Collaborative care for co-morbid depression and diabetes: a systematic review and meta-analysis

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Article title: Collaborative care for co-morbid depression and diabetes: a systematic review and meta-analysis

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ABSTRACT

Objective: The collaborative care model is recommended for depression in adults with a chronic physical health problem like diabetes. We sought to systematically assess the effect of collaborative care on depression and glycaemia in adults with co-morbid depression and diabetes to inform guidelines and practice.

Design: Systematic review and meta-analysis.

Data sources: We searched PubMed, Scopus, Cochrane Library, Cinahl, Health Source Nursing, Medline, PsychINFO and reference lists of retrieved articles published before August 2013.

Inclusion criteria: Randomised controlled trials (RCTs) on collaborative care (i.e. co-ordinated multi-disciplinary model of care) for depression that reported the effects on depression and glycaemic outcomes in adults with co-morbid clinically relevant depression and diabetes were eligible.

Data extraction and analysis: Data on the mean difference in depression and glycaemic outcomes were extracted and pooled using random effects meta-analysis.

Results: Seven RCTs included for review reported effects on depression outcomes in 1895 participants, and glycated haemoglobin (HbA1c) level in 1556 participants. Collaborative care significantly improved depression score (standardised mean difference was -0.32 [95% CI: -0.53 to -0.11]; I-squared=79.0%) and HbA1c level (weighted mean difference was -0.33% [95% CI: -0.66% to -0.00%]; I-squared=72.9%) compared with control conditions. Depression remission did not predict better glycaemic control across the studies.

Conclusions: Limited evidence from short-to-medium term RCTs predominately conducted in the United States suggests that collaborative care for depression significantly improves both depression and glycaemia outcomes, independently, in people with co-morbid depression and diabetes.

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ARTICLE SUMMARY

Article focus

- To systematically assess the effect of collaborative care on depression and glycaemia in adults with co-morbid depression and diabetes.

Key messages

- Limited evidence from short-to-medium term RCTs predominately conducted in the United States suggests that collaborative care for depression significantly improves both depression and glycaemia outcomes.

Strengths and limitations of this study

- Key findings were based on a high-quality systematic review and meta-analysis level of evidence
- Since only a small number of short-to-medium term studies predominately conducted in the United States were included, the findings of this review may not be relevant to health care settings in other countries, requiring further research.

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INTRODUCTION

Diabetes is currently ranked the 14th leading cause of global disease burden (assessed using a summary measure of healthy years of life lost due to premature death and years lived with disability), and has moved up several places in the rankings for leading causes since 1990 [1]. The International Diabetes Federation estimated that more than 371 million people (or 8.3% of the adult population worldwide) had diabetes in 2012 [2]. Major depression, currently ranked the 11th leading cause of global disease burden, has also moved up several places in the rankings for leading causes since 1990 [1]. Although rankings varied substantially across regions, health care practitioners in these countries need guidance to better deal with the rising burden of diabetes and depression.

Diabetes is a chronic physical health condition that is often co-morbid with clinically relevant symptoms of depression [3-5]. Practitioners should be aware that depression co-morbidity can significantly worsen the self-care [6], health [7-9] and economic burden of diabetes [10]. This suggests that effective management of depression in people with co-morbid diabetes could potentially reverse several of these adverse outcomes, resulting in better glycaemic control among other benefits.

Current National Institute for Health and Clinical Excellence (NICE) guidelines for depression in adults with a chronic physical health problem, like diabetes, recommend collaborative care in a 'stepped care framework' in which to organise health services [11]. Patients with inadequate response to one or more treatments are 'stepped up' from low intensity care to a more intensive form of management (including lifestyle, psychological and pharmacological therapies). Practitioners should consider collaborative care for patients with co-morbid diabetes and depression, since they typically need more intensive care.

Randomized controlled trial (RCT) evidence shows that collaborative care is more effective than usual care for improving depression outcomes at both short and longer terms in

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American primary care settings [12]. Systematic reviews of RCTs have also confirmed that collaborative care is more effective than usual care for improving depression outcomes in people with co-morbid diabetes [13, 14], but there was a lack of consistent evidence for improving glucose control [13, 15]. However, the results of newly published RCTs suggest that collaborative care for depression also leads to significant improvements in glycaemic control [16, 17]. We therefore sought to systematically assess the total body of RCT evidence on collaborative care for depression in adults with co-morbid depression and diabetes to inform guidelines and practice.

METHODS

Search strategy

We searched PubMed, Scopus, Cochrane Library, Cinahl, Health Source Nursing, Medline, PsychINFO and reference lists of retrieved articles published before August 2013. Search syntaxes were developed in consultation with an experienced university research librarian taking into account a broad range of terms and phrases used in definitions of RCTs, collaborative care, depression and diabetes (full electronic search strategies for PubMed and Scopus databases; appendix page 1). Reference lists of potentially eligible articles were searched by hand to identify additional studies missed by our search strategy.

Study selection

Two reviewers (EA and JF) identified potentially relevant studies for inclusion by screening titles and/or abstracts of all citations identified with our database searches. A second screening was performed on the full text of these articles. Articles for RCTs on collaborative care (i.e. evidence showing that the intervention was a co-ordinated multi-disciplinary model

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of care) for depression that reported the effects on both depression and glycaemic outcomes in adults were eligible. There were no language restrictions for articles.

Data extraction

Data extraction and quality assessment of included studies were performed and/or verified independently by three reviewers (EA, JF and PF). Discrepancies were resolved through discussion. Authors of relevant studies were contacted, where possible, for data that could not be extracted from the published articles.

Quality assessment

For methodology and quality assessment, a quality checklist was developed to identify potential sources of bias (table; appendix page 2). Quality items for RCTs reviewed were as follows (each worth 1.0 numerical point): 1) study eligibility criteria were adequately described, 2) randomization methodology was adequate (i.e., evidence suggesting "random" method was used to generate and implement random allocation sequence), 3) allocation concealment was adequate (i.e., evidence to suggest that a robust method was used for concealing the sequence of treatment allocation (e.g., independent IT or telephone service or sealed opaque envelopes only opened in front of the participant), 4) between-group were balanced at baseline for primary outcomes (i.e., evidence showing that groups were similar at the outset for primary outcomes), 5) between-group drop-out rates were balanced, and 6) intention to treat analysis was included.

Our quality item checklist was designed based on criteria for assessment of RCTs [18, 19] and allowed summed scores to range from 0 to 6 points, reflecting lowest to highest quality. Studies were considered 'better quality' if they received a score higher than 4, since that meant that they had most of our quality items.

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Primary outcomes

Data on the mean difference in depression and glycated haemoglobin (HbA1c) outcomes between the treatment and control groups were extracted and pooled using random effects meta-analysis. In one study [16], the post-treatment means were derived from the within group changes and the control group standard deviation carried forward from the baseline values [20]. Standardised mean differences were calculated using Glass's Delta method.

Data synthesis

Three reviewers (EA, PF and JF) independently collated and/or verified extracted data to present a descriptive synthesis of important study characteristics and a quantitative synthesis of effect estimates.

Statistical methods

We pooled and weighted studies first using random effects meta-analysis models, and second using fixed effects models for verification [21]. Hb1Ac results were pooled to estimate the inverse variance weighted mean difference (WMD), including the DerSimonian and Laird 95% confidence interval (95% CI), between treatment and control groups.

In examining the effects of collaborative care treatment on depression scores, the standardised mean difference (SMD) from each RCT were pooled to produce an overall estimate of effect, and associated 95% CI, between treatment and control groups. We used meta-regression to test the hypothesis that SMD of the depression score is a predictor of the WMD of Hb1Ac.

For each meta-analysis model, the degree of heterogeneity in WMD or SMD was assessed by visual inspection, the *I*-squared statistic (moderate being < 50% [22]) and the χ^2-test of

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goodness of fit [23]. Where evidence of heterogeneity was observed, we checked data extracted from individual outlier studies, qualitatively investigated reasons for their different results, and explored the effects of study exclusion in sensitivity analyses.

We also used sensitivity analysis to investigate the robustness of the meta-analyses models. We variously excluded lower quality studies (score of ≤4.0), one study conducted outside the United States (Australia), studies that integrated diabetes care, studies which considered lifestyle risk factors, and studies of less than one-year duration. Publication bias, which reflects the tendency for smaller studies to be published in the literature only when findings are positive, was assessed visually using funnel plots [24]. All calculations were performed in Stata version 12 (StataCorp, College Station, TX, USA) using the 'metan', 'metareg' and 'metafunnel' commands. A two-tailed *P*-value < 0.05 was considered statistically significant throughout the analyses.

RESULTS

Figure 1 presents a flowchart summarizing identification of potentially relevant studies, and those included and excluded. Our search strategy identified 264 citations after duplicates were removed. Of these, 246 citations were excluded after the first screening of titles and/or abstracts for inclusion and exclusion criteria, leaving 18 citations for a second full text screening. After further assessment, 11 citations were excluded for reasons listed in figure 1 leaving seven RCTs for final inclusion in the systematic review. Most studies were excluded for inadequate study design or intervention (i.e. did not qualify as collaborative care model), and a couple of studies were excluded for being redundant duplicate citations and for incomplete data available for extraction (list of excluded citations and reasons; appendix pages 3-4).

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<< Figure 1 >>

Descriptive data synthesis

Table 1 presents study characteristics of seven RCTs included for review, which were published between 2004 and 2013. All studies except one [25] were conducted in the United States. Major inclusion criteria were various case definitions of diabetes in five studies [16, 26-29], diabetes and/or coronary heart disease (CHD) in two studies [17, 25], and co-morbid clinically relevant depression in all studies. Major exclusion criteria were cognitive impairment in four studies [16, 17, 28, 29], co-morbid psychiatric disorder or suicidal ideation in four studies [17, 27-29], alcohol problems in two studies [27, 29], and living in residential care in two studies [17, 25], among others. The sample sizes ranged from 58 to 417, resulting in a total of 1895 participants for depression outcomes and 1556 participants for HbA1c outcome across studies. Mean age of the samples ranged from 54 to 71 years. All of the study samples contained both male and female participants. Baseline mean depression scores ranged from 15.6 to 19.7 by the CES-D 20 [26], from 9.9 to 11.6 by the PHQ-9 [16, 25], and from 1.4 to 1.7 by the SCL-20 [17, 27-29]. Baseline mean HbA1c levels ranged from 6.9 to 9.1%. Defining features of collaborative care models investigated were a case manager/officer (usually a nurse or non-physician mental health worker for co-ordination of care) with proactive follow-ups in all studies, a structured management plan delivered within a stepped care framework and relapse prevention in four studies [17, 27-29], an integrated diabetes care program in three studies [16, 17, 26], and consideration for lifestyle risk factors in two studies [17, 25]. Control conditions were “usual care” in four studies [16, 25, 26, 29], whereas usual care was enhanced in the three other studies [17, 27, 28]. Trial durations ranged from 12 to 52 weeks. Primary outcomes were depression score assessed by the CES-D 20 in one study [26], by the PHQ-9 in two studies [16, 25], and by the SCL-20 in four studies

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[17, 27-29]; and glycaemic control by HbA1c in all of the studies. Mean quality scores ranged from 3.5 to 5.5, and all but three studies [25, 26, 29] received a score of 4.5 or higher.

<< Table 1 >>

Quantitative data synthesis

Effect of collaborative care on depression

Figure 2 presents the SMD in depression outcomes after collaborative care between the treatment and control groups. Collaborative care significantly improved standardised depression outcomes compared with control conditions (pooled SMD was -0.32 [95% CI: -0.53 to -0.11]). There was statistical heterogeneity between studies (I-squared=79.0%, P<0.001) that was mostly a result of variation in the degree of benefit favouring collaborative care in all but one study [27], which had significant between-group differences in mean depression scores at baseline. Correcting for these differences substantially changed the SMD for that study (from 0.00 [95% CI: -0.20 to 0.20] to -0.60 [95% CI: -0.81 to -0.39]) in a sensitivity analysis. In addition, the sensitivity analyses presented in table 2 shows that the pooled SMD was substantially changed only after exclusion of lower quality studies (decreased to -0.17 [95% CI: -0.35 to 0.00]). A funnel plot was produced and confirmed widespread heterogeneity of effect estimates between studies, but did not suggest any publication bias (appendix page 5).

<< Figure 2 >>

<< Table 2 >>

Effect of collaborative care on HbA1c

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Figure 3 presents the WMD in HbA1c level after collaborative care between the treatment and control groups. Collaborative care significantly reduced HbA1c level compared with control conditions (pooled WMD was -0.33% [95% CI: -0.66% to -0.00%]). There was statistical heterogeneity between studies (I-squared=72.9%, P=0.001) that was mostly a result of variation in the degree of benefit favouring collaborative care in all but two studies [28, 29]. The sensitivity analyses presented in table 3 shows that the pooled WMD was slightly decreased in the fixed effect model (-0.21 [95% CI: -0.37 to -0.05]), but no longer statistically significant after each of the various studies was excluded. This was particularly so after exclusion of three studies that integrated diabetes care (decreased to -0.07 [95% CI: -0.35 to 0.21]). A funnel plot was produced and confirmed widespread heterogeneity of effect estimates between studies, but did not suggest any publication bias (appendix page 6).

<< Figure 3 >>

<< Table 3 >>

Effect of depression remission on HbA1c

Figure 4 presents a scatter plot displaying the association between the SMD in depression outcomes and the WMD in HbA1c values in each study. Results of a meta-regression model suggest that the SMD for depression scores failed to predict the WMD in HbA1c values across studies (P=0.828, coefficient was 0.19 [95% CI: -1.93 to 2.31]).

<< Figure 4 >>

DISCUSSION

Summary of evidence

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Based on limited evidence from short-to-medium term RCTs predominately conducted in the United States, our results suggest that collaborative care for depression significantly improves both depression and glycaemia outcomes in people with co-morbid depression and diabetes. Furthermore, we found evidence from a sensitivity analysis that future high-quality RCTs [30] will likely strengthen rather than weaken this evidence base. The size of the effect of collaborative care on depression and HbA1c outcomes that can be expected in practice is small-to-moderate, but comparable with pharmacological, psychological and behavioural therapies alone [13, 14, 31, 32], and likely to be clinically relevant. For instance, several of the RCTs we reviewed have also shown that collaborative care for depression in people with co-morbid diabetes is more effective than usual care for improving functional health outcomes [33] and were cost effective [34, 35], consistent with previous economic modelling [36]. In addition, a recent meta-analysis found a positive dose-response trend between HbA1c level and adverse cardiovascular outcomes [37]. This suggests that improvements in glycaemic control from collaborative care for depression could theoretically protect patients with co-morbid diabetes against future cardiovascular risk.

In contrast, we found no evidence to suggest that improved depression outcomes results in better glycaemic control (lower HbA1c values) among people with co-morbid diabetes. This null finding for reversibility of the effect of depression on glycaemia weakens the evidence base for causality in terms of worsening the burden of diabetes. Alternatively, collaborative care for depression may improve glycaemia in people with diabetes by increasing self-management, independent of the depression prognosis. For example, collaborative care for depression [17] was more effective than usual care for improving blood pressure and blood glucose self-monitoring rates [38]. Quality improvement strategies for diabetes care that promote glucose self-monitoring among patients can significantly improve HbA1c level (SMD was 0.57% [0.31% to 0.83]) [39]. Indeed, evidence from our sensitivity analysis

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showed that the effect of collaborative care on HbA1c was almost entirely confined to the three studies that integrated diabetes care within the collaborative care model [16, 17, 26]. Second, none of the RCTs we reviewed properly integrated lifestyle intervention within the collaborative care. In high-income countries like the United States and Australia, depression is associated with overweight or obesity, physical inactivity, smoking cigarettes and drinking excessive amounts of sugar-sweetened and alcoholic beverages [40, 41], all of which are well-established lifestyle risk factors for diabetes. Indeed, there is international consensus supporting the effectiveness of lifestyle intervention in the prevention and management of type 2 diabetes [42]. In addition, previous systematic reviews of RCTs have shown that exercise (an integral component of lifestyle intervention) is effective for improving both depression score (SMD was -0.82 [95% CI: -1.12 to -0.51]) and HbA1c level (WMD was -0.67% [95% CI: -0.84 to -0.49%]) [43, 44], and the size of these effects are substantially larger than what we found for collaborative care for depression. There is now sufficient evidence to suggest that diabetes care and lifestyle intervention integrated within collaborative care for depression would be the most effective way to manage care for co-morbid depression and diabetes.

