; PCP informed of patient preference; structured telephone call and f/up to monitor symptoms, promote adherence and engagement;	Enhanced usual care, PCP informed of psychiatric status at baseline and subsequent screening
SUCCEED Huffman et al 2011, USA [17 50]	Single-blind effectiveness RCT, 3 months	UA, MI, HF, arrhythmia (52.6%)	90 CC vs. 85 UC (48.6)	Two-step screening process; PHQ-2 positive screen and PHQ-9 score ≥ 10 as an inpatient	Social worker and psychiatrist individualized depression treatment recommendations based on history and patient preference (SSRI or psychotherapy); study team provided the PCP or cardiologist with treatment recommendations; verbal and written recommendations to the inpatient treatment team; depression education for pleasant activities scheduling; monitored for	Usual care, PCP informed of depression status

					adequate depression response;	
TrueBlue, Morgan et al., AUS [19 36]	Cluster randomized RCT, 12 months	CHD and diabetes (57.8)	170 CC vs. 147 WLC (46.7)	PHQ-9 score ≥ 5 as a primary care patient	Scheduled visits to PN and PCP every 3 months over 12-months; referrals to MHS; development and recording of patient goals;	Usual care, PN monitor depression by screening at scheduled intervals

BDI-I; Beck Depression Inventory-I; CABG, coronary artery bypass graft; CC, collaborative care; CHD, coronary heart disease; COPES, Coronary Psychosocial Evaluation Studies; CODIACS, Centralized, Stepped, Patient Preference–Based Treatment for Patients With Post–Acute Coronary Syndrome Depression; GAD, generalized anxiety disorder; HF, heart failure; MHS, mental health services; MI, myocardial infarction; MOSAIC, Management of Sadness and Anxiety in Cardiology; PCP, primary care physician; PD, panic disorder; PHQ, Patient Health Questionnaire; PN, practice nurse; PRIME-MD, Primary Care Evaluation of Mental Disorders; PST, problem-solving therapy; RCT, randomized controlled trial; SSRI, selectoive serotonin reuptake inhibitors; SNRI, serotonin norepinephrine reuptake inhibitor; SUCCEED, Screening Utilization and Collaborative Care for More Effective and Efficient Treatment of Depression; UA, unstable angina; WLC, wait-list control;



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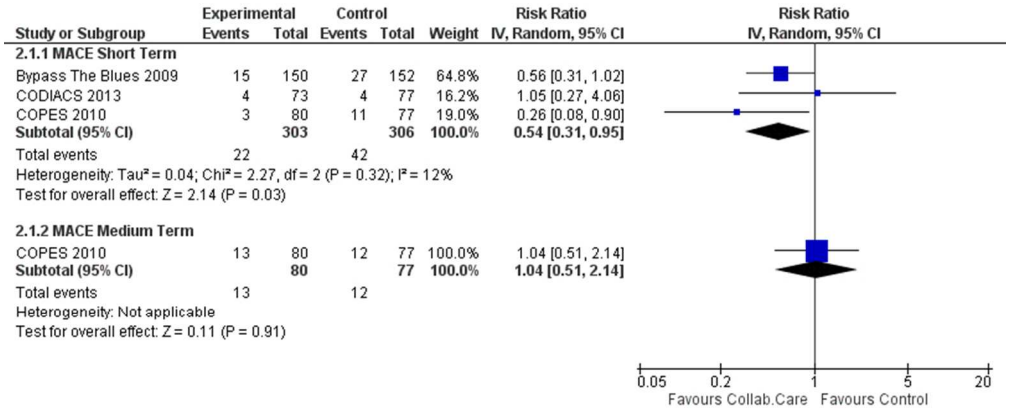

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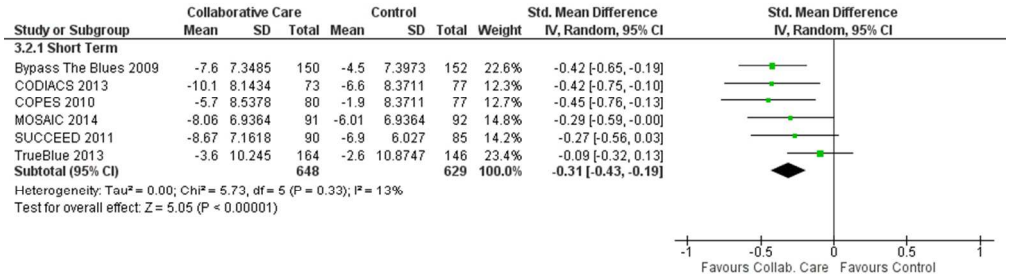

