JAMA Psychiatry | Original Investigation | META-ANALYSIS

Association Between Chronic Physical Conditions and the Effectiveness of Collaborative Care for Depression
An Individual Participant Data Meta-analysis

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IMPORTANCE Collaborative care is an intensive care model involving several health care professionals working together, typically a physician, a case manager, and a mental health professional. Meta-analyses of aggregate data have shown that collaborative care is particularly effective in people with depression and comorbid chronic physical conditions. However, only participant-level analyses can rigorously test whether the treatment effect is influenced by participant characteristics, such as chronic physical conditions.

OBJECTIVE To assess whether the effectiveness of collaborative care for depression is moderated by the presence, type, and number of chronic physical conditions.

DATA SOURCES Data were obtained from MEDLINE, EMBASE, PubMed, PsycINFO, CINAHL Complete, and Cochrane Central Register of Controlled Trials, and references from relevant systematic reviews. The search and collection of eligible studies was ongoing until May 22, 2015.

STUDY SELECTION This was an update to a previous meta-analysis. Two independent reviewers were involved in the study selection process. Randomized clinical trials that compared the effectiveness of collaborative care with usual care in adults with depression and reported measured changes in depression severity symptoms at 4 to 6 months after randomization were included in the analysis. Key search terms included *depression, dysthymia, anxiety, panic, phobia, obsession, compulsion, posttraumatic, care management, case management, collaborative care, enhanced care*, and *managed care*.

DATA EXTRACTION AND SYNTHESIS Individual participant data on baseline demographics and chronic physical conditions as well as baseline and follow-up depression severity symptoms were requested from authors of the eligible studies. One-step meta-analysis of individual participant data using appropriate mixed-effects models was performed.

MAIN OUTCOMES AND MEASURES Continuous outcomes of depression severity symptoms measured using self-reported or observer-rated measures.

RESULTS Data sets from 31 randomized clinical trials including 36 independent comparisons (N = 10 962 participants) were analyzed. Individual participant data analyses found no significant interaction effects, indicating that the presence (interaction coefficient, 0.02 [95% CI, −0.10 to 0.13]), numbers (interaction coefficient, 0.01 [95% CI, −0.01 to 0.02]), and types of chronic physical conditions do not influence the treatment effect.

CONCLUSIONS AND RELEVANCE There is evidence that collaborative care is effective for people with depression alone and also for people with depression and chronic physical conditions. Existing guidance that recommends limiting collaborative care to people with depression and physical comorbidities is not supported by this individual participant data meta-analysis.

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Depression is the leading global cause of disease burden accounting for most disability-adjusted life years.[1,2] The combination of depression with a chronic physical condition (hereinafter termed *physical condition*), such as cardiovascular diseases, respiratory diseases, and diabetes, is associated with the greatest decrements in quality of life, years lost owing to disability,[3] patient safety failures, and unscheduled care.[4-8]

A promising intervention for depression in primary care is collaborative care,[9] which involves the use of a case manager (usually nonmedical but also medical; eg, clinical social workers) working with primary care professionals, often supervised by a mental health specialist and supported by care management systems. A Cochrane review[10] showed that collaborative care is more effective than usual care for depression.

Finding feasible and effective ways of integrating care for patients with depression and comorbid physical conditions remains a critical goal for health systems worldwide. There has been significant interest in the ability of collaborative care to improve care for people with depression and physical conditions.[11,12] In the United States, the Community Preventive Services Task Force[13,14] recommends collaborative care for the treatment of major depression in adults but concedes that there are evidence gaps about the effectiveness of this approach in people with comorbid physical conditions. In the United Kingdom, the English organization responsible for clinical guidelines (National Institute for Health and Care Excellence)[15] recommends that collaborative care should be considered only for people with depression and comorbid physical conditions based on results from aggregate-data meta-analyses of 2 sets of trials: collaborative care for patients with depression and collaborative care for patients with depression and physical conditions. Although these recommendations were based on the best available evidence at the time, conducting 2 separate meta-analyses means that any differences in effectiveness may be confounded by differences between the trials (eg, location, quality, and intervention format) and may not be due to physical conditions.[16] In addition, some collaborative care trials that recruited people with depression would not necessarily have excluded those with physical conditions, especially trials conducted in older populations in whom such conditions are highly prevalent.[17-25]

To reach international consensus about the most effective ways to manage depression it is critical that guidelines reflect the most robust analysis of the most current data. There is increasing recognition that individual participant data (IPD) meta-analysis is a better basis for modeling treatment effects than are aggregate data meta-analyses.[26] Individual participant data meta-analysis is more precise because it involves the application of standardized analyses across multiple data sets, overcomes sample size and reporting issues, and allows more sophisticated modeling of moderator effects.[26-28] In this context, IPD allows for more accurate coding of comorbidity based on actual patient health.

In the present study, we used IPD meta-analysis to test whether physical conditions moderate the effectiveness of collaborative care for depression outcomes. First, we examined whether studies that recruited individuals with physical conditions as part of inclusion criteria demonstrated greater effect of collaborative care on depression outcomes (ie, a study-level moderator analysis). Subsequently, we examined whether the effectiveness of collaborative care on depression outcomes was moderated by the presence, number, and type of physical conditions reported by individual participants within trials (ie, participant-level moderator analyses). The results will provide a rigorous basis for recommendations about the types of people most likely to benefit from collaborative care and contribute to the wider debate about how multimorbidity influences treatment effectiveness.[29,30]

Key Points

Question Is collaborative care more effective for patients with depression and chronic physical conditions compared with patients with depression alone?

Findings This meta-analysis of individual participant data from 10 960 patients found no significant differences in the treatment effects of collaborative care between patients with depression alone and patients with depression and chronic physical conditions.