Limitations

Several limitations require further consideration. Since only a small number of short-to-medium term studies predominately conducted in the United States were included, the findings of this review may not be relevant to health care settings in other countries, requiring further research. In particular, health care systems in most countries are not properly set up to optimize the co-ordination between practitioners [45]. Integration of therapies including collaborative care, diabetes care and lifestyle intervention is required for managing co-morbid depression diabetes. Finally, reviewer-level limitations include incomplete retrieval of

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information for several of the 11 citations excluded, and the existence of other relevant studies not identified with our search strategy resulting in bias. However, the results and conclusions reported in most of the excluded studies were in line with those reported here, search strategy bias was unlikely.

Conclusions

Limited evidence from short-to-medium term RCTs predominately conducted in the United States suggest that collaborative care for depression significantly improves both depression and glycaemia outcomes, independently, in people with co-morbid depression and diabetes. Future research should investigate the effectiveness, feasibility and appropriateness of collaborative care integration with diabetes care and lifestyle intervention for co-morbid depression and diabetes in routine clinical practice in specific health care settings worldwide.

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Authorship order is according to percentage contribution. EA is guarantor of the paper, taking responsibility for the integrity of the work as a whole, from inception to published article. EA conceived and designed the review, identified studies for inclusion, extracted and interpreted data, and drafted the article. PF analysed and interpreted data, and revised the article. JF extracted and interpreted data, and revised the article. All authors approved the final completed article. We are grateful to Mrs Rohini Patil for her work on developing and conducting the electronic database searches.

CONTRIBUTORSHIP STATEMENT

Authorship order is according to percentage contribution. EA is guarantor of the paper, taking responsibility for the integrity of the work as a whole, from inception to published article. EA conceived and designed the review, identified studies for inclusion, extracted and interpreted data, and drafted the article. PF analysed and interpreted data, and revised the article. JF extracted and interpreted data, and revised the article. All authors approved the final completed article. We are grateful to Mrs Rohini Patil for her work on developing and conducting the electronic database searches.

COMPETING INTERESTS

EA has received honoraria for speaking at events for Eli Lilly Australia Pty Ltd (Lilly).

DATA SHARING STATEMENT

Not applicable

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TABLE 2: Characteristics of randomised controlled trials reviewed

adjacent.....continued →

Study identification	Country	Sample size	Population		Men (%); Mean age (years)	Baseline mean depression score		Baseline mean HbA1c (%)	
			Major inclusion criteria (all)	Major exclusion criteria (any)		Treated	Controls	Treated	Controls
Bogner et al, 2010[26]	United States	58	Aged ≥50 years, recent HbA1c >7 or an oral hypoglycaemic prescription within past year, diagnosed depression or an antidepressant prescription within past year	None specified	16; 60	15.6	19.7	7.3	7.3
Bogner et al, 2012[16]	United States	180	Aged ≥30 years, diagnosis of type 2 diabetes and current oral hypoglycaemic prescription, current antidepressant prescription	No informed consent, cognitive impairment (Mini-Mental State Examination <21), residence in care facility providing medications, unwillingness or inability to use the Medication Event Monitoring System	32; 57	10.6	9.9	7.2	7.0
Ell et al, 2010[27]*	United States	387	Aged ≥18 years, "with diabetes", one of two cardinal depressive symptoms most days and depression score ≥10 by the PHQ-9, informed consent	Acute suicidal ideation, score of ≥8 by the Alcohol Use Disorders Identification Test, inability to speak Spanish or English	18; 54	1.7	1.4	9.0	9.1
Katon et al, 2004[28]*	United States	329	Diabetes (by registry), depression score of ≥10 by the PHQ-9 at first screening and score of ≥1.1 by the SCL-90 at second telephone screening, ambulatory, English speaking, adequate hearing for telephone interview, planned continued enrolment in the clinic during the next year	Currently in care of psychiatrist, diagnosed bipolar disorder or schizophrenia, current antipsychotic or mood stabilizer medications, symptoms of dementia	35; 58	1.7	1.6	8.0	8.0
Katon et al, 2010[17]	United States	214	Diabetes, coronary heart disease or both (by registry), depression score of ≥3 by the PHQ-2 and ≥10 by the PHQ-9, ambulatory, spoke English, and planned be enrolled in the Health Maintenance Organization for 12 months	Terminal illness, residence in long-term facility, severe hearing loss, planned bariatric surgery within three months, pregnancy or breast feeding, ongoing psychiatric care, bipolar disorder or schizophrenia, current antipsychotic or mood stabilizer medications, symptoms of dementia	48; 57	1.7	1.7	8.1	8.0
Morgan et al, 2013[25]	Australia	156 (glycaemia); 310 (depression)	Type 2 diabetes, coronary heart disease or both (by registry), depression score of ≥5 by the PHQ-9, informed consent	Aged <18 years, in residential care	55; 68	10.7	11.6	7.0	6.9

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Williams et al, 2004[29]*	United States	232 (glycaemia); 417 (depression)	Diagnosed or treated diabetes or high blood sugar in past three years by self-report, current major depression or dysthymic disorder by structured clinical interview according to DSM-IV	Current drinking problem (score of ≥2 by the CAGE questionnaire), history of bipolar disorder or psychosis, ongoing psychiatric care, or severe cognitive impairment (score of <3 by questionnaire)	47; 71	1.7	1.7	7.3	7.3

Abbreviations: HbA1c, glycated haemoglobin; CES-D, Center for Epidemiological Studies Depression scale; PHQ, Patient Health Questionnaire; SCL, Symptom Checklist; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, fourth edition
*Raw data was provided by the author

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→ adjacent.....continued

Treatments	Control conditions	Trial duration (weeks)	Outcomes (assessments)	Quality score (out of 6)
"Integrated care"; consisted of supervised case manager, patient-centred care, education and integrated care for depression and diabetes; three 30 min in person and two 15 min telephone follow-up sessions over four weeks	"Usual care"; and study assessments	12	Glycaemia (HbA1c); depression score (CES-D 20)	4.0
"Integrated care"; consisted of supervised case manager, patient-centred care, education and integrated care for depression and diabetes; three 30 min in person and two 15 min telephone follow-up sessions over three months	"Usual care"; and study assessments	12	Glycaemia (HbA1c); depression score (PHQ-9)	5.0
"Collaborative care"; consisted of supervised nurse case manager, patient-centred care, problem solving therapy, self-monitoring education, and coordination of care and services for depression and diabetes within a stepped-care framework; monthly telephone symptom monitoring, treatment maintenance and relapse prevention up to 12 months	"Enhanced usual care"; and patient and family-focused depression education pamphlets	52	Glycaemia (HbA1c); depression score (SCL-20)	5.5
"Collaborative care"; consisted of supervised nurse case manager, patient-centred care (initial choice of antidepressant or problem solving therapy), within a stepped-care framework; initial one hour visit, followed by twice monthly half-hour follow-ups (telephone or in-person) up to 12 weeks and referral to speciality care thereafter if necessary	"Usual care"; and advice to consult their physician for depression care	26	Glycaemia (HbA1c); depression score (SCL-20)	4.5
"Collaborative care"; consisted of supervised nurse case manager, "treat-to-target program" integrated care for specific conditions, within a stepped-care framework, motivational problem solving and goal setting for self-care (including exercise, and "The Depression Helpbook", video and written material); structured visits every two to three weeks, and maintenance plan once targeted levels were achieved including telephone follow-ups every four weeks	"Enhanced usual care"; patients could self-refer to mental health care or be referred by primary care physicians at the clinic; and study assessments	52	Glycaemia (HbA1c); depression score (SCL-20)	5.0
"Collaborative care"; consisted of collaborative care trained nurse case manager, 45 min nurse consult every three months followed (for assessment of lifestyle, physical and biochemical risk factors, and referrals, self-care of depression and setting personal goals for review and discussion of educational resources), followed by a 15 min consult with their usual general practitioner	"Usual care"; baseline data collected retrospectively	26	Glycaemia (HbA1c); depression score (PHQ-9)	3.5

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Collaborative care; consisted of trained nurse or psychologist case manager, patient-centred care, problem solving therapy, 20 min educational video tape and written material on late-life depression, and coordination of care and services for depression within a stepped-care framework; monthly telephone symptom monitoring, treatment maintenance and relapse prevention up to 12 months; diabetes care not specifically enhanced	"Usual care"; and study assessments	52	Glycaemia (HbA1c); depression score (SCL-20)	4.0	

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TABLE 2: Sensitivity analysis of randomized controlled trials of collaborative care → depression score outcome meta-analysis

	N studies	N sample	SMD	(95% confidence interval)	P-value for heterogeneity
Fixed effects model	7	1895	-0.31	(-0.40 to -0.22)	<0.001
Exclusion of 3 lower quality studies (score ≤4.0)	4	1110	-0.17	(-0.35 to 0.00)	0.101
Exclusion of 1 study outside the United States (Australia)	6	1585	-0.32	(-0.57 to -0.07)	<0.001
Exclusion of 3 studies that integrated diabetes care	4	1443	-0.30	(-0.62 to 0.01)	<0.001
Exclusion of 2 studies that considered lifestyle risk factors	5	1371	-0.30	(-0.59 to 0.00)	<0.001
Exclusion of 4 studies less than 1 year duration	3	1018	-0.34	(-0.68 to 0.01)	<0.001

Abbreviations: N, number; SMD, standardized mean difference

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TABLE 3: Sensitivity analysis of randomised controlled trials of collaborative care → HbA1c outcome meta-analysis

	N studies	N sample	WMD	(95% confidence interval)	P-value for heterogeneity
Fixed effects model	7	1556	-0.21	(-0.37 to -0.05)	0.001
Exclusion of 3 lower quality studies (score ≤4.0)	4	1110	-0.32	(-0.81 to 0.17)	0.001
Exclusion of 1 study outside the United States (Australia)	6	1400	-0.31	(-0.68 to 0.07)	0.001
Exclusion of 3 studies that integrated diabetes care	4	1104	-0.07	(-0.35 to 0.21)	0.086
Exclusion of 2 studies that considered lifestyle risk factors	5	1186	-0.27	(-0.71 to 0.16)	0.002
Exclusion of 4 studies less than 1 year duration	3	833	-0.18	(-0.48 to 0.11)	0.189

Abbreviations: N, number; WMD, weighted mean difference

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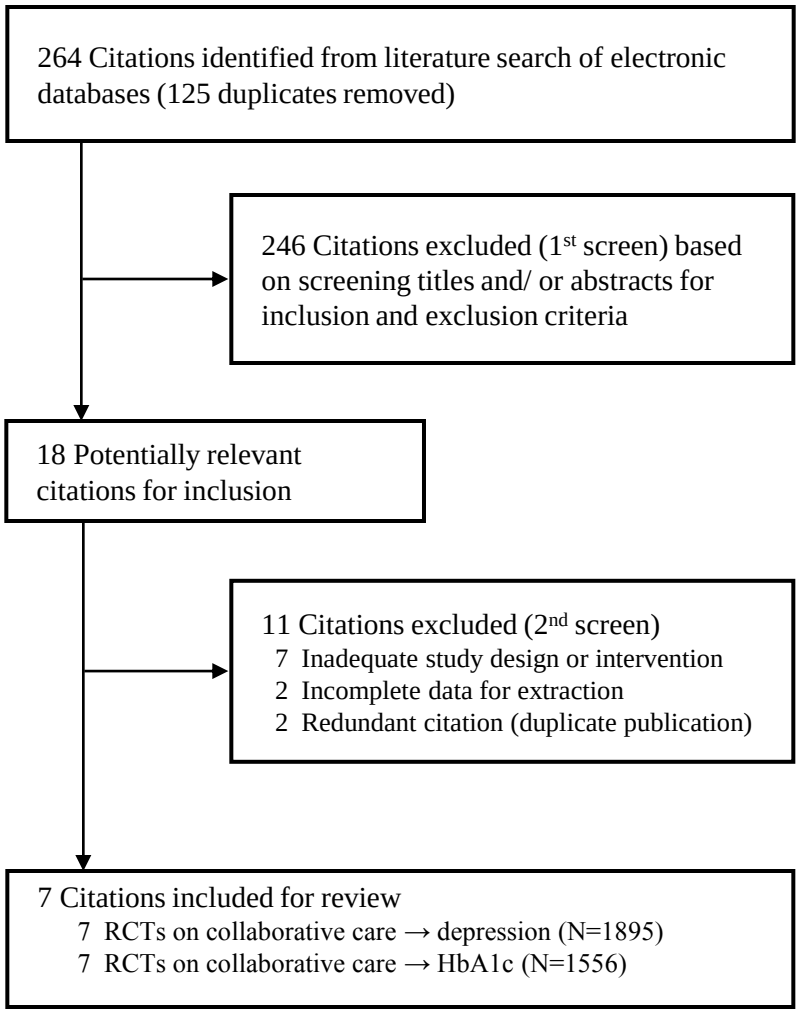

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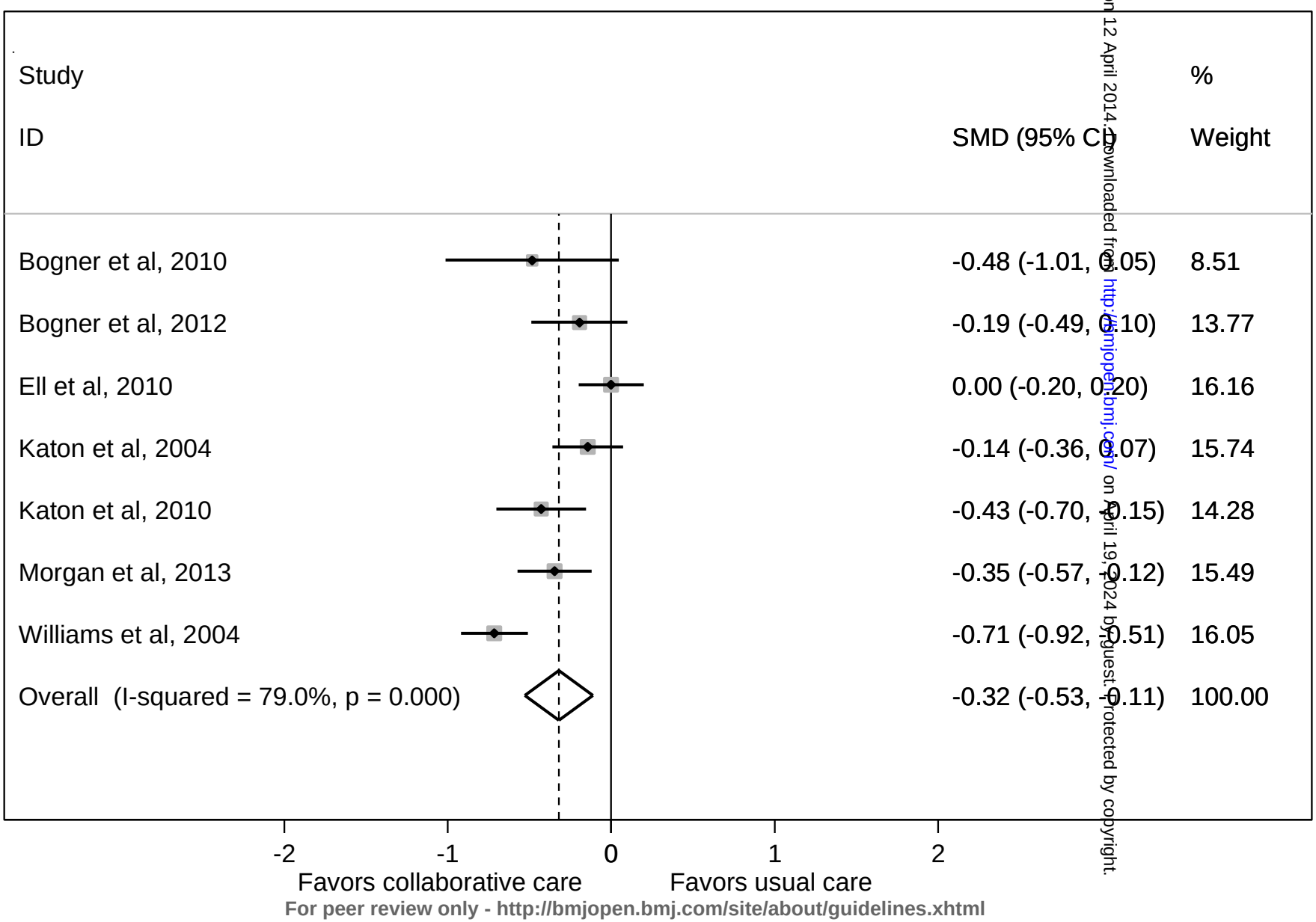