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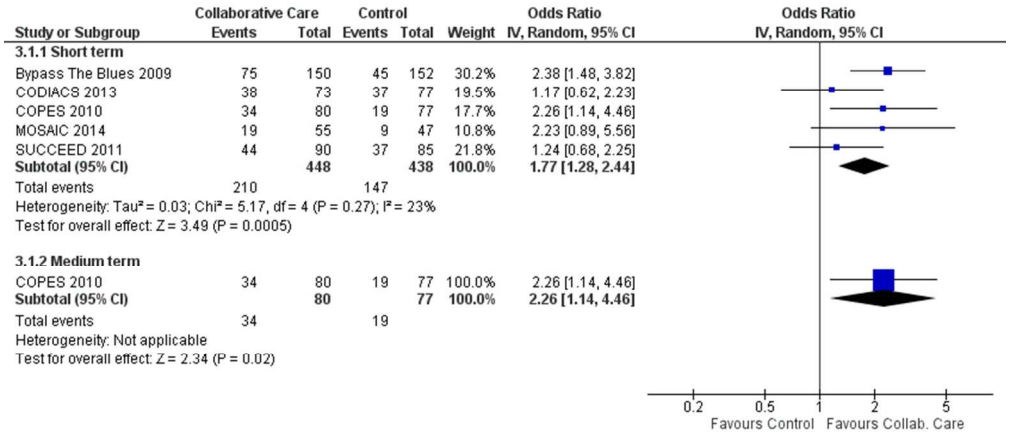

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eSupplement 1. Risk of Bias Adjudication for Included Trials

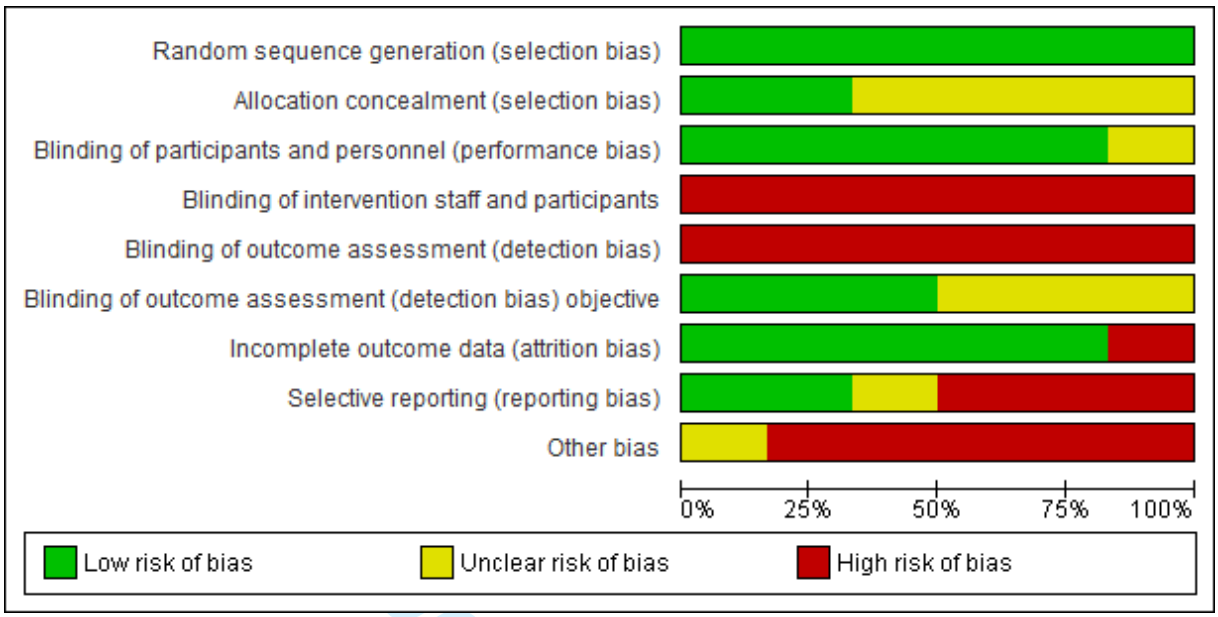
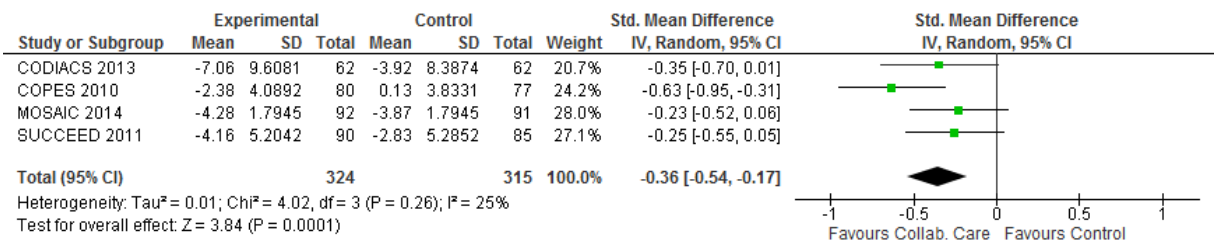