Meaning Collaborative care is an equally effective way to deliver depression care for patient with and without comorbid chronic physical conditions; existing guidance that recommends limiting access to collaborative care for patients with depression and chronic physical conditions should be updated.

Methods

This IPD meta-analysis was conducted and reported according to published methodological guidelines.[31,32] The PRISMA-D was completed (eTable 1 in the Supplement).

Information Sources

The published Cochrane review[10] of collaborative care was used to identify eligible randomized clinical trials (RCTs). The Cochrane review searches were updated in March 2014 (MEDLINE, EMBASE, PsycINFO, Cochrane Central Register of Controlled Trials, and CINAHL Complete) but search and collection of eligible studies was ongoing until May 22, 2015. Key search terms included *depression, dysthymia, anxiety, panic, phobia, obsession, compulsion, posttraumatic, care management, case management, collaborative care, enhanced care*, and *managed care*. The reference lists of reports of all included studies were screened for additional studies. We also asked authors of studies reviewed to identify additional published studies and trials in progress.

Eligibility Criteria

We used the same inclusion criteria reported by the Cochrane review,[10] except we excluded studies conducted in adolescents and studies that did not report a depression outcome (eMethods in the Supplement). The following factors were evaluated in study selection:

1. Adults (age ≥18 years) with depression or mixed anxiety and depressive disorder,
2. Collaborative care interventions (multiprofessional approach to patient care, structured management plan, scheduled patient follow-ups, and enhanced interprofessional communication),
3. Comparison (usual or enhanced usual care),
4. Outcome (continuous depression scores), and
5. Research design (RCTs or cluster RCTs).

Measuring Depression and Physical Conditions

All studies provided continuous depression scores measured using validated scales, including the Beck Depression Inventory,[33] the Center for Epidemiologic Studies Depression Scale,[34] the Hamilton Rating Scale for Depression,[35] and the Patient Health Questionnaire-9.[36] We focused on short-term depression outcomes reported between 4 and 6 months after randomization. Depression scores were standardized within each study, using the baseline SD and the follow-up mean score.

At study level, 9 of the 36 comparisons recruited participants with a physical condition. Thirty of the 36 comparisons reported data on the presence and number of physical conditions at individual participant level. Of these, most comparisons (21 [58%]) used validated comorbidity indices, such as the Charlson Comorbidity Index,[37] and 6 (17%) used empirical lists of physical conditions. Seventeen comparisons (47%) identified the type of physical conditions among participants. Based on these data, we were able to create 5 categories of physical conditions: cancer (10 comparisons), cardiac disease (16 comparisons), diabetes (17 comparisons), hypertension (11 comparisons), and respiratory disease (11 comparisons).

Data Extraction and Preparation

We contacted the study authors to obtain primary data sets for the following data: treatment group, age, sex, baseline and follow-up depression scores, and number and types of physical conditions (eTable 2 in the Supplement). Received data were cleaned, converted into the same reporting format, and aggregated into a single data set. Initial separate analyses on depression outcomes were conducted for each study to ensure that our analyses were consistent with those reported in the original study. We extracted data from the published reports of all the eligible studies using a standardized Excel (Microsoft Inc) data extraction form. Data on populations, interventions, chronic conditions (used as moderator in the analyses), risk of bias, and outcome effect sizes were also extracted. Studies with data available to us were compared with studies with unavailable data in terms of outcome effect sizes and moderator analyses.

Missing Data

Multiple imputation techniques were used to obtain more complete data sets and to better protect against bias due to data missing at random mechanisms. Missing values for age and depression scores at follow-up were imputed with a multivariate imputation algorithm (*mi impute mvn* in Stata, version 14; StataCorp LP) using Markov chain Monte Carlo.[38,39] This process produces several data sets, each of which is analyzed separately using the prespecified model; the results are then combined using Rubin's rules,[40] which account for uncertainty in imputed values. A total of 1000 new data sets with the observed and imputed scores for age and depression at follow-up were generated based on values obtained from study identification number, treatment group, baseline depression score, and sex. The range of imputed values was limited to the range of observed values of the variables. Time series and autocorrelation plots of the worst linear function were performed to monitor the convergence of the generated imputation algorithms.[41,42] We examined whether baseline variables (study, treatment group, age, sex, and baseline depression scores) predicted missing data to confirm that the assumptions underlying imputations were met. Sensitivity analyses were performed using only cases with available data; no significant differences were detected in any of the reported results.