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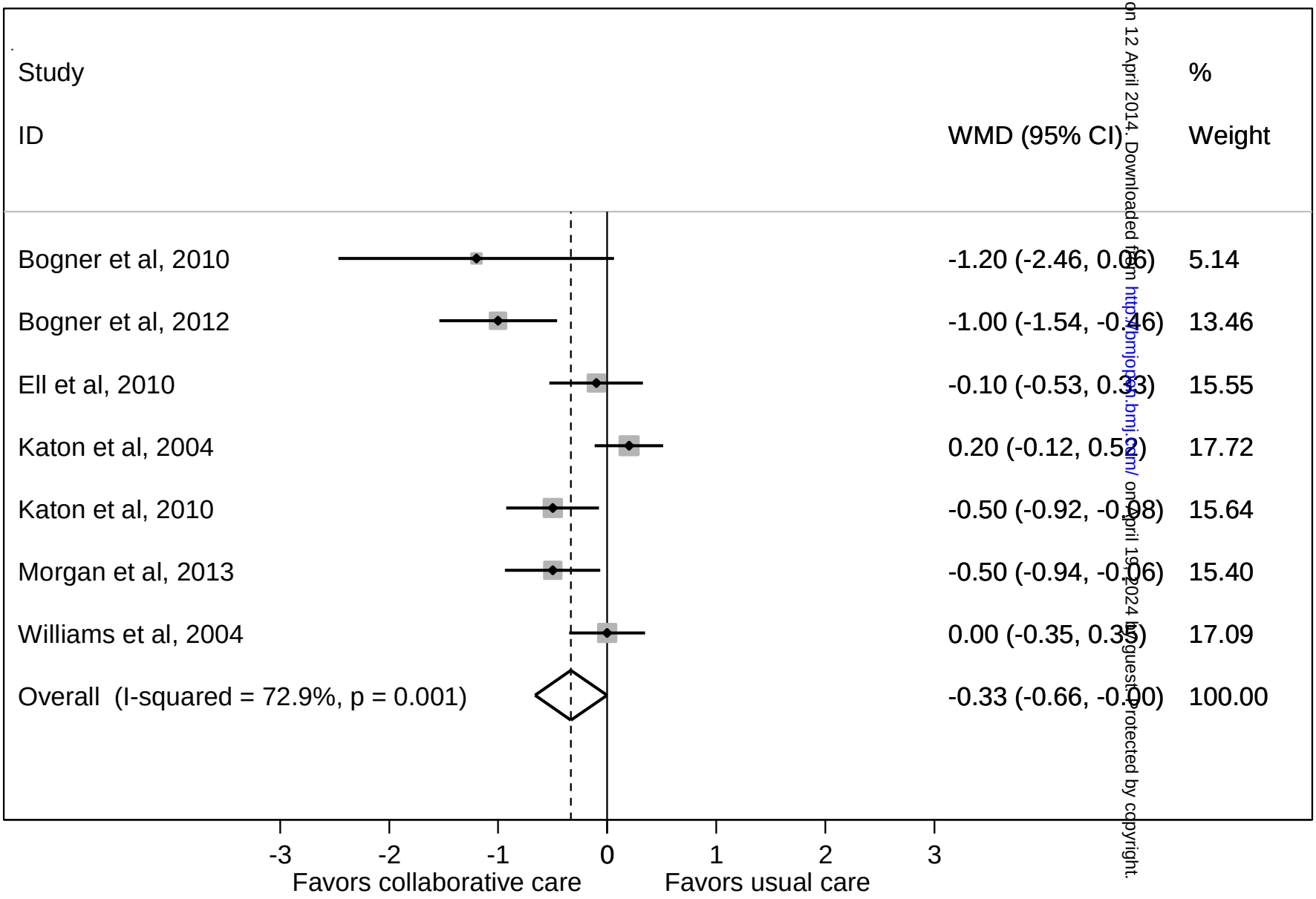

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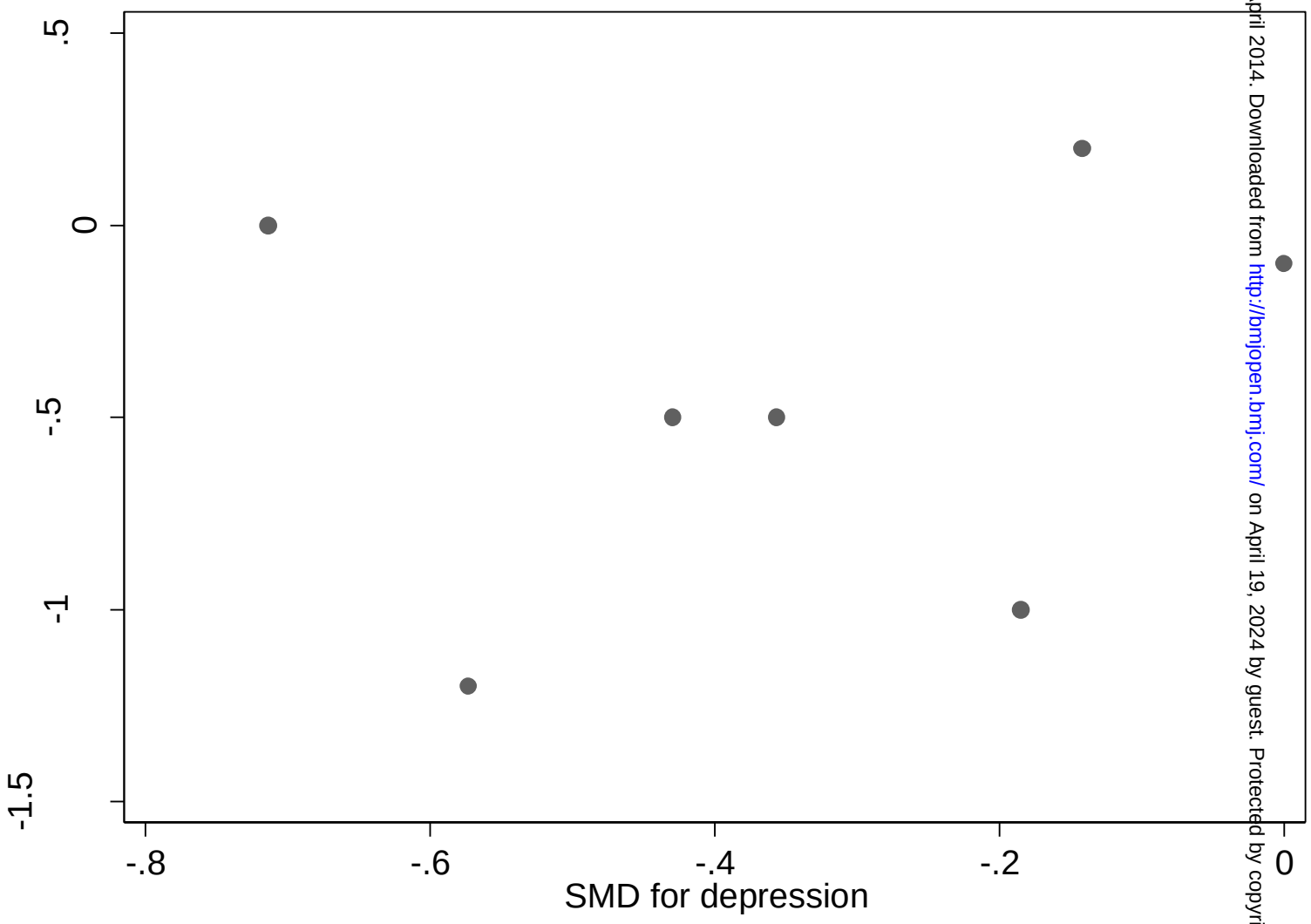

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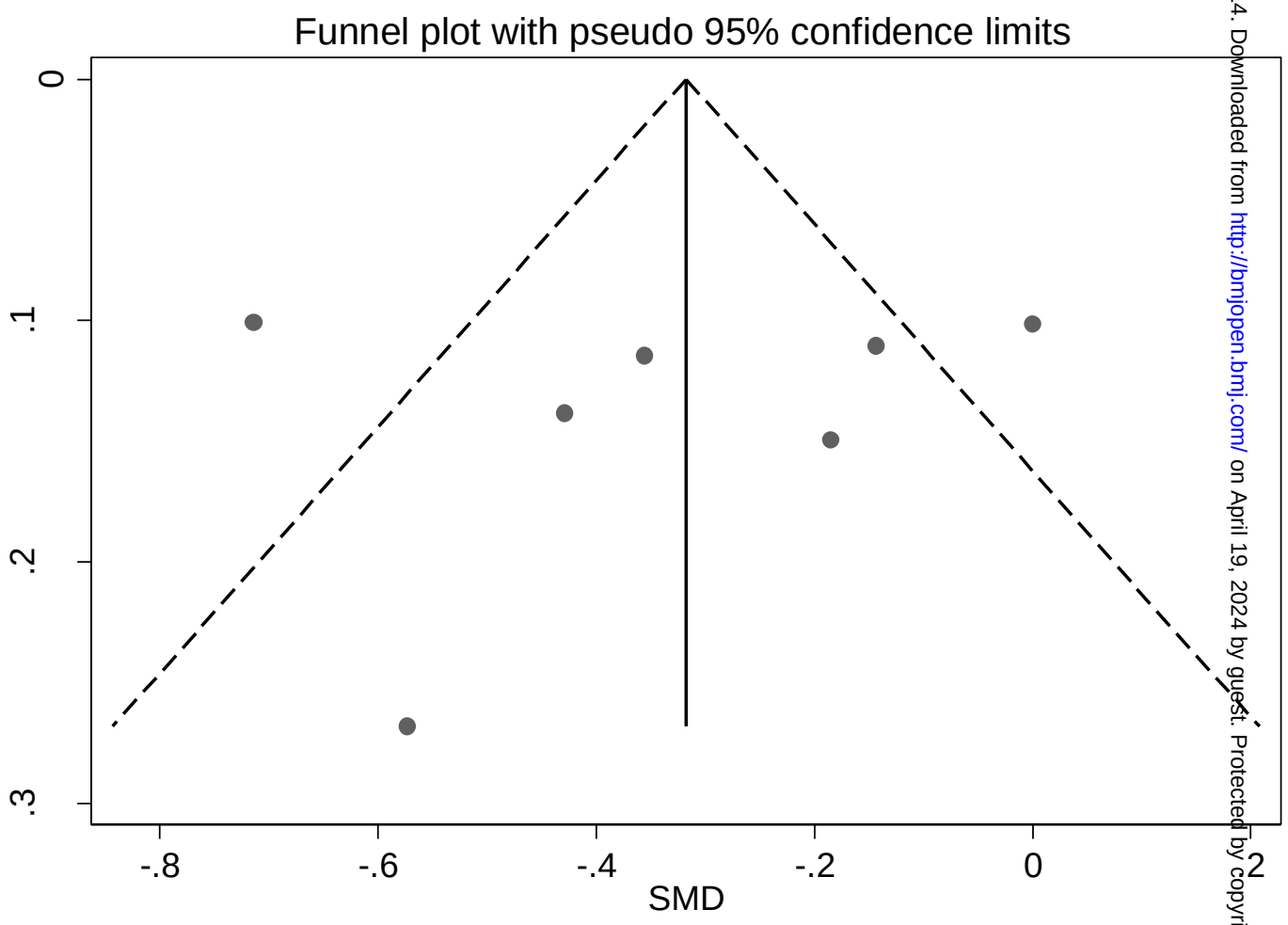

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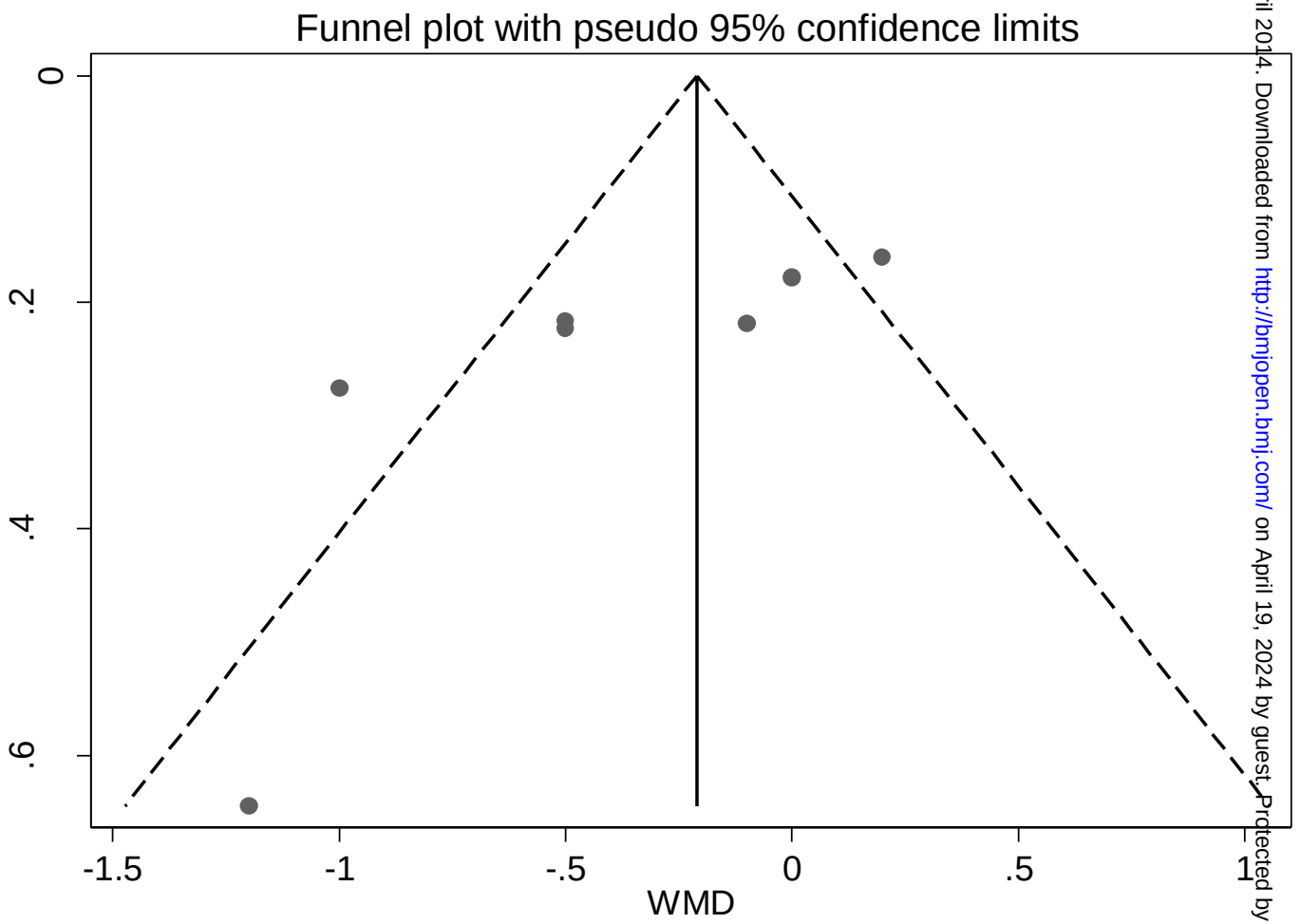