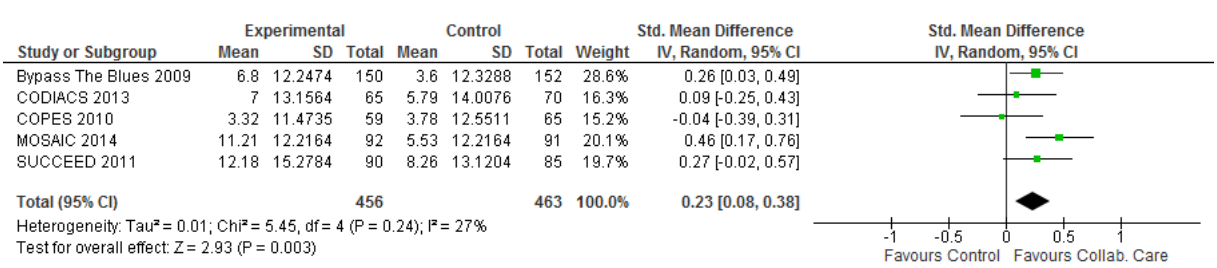
Figure showing the adjudication of risk of bias in included trials. Risk of bias independently adjudicated by PJT and HB using Cochrane Review Manager 5.3. Final risk of bias determined by consensus between the two raters.

eSupplement 2. Forest plot showing anxiety symptoms in collaborative care studies versus usual care or waiting list control (short term)



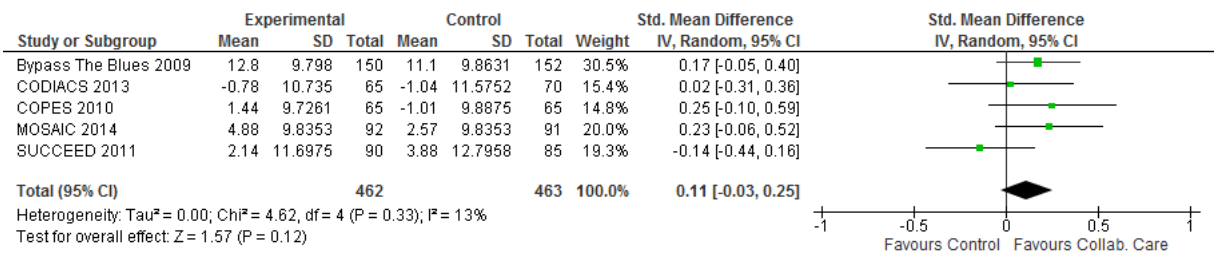
CI, confidence interval; IV, inverse variance;

eSupplement 3. Forest plot showing mental quality of life symptoms in collaborative care studies versus usual care or waiting list control (short term)