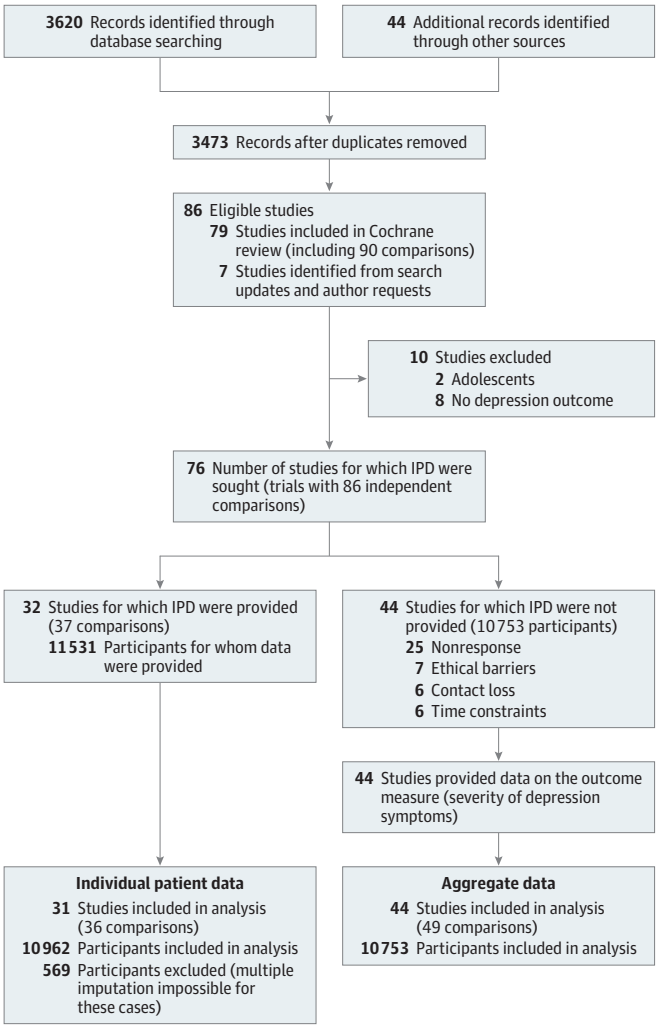
Statistical Analysis

One-step meta-analysis was undertaken because it is less susceptible to bias, is most efficient in terms of power, and allows for sophisticated modeling of covariates (age, sex, and baseline depression scores in the present study).[43,44] A 1-step IPD meta-analysis constructs a model for the hypothesized treatment-covariate associations across all IPD sets while statistically accounting for clustering at the level of each included data set.[28,45]

Appropriate mixed-effects models (fixed study-specific intercepts, random treatment effect, and fixed study-specific effects for baseline depression) were used to meta-analyze the participant-level data and estimate the between-study and within-study variances and the effects of covariates.[46] Clustered RCTs were statistically accounted for in the model by adhering to the methodologic recommendations of Sutton et al.[47] The Stata, version 14, command *mixed* was used through the *ipdforest* command to summarize the evidence by study and obtain forest plots.[48,49] A 1-stage meta-analysis variant of the I^2 statistic was used to assess heterogeneity.[50] We examined the impact of covariates separately, building a model based on both statistical and theoretical criteria. If studies included multiple treatment groups and a single control group, the treatment groups were treated as separate comparisons in the analyses, whereas, the control groups were halved at random to avoid double counting in the analyses. In accordance with published guidelines,[51] funnel plots were constructed to assess the potential for publication bias.

Several prespecified primary analyses were performed. One analysis examined a study-level moderator (binary variable; participants with physical conditions as part of the study's inclusion criteria: yes, 1; no, 0). The other analyses examined moderators at patient level including the presence (binary variable; present, 1; absent, 0), number (continuous variable), and types of physical conditions (binary variables for each condition; present, 1; absent, 0).

Figure 1. PRISMA Flowchart



Flowchart of the inclusion of studies in the review. IPD indicates individual participant data.

We conducted 2 secondary analyses to examine the robustness of the results and assessed whether the results remained the same after controlling for the risk of bias scores of the studies (based on allocation concealment item). Allocation concealment was selected as an indicator of risk of bias because it is the most sensitive item to changes in the treatment effect, especially when based on self-reported outcomes.[52-54] We also explored whether the main effects were influenced by the measure used to assess physical conditions (use of validated comorbidity severity indices).

Results

Figure 1 presents the flowchart of the study selection process. A total of 76 RCTs (22 284 patients) including 86 independent comparisons were eligible for inclusion in the IPD meta-analysis. We found no evidence of asymmetry in the funnel plot for these studies (Egger regression test intercept [SE], −0.54 [0.42]; *P* = .21) (eFigure 1 in the Supplement). We collected data from 32 trials (11 531 [51.7%] of the total number of participants) that included 37 comparisons. One RCT[55] (a pilot study based on 49 participants) was excluded from the analyses because it did not include data on age and sex, leaving 36 comparisons. A total of 569 individual cases (4.9%) were excluded from the analyses because of missing baseline values on depression or age, leaving 10 962 unique cases (of which 1819 [16.6%] were imputed using multiple imputations).

Baseline Characteristics and Comparisons Between Available and Unavailable Data

Eighteen studies were conducted in the United States, 11 in Europe, 1 in Canada, and 1 in India. Most participants were women (7749 [70.7%]); mean (SD) age was 51 (15) years (range, 17-97 years). Most participants (8099 [78.1%]) had at least 1 physical condition with a mean of 2.5 (2.3) conditions. We identified no important issues while checking the IPD. Details on the characteristics of the studies are presented in eTable 3 and eTable 4 in the Supplement.

Table. Comparison of Studies Providing Data for the IPD Analyses and Those Not Providing Data

Variable	Data Unavailable (n = 49)	Data Available (n = 36)	Statistical Test	*P* Value
Country, United States	36 (78)	23 (62)	$\chi^2_{1,85} = 3.17$	.08
Publication date, y				
Mean (SD)	2006 (4.03)	2007 (5.29)	$t_{83} = 1.01$	.32
Median (range)	2007 (1995-2013)	2008 (1995-2015)		
Systematic recruitment method, No. (%)	41 (84)	31 (84)	$\chi^2_{1,85} = 0.01$	.98
Chronic physical condition present, No. (%)	12 (24)	9 (24)	$\chi^2_{1,85} = 0.01$	.97
Intervention content psychological or both, No. (%)	20 (41)	28 (76)	$\chi^2_{1,85} = 12.79$	<.01
Frequency of scheduled supervision, mean (SD)	1.64 (0.82)	1.76 (0.91)	$t_{83} = 0.65$	.52
Allocation concealment low risk, No. (%)	30 (61)	18 (49)	$\chi^2_{1,85} = 3.17$	.24
Sample size				
Mean (SD)	220 (305)	292 (192)	$t_{83} = 1.63$	.11
Median (range)	165 (23 to 1570)	227 (64 to 783)		
Effect size				
SMD (SE)	−0.32 (0.31)	−0.24 (0.30)	$t_{83} = 1.22$	.23
SMD (95% CI)	(−0.40 to −0.23)	(−0.29 to −0.10)		

Abbreviations: IPD, individual participant data; SMD, standardized mean difference.