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APPENDIX

PubMed search syntax

((((("randomized controlled trials as topic"[MeSH Terms] OR randomised controlled trial OR RCT)) AND ((((((comprehensive health care[MeSH Terms]) OR collaborative care[Title/Abstract]) OR multidisciplinary care[Title/Abstract]) OR team care.[Title/Abstract]) OR integrated care[Title/Abstract]) OR complex care[Title/Abstract])) AND (((((("blood glucose"[MeSH Terms] OR "diabetes complications"[MeSH Terms]) OR "hemoglobin a, glycosylated"[MeSH Terms]) OR hemoglobin A1c[Title/Abstract]) OR "Hemoglobin A, Glycosylated"[Mesh]) OR HbA1c[Title/Abstract]) OR glucose blood level[Title/Abstract]) OR diabetes[Title/Abstract] OR diabetic[Title/Abstract])) AND (((((((psychological distress[Title/Abstract]) OR hypervigilance[Title/Abstract]) OR nervousness[Title/Abstract]) OR anxieties[Title/Abstract]) OR anxious[Title/Abstract]) OR anxiety[MeSH Terms]) OR ("depressive disorder"[MeSH Terms] OR "depression"[MeSH Terms]))

Scopus search syntax

(TITLE-ABS-KEY(depression OR depressi* OR anxiety OR "psychological distress" OR hypervigilance OR nervousness OR anxieties OR melancholi* OR dysthymi*) AND TITLE-ABS-KEY("blood glucose" OR "hb a1c" OR "hemoglobin a glycosylated" OR glycaemic OR diabet*) AND TITLE-ABS-KEY("collaborative care" OR "multidisciplinary care" OR "transmural care" OR "complex care" OR "seamless care" OR "team care") AND TITLE-ABS-KEY(randomi?ed controlled trial OR rct))

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Quality item checklist for randomised controlled trials reviewed (each worth 1 numerical point)

Study identification	Description of eligibility criteria adequate? (each worth 0.5 points): (1) inclusion criteria; (2) exclusion criteria	Randomization adequate? (each worth 0.5 points): (1) evidence suggesting "random" allocation; (2) evidence suggesting method used to generate random allocation sequence	Allocation concealment adequate?	Between-group prognostic indicators balanced? (each worth 0.5 points): (1) Depression score; (2) HbA1c level	Between-group drop-outs balanced?	Intention to treat analysis included?	Total quality score (out of 6)
Bogner et al, 2010	0.5	0.5	0.0	1.0	1.0	1.0	4.0
Bogner et al, 2012	1.0	1.0	0.0	1.0	1.0	1.0	5.0
Ell et al, 2010	1.0	1.0	1.0	0.5	1.0	1.0	5.5
Katon et al, 2004	1.0	1.0	0.0	1.0	1.0	0.5	4.5
Katon et al, 2010	1.0	1.0	0.0	1.0	1.0	1.0	5.0
Morgan et al, 2013	1.0	0.5	0.0	1.0	1.0	0.0	3.5
Williams et al, 2004	1.0	1.0	1.0	1.0	0.0	0.0	4.0

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EXCLUDED CITATIONS (REASONS)

1. Ciechanowski PS, Russo JE, Katon WJ, *et al*. The association of patient relationship style and outcomes in collaborative care treatment for depression in patients with diabetes. *Medical care*. 2006;44(3):283-91.

(Redundant citation; duplicate publication)

2. Ell K, Aranda MP, Xie B, Lee PJ, Chou CP**.** Collaborative depression treatment in older and younger adults with physical illness: pooled comparative analysis of three randomized clinical trials. *American Journal of Geriatric Psychiatry*. 2010;18(6):520-30.

(Inadequate study design; meta-analysis of RCTs)

3. Fisher L, Polonsky W, Parkin CG, *et al***.** The impact of blood glucose monitoring on depression and distress in insulin-nave patients with type 2 diabetes. *Current Medical Research and Opinion*. 2011;27(SUPPL. 3):39-46.

(Inadequate collaborative care model; structured self-monitoring of blood glucose alone)

4. Lamers F, Jonkers CC, Bosma H, Knottnerus JA, van Eijk JT**.** Treating depression in diabetes patients: does a nurse-administered minimal psychological intervention affect diabetes-specific quality of life and glycaemic control? A randomized controlled trial. *J Adv Nurs*. 2011;67(4):788-99.

(Inadequate collaborative care model; psychological therapy alone)

5. Lin EH, Korff M, Ciechanowski P, *et al*. Treatment adjustment and medication adherence for complex patients with diabetes, heart disease, and depression: a randomized controlled trial. *Annals of family medicine*; 2012:6-14.

(Redundant citation; duplicate publication)

6. Naji S**.** Integrated care for diabetes: Clinical, psychosocial, and economic evaluation. *British Medical Journal*. 1994;308(6938):1208-12.

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(Inadequate collaborative care model; not specifically for depression)

7. Solberg LI, Crain AL, Sperl-Hillen JM, *et al***.** Care quality and implementation of the Chronic Care Model: a quantitative study. Annals of Family Medicine. 2006;4(4):310-6.

(Inadequate study design; not an RCT)

8. Stiefel F, Zdrojewski C, Bel Hadj F, *et al*. Effects of a multifaceted psychiatric intervention targeted for the complex medically ill: a randomized controlled trial. *Psychotherapy & Psychosomatics*. 2008;77(4):247-56.

(Incomplete data for extraction, contacted author 4 Sep 2013)

9. Tapp H, Phillips SE, Waxman D, *et al***.** Multidisciplinary team approach to improved chronic care management for diabetic patients in an urban safety net ambulatory care clinic. *Journal of the American Board of Family Medicine*. 2012;25(2):245-6.

(Inadequate study design; feasibility and study design)

10. Taveira TH, Dooley AG, Cohen LB, Khatana SA, Wu WC**.** Pharmacist-led group medical appointments for the management of type 2 diabetes with comorbid depression in older adults. *Ann Pharmacother*. 2011;45(11):1346-55.

(Inadequate collaborative care; lacked evidence of co-ordination of care)

11. Trief PM, Morin PC, Izquierdo R, *et al*. Depression and glycemic control in elderly ethnically diverse patients with diabetes: the IDEATel project. *Diabetes Care*. 2006;29(4):830-5.

(Incomplete data for extraction, contacted author 5 Sep 2013

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Funnel plot assessing symmetry of 7 RCTs on effectiveness of collaborative care for depression outcome

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Funnel plot assessing symmetry of 7 RCTs on effectiveness of collaborative care for improving HbA1c outcome

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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.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4,5
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.	No
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.	5,6
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.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 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).	5,6
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.	6
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
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.	6, appendix 2
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7

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PRISMA 2009 Checklist

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.	7,8

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).	7, 8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Appendix 5,6
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.	8,9
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.	23-26
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).	Appendix 5,6
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.	10,11
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10,11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10,11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	27,28
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).	11-13
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).	13,14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14
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.	None

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Collaborative care for co-morbid depression and diabetes: a systematic review and meta-analysis

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Article title: Collaborative care for co-morbid depression and diabetes: a systematic review and meta-analysis

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ABSTRACT

Objective: The collaborative care model is recommended for depression in adults with a chronic physical health problem like diabetes. We sought to systematically assess the effect of collaborative care on depression and glycaemia in adults with co-morbid depression and diabetes to inform guidelines and practice.

Design: Systematic review and meta-analysis.

Data sources: We searched PubMed, Scopus, Cochrane Library, Cinahl, Health Source Nursing, Medline, PsychINFO and reference lists of retrieved articles published before August 2013.

Inclusion criteria: Randomised controlled trials (RCTs) on collaborative care (i.e. co-ordinated multi-disciplinary model of care) for depression that reported the effects on depression and glycaemic outcomes in adults with co-morbid clinically relevant depression and diabetes were eligible.

Data extraction and analysis: Data on the mean difference in depression and glycaemic outcomes were extracted and pooled using random effects meta-analysis.

Results: Seven RCTs included for review reported effects on depression outcomes in 1895 participants, and glycated haemoglobin (HbA1c) level in 1556 participants. Collaborative care significantly improved depression score (standardised mean difference was -0.32 [95% CI: -0.53 to -0.11]; I-squared=79.0%) and HbA1c level (weighted mean difference was -0.33% [95% CI: -0.66% to -0.00%]; I-squared=72.9%) compared with control conditions. Depression remission did not predict better glycaemic control across the studies.

Conclusions: Limited evidence from short-to-medium term RCTs predominately conducted in the United States suggests that collaborative care for depression significantly improves both depression and glycaemia outcomes, independently, in people with co-morbid depression and diabetes.

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ARTICLE SUMMARY

Article focus

- To systematically assess the effect of collaborative care on depression and glycaemia in adults with co-morbid depression and diabetes.

Key messages

- Limited evidence from short-to-medium term RCTs predominately conducted in the United States suggests that collaborative care for depression significantly improves both depression and glycaemia outcomes.

Strengths and limitations of this study

- Key findings were based on a high-quality systematic review and meta-analysis level of evidence
- Since only a small number of short-to-medium term studies predominately conducted in the United States were included, the findings of this review may not be relevant to health care settings in other countries, requiring further research.

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INTRODUCTION

Diabetes is currently ranked the 14th leading cause of global disease burden (assessed using a summary measure of healthy years of life lost due to premature death and years lived with disability), and has moved up several places in the rankings for leading causes since 1990 [1]. The International Diabetes Federation estimated that more than 371 million people (or 8.3% of the adult population worldwide) had diabetes in 2012 [2]. Major depression, currently ranked the 11th leading cause of global disease burden, has also moved up several places in the rankings for leading causes since 1990 [1]. Although rankings varied substantially across regions, health care practitioners in these countries need guidance to better deal with the rising burden of diabetes and depression.

Diabetes is a chronic physical health condition that is often co-morbid with clinically relevant symptoms of depression [3-5]. Practitioners should be aware that depression co-morbidity can significantly worsen the self-care [6], health [7-9] and economic burden of diabetes [10]. This suggests that effective management of depression in people with co-morbid diabetes could potentially reverse several of these adverse outcomes, resulting in better glycaemic control among other benefits.

Current National Institute for Health and Clinical Excellence (NICE) guidelines for depression in adults with a chronic physical health problem, like diabetes, recommend collaborative care in a 'stepped care framework' in which to organise health services [11]. Patients with inadequate response to one or more treatments are 'stepped up' from low intensity care to a more intensive form of management (including lifestyle, psychological and pharmacological therapies). Practitioners should consider collaborative care for patients with co-morbid diabetes and depression, since they typically need more intensive care.

Randomized controlled trial (RCT) evidence shows that collaborative care is more effective than usual care for improving depression outcomes at both short and longer terms in

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American primary care settings [12]. Systematic reviews of RCTs have also confirmed that collaborative care is more effective than usual care for improving depression outcomes in people with co-morbid diabetes [13, 14], but there was a lack of consistent evidence for improving glucose control [13, 15]. However, the results of newly published RCTs suggest that collaborative care for depression also leads to significant improvements in glycaemic control [16, 17]. We therefore sought to systematically assess the total body of RCT evidence on collaborative care for depression in adults with co-morbid depression and diabetes to inform guidelines and practice.

METHODS

Search strategy

We searched PubMed, Scopus, Cochrane Library, Cinahl, Health Source Nursing, Medline, PsychINFO and reference lists of retrieved articles published before August 2013. Search syntaxes were developed in consultation with an experienced university research librarian taking into account a broad range of terms and phrases used in definitions of RCTs, collaborative care, depression and diabetes (full electronic search strategies for PubMed and Scopus databases; appendix page 1). Reference lists of potentially eligible articles were searched by hand to identify additional studies missed by our search strategy.

Study selection

Two reviewers (EA and JF) identified potentially relevant studies for inclusion by screening titles and/or abstracts of all citations identified with our database searches. A second screening was performed on the full text of these articles. Articles for RCTs on collaborative care (i.e. evidence showing that the intervention was a co-ordinated multi-disciplinary model of care) for depression that reported the effects on both depression and glycaemic outcomes

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in adults, in adults, most of who had to have had co-morbid diabetes, were eligible. There were no language restrictions for articles.

Data extraction

Data extraction and quality assessment of included studies were performed and/or verified independently by three reviewers (EA, JF and PF). Discrepancies were resolved through discussion. Authors of relevant studies were contacted, where possible, for data that could not be extracted from the published articles.

Quality assessment

For methodology and quality assessment, a quality checklist was developed to identify potential sources of bias (table; appendix page 2). Quality items for RCTs reviewed were as follows (each worth 1.0 numerical point): 1) study eligibility criteria were adequately described, 2) randomization methodology was adequate (i.e., evidence suggesting "random" method was used to generate and implement random allocation sequence), 3) allocation concealment was adequate (i.e., evidence to suggest that a robust method was used for concealing the sequence of treatment allocation (e.g., independent IT or telephone service or sealed opaque envelopes only opened in front of the participant), 4) between-group primary outcomes were balanced at baseline (i.e., evidence showing that groups were similar at the outset for primary outcomes), 5) between-group drop-out rates were balanced, and 6) intention to treat analysis was included.

Our quality item checklist was designed based on criteria for assessment of RCTs [18, 19] and allowed summed scores to range from 0 to 6 points, reflecting lowest to highest quality. Studies were considered 'better quality' if they received a score higher than 4, since that meant that they had most of our quality items.

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Primary outcomes

Data on the mean difference in depression and glycated haemoglobin (HbA1c) outcomes between the treatment and control groups were extracted and pooled using random effects meta-analysis. In one study [16], the post-treatment means were derived from the within group changes and the control group standard deviation carried forward from the baseline values [20]. Standardised mean differences were calculated using Glass's Delta method.

Data synthesis

Three reviewers (EA, PF and JF) independently collated and/or verified extracted data to present a descriptive synthesis of important study characteristics and a quantitative synthesis of effect estimates.

Statistical methods

We pooled and weighted studies first using random effects meta-analysis models, and second using fixed effects models for verification [21]. Results for HbA1c were pooled to estimate the inverse variance weighted mean difference (WMD), including the DerSimonian and Laird 95% confidence interval (95% CI), between treatment and control groups.

In examining the effects of collaborative care treatment on depression scores, the standardised mean difference (SMD) from each RCT were pooled to produce an overall estimate of effect, and associated 95% CI, between treatment and control groups. We used meta-regression to test the hypothesis that the SMD in depression score is a predictor of the WMD in HbA1c level.

For each meta-analysis model, the degree of heterogeneity in WMD or SMD was assessed by visual inspection, the *I*-squared statistic (moderate being < 50% [22]) and the χ^2-test of

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goodness of fit [23]. Where evidence of heterogeneity was observed, we checked data extracted from individual outlier studies, qualitatively investigated reasons for their different results, and explored the effects of study exclusion in sensitivity analyses.

We also used sensitivity analysis to investigate the robustness of the meta-analyses models. We variously excluded lower quality studies (score of ≤4.0), one study conducted outside the United States (Australia), studies that integrated diabetes care, studies which considered lifestyle risk factors, and studies of less than one-year duration. Publication bias, which reflects the tendency for smaller studies to be published in the literature only when findings are positive, was assessed visually using funnel plots [24]. All calculations were performed in Stata version 12 (StataCorp, College Station, TX, USA) using the 'metan', 'metareg' and 'metafunnel' commands. Effects were considered statistical significant when the associated 95% confidence intervals did not include zero and heterogeneity was considered statistically significant where the associated P-value was less than 0.05.

RESULTS

Figure 1 presents a flowchart summarizing identification of potentially relevant studies, and those included and excluded. Our search strategy identified 264 citations after duplicates were removed. Of these, 246 citations were excluded after the first screening of titles and/or abstracts for inclusion and exclusion criteria, leaving 18 citations for a second full text screening. After further assessment, 11 citations were excluded for reasons listed in figure 1 leaving seven RCTs for final inclusion in the systematic review. Most studies were excluded for inadequate study design or intervention (i.e. did not qualify as collaborative care model), and a couple of studies were excluded for being redundant duplicate citations and for incomplete data available for extraction (list of excluded citations and reasons; appendix pages 3-4).