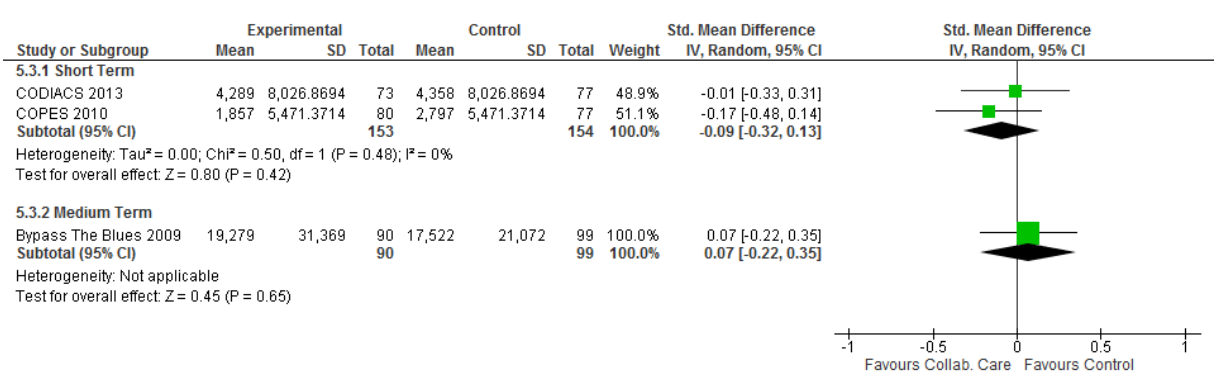
CI, confidence interval; IV, inverse variance;

eSupplement 4. Forest plot showing physical quality of life symptoms in collaborative care studies versus usual care or waiting list control (short term)



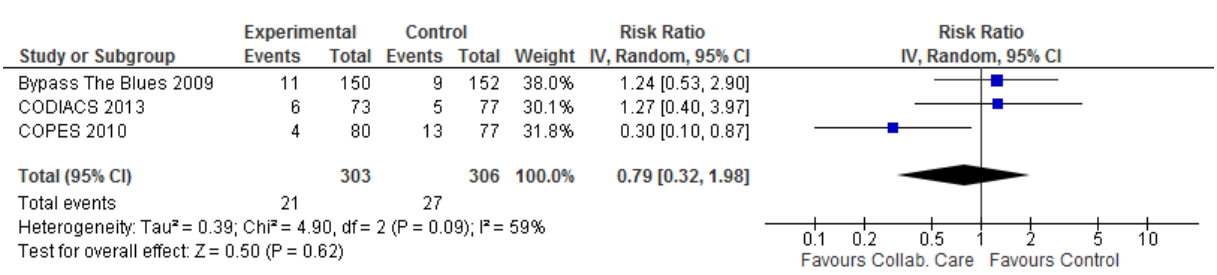
CI, confidence interval; IV, inverse variance;

eSupplement 5. Forest plot showing healthcare costs in collaborative care studies versus usual care or waiting list control (short term and medium term)



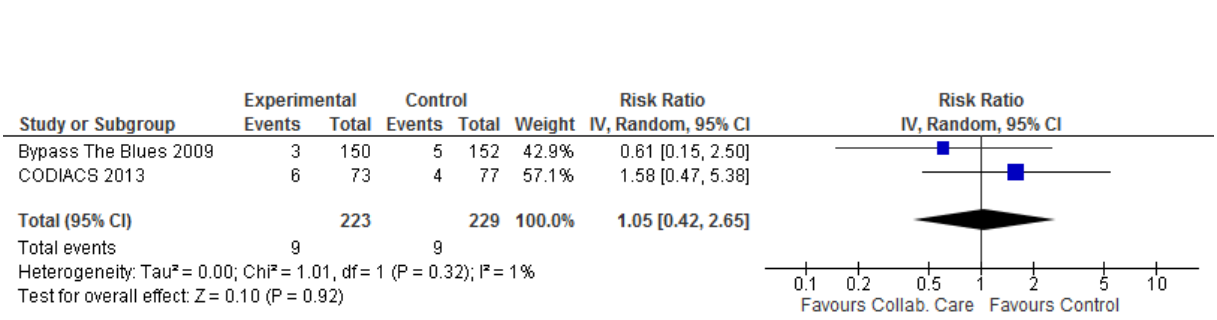
CI, confidence interval; IV, inverse variance;

eSupplement 6. Forest plot showing the risk ratio for acute coronary syndrome post intervention in collaborative care studies versus usual care or waiting list control (short term)