Available and unavailable studies were compared in terms of population, intervention, and risk of bias characteristics, as well as outcome data. We selected these specific characteristics based on the results of 2 previous reviews[12,16] that applied meta-regression analyses to identify moderators of the main effect of collaborative care interventions. As reported in the **Table**, the only statistically significant difference identified was for the intervention content; a larger proportion of trials that incorporated psychological interventions made data available.

Effects of Collaborative Care on 3 Depressive Symptoms at 4- to 6-Month Follow-up

Collaborative care was associated with a small but significant effect on depression outcomes compared with usual care (standardized mean difference [SMD], −0.22 [95% CI, −0.25 to −0.18]; I^2 = 0.8%; 0.3%-3.5%) (eFigure 2 in the Supplement) equal to a drop of approximately 2 points on the Patient Health Questionnaire-9 above the change in the controls. This effect size was smaller but not significantly different from the effect size reported in a Cochrane review[10] (−0.28 [95% CI, −0.31 to −0.25]; *P* = .227) (Table).

Association Between Systematic Identification of Patients with Chronic Physical Conditions and the Effectiveness of Collaborative Care on Depression Scores

A statistically significant interaction was found between systematic identification of participants with physical conditions in the study and treatment effect (interaction coefficient, −0.12 [95% CI, −0.23 to −0.02]) (**Figure 2**).[12,19,21,24,56-82] Randomized clinical trials that explicitly recruited people with physical conditions were associated with significantly larger treatment effects for depression (SMD, −0.29 [95% CI, −0.37 to −0.21]) compared with RCTs that did not explicitly recruit people with physical conditions (SMD, −0.19 [95% CI, −0.23 to −0.15]). The moderating effect of inclusion of physical conditions was even larger in trials with adequate concealment of allocation (interaction coefficient, −0.14 [95% CI, −0.26 to −0.02]).

Association Between Presence of Chronic Physical Conditions and the Effectiveness of Collaborative Care on Depression Scores

When we compared the effects of collaborative care in participants with and without physical conditions, the interaction term with the treatment effect was nonsignificant (interaction coefficient, 0.02 [95% CI, −0.10 to 0.13]) (**Figure 3**) (References 12, 19, 21, 24, 56, 57, 59, 60, 63, 65-72, 74-82). We could not demonstrate any statistically significant moderating effect of the presence of physical conditions on depression outcomes at follow-up (effect in those with physical conditions: SMD, −0.21 [95% CI, −0.27 to −0.15], in those without physical conditions: SMD, −0.23 [95% CI, −0.32 to −0.12]) (Figure 3).

This result was not sensitive to allocation concealment ratings (adequate: interaction coefficient, −0.06 [95% CI, −0.04 to 0.02]) or to the measure used to assess physical conditions (validated: 0.05 [95% CI, −0.08 to 0.10]).

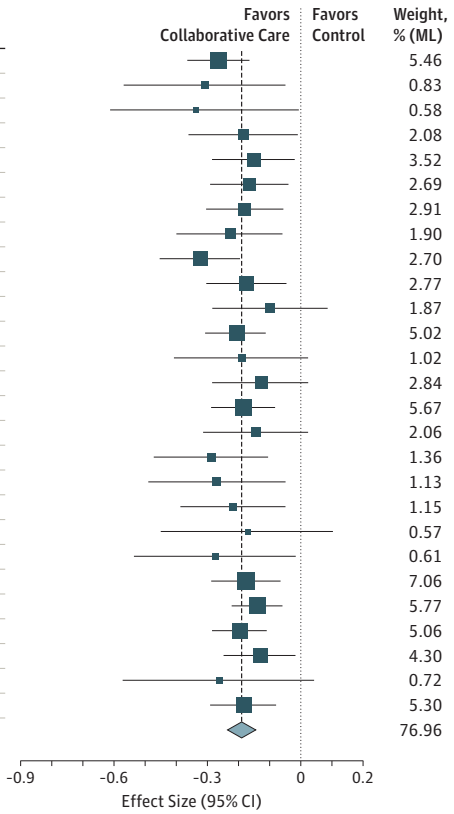
Association Between Number of Chronic Physical Conditions and the Effectiveness of Collaborative Care on Depression Scores

The interaction term between number of physical conditions and treatment effect was nonsignificant (interaction coefficient, 0.00 [95% CI, −0.01 to 0.02]) (**Figure 4**) (References 12, 19, 21, 24, 56, 57, 59, 60, 63, 65-72, 74-82). This finding suggests that the improvement of depression scores at follow-up does not differ according to the number of physical condi-

Figure 2. Study-Level Analysis Examining the Effect of the Presence Chronic Physical Conditions on the Effectiveness of Collaborative Care

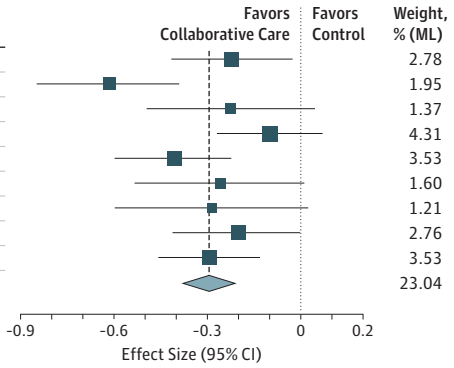
A Studies did not explicitly recruit patients with chronic physical conditions