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<< Figure 1 >>

Descriptive data synthesis

Table 1 presents study characteristics of seven RCTs included for review, which were published between 2004 and 2013. All studies except one [25] were conducted in the United States. Major inclusion criteria were various case definitions of diabetes in five studies [16, 26-29], diabetes and/or coronary heart disease (CHD) in two studies [17, 25], and co-morbid clinically relevant depression in all studies. Major exclusion criteria were cognitive impairment in four studies [16, 17, 28, 29], co-morbid psychiatric disorder or suicidal ideation in four studies [17, 27-29], alcohol problems in two studies [27, 29], and living in residential care in two studies [17, 25], among others. The sample sizes ranged from 58 to 417, resulting in a total of 1895 participants for depression outcomes and 1556 participants for HbA1c outcome across studies. Mean age of the samples ranged from 54 to 71 years. All of the study samples contained both male and female participants. Baseline mean depression scores ranged from 15.6 to 19.7 by the CES-D 20 [26], from 9.9 to 11.6 by the PHQ-9 [16, 25], and from 1.4 to 1.7 by the SCL-20 [17, 27-29]. Baseline mean HbA1c levels ranged from 6.9 to 9.1%. Defining features of collaborative care models investigated were a case manager/officer (usually a nurse or non-physician mental health worker for co-ordination of care) with proactive follow-ups in all studies, a structured management plan delivered within a stepped care framework and relapse prevention in four studies [17, 27-29], an integrated diabetes care program in three studies [16, 17, 26], and consideration for lifestyle risk factors in two studies [17, 25]. Control conditions were “usual care” in four studies [16, 25, 26, 29], whereas usual care was enhanced in the three other studies [17, 27, 28]. Trial durations ranged from 12 to 52 weeks. Primary outcomes were depression score assessed by the CES-D

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20 in one study [26], by the PHQ-9 in two studies [16, 25], and by the SCL-20 in four studies [17, 27-29]; and glycaemic control by HbA1c in all of the studies. Mean quality scores ranged from 3.5 to 5.5, and all but three studies [25, 26, 29] received a score of 4.5 or higher.

<< Table 1 >>

Quantitative data synthesis

Effect of collaborative care on depression

Figure 2 presents the SMD in depression outcomes after collaborative care between the treatment and control groups. Collaborative care significantly improved standardised depression outcomes compared with control conditions (pooled SMD was -0.32 [95% CI: -0.53 to -0.11]). There was statistical heterogeneity between studies (I-squared=79.0%, P<0.001) that was mostly a result of variation in the degree of benefit favouring collaborative care in all but one study [27], which had significant between-group differences in mean depression scores at baseline. Correcting for these differences substantially changed the SMD for that study (from 0.00 [95% CI: -0.20 to 0.20] to -0.60 [95% CI: -0.81 to -0.39]) in a sensitivity analysis. In addition, the sensitivity analyses presented in table 2 shows that the pooled SMD was substantially changed only after exclusion of lower quality studies (decreased to -0.17 [95% CI: -0.35 to 0.00]). A funnel plot was produced and confirmed widespread heterogeneity of effect estimates between studies, but did not suggest any publication bias (appendix page 5).

<< Figure 2 >>

<< Table 2 >>

Effect of collaborative care on HbA1c

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Figure 3 presents the WMD in HbA1c level after collaborative care between the treatment and control groups. Collaborative care significantly reduced HbA1c level compared with control conditions (pooled WMD was -0.33% [95% CI: -0.66% to -0.00%]). There was statistical heterogeneity between studies (I-squared=72.9%, P=0.001) that was mostly a result of variation in the degree of benefit favouring collaborative care in all but two studies [28, 29]. The sensitivity analyses presented in table 3 shows that the pooled WMD was slightly decreased in the fixed effect model (-0.21 [95% CI: -0.37 to -0.05]), but no longer statistically significant after each of the various studies was excluded. This was particularly so after exclusion of three studies that integrated diabetes care (decreased to -0.07 [95% CI: -0.35 to 0.21]). A funnel plot was produced and confirmed widespread heterogeneity of effect estimates between studies, but did not suggest any publication bias (appendix page 6).

<< Figure 3 >>

<< Table 3 >>

Effect of depression remission on HbA1c

Figure 4 presents a scatter plot displaying the association between the SMD in depression outcomes and the WMD in HbA1c values in each study. Results of a meta-regression model suggest that the SMD for depression scores failed to predict the WMD in HbA1c values across studies (P=0.828, coefficient was 0.19 [95% CI: -1.93 to 2.31]).

<< Figure 4 >>

DISCUSSION

Summary of evidence

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Based on limited evidence from short-to-medium term RCTs predominately conducted in the United States, our results suggest that collaborative care for depression significantly improves both depression and glycaemia outcomes in people with co-morbid depression and diabetes. Our results for better glycaemic control are novel and more comprehensive than those published from previous meta-analyses because we sought and obtained raw unpublished data from the authors of three studies [27-29]. Furthermore, we found evidence from a sensitivity analysis that future high-quality RCTs [30] will likely strengthen rather than weaken this evidence base. The size of the effect of collaborative care on depression and HbA1c outcomes that can be expected in practice is small-to-moderate, but comparable with pharmacological, psychological and behavioural therapies alone [13, 14, 31, 32], and likely to be clinically relevant. For instance, several of the RCTs we reviewed have also shown that collaborative care for depression in people with co-morbid diabetes is more effective than usual care for improving functional health outcomes [33] and were cost effective [34, 35], consistent with previous economic modelling [36]. In addition, a recent meta-analysis found a positive dose-response trend between HbA1c level and adverse cardiovascular outcomes [37]. This suggests that improvements in glycaemic control from collaborative care for depression could theoretically protect patients with co-morbid diabetes against future cardiovascular risk.

In contrast, we found no evidence to suggest that improved depression outcomes results in better glycaemic control (lower HbA1c values) among people with co-morbid diabetes. This null finding for reversibility of the effect of depression on glycaemia weakens the evidence base for causality in terms of worsening the burden of diabetes. Alternatively, collaborative care for depression may improve glycaemia in people with diabetes by increasing self-management, independent of the depression prognosis. For example, collaborative care for depression [17] was more effective than usual care for improving blood pressure and blood

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glucose self-monitoring rates [38]. Quality improvement strategies for diabetes care that promote glucose self-monitoring among patients can significantly improve HbA1c level (SMD was 0.57% [0.31% to 0.83]) [39]. Indeed, evidence from our sensitivity analysis showed that the effect of collaborative care on HbA1c was almost entirely confined to the three studies that integrated diabetes care within the collaborative care model [16, 17, 26]. Second, none of the RCTs we reviewed properly integrated lifestyle intervention, as per the current global guideline for effective management of type 2 diabetes,[40] within the collaborative care. In high-income countries like the United States and Australia, depression is associated with overweight or obesity, physical inactivity, smoking cigarettes and drinking excessive amounts of sugar-sweetened and alcoholic beverages [41, 42], all of which are well-established lifestyle risk factors for diabetes. Indeed, there is international consensus supporting the effectiveness of lifestyle intervention in the prevention and management of type 2 diabetes [40]. In addition, previous systematic reviews of RCTs have shown that exercise (an integral component of lifestyle intervention) is effective for improving both depression score (SMD was -0.82 [95% CI: -1.12 to -0.51]) and HbA1c level (WMD was -0.67% [95% CI: -0.84 to -0.49%]) [43, 44], and the size of these effects are substantially larger than what we found for collaborative care for depression. There is now sufficient evidence to suggest that diabetes care and lifestyle intervention integrated within collaborative care for depression would be the most effective way to manage care for co-morbid depression and diabetes.

Limitations

Several limitations require further consideration. Since only a small number of short-to-medium term studies predominately conducted in the United States were included, the findings of this review may not be relevant to health care settings in other countries, requiring

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further research. In particular, health care systems in most countries are not properly set up to optimize the co-ordination between practitioners [45]. Integration of therapies including collaborative care, diabetes care and lifestyle intervention is required to effectively manage co-morbid depression diabetes. Secondly, baseline mean HbA1c level was close to the upper limit of the normal range in several studies, which would have underestimated the effect size for, and therapeutic benefit of, collaborative care for glycaemic control. Finally, reviewer-level limitations include incomplete retrieval of information for several of the 11 citations excluded, and the existence of other relevant studies not identified with our search strategy resulting in bias. However, the results and conclusions reported in most of the excluded studies were in line with those reported here, search strategy bias was unlikely.

Conclusions

Limited evidence from short-to-medium term RCTs predominately conducted in the United States suggest that collaborative care for depression significantly improves both depression and glycaemia outcomes, independently, in people with co-morbid depression and diabetes. Future research should investigate the effectiveness, feasibility and appropriateness of collaborative care integration with diabetes care and lifestyle intervention for co-morbid depression and diabetes, and other co-morbid cardiovascular risk conditions, in routine clinical practice in specific health care settings worldwide.

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Figure 1: Flowchart summarizing identification of studies included for review.

Figure 2: SMD in depression outcomes after collaborative care between the treatment and control groups.

Figure 3: WMD in HbA1c level after collaborative care between the treatment and control groups.

Figure 4: Scatter plot displaying the association between the SMD in depression outcomes and the WMD in HbA1c values in each study.

Appendix page 5: Funnel plot assessing symmetry of 7 RCTs on effectiveness of collaborative care for depression outcome.

Appendix page 6: Funnel plot assessing symmetry of 7 RCTs on effectiveness of collaborative care for improving HbA1c outcome.

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Authorship order is according to percentage contribution. EA is guarantor of the paper, taking responsibility for the integrity of the work as a whole, from inception to published article. EA conceived and designed the review, identified studies for inclusion, extracted and interpreted data, and drafted the article. PF analysed and interpreted data, and revised the article. JF extracted and interpreted data, and revised the article. All authors approved the final completed article. We are grateful to Mrs Rohini Patil for her work on developing and conducting the electronic database searches.

COMPETING INTERESTS

EA has received honoraria for speaking at events for Eli Lilly Australia Pty Ltd (Lilly).

CONTRIBUTORSHIP

Authorship order is according to percentage contribution. EA is guarantor of the paper, taking responsibility for the integrity of the work as a whole, from inception to published article. EA conceived and designed the review, identified studies for inclusion, extracted and interpreted data, and drafted the article. PF analysed and interpreted data, and revised the article. JF extracted and interpreted data, and revised the article. All authors approved the final completed article. We are grateful to Mrs Rohini Patil for her work on developing and conducting the electronic database searches.

DATA SHARING

No additional data available.

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TABLE 1: Characteristics of randomised controlled trials reviewed

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Study identification	Country	Sample size	Population		Men (%); Mean age (years)	Baseline mean depression score		Baseline mean HbA1c (%)	
			Major inclusion criteria (all)	Major exclusion criteria (any)		Treated	Controls	Treated	Controls
Bogner et al, 2010[26]	United States	58	Aged ≥50 years, recent HbA1c >7 or an oral hypoglycaemic prescription within past year, diagnosed depression or an antidepressant prescription within past year	None specified	16; 60	15.6	19.7	7.3	7.3
Bogner et al, 2012[16]	United States	180	Aged ≥30 years, diagnosis of type 2 diabetes and current oral hypoglycaemic prescription, current antidepressant prescription	No informed consent, cognitive impairment (Mini-Mental State Examination <21), residence in care facility providing medications, unwillingness or inability to use the Medication Event Monitoring System	32; 57	10.6	9.9	7.2	7.0
Ell et al, 2010[27]*	United States	387	Aged ≥18 years, "with diabetes", one of two cardinal depressive symptoms most days and depression score ≥10 by the PHQ-9, informed consent	Acute suicidal ideation, score of ≥8 by the Alcohol Use Disorders Identification Test, inability to speak Spanish or English	18; 54	1.7	1.4	9.0	9.1
Katon et al, 2004[28]*	United States	329	Diabetes (by registry), depression score of ≥10 by the PHQ-9 at first screening and score of ≥1.1 by the SCL-90 at second telephone screening, ambulatory, English speaking, adequate hearing for telephone interview, planned continued enrolment in the clinic during the next year	Currently in care of psychiatrist, diagnosed bipolar disorder or schizophrenia, current antipsychotic or mood stabilizer medications, symptoms of dementia	35; 58	1.7	1.6	8.0	8.0
Katon et al, 2010[17]	United States	214	Diabetes, coronary heart disease or both (by registry), depression score of ≥3 by the PHQ-2 and ≥10 by the PHQ-9, ambulatory, spoke English, and planned be enrolled in the Health Maintenance Organization for 12 months	Terminal illness, residence in long-term facility, severe hearing loss, planned bariatric surgery within three months, pregnancy or breast feeding, ongoing psychiatric care, bipolar disorder or schizophrenia, current antipsychotic or mood stabilizer medications, symptoms of dementia	48; 57	1.7	1.7	8.1	8.0
Morgan et al, 2013[25]	Australia	156 (glycaemia); 310 (depression)	Type 2 diabetes, coronary heart disease or both (by registry), depression score of ≥5 by the PHQ-9, informed consent	Aged <18 years, in residential care	55; 68	10.7	11.6	7.0	6.9

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Williams et al, 2004[29]*	United States	232 (glycaemia); 417 (depression)	Diagnosed or treated diabetes or high blood sugar in past three years by self-report, current major depression or dysthymic disorder by structured clinical interview according to DSM-IV	Current drinking problem (score of ≥2 by the CAGE questionnaire), history of bipolar disorder or psychosis, ongoing psychiatric care, or severe cognitive impairment (score of <3 by questionnaire)	47; 71	1.7	1.7	7.3	7.3

Abbreviations: HbA1c, glycated haemoglobin; CES-D, Center for Epidemiological Studies Depression scale; PHQ, Patient Health Questionnaire; SCL, Symptom Checklist; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, fourth edition
*Raw data was provided by the author

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Treatments	Control conditions	Trial duration (weeks)	Outcomes (assessments)	Quality score (out of 6)
"Integrated care"; consisted of supervised case manager, patient-centred care, education and integrated care for depression and diabetes; three 30 min in person and two 15 min telephone follow-up sessions over four weeks	"Usual care"; and study assessments	12	Glycaemia (HbA1c); depression score (CES-D 20)	4.0
"Integrated care"; consisted of supervised case manager, patient-centred care, education and integrated care for depression and diabetes; three 30 min in person and two 15 min telephone follow-up sessions over three months	"Usual care"; and study assessments	12	Glycaemia (HbA1c); depression score (PHQ-9)	5.0
"Collaborative care"; consisted of supervised nurse case manager, patient-centred care, problem solving therapy, self-monitoring education, and coordination of care and services for depression and diabetes within a stepped-care framework; monthly telephone symptom monitoring, treatment maintenance and relapse prevention up to 12 months	"Enhanced usual care"; and patient and family-focused depression education pamphlets	52	Glycaemia (HbA1c); depression score (SCL-20)	5.5
"Collaborative care"; consisted of supervised nurse case manager, patient-centred care (initial choice of antidepressant or problem solving therapy), within a stepped-care framework; initial one hour visit, followed by twice monthly half-hour follow-ups (telephone or in-person) up to 12 weeks and referral to speciality care thereafter if necessary	"Usual care"; and advice to consult their physician for depression care	26	Glycaemia (HbA1c); depression score (SCL-20)	4.5
"Collaborative care"; consisted of supervised nurse case manager, "treat-to-target program" integrated care for specific conditions, within a stepped-care framework, motivational problem solving and goal setting for self-care (including exercise, and "The Depression Helpbook", video and written material); structured visits every two to three weeks, and maintenance plan once targeted levels were achieved including telephone follow-ups every four weeks	"Enhanced usual care"; patients could self-refer to mental health care or be referred by primary care physicians at the clinic; and study assessments	52	Glycaemia (HbA1c); depression score (SCL-20)	5.0
"Collaborative care"; consisted of collaborative care trained nurse case manager, 45 min nurse consult every three months followed (for assessment of lifestyle, physical and biochemical risk factors, and referrals, self-care of depression and setting personal goals for review and discussion of educational resources), followed by a 15 min consult with their usual general practitioner	"Usual care"; baseline data collected retrospectively	26	Glycaemia (HbA1c); depression score (PHQ-9)	3.5