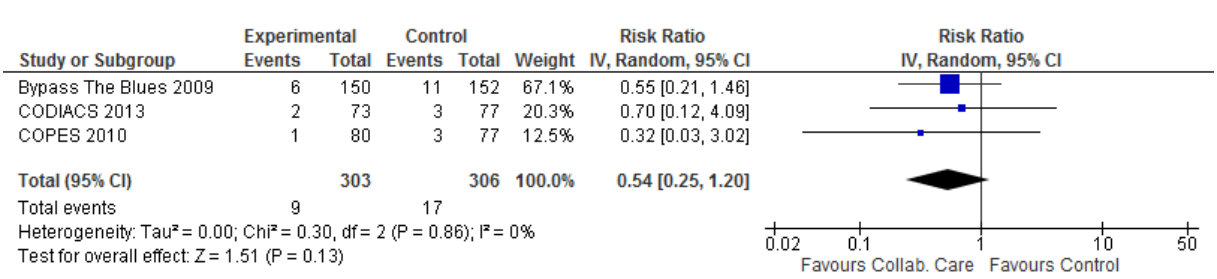
CI, confidence interval; IV, inverse variance;

eSupplement 7. Forest plot showing the risk ratio for coronary revascularization post intervention in collaborative care studies versus usual care or waiting list control (short term)



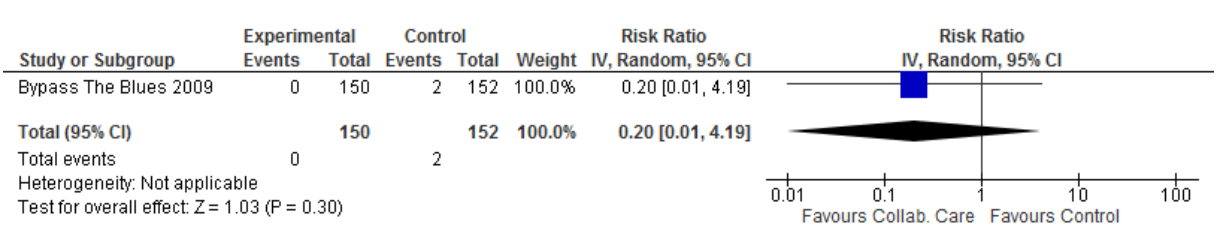
CI, confidence interval; IV, inverse variance;

eSupplement 8. Forest plot showing the risk ratio for heart failure post intervention in collaborative care studies versus usual care or waiting list control (short term)



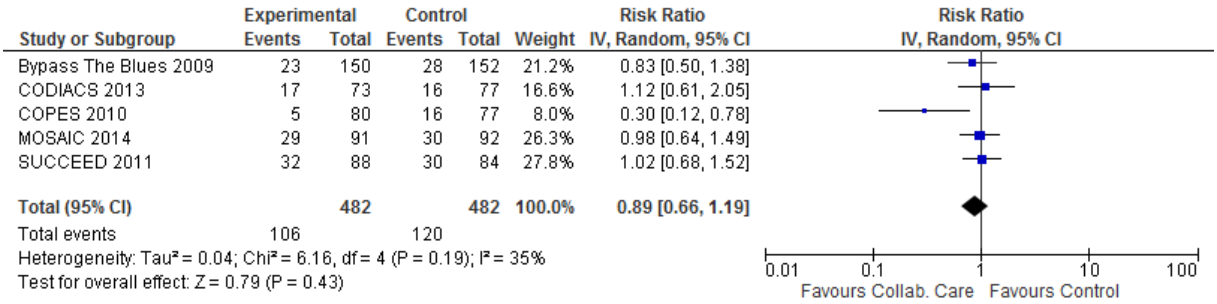
CI, confidence interval; IV, inverse variance;

eSupplement 9. Forest plot showing the risk ratio for stroke post intervention in collaborative care studies versus usual care or waiting list control (short term)