Source	Effect Size (95% CI)	Weight, % (ML)
Bruce et al,[19] 2004	-0.27 (-0.36 to -0.17)	5.46
Katon et al,[56] 1995	-0.31 (-0.57 to -0.05)	0.83
Katon et al,[57] 1996	-0.34 (-0.67 to -0.01)	0.58
Katon et al,[58] 1999	-0.19 (-0.36 to -0.01)	2.08
Katon et al,[59] 2001	-0.15 (-0.28 to -0.02)	3.52
Simon et al,[60] 2000	-0.17 (-0.29 to -0.04)	2.69
Simon et al,[60] 2000	-0.18 (-0.31 to -0.06)	2.91
Simon et al,[61] 2011	-0.23 (-0.40 to -0.06)	1.90
Simon et al,[62] 2004	-0.32 (-0.45 to -0.20)	2.70
Simon et al,[62] 2004	-0.18 (-0.30 to -0.05)	2.77
Melville et al,[63] 2014	-0.10 (-0.28 to 0.09)	1.87
Buszewicz et al,[64] 2010	-0.21 (-0.31 to -0.11)	5.02
Cole et al,[24] 2006	-0.19 (-0.41 to 0.02)	1.02
Ell et al,[21] 2007	-0.13 (-0.28 to 0.02)	2.84
Gensichen et al,[65] 2009	-0.19 (-0.29 to -0.08)	5.67
Menchetti et al,[66] 2013	-0.15 (-0.31 to 0.02)	2.06
Huijbregts et al,[67] 2013	-0.29 (-0.47 to -0.11)	1.36
Vlasveld et al,[68] 2012	-0.27 (-0.49 to -0.05)	1.13
Smit et al,[69] 2006	-0.22 (-0.39 to -0.05)	1.15
Smit et al,[69] 2006	-0.17 (-0.45 to 0.10)	0.57
Smit et al,[69] 2006	-0.28 (-0.54 to -0.02)	0.61
Patel et al,[70] 2010	-0.18 (-0.29 to -0.07)	7.06
Wells et al,[71] 2000	-0.14 (-0.22 to -0.06)	5.77
Wells et al,[71] 2000	-0.20 (-0.29 to -0.11)	5.06
Adler et al,[72] 2004	-0.13 (-0.25 to -0.02)	4.30
Richards et al,[73] 2009	-0.27 (-0.57 to 0.04)	0.72
Richards et al,[74] 2013	-0.19 (-0.29 to -0.08)	5.30
ML Overall I^2 = 0%	-0.19 (-0.23 to -0.15)	76.96



B Studies explicitly recruited patients with chronic physical conditions

Source	Effect Size (95% CI)	Weight, % (ML)
Katon et al,[75] 2004	-0.22 (-0.42 to -0.03)	2.78
Katon et al,[76] 2010	-0.62 (-0.85 to -0.39)	1.95
Davidson et al,[77] 2013	-0.23 (-0.50 to 0.04)	1.37
Ell et al,[78] 2008	-0.10 (-0.27 to 0.07)	4.31
Ell et al,[79] 2010	-0.41 (-0.60 to -0.22)	3.53
Huffman et al,[80] 2011	-0.26 (-0.53 to 0.01)	1.60
Huffman et al,[81] 2014	-0.29 (-0.60 to 0.02)	1.21
Rollman et al,[82] 2009	-0.20 (-0.41 to 0.01)	2.76
Coventry et al,[12] 2014	-0.29 (-0.46 to -0.13)	3.53
ML Overall I^2 = 0%	-0.29 (-0.37 to -0.21)	23.04



Study-level data and pooled effects across 36 comparisons. A, Studies that did not explicitly recruit patients with chronic physical conditions. B, Studies that explicitly recruited patients with chronic physical conditions; mixed-effects model used. Weights are from random-effects analysis. ML indicates maximum likelihood.

tions. The interaction effect was not significantly affected by the allocation concealment rating (interaction coefficient, −0.00 [95% CI, −0.03 to 0.03]) or by the measure used to assess physical conditions (interaction coefficient, −0.01 [95% CI, −0.04 to 0.02]).

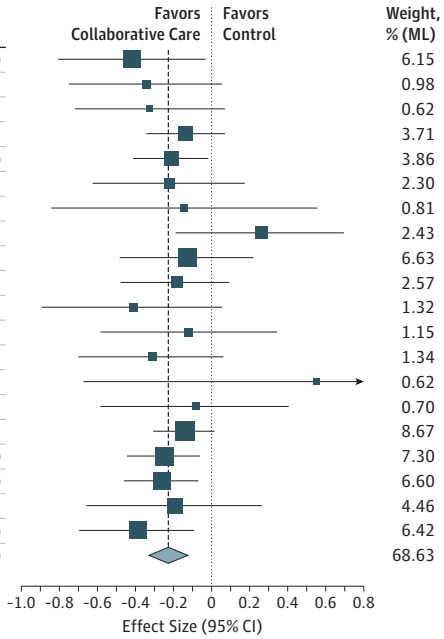
Association Between Types of Chronic Physical Conditions and the Effectiveness of Collaborative Care on Depression Scores

We found no evidence that the effects of collaborative care on depression outcomes are moderated by the types of physical conditions among participants. None of the interaction effects between treatment effect and types of physical conditions were significant: cancer (interaction coefficient, −0.11 [95% CI, −0.02 to 0.22]), cardiac disease (interaction coefficient, −0.02 [95% CI, −0.14 to 0.09]), diabetes (interaction coefficient, −0.02 [95% CI, −0.08 to 0.09]), hypertension (interaction coefficient, −0.09 [95% CI, −0.21 to 0.03]), and respiratory disease (interaction coefficient, −0.08 [95% CI, −0.21 to 0.07]). These findings suggest that the benefits derived by collaborative care do not differ significantly across subgroups of people with certain types of physical conditions. None of the interaction effects were