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Collaborative care; consisted of trained nurse or psychologist case manager, patient-centred care, problem solving therapy, 20 min educational video tape and written material on late-life depression, and coordination of care and services for depression within a stepped-care framework; monthly telephone symptom monitoring, treatment maintenance and relapse prevention up to 12 months; diabetes care not specifically enhanced	"Usual care"; and study assessments	52	Glycaemia (HbA1c); depression score (SCL-20)	4.0

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TABLE 2: Sensitivity analysis of randomized controlled trials of collaborative care → depression score outcome meta-analysis

	N studies	N sample	SMD	(95% confidence interval)	P-value for heterogeneity
Fixed effects model	7	1895	-0.31	(-0.40 to -0.22)	<0.001
Exclusion of 3 lower quality studies (score ≤4.0)	4	1110	-0.17	(-0.35 to 0.00)	0.101
Exclusion of 1 study outside the United States (Australia)	6	1585	-0.32	(-0.57 to -0.07)	<0.001
Exclusion of 3 studies that integrated diabetes care	4	1443	-0.30	(-0.62 to 0.01)	<0.001
Exclusion of 2 studies that considered lifestyle risk factors	5	1371	-0.30	(-0.59 to 0.00)	<0.001
Exclusion of 4 studies less than 1 year duration	3	1018	-0.34	(-0.68 to 0.01)	<0.001

Abbreviations: N, number; SMD, standardized mean difference

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TABLE 3: Sensitivity analysis of randomised controlled trials of collaborative care → HbA1c outcome meta-analysis

	N studies	N sample	WMD	(95% confidence interval)	P-value for heterogeneity
Fixed effects model	7	1556	-0.21	(-0.37 to -0.05)	0.001
Exclusion of 3 lower quality studies (score ≤4.0)	4	1110	-0.32	(-0.81 to 0.17)	0.001
Exclusion of 1 study outside the United States (Australia)	6	1400	-0.31	(-0.68 to 0.07)	0.001
Exclusion of 3 studies that integrated diabetes care	4	1104	-0.07	(-0.35 to 0.21)	0.086
Exclusion of 2 studies that considered lifestyle risk factors	5	1186	-0.27	(-0.71 to 0.16)	0.002
Exclusion of 4 studies less than 1 year duration	3	833	-0.18	(-0.48 to 0.11)	0.189

Abbreviations: N, number; WMD, weighted mean difference

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Article title: Collaborative care for co-morbid depression and diabetes: a systematic review and meta-analysis

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ABSTRACT

Objective: The collaborative care model is recommended for depression in adults with a chronic physical health problem like diabetes. We sought to systematically assess the effect of collaborative care on depression and glycaemia in adults with co-morbid depression and diabetes to inform guidelines and practice.

Design: Systematic review and meta-analysis.

Data sources: We searched PubMed, Scopus, Cochrane Library, Cinahl, Health Source Nursing, Medline, PsychINFO and reference lists of retrieved articles published before August 2013.

Inclusion criteria: Randomised controlled trials (RCTs) on collaborative care (i.e. co-ordinated multi-disciplinary model of care) for depression that reported the effects on depression and glycaemic outcomes in adults with co-morbid clinically relevant depression and diabetes were eligible.

Data extraction and analysis: Data on the mean difference in depression and glycaemic outcomes were extracted and pooled using random effects meta-analysis.

Results: Seven RCTs included for review reported effects on depression outcomes in 1895 participants, and glycated haemoglobin (HbA1c) level in 1556 participants. Collaborative care significantly improved depression score (standardised mean difference was -0.32 [95% CI: -0.53 to -0.11]; I-squared=79.0%) and HbA1c level (weighted mean difference was -0.33% [95% CI: -0.66% to -0.00%]; I-squared=72.9%) compared with control conditions. Depression remission did not predict better glycaemic control across the studies.

Conclusions: Limited evidence from short-to-medium term RCTs predominately conducted in the United States suggests that collaborative care for depression significantly improves both depression and glycaemia outcomes, independently, in people with co-morbid depression and diabetes.

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ARTICLE SUMMARY

Article focus

- To systematically assess the effect of collaborative care on depression and glycaemia in adults with co-morbid depression and diabetes.

Key messages

- Limited evidence from short-to-medium term RCTs predominately conducted in the United States suggests that collaborative care for depression significantly improves both depression and glycaemia outcomes.

Strengths and limitations of this study

- Key findings were based on a high-quality systematic review and meta-analysis level of evidence
- Since only a small number of short-to-medium term studies predominately conducted in the United States were included, the findings of this review may not be relevant to health care settings in other countries, requiring further research.

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INTRODUCTION

Diabetes is currently ranked the 14th leading cause of global disease burden (assessed using a summary measure of healthy years of life lost due to premature death and years lived with disability), and has moved up several places in the rankings for leading causes since 1990 [1]. The International Diabetes Federation estimated that more than 371 million people (or 8.3% of the adult population worldwide) had diabetes in 2012 [2]. Major depression, currently ranked the 11th leading cause of global disease burden, has also moved up several places in the rankings for leading causes since 1990 [1]. Although rankings varied substantially across regions, health care practitioners in these countries need guidance to better deal with the rising burden of diabetes and depression.

Diabetes is a chronic physical health condition that is often co-morbid with clinically relevant symptoms of depression [3-5]. Practitioners should be aware that depression co-morbidity can significantly worsen the self-care [6], health [7-9] and economic burden of diabetes [10]. This suggests that effective management of depression in people with co-morbid diabetes could potentially reverse several of these adverse outcomes, resulting in better glycaemic control among other benefits.

Current National Institute for Health and Clinical Excellence (NICE) guidelines for depression in adults with a chronic physical health problem, like diabetes, recommend collaborative care in a 'stepped care framework' in which to organise health services [11]. Patients with inadequate response to one or more treatments are 'stepped up' from low intensity care to a more intensive form of management (including lifestyle, psychological and pharmacological therapies). Practitioners should consider collaborative care for patients with co-morbid diabetes and depression, since they typically need more intensive care.

Randomized controlled trial (RCT) evidence shows that collaborative care is more effective than usual care for improving depression outcomes at both short and longer terms in

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American primary care settings [12]. Systematic reviews of RCTs have also confirmed that collaborative care is more effective than usual care for improving depression outcomes in people with co-morbid diabetes [13, 14], but there was a lack of consistent evidence for improving glucose control [13, 15]. However, the results of newly published RCTs suggest that collaborative care for depression also leads to significant improvements in glycaemic control [16, 17]. We therefore sought to systematically assess the total body of RCT evidence on collaborative care for depression in adults with co-morbid depression and diabetes to inform guidelines and practice.

METHODS

Search strategy

We searched PubMed, Scopus, Cochrane Library, Cinahl, Health Source Nursing, Medline, PsychINFO and reference lists of retrieved articles published before August 2013. Search syntaxes were developed in consultation with an experienced university research librarian taking into account a broad range of terms and phrases used in definitions of RCTs, collaborative care, depression and diabetes (full electronic search strategies for PubMed and Scopus databases; appendix page 1). Reference lists of potentially eligible articles were searched by hand to identify additional studies missed by our search strategy.

Study selection

Two reviewers (EA and JF) identified potentially relevant studies for inclusion by screening titles and/or abstracts of all citations identified with our database searches. A second screening was performed on the full text of these articles. Articles for RCTs on collaborative care (i.e. evidence showing that the intervention was a co-ordinated multi-disciplinary model of care) for depression that reported the effects on both depression and glycaemic outcomes

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in adults, in adults, most of who had to have had co-morbid diabetes, were eligible. There were no language restrictions for articles.

Data extraction

Data extraction and quality assessment of included studies were performed and/or verified independently by three reviewers (EA, JF and PF). Discrepancies were resolved through discussion. Authors of relevant studies were contacted, where possible, for data that could not be extracted from the published articles.

Quality assessment

For methodology and quality assessment, a quality checklist was developed to identify potential sources of bias (table; appendix page 2). Quality items for RCTs reviewed were as follows (each worth 1.0 numerical point): 1) study eligibility criteria were adequately described, 2) randomization methodology was adequate (i.e., evidence suggesting "random" method was used to generate and implement random allocation sequence), 3) allocation concealment was adequate (i.e., evidence to suggest that a robust method was used for concealing the sequence of treatment allocation (e.g., independent IT or telephone service or sealed opaque envelopes only opened in front of the participant), 4) between-group primary outcomes were balanced at baseline (i.e., evidence showing that groups were similar at the outset for primary outcomes), 5) between-group drop-out rates were balanced, and 6) intention to treat analysis was included.

Our quality item checklist was designed based on criteria for assessment of RCTs [18, 19] and allowed summed scores to range from 0 to 6 points, reflecting lowest to highest quality. Studies were considered 'better quality' if they received a score higher than 4, since that meant that they had most of our quality items.

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Primary outcomes

Data on the mean difference in depression and glycated haemoglobin (HbA1c) outcomes between the treatment and control groups were extracted and pooled using random effects meta-analysis. In one study [16], the post-treatment means were derived from the within group changes and the control group standard deviation carried forward from the baseline values [20]. Standardised mean differences were calculated using Glass's Delta method.

Data synthesis

Three reviewers (EA, PF and JF) independently collated and/or verified extracted data to present a descriptive synthesis of important study characteristics and a quantitative synthesis of effect estimates.

Statistical methods

We pooled and weighted studies first using random effects meta-analysis models, and second using fixed effects models for verification [21]. Results for HbA1c were pooled to estimate the inverse variance weighted mean difference (WMD), including the DerSimonian and Laird 95% confidence interval (95% CI), between treatment and control groups.

In examining the effects of collaborative care treatment on depression scores, the standardised mean difference (SMD) from each RCT were pooled to produce an overall estimate of effect, and associated 95% CI, between treatment and control groups. We used meta-regression to test the hypothesis that the SMD in depression score is a predictor of the WMD in HbA1c level.

For each meta-analysis model, the degree of heterogeneity in WMD or SMD was assessed by visual inspection, the *I*-squared statistic (moderate being < 50% [22]) and the χ^2-test of

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goodness of fit [23]. Where evidence of heterogeneity was observed, we checked data extracted from individual outlier studies, qualitatively investigated reasons for their different results, and explored the effects of study exclusion in sensitivity analyses.

We also used sensitivity analysis to investigate the robustness of the meta-analyses models. We variously excluded lower quality studies (score of ≤4.0), one study conducted outside the United States (Australia), studies that integrated diabetes care, studies which considered lifestyle risk factors, and studies of less than one-year duration. Publication bias, which reflects the tendency for smaller studies to be published in the literature only when findings are positive, was assessed visually using funnel plots [24]. All calculations were performed in Stata version 12 (StataCorp, College Station, TX, USA) using the 'metan', 'metareg' and 'metafunnel' commands. Effects were considered statistical significant when the associated 95% confidence intervals did not include zero and heterogeneity was considered statistically significant where the associated P-value was less than 0.05.

RESULTS

Figure 1 presents a flowchart summarizing identification of potentially relevant studies, and those included and excluded. Our search strategy identified 264 citations after duplicates were removed. Of these, 246 citations were excluded after the first screening of titles and/or abstracts for inclusion and exclusion criteria, leaving 18 citations for a second full text screening. After further assessment, 11 citations were excluded for reasons listed in figure 1 leaving seven RCTs for final inclusion in the systematic review. Most studies were excluded for inadequate study design or intervention (i.e. did not qualify as collaborative care model), and a couple of studies were excluded for being redundant duplicate citations and for incomplete data available for extraction (list of excluded citations and reasons; appendix pages 3-4).

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<< Figure 1 >>

Descriptive data synthesis

Table 1 presents study characteristics of seven RCTs included for review, which were published between 2004 and 2013. All studies except one [25] were conducted in the United States. Major inclusion criteria were various case definitions of diabetes in five studies [16, 26-29], diabetes and/or coronary heart disease (CHD) in two studies [17, 25], and co-morbid clinically relevant depression in all studies. Major exclusion criteria were cognitive impairment in four studies [16, 17, 28, 29], co-morbid psychiatric disorder or suicidal ideation in four studies [17, 27-29], alcohol problems in two studies [27, 29], and living in residential care in two studies [17, 25], among others. The sample sizes ranged from 58 to 417, resulting in a total of 1895 participants for depression outcomes and 1556 participants for HbA1c outcome across studies. Mean age of the samples ranged from 54 to 71 years. All of the study samples contained both male and female participants. Baseline mean depression scores ranged from 15.6 to 19.7 by the CES-D 20 [26], from 9.9 to 11.6 by the PHQ-9 [16, 25], and from 1.4 to 1.7 by the SCL-20 [17, 27-29]. Baseline mean HbA1c levels ranged from 6.9 to 9.1%. Defining features of collaborative care models investigated were a case manager/officer (usually a nurse or non-physician mental health worker for co-ordination of care) with proactive follow-ups in all studies, a structured management plan delivered within a stepped care framework and relapse prevention in four studies [17, 27-29], an integrated diabetes care program in three studies [16, 17, 26], and consideration for lifestyle risk factors in two studies [17, 25]. Control conditions were “usual care” in four studies [16, 25, 26, 29], whereas usual care was enhanced in the three other studies [17, 27, 28]. Trial durations ranged from 12 to 52 weeks. Primary outcomes were depression score assessed by the CES-D

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20 in one study [26], by the PHQ-9 in two studies [16, 25], and by the SCL-20 in four studies [17, 27-29]; and glycaemic control by HbA1c in all of the studies. Mean quality scores ranged from 3.5 to 5.5, and all but three studies [25, 26, 29] received a score of 4.5 or higher.

<< Table 1 >>

Quantitative data synthesis

Effect of collaborative care on depression

Figure 2 presents the SMD in depression outcomes after collaborative care between the treatment and control groups. Collaborative care significantly improved standardised depression outcomes compared with control conditions (pooled SMD was -0.32 [95% CI: -0.53 to -0.11]). There was statistical heterogeneity between studies (I-squared=79.0%, P<0.001) that was mostly a result of variation in the degree of benefit favouring collaborative care in all but one study [27], which had significant between-group differences in mean depression scores at baseline. Correcting for these differences substantially changed the SMD for that study (from 0.00 [95% CI: -0.20 to 0.20] to -0.60 [95% CI: -0.81 to -0.39]) in a sensitivity analysis. In addition, the sensitivity analyses presented in table 2 shows that the pooled SMD was substantially changed only after exclusion of lower quality studies (decreased to -0.17 [95% CI: -0.35 to 0.00]). A funnel plot was produced and confirmed widespread heterogeneity of effect estimates between studies, but did not suggest any publication bias (appendix page 5).

<< Figure 2 >>

<< Table 2 >>

Effect of collaborative care on HbA1c

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Figure 3 presents the WMD in HbA1c level after collaborative care between the treatment and control groups. Collaborative care significantly reduced HbA1c level compared with control conditions (pooled WMD was -0.33% [95% CI: -0.66% to -0.00%]). There was statistical heterogeneity between studies (I-squared=72.9%, P=0.001) that was mostly a result of variation in the degree of benefit favouring collaborative care in all but two studies [28, 29]. The sensitivity analyses presented in table 3 shows that the pooled WMD was slightly decreased in the fixed effect model (-0.21 [95% CI: -0.37 to -0.05]), but no longer statistically significant after each of the various studies was excluded. This was particularly so after exclusion of three studies that integrated diabetes care (decreased to -0.07 [95% CI: -0.35 to 0.21]). A funnel plot was produced and confirmed widespread heterogeneity of effect estimates between studies, but did not suggest any publication bias (appendix page 6).

<< Figure 3 >>

<< Table 3 >>

Effect of depression remission on HbA1c

Figure 4 presents a scatter plot displaying the association between the SMD in depression outcomes and the WMD in HbA1c values in each study. Results of a meta-regression model suggest that the SMD for depression scores failed to predict the WMD in HbA1c values across studies (P=0.828, coefficient was 0.19 [95% CI: -1.93 to 2.31]).