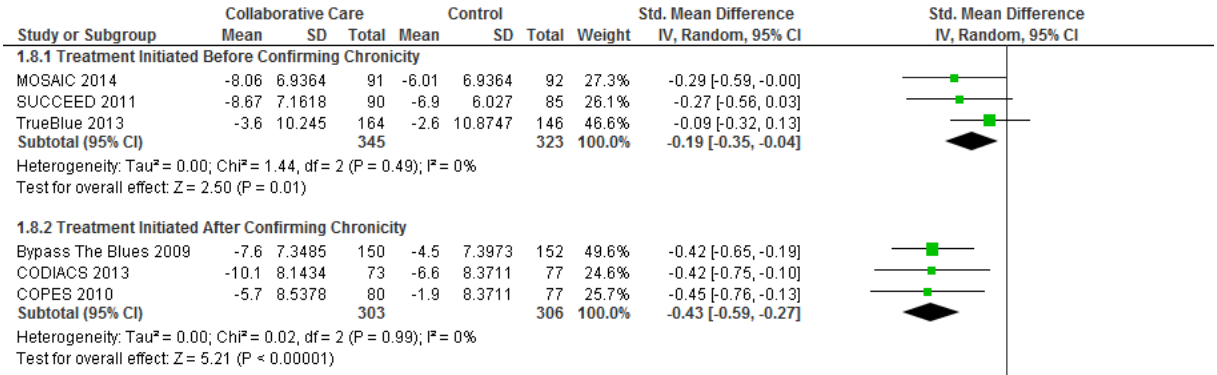
CI, confidence interval; IV, inverse variance;

eSupplement 10. Forest plot showing the risk ratio for cardiac-cause hospital admission post intervention in collaborative care studies versus usual care or waiting list control (short term)

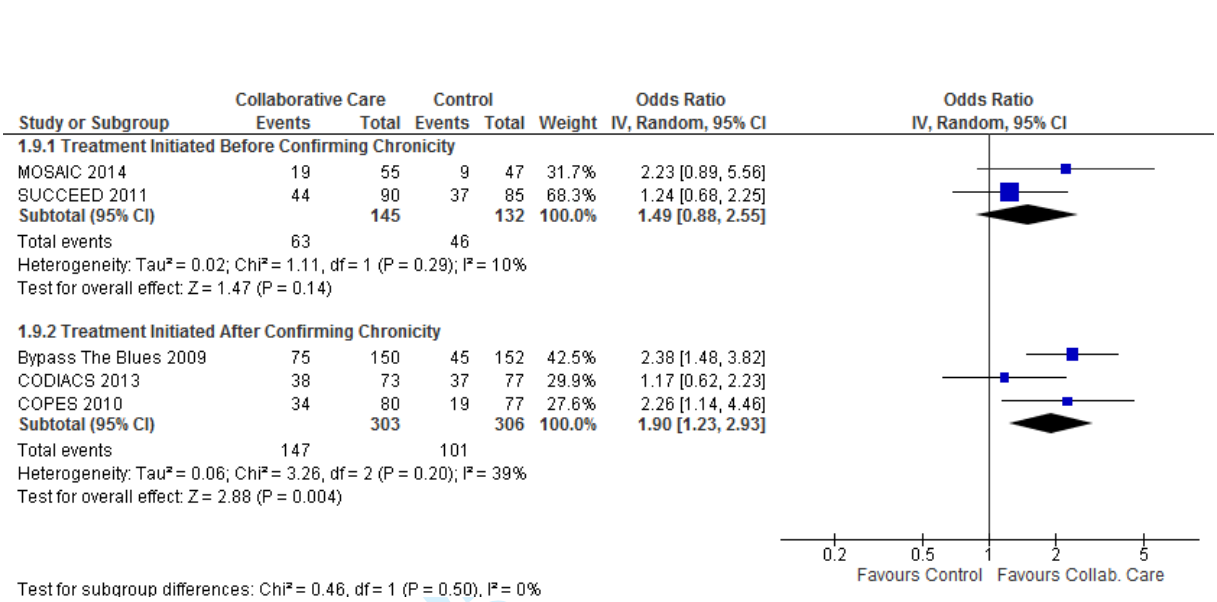


CI, confidence interval; IV, inverse variance;