Figure 3. Individual Participant-Level Analysis Examining the Effect of the Presence of Chronic Physical Conditions on the Effectiveness of Collaborative Care

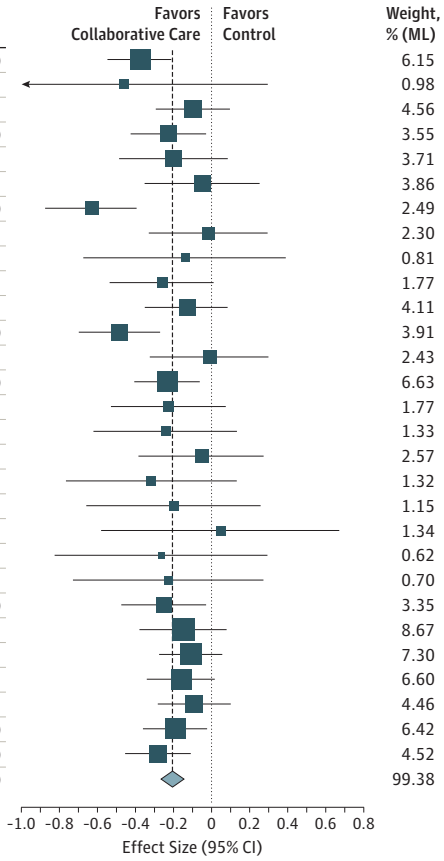
A Participants did not have chronic physical conditions

Source	Effect Size (95% CI)	Weight, % (ML)
Bruce et al,[19] 2004	-0.42 (-0.80 to -0.03)	6.15
Katon et al,[56] 1995	-0.34 (-0.74 to 0.06)	0.98
Katon et al,[57] 1996	-0.32 (-0.71 to 0.07)	0.62
Simon et al,[60] 2000	-0.14 (-0.34 to 0.07)	3.71
Simon et al,[60] 2000	-0.21 (-0.41 to -0.01)	3.86
Melville et al,[63] 2014	-0.22 (-0.62 to 0.17)	2.30
Cole et al,[24] 2006	-0.14 (-0.84 to 0.55)	0.81
Ell et al,[21] 2007	0.26 (-0.18 to 0.69)	2.43
Gensichen et al,[65] 2009	-0.13 (-0.48 to 0.22)	6.63
Menchetti et al,[66] 2013	-0.19 (-0.47 to 0.10)	2.57
Huijbregts et al,[67] 2013	-0.41 (-0.89 to 0.06)	1.32
Vlasveld et al,[68] 2012	-0.12 (-0.59 to 0.35)	1.15
Smit et al,[69] 2006	-0.31 (-0.69 to 0.07)	1.34
Smit et al,[69] 2006	0.55 (-0.66 to 1.75)	0.62
Smit et al,[69] 2006	-0.09 (-0.58 to 0.40)	0.70
Patel et al,[70] 2010	-0.14 (-0.30 to 0.02)	8.67
Wells et al,[71] 2000	-0.25 (-0.44 to -0.06)	7.30
Wells et al,[71] 2000	-0.26 (-0.45 to -0.07)	6.60
Adler et al,[72] 2004	-0.19 (-0.65 to 0.27)	4.46
Richards et al,[74] 2013	-0.39 (-0.69 to -0.09)	6.42
REML Overall I^2 = 0.9%	-0.23 (-0.33 to -0.12)	68.63



B Participants had a chronic physical condition

Source	Effect Size (95% CI)	Weight, % (ML)
Bruce et al,[19] 2004	-0.38 (-0.55 to -0.21)	6.15
Katon et al,[56] 1995	-0.47 (-1.23 to 0.29)	0.98
Katon et al,[59] 2001	-0.10 (-0.29 to 0.10)	4.56
Katon et al,[75] 2004	-0.23 (-0.43 to -0.03)	3.55
Simon et al,[60] 2000	-0.20 (-0.49 to 0.08)	3.71
Simon et al,[60] 2000	-0.05 (-0.35 to 0.25)	3.86
Katon et al,[76] 2010	-0.64 (-0.88 to -0.40)	2.49
Melville et al,[63] 2014	-0.02 (-0.33 to 0.29)	2.30
Cole et al,[24] 2006	-0.14 (-0.68 to 0.39)	0.81
Davidson et al,[77] 2013	-0.26 (-0.54 to 0.01)	1.77
Ell et al,[78] 2008	-0.13 (-0.35 to 0.08)	4.11
Ell et al,[79] 2010	-0.49 (-0.70 to -0.27)	3.91
Ell et al,[21] 2007	-0.01 (-0.33 to 0.30)	2.43
Gensichen et al,[65] 2009	-0.23 (-0.41 to -0.06)	6.63
Huffman et al,[80] 2011	-0.23 (-0.53 to 0.07)	1.77
Huffman et al,[81] 2014	-0.24 (-0.62 to 0.13)	1.33
Menchetti et al,[66] 2013	-0.06 (-0.39 to 0.28)	2.57
Huijbregts et al,[67] 2013	-0.32 (-0.77 to 0.13)	1.32
Vlasveld et al,[68] 2012	-0.20 (-0.67 to 0.26)	1.15
Smit et al,[69] 2006	0.05 (-0.59 to 0.68)	1.34
Smit et al,[69] 2006	-0.27 (-0.83 to 0.29)	0.62
Smit et al,[69] 2006	-0.23 (-0.73 to 0.28)	0.70
Rollman et al,[82] 2009	-0.25 (-0.48 to -0.03)	3.35
Patel et al,[70] 2010	-0.15 (-0.38 to 0.08)	8.67
Wells et al,[71] 2000	-0.11 (-0.28 to 0.06)	7.30
Wells et al,[71] 2000	-0.16 (-0.34 to 0.01)	6.60
Adler et al,[72] 2004	-0.09 (-0.28 to 0.10)	4.46
Richards et al,[74] 2013	-0.19 (-0.37 to -0.02)	6.42
Coventry et al,[12] 2014	-0.28 (-0.45 to -0.11)	4.52
REML Overall I^2 = 0.9%	-0.21 (-0.27 to -0.15)	99.38