<< Figure 4 >>

DISCUSSION

Summary of evidence

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Based on limited evidence from short-to-medium term RCTs predominately conducted in the United States, our results suggest that collaborative care for depression significantly improves both depression and glycaemia outcomes in people with co-morbid depression and diabetes. Our results for better glycaemic control are novel and more comprehensive than those published from previous meta-analyses because we sought and obtained raw unpublished data from the authors of three studies [27-29]. Furthermore, we found evidence from a sensitivity analysis that future high-quality RCTs [30] will likely strengthen rather than weaken this evidence base. The size of the effect of collaborative care on depression and HbA1c outcomes that can be expected in practice is small-to-moderate, but comparable with pharmacological, psychological and behavioural therapies alone [13, 14, 31, 32], and likely to be clinically relevant. For instance, several of the RCTs we reviewed have also shown that collaborative care for depression in people with co-morbid diabetes is more effective than usual care for improving functional health outcomes [33] and were cost effective [34, 35], consistent with previous economic modelling [36]. In addition, a recent meta-analysis found a positive dose-response trend between HbA1c level and adverse cardiovascular outcomes [37]. This suggests that improvements in glycaemic control from collaborative care for depression could theoretically protect patients with co-morbid diabetes against future cardiovascular risk.

In contrast, we found no evidence to suggest that improved depression outcomes results in better glycaemic control (lower HbA1c values) among people with co-morbid diabetes. This null finding for reversibility of the effect of depression on glycaemia weakens the evidence base for causality in terms of worsening the burden of diabetes. Alternatively, collaborative care for depression may improve glycaemia in people with diabetes by increasing self-management, independent of the depression prognosis. For example, collaborative care for depression [17] was more effective than usual care for improving blood pressure and blood

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glucose self-monitoring rates [38]. Quality improvement strategies for diabetes care that promote glucose self-monitoring among patients can significantly improve HbA1c level (SMD was 0.57% [0.31% to 0.83]) [39]. Indeed, evidence from our sensitivity analysis showed that the effect of collaborative care on HbA1c was almost entirely confined to the three studies that integrated diabetes care within the collaborative care model [16, 17, 26]. Second, none of the RCTs we reviewed properly integrated lifestyle intervention, as per the current global guideline for effective management of type 2 diabetes,[40] within the collaborative care. In high-income countries like the United States and Australia, depression is associated with overweight or obesity, physical inactivity, smoking cigarettes and drinking excessive amounts of sugar-sweetened and alcoholic beverages [41, 42], all of which are well-established lifestyle risk factors for diabetes. Indeed, there is international consensus supporting the effectiveness of lifestyle intervention in the prevention and management of type 2 diabetes [40]. In addition, previous systematic reviews of RCTs have shown that exercise (an integral component of lifestyle intervention) is effective for improving both depression score (SMD was -0.82 [95% CI: -1.12 to -0.51]) and HbA1c level (WMD was -0.67% [95% CI: -0.84 to -0.49%]) [43, 44], and the size of these effects are substantially larger than what we found for collaborative care for depression. There is now sufficient evidence to suggest that diabetes care and lifestyle intervention integrated within collaborative care for depression would be the most effective way to manage care for co-morbid depression and diabetes.

Limitations

Several limitations require further consideration. Since only a small number of short-to-medium term studies predominately conducted in the United States were included, the findings of this review may not be relevant to health care settings in other countries, requiring

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further research. In particular, health care systems in most countries are not properly set up to optimize the co-ordination between practitioners [45]. Integration of therapies including collaborative care, diabetes care and lifestyle intervention is required to effectively manage co-morbid depression diabetes. Secondly, baseline mean HbA1c level was close to the upper limit of the normal range in several studies, which would have underestimated the effect size for, and therapeutic benefit of, collaborative care for glycaemic control. Finally, reviewer-level limitations include incomplete retrieval of information for several of the 11 citations excluded, and the existence of other relevant studies not identified with our search strategy resulting in bias. However, the results and conclusions reported in most of the excluded studies were in line with those reported here, search strategy bias was unlikely.

Conclusions

Limited evidence from short-to-medium term RCTs predominately conducted in the United States suggest that collaborative care for depression significantly improves both depression and glycaemia outcomes, independently, in people with co-morbid depression and diabetes. Future research should investigate the effectiveness, feasibility and appropriateness of collaborative care integration with diabetes care and lifestyle intervention for co-morbid depression and diabetes, and other co-morbid cardiovascular risk conditions, in routine clinical practice in specific health care settings worldwide.

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Figure 1: Flowchart summarizing identification of studies included for review.

Figure 2: SMD in depression outcomes after collaborative care between the treatment and control groups.

Figure 3: WMD in HbA1c level after collaborative care between the treatment and control groups.

Figure 4: Scatter plot displaying the association between the SMD in depression outcomes and the WMD in HbA1c values in each study.

Appendix page 5: Funnel plot assessing symmetry of 7 RCTs on effectiveness of collaborative care for depression outcome.

Appendix page 6: Funnel plot assessing symmetry of 7 RCTs on effectiveness of collaborative care for improving HbA1c outcome.

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Authorship order is according to percentage contribution. EA is guarantor of the paper, taking responsibility for the integrity of the work as a whole, from inception to published article. EA conceived and designed the review, identified studies for inclusion, extracted and interpreted data, and drafted the article. PF analysed and interpreted data, and revised the article. JF extracted and interpreted data, and revised the article. All authors approved the final completed article. We are grateful to Mrs Rohini Patil for her work on developing and conducting the electronic database searches.

COMPETING INTERESTS

EA has received honoraria for speaking at events for Eli Lilly Australia Pty Ltd (Lilly).

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TABLE 2: Characteristics of randomised controlled trials reviewed

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Study identification	Country	Sample size	Population		Men (%); Mean age (years)	Baseline mean depression score		Baseline mean HbA1c (%)	
			Major inclusion criteria (all)	Major exclusion criteria (any)		Treated	Controls	Treated	Controls
Bogner et al, 2010[26]	United States	58	Aged ≥50 years, recent HbA1c >7 or an oral hypoglycaemic prescription within past year, diagnosed depression or an antidepressant prescription within past year	None specified	16; 60	15.6	19.7	7.3	7.3
Bogner et al, 2012[16]	United States	180	Aged ≥30 years, diagnosis of type 2 diabetes and current oral hypoglycaemic prescription, current antidepressant prescription	No informed consent, cognitive impairment (Mini-Mental State Examination <21), residence in care facility providing medications, unwillingness or inability to use the Medication Event Monitoring System	32; 57	10.6	9.9	7.2	7.0
Ell et al, 2010[27]*	United States	387	Aged ≥18 years, "with diabetes", one of two cardinal depressive symptoms most days and depression score ≥10 by the PHQ-9, informed consent	Acute suicidal ideation, score of ≥8 by the Alcohol Use Disorders Identification Test, inability to speak Spanish or English	18; 54	1.7	1.4	9.0	9.1
Katon et al, 2004[28]*	United States	329	Diabetes (by registry), depression score of ≥10 by the PHQ-9 at first screening and score of ≥1.1 by the SCL-90 at second telephone screening, ambulatory, English speaking, adequate hearing for telephone interview, planned continued enrolment in the clinic during the next year	Currently in care of psychiatrist, diagnosed bipolar disorder or schizophrenia, current antipsychotic or mood stabilizer medications, symptoms of dementia	35; 58	1.7	1.6	8.0	8.0
Katon et al, 2010[17]	United States	214	Diabetes, coronary heart disease or both (by registry), depression score of ≥3 by the PHQ-2 and ≥10 by the PHQ-9, ambulatory, spoke English, and planned be enrolled in the Health Maintenance Organization for 12 months	Terminal illness, residence in long-term facility, severe hearing loss, planned bariatric surgery within three months, pregnancy or breast feeding, ongoing psychiatric care, bipolar disorder or schizophrenia, current antipsychotic or mood stabilizer medications, symptoms of dementia	48; 57	1.7	1.7	8.1	8.0
Morgan et al, 2013[25]	Australia	156 (glycaemia); 310 (depression)	Type 2 diabetes, coronary heart disease or both (by registry), depression score of ≥5 by the PHQ-9, informed consent	Aged <18 years, in residential care	55; 68	10.7	11.6	7.0	6.9

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Williams et al, 2004[29]*	United States	232 (glycaemia); 417 (depression)	Diagnosed or treated diabetes or high blood sugar in past three years by self-report, current major depression or dysthymic disorder by structured clinical interview according to DSM-IV	Current drinking problem (score of ≥2 by the CAGE questionnaire), history of bipolar disorder or psychosis, ongoing psychiatric care, or severe cognitive impairment (score of <3 by questionnaire)	47; 71	1.7	1.7	7.3	7.3

Abbreviations: HbA1c, glycated haemoglobin; CES-D, Center for Epidemiological Studies Depression scale; PHQ, Patient Health Questionnaire; SCL, Symptom Checklist; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, fourth edition
*Raw data was provided by the author

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→ adjacent.....continued

Treatments	Control conditions	Trial duration (weeks)	Outcomes (assessments)	Quality score (out of 6)
"Integrated care"; consisted of supervised case manager, patient-centred care, education and integrated care for depression and diabetes; three 30 min in person and two 15 min telephone follow-up sessions over four weeks	"Usual care"; and study assessments	12	Glycaemia (HbA1c); depression score (CES-D 20)	4.0
"Integrated care"; consisted of supervised case manager, patient-centred care, education and integrated care for depression and diabetes; three 30 min in person and two 15 min telephone follow-up sessions over three months	"Usual care"; and study assessments	12	Glycaemia (HbA1c); depression score (PHQ-9)	5.0
"Collaborative care"; consisted of supervised nurse case manager, patient-centred care, problem solving therapy, self-monitoring education, and coordination of care and services for depression and diabetes within a stepped-care framework; monthly telephone symptom monitoring, treatment maintenance and relapse prevention up to 12 months	"Enhanced usual care"; and patient and family-focused depression education pamphlets	52	Glycaemia (HbA1c); depression score (SCL-20)	5.5
"Collaborative care"; consisted of supervised nurse case manager, patient-centred care (initial choice of antidepressant or problem solving therapy), within a stepped-care framework; initial one hour visit, followed by twice monthly half-hour follow-ups (telephone or in-person) up to 12 weeks and referral to speciality care thereafter if necessary	"Usual care"; and advice to consult their physician for depression care	26	Glycaemia (HbA1c); depression score (SCL-20)	4.5
"Collaborative care"; consisted of supervised nurse case manager, "treat-to-target program" integrated care for specific conditions, within a stepped-care framework, motivational problem solving and goal setting for self-care (including exercise, and "The Depression Helpbook", video and written material); structured visits every two to three weeks, and maintenance plan once targeted levels were achieved including telephone follow-ups every four weeks	"Enhanced usual care"; patients could self-refer to mental health care or be referred by primary care physicians at the clinic; and study assessments	52	Glycaemia (HbA1c); depression score (SCL-20)	5.0
"Collaborative care"; consisted of collaborative care trained nurse case manager, 45 min nurse consult every three months followed (for assessment of lifestyle, physical and biochemical risk factors, and referrals, self-care of depression and setting personal goals for review and discussion of educational resources), followed by a 15 min consult with their usual general practitioner	"Usual care"; baseline data collected retrospectively	26	Glycaemia (HbA1c); depression score (PHQ-9)	3.5

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Collaborative care; consisted of trained nurse or psychologist case manager, patient-centred care, problem solving therapy, 20 min educational video tape and written material on late-life depression, and coordination of care and services for depression within a stepped-care framework; monthly telephone symptom monitoring, treatment maintenance and relapse prevention up to 12 months; diabetes care not specifically enhanced	"Usual care"; and study assessments	52	Glycaemia (HbA1c); depression score (SCL-20)	4.0	

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TABLE 2: Sensitivity analysis of randomized controlled trials of collaborative care → depression score outcome meta-analysis

	N studies	N sample	SMD	(95% confidence interval)	P-value for heterogeneity
Fixed effects model	7	1895	-0.31	(-0.40 to -0.22)	<0.001
Exclusion of 3 lower quality studies (score ≤4.0)	4	1110	-0.17	(-0.35 to 0.00)	0.101
Exclusion of 1 study outside the United States (Australia)	6	1585	-0.32	(-0.57 to -0.07)	<0.001
Exclusion of 3 studies that integrated diabetes care	4	1443	-0.30	(-0.62 to 0.01)	<0.001
Exclusion of 2 studies that considered lifestyle risk factors	5	1371	-0.30	(-0.59 to 0.00)	<0.001
Exclusion of 4 studies less than 1 year duration	3	1018	-0.34	(-0.68 to 0.01)	<0.001

Abbreviations: N, number; SMD, standardized mean difference

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TABLE 3: Sensitivity analysis of randomised controlled trials of collaborative care → HbA1c outcome meta-analysis

	N studies	N sample	WMD	(95% confidence interval)	P-value for heterogeneity
Fixed effects model	7	1556	-0.21	(-0.37 to -0.05)	0.001
Exclusion of 3 lower quality studies (score ≤4.0)	4	1110	-0.32	(-0.81 to 0.17)	0.001
Exclusion of 1 study outside the United States (Australia)	6	1400	-0.31	(-0.68 to 0.07)	0.001
Exclusion of 3 studies that integrated diabetes care	4	1104	-0.07	(-0.35 to 0.21)	0.086
Exclusion of 2 studies that considered lifestyle risk factors	5	1186	-0.27	(-0.71 to 0.16)	0.002
Exclusion of 4 studies less than 1 year duration	3	833	-0.18	(-0.48 to 0.11)	0.189

Abbreviations: N, number; WMD, weighted mean difference

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APPENDIX

PubMed search syntax

((((("randomized controlled trials as topic"[MeSH Terms] OR randomised controlled trial OR RCT)) AND ((((((comprehensive health care[MeSH Terms]) OR collaborative care[Title/Abstract]) OR multidisciplinary care[Title/Abstract]) OR team care.[Title/Abstract]) OR integrated care[Title/Abstract]) OR complex care[Title/Abstract])) AND (((((("blood glucose"[MeSH Terms] OR "diabetes complications"[MeSH Terms]) OR "hemoglobin a, glycosylated"[MeSH Terms]) OR hemoglobin A1c[Title/Abstract]) OR "Hemoglobin A, Glycosylated"[Mesh]) OR HbA1c[Title/Abstract]) OR glucose blood level[Title/Abstract]) OR diabetes[Title/Abstract] OR diabetic[Title/Abstract])) AND (((((((psychological distress[Title/Abstract]) OR hypervigilance[Title/Abstract]) OR nervousness[Title/Abstract]) OR anxieties[Title/Abstract]) OR anxious[Title/Abstract]) OR anxiety[MeSH Terms]) OR ("depressive disorder"[MeSH Terms] OR "depression"[MeSH Terms]))

Scopus search syntax

(TITLE-ABS-KEY(depression OR depressi* OR anxiety OR "psychological distress" OR hypervigilance OR nervousness OR anxieties OR melancholi* OR dysthymi*) AND TITLE-ABS-KEY("blood glucose" OR "hb a1c" OR "hemoglobin a glycosylated" OR glycaemic OR diabet*) AND TITLE-ABS-KEY("collaborative care" OR "multidisciplinary care" OR "transmural care" OR "complex care" OR "seamless care" OR "team care") AND TITLE-ABS-KEY(randomi?ed controlled trial OR rct))

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Quality item checklist for randomised controlled trials reviewed (each worth 1 numerical point)

Study identification	Description of eligibility criteria adequate? (each worth 0.5 points): (1) inclusion criteria; (2) exclusion criteria	Randomization adequate? (each worth 0.5 points): (1) evidence suggesting "random" allocation; (2) evidence suggesting method used to generate random allocation sequence	Allocation concealment adequate?	Between-group prognostic indicators balanced? (each worth 0.5 points): (1) Depression score; (2) HbA1c level	Between-group drop-outs balanced?	Intention to treat analysis included?	Total quality score (out of 6)
Bogner et al, 2010	0.5	0.5	0.0	1.0	1.0	1.0	4.0
Bogner et al, 2012	1.0	1.0	0.0	1.0	1.0	1.0	5.0
Ell et al, 2010	1.0	1.0	1.0	0.5	1.0	1.0	5.5
Katon et al, 2004	1.0	1.0	0.0	1.0	1.0	0.5	4.5
Katon et al, 2010	1.0	1.0	0.0	1.0	1.0	1.0	5.0
Morgan et al, 2013	1.0	0.5	0.0	1.0	1.0	0.0	3.5
Williams et al, 2004	1.0	1.0	1.0	1.0	0.0	0.0	4.0

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EXCLUDED CITATIONS (REASONS)

1. Ciechanowski PS, Russo JE, Katon WJ, *et al*. The association of patient relationship style and outcomes in collaborative care treatment for depression in patients with diabetes. *Medical care*. 2006;44(3):283-91.