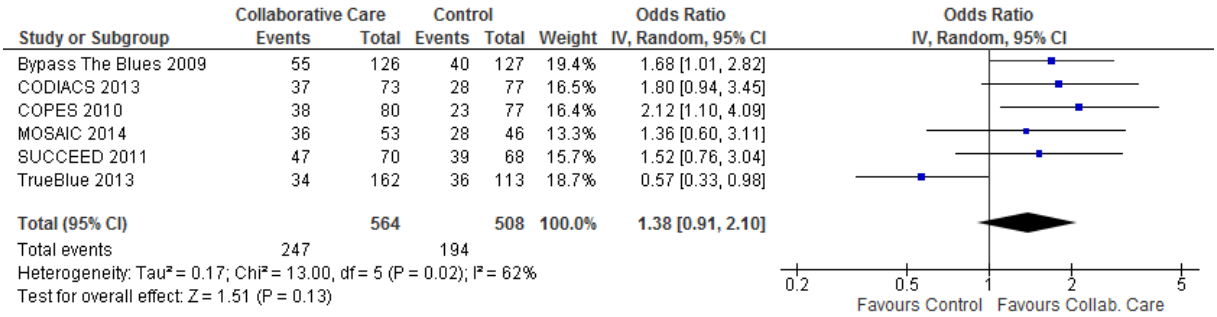
eSupplement 11. Forest plot of sensitivity analysis showing depression symptoms post intervention in collaborative care studies versus usual care or waiting list control (short term)



eSupplement 12. Forest plot of sensitivity analysis showing depression remission post intervention in collaborative care studies versus usual care or waiting list control (short term)

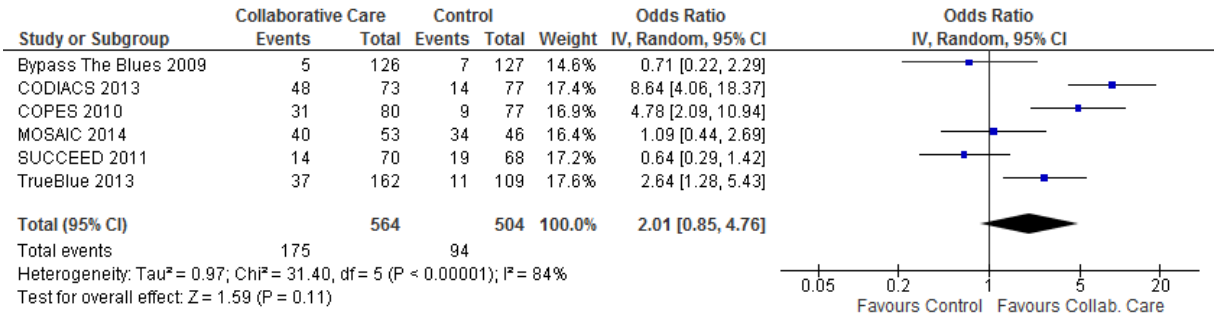


eSupplement 13. Forest plot showing the odds ratio for anti-depressant therapy post intervention in collaborative care studies versus usual care or waiting list control (short term)



CI, confidence interval; IV, inverse variance;

eSupplement 14. Forest plot showing the odds ratio for psychotherapy post intervention in collaborative care studies versus usual care or waiting list control (short term)



CI, confidence interval; IV, inverse variance;

eSupplement 15. GRADE assessment of each endpoint

GRADE Item	MACE Endpoint	Depression	Anxiety	Mental QOL	Physical QOL	Cost Effectiveness
Risk of bias	Serious (-1)	Serious (-1)	Serious (-1)	Serious (-1)	Serious (-1)	Serious (-1)
Inconsistency	No	No	No	No	No	No
Indirectness	No	No	No	No	No	No
Imprecision	No	No	No	No	No	No
Publication bias	Undetected	Undetected	Undetected	Undetected	Undetected	Undetected
Large effect	No	No	No	No	No	No
Plausible confounding would change the effect	No	No	No	No	No	No
Dose response gradient	No	No	No	No	No	No
Quality of evidence	**Moderate**	**Moderate**	**Moderate**	**Moderate**	**Moderate**	**Moderate**

GRADE assessment made using GRADE profiler 3.6.1 [27]

MACE included myocardial infarction, coronary revascularization procedure, incident heart failure, stroke

MACE, major adverse cardiac events; QOL, quality of life

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6 and abstract
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6 - 7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	eSupplement 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8, Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8-10, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10, eSupplement 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Fig 2 - 4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10 - 13 Fig 2 – 4;
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10, eSupplement 1
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11-13, eSupplements 2-14
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14-16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13-16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

PRISMA 2009 Checklist

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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