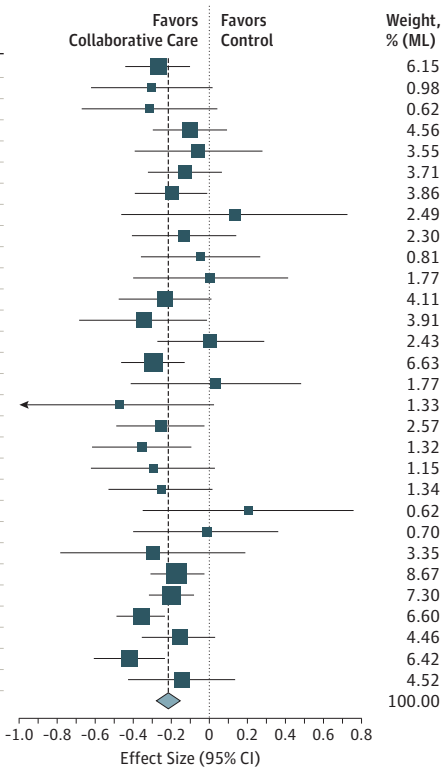


Individual participant data and pooled effects across 30 comparisons. A, Studies in which participants did not have a chronic physical condition. B, Studies in which participants had a chronic physical condition. Mixed-effects model used. Weights are from random-effects analysis. REML indicates restricted maximum likelihood.

Figure 4. Individual Participant–Level Analysis Examining the Effect of the Number of Chronic Physical Conditions on the Effectiveness of Collaborative Care

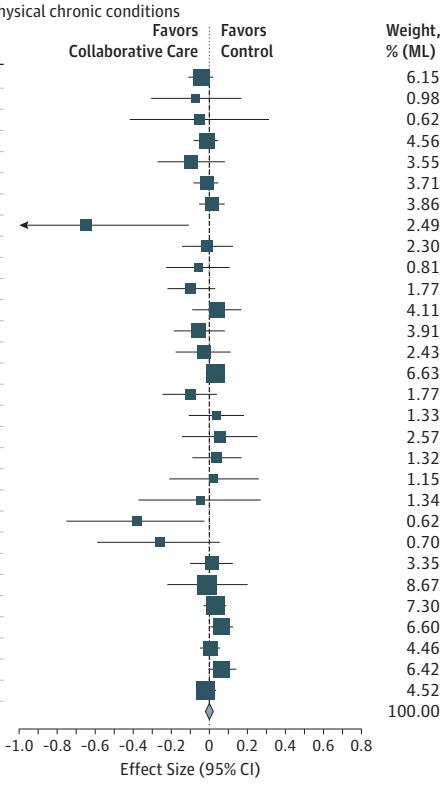
A Main effect of the individual participant data analysis

Source	Effect Size (95% CI)	Weight, % (ML)
Bruce et al,[19] 2004	-0.28 (-0.47 to -0.10)	6.15
Katon et al,[56] 1995	-0.37 (-0.72 to -0.02)	0.98
Katon et al,[57] 1996	-0.28 (-0.71 to 0.15)	0.62
Katon et al,[59] 2001	-0.05 (-0.25 to 0.15)	4.56
Katon et al,[75] 2004	-0.04 (-0.39 to 0.32)	3.55
Simon et al,[60] 2000	-0.12 (-0.28 to 0.05)	3.71
Simon et al,[60] 2000	-0.17 (-0.33 to -0.01)	3.86
Katon et al,[76] 2010	0.06 (-0.54 to 0.66)	2.49
Melville et al,[63] 2014	-0.10 (-0.40 to 0.21)	2.30
Cole et al,[24] 2006	-0.16 (-0.65 to 0.33)	0.81
Davidson et al,[77] 2013	-0.03 (-0.45 to 0.39)	1.77
Ell et al,[78] 2008	-0.26 (-0.56 to 0.05)	4.11
Ell et al,[79] 2010	-0.44 (-0.85 to -0.04)	3.91
Ell et al,[21] 2007	0.13 (-0.20 to 0.47)	2.43
Gensichen et al,[65] 2009	-0.35 (-0.55 to -0.15)	6.63
Huffman et al,[80] 2011	0.14 (-0.35 to 0.63)	1.77
Huffman et al,[81] 2014	-0.48 (-1.06 to 0.11)	1.33
Menchetti et al,[66] 2013	-0.22 (-0.46 to 0.02)	2.57
Huijbregts et al,[67] 2013	-0.44 (-0.79 to -0.09)	1.32
Vlasveld et al,[68] 2012	-0.18 (-0.58 to 0.21)	1.15
Smit et al,[69] 2006	-0.25 (-0.56 to 0.06)	1.34
Smit et al,[69] 2006	0.13 (-0.51 to 0.76)	0.62
Smit et al,[69] 2006	0.14 (-0.26 to 0.55)	0.70
Rollman et al,[82] 2009	-0.35 (-0.88 to 0.19)	3.35
Patel et al,[70] 2010	-0.19 (-0.34 to -0.03)	8.67
Wells et al,[71] 2000	-0.16 (-0.28 to -0.03)	7.30
Wells et al,[71] 2000	-0.35 (-0.48 to -0.21)	6.60
Adler et al,[72] 2004	-0.17 (-0.39 to 0.06)	4.46
Richards et al,[74] 2013	-0.40 (-0.60 to -0.21)	6.42
Coventry et al,[12] 2014	-0.10 (-0.40 to 0.20)	4.52
REML Overall I^2 = 0.8%	-0.22 (-0.29 to -0.15)	100.00