(Redundant citation; duplicate publication)

2. Ell K, Aranda MP, Xie B, Lee PJ, Chou CP**.** Collaborative depression treatment in older and younger adults with physical illness: pooled comparative analysis of three randomized clinical trials. *American Journal of Geriatric Psychiatry*. 2010;18(6):520-30.

(Inadequate study design; meta-analysis of RCTs)

3. Fisher L, Polonsky W, Parkin CG, *et al***.** The impact of blood glucose monitoring on depression and distress in insulin-nave patients with type 2 diabetes. *Current Medical Research and Opinion*. 2011;27(SUPPL. 3):39-46.

(Inadequate collaborative care model; structured self-monitoring of blood glucose alone)

4. Lamers F, Jonkers CC, Bosma H, Knottnerus JA, van Eijk JT**.** Treating depression in diabetes patients: does a nurse-administered minimal psychological intervention affect diabetes-specific quality of life and glycaemic control? A randomized controlled trial. *J Adv Nurs*. 2011;67(4):788-99.

(Inadequate collaborative care model; psychological therapy alone)

5. Lin EH, Korff M, Ciechanowski P, *et al*. Treatment adjustment and medication adherence for complex patients with diabetes, heart disease, and depression: a randomized controlled trial. *Annals of family medicine*; 2012:6-14.

(Redundant citation; duplicate publication)

6. Naji S**.** Integrated care for diabetes: Clinical, psychosocial, and economic evaluation. *British Medical Journal*. 1994;308(6938):1208-12.

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(Inadequate collaborative care model; not specifically for depression)

7. Solberg LI, Crain AL, Sperl-Hillen JM, *et al***.** Care quality and implementation of the Chronic Care Model: a quantitative study. Annals of Family Medicine. 2006;4(4):310-6.

(Inadequate study design; not an RCT)

8. Stiefel F, Zdrojewski C, Bel Hadj F, *et al*. Effects of a multifaceted psychiatric intervention targeted for the complex medically ill: a randomized controlled trial. *Psychotherapy & Psychosomatics*. 2008;77(4):247-56.

(Incomplete data for extraction, contacted author 4 Sep 2013)

9. Tapp H, Phillips SE, Waxman D, *et al***.** Multidisciplinary team approach to improved chronic care management for diabetic patients in an urban safety net ambulatory care clinic. *Journal of the American Board of Family Medicine*. 2012;25(2):245-6.

(Inadequate study design; feasibility and study design)

10. Taveira TH, Dooley AG, Cohen LB, Khatana SA, Wu WC**.** Pharmacist-led group medical appointments for the management of type 2 diabetes with comorbid depression in older adults. *Ann Pharmacother*. 2011;45(11):1346-55.

(Inadequate collaborative care; lacked evidence of co-ordination of care)

11. Trief PM, Morin PC, Izquierdo R, *et al*. Depression and glycemic control in elderly ethnically diverse patients with diabetes: the IDEATel project. *Diabetes Care*. 2006;29(4):830-5.

(Incomplete data for extraction, contacted author 5 Sep 2013

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Funnel plot assessing symmetry of 7 RCTs on effectiveness of collaborative care for depression outcome

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Funnel plot assessing symmetry of 7 RCTs on effectiveness of collaborative care for improving HbA1c outcome

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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.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4,5
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.	No
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.	5,6
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.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 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).	5,6
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.	6
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
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.	6, appendix 2
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7

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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.	7,8

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).	7, 8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Appendix 5,6
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.	8,9
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.	23-26
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).	Appendix 5,6
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.	10,11
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10,11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10,11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	27,28
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).	11-13
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).	13,14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14
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.	None

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.

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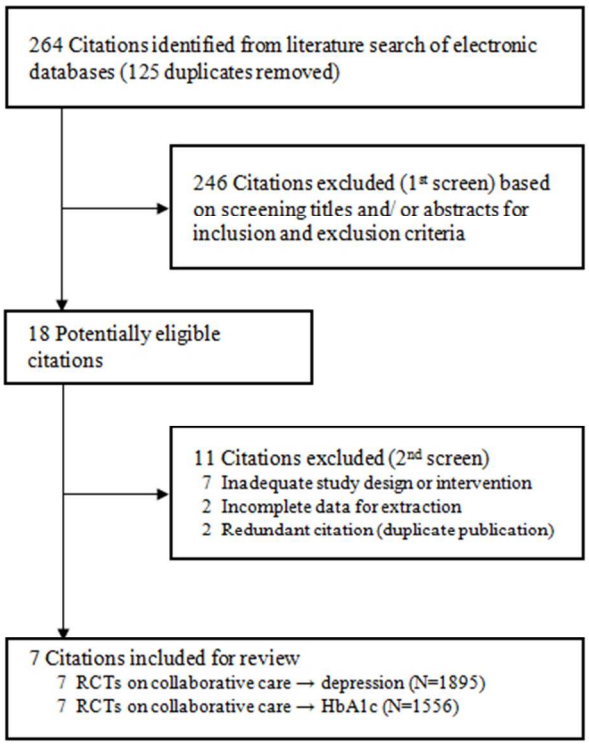

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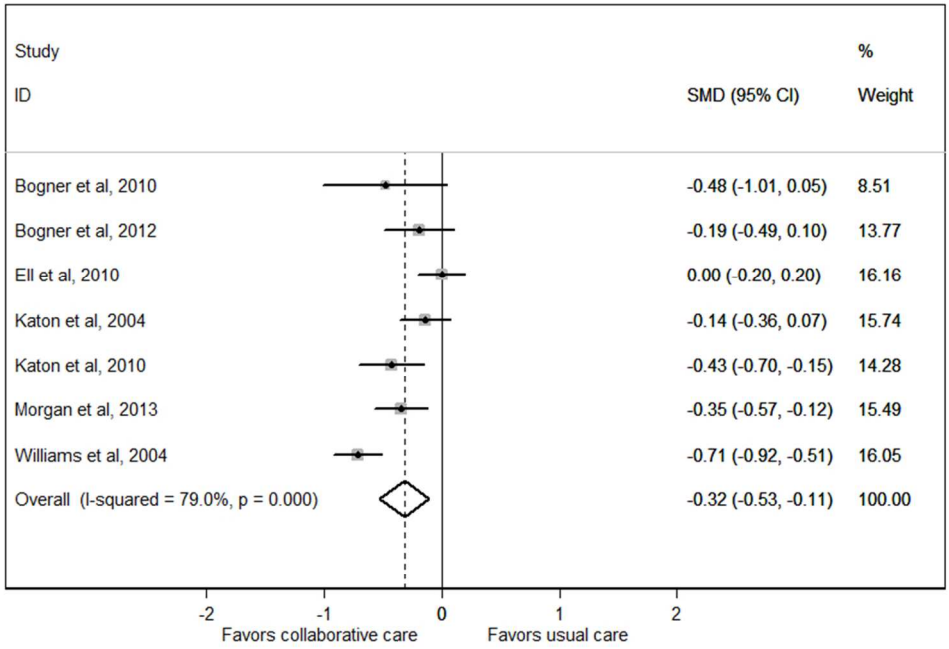

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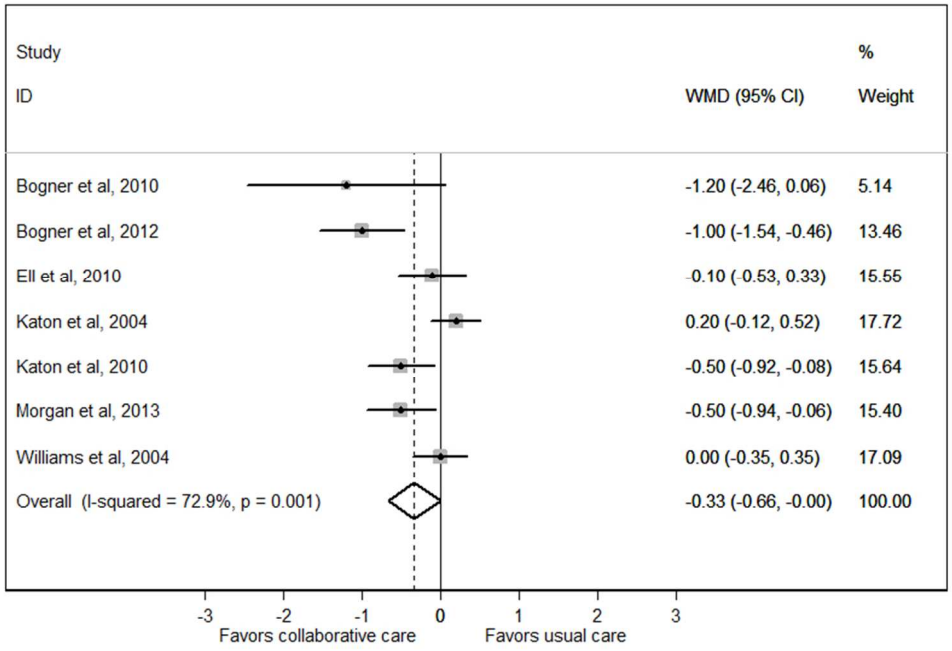

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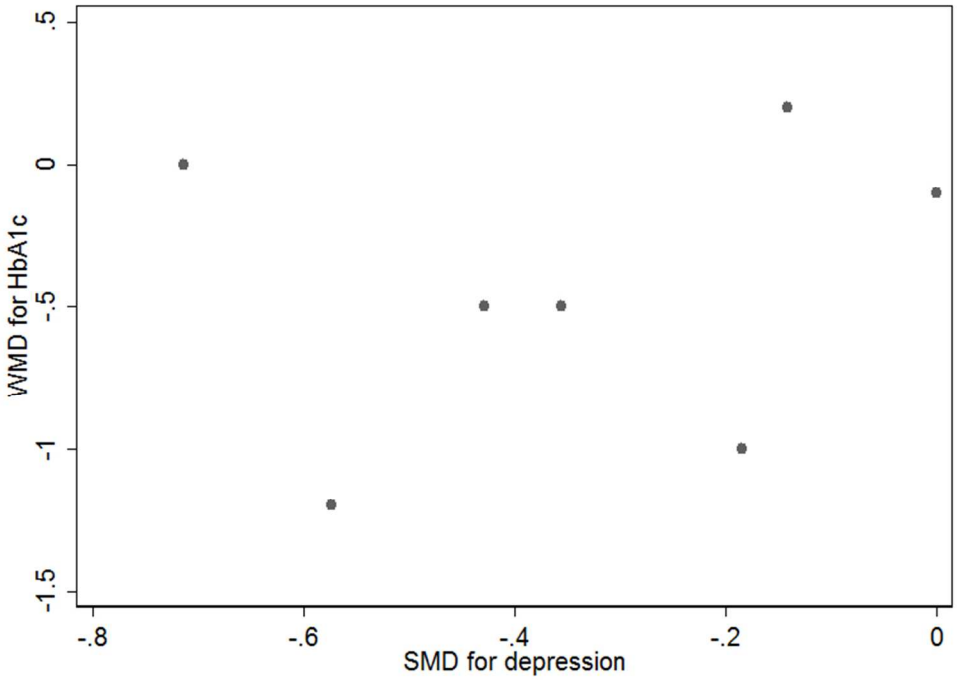

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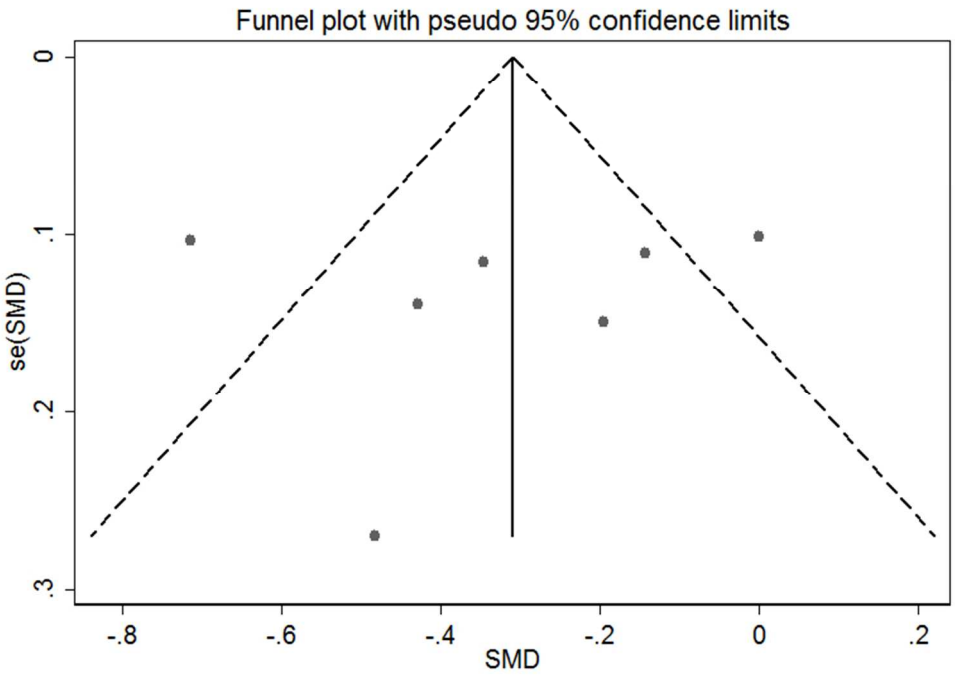

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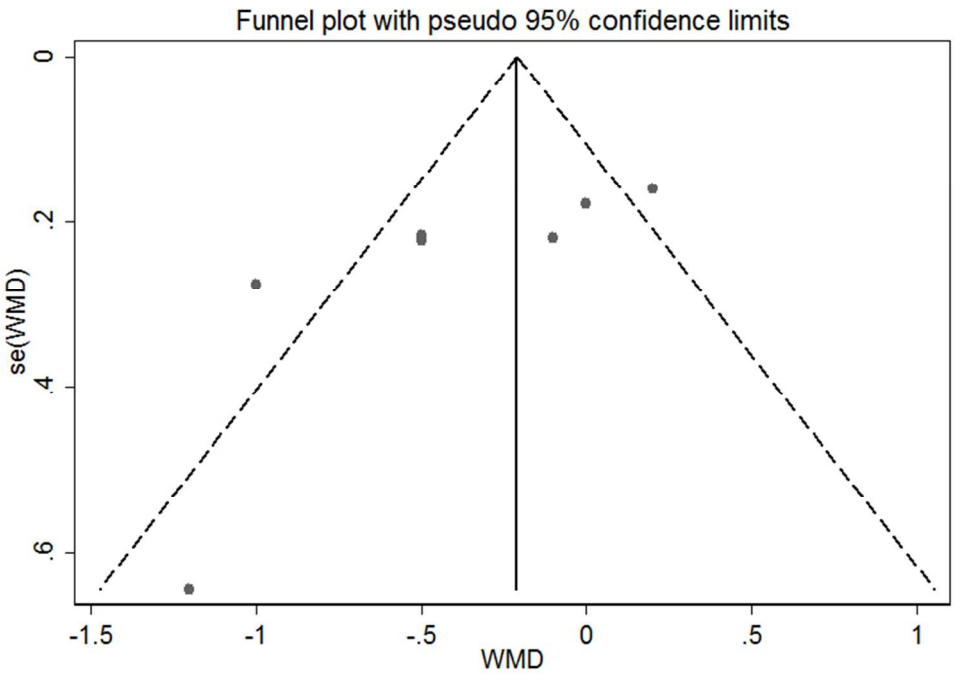

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