B Interaction effect of the study group and the number of physical chronic conditions

Source	Effect Size (95% CI)	Weight, % (ML)
Bruce et al,[19] 2004	-0.04 (-0.11 to 0.03)	6.15
Katon et al,[56] 1995	-0.03 (-0.28 to 0.23)	0.98
Katon et al,[57] 1996	-0.09 (-0.53 to 0.36)	0.62
Katon et al,[59] 2001	-0.01 (-0.08 to 0.06)	4.56
Katon et al,[75] 2004	-0.10 (-0.28 to 0.09)	3.55
Simon et al,[60] 2000	-0.02 (-0.10 to 0.05)	3.71
Simon et al,[60] 2000	0.03 (-0.05 to 0.11)	3.86
Katon et al,[76] 2010	-0.57 (-1.11 to -0.04)	2.49
Melville et al,[63] 2014	0.00 (-0.14 to 0.14)	2.30
Cole et al,[24] 2006	-0.01 (-0.29 to 0.27)	0.81
Davidson et al,[77] 2013	-0.07 (-0.20 to 0.05)	1.77
Ell et al,[78] 2008	0.05 (-0.11 to 0.20)	4.11
Ell et al,[79] 2010	-0.03 (-0.20 to 0.13)	3.91
Ell et al,[21] 2007	-0.05 (-0.24 to 0.13)	2.43
Gensichen et al,[65] 2009	0.04 (-0.02 to 0.10)	6.63
Huffman et al,[80] 2011	-0.13 (-0.29 to 0.03)	1.77
Huffman et al,[81] 2014	0.07 (-0.11 to 0.25)	1.33
Menchetti et al,[66] 2013	0.07 (-0.13 to 0.28)	2.57
Huijbregts et al,[67] 2013	0.11 (-0.06 to 0.28)	1.32
Vlasveld et al,[68] 2012	0.00 (-0.28 to 0.28)	1.15
Smit et al,[69] 2006	0.06 (-0.30 to 0.42)	1.34
Smit et al,[69] 2006	-0.37 (-0.80 to 0.06)	0.62
Smit et al,[69] 2006	-0.26 (-0.57 to 0.05)	0.70
Rollman et al,[82] 2009	0.02 (-0.10 to 0.14)	3.35
Patel et al,[70] 2010	0.00 (-0.22 to 0.23)	8.67
Wells et al,[71] 2000	0.02 (-0.04 to 0.08)	7.30
Wells et al,[71] 2000	0.08 (0.02 to 0.14)	6.60
Adler et al,[72] 2004	0.02 (-0.04 to 0.07)	4.46
Richards et al,[74] 2013	0.07 (0.00 to 0.15)	6.42
Coventry et al,[12] 2014	-0.02 (-0.06 to 0.02)	4.52
REML Overall I^2 = 0.8%	0.00 (-0.01 to 0.02)	100.00



Individual participant data and pooled effects across 30 comparisons. A, Main effect of the individual participant data analysis. B, Interaction effect of the study group and the number of physical chronic conditions. Mixed-effects model used. Weights are from random-effects analysis. REML indicates restricted maximum likelihood.

affected by allocation concealment or by the measure used to assess physical conditions.

Discussion

Analyzing data from 36 comparisons of collaborative care and 10 962 participants, this IPD meta-analysis showed that collaborative care is associated with significant short-term improvements in depression outcomes across all people with or without comorbid physical conditions. At study level, trials that recruited only participants with comorbid physical conditions were associated with larger treatment effects compared with trials that did not include those with comorbid conditions, confirming previous findings.[12,15] However, when a more accurate analysis at the individual participant level was undertaken, the presence, number, and type of physical conditions did not moderate the main effect of collaborative care on depression outcomes. Overall, the findings of this IPD meta-analysis do not support existing recommendations based on meta-analyses of aggregate data that collaborative care should be considered only for patients with comorbid depression and physical conditions. Our findings highlight the importance of undertaking IPD analyses in developing rigorous recommendations, especially for subgroups of complex patients.

Strengths and Limitations

To our knowledge, this study is the most methodologically rigorous test of the influence of physical conditions on the effects of collaborative care on depression outcomes.[26,83] However, there are several limitations. Individual participant data meta-analysis remains vulnerable to important sources of bias, including publication, study or reviewer selection, and data availability bias.[51] No funnel plot asymmetry was detected, suggesting that publication bias is not likely to be present in the overall data set. Study selection bias was minimized by including studies through multiple sources (ie, an existing standard Cochrane review,[10] top-up database searches, and author requests) using strict prespecification of trial eligibility criteria. These efforts facilitated access to data from approximately half of the participants included in published RCTs of collaborative care for depression, which is below the recommended recruitment target (80% of data requested).[51] We observed some differences between available and unavailable studies, but these differences rarely reached statistical significance. For example, the overall effect size was smaller than that found in the previous Cochrane review.[10] This difference is likely to be explained by the fact that less than half of all collaborative care trials were included in this IPD analysis, and these trials were generally larger than those that were not included. It is important to continue to develop effective methods and agreements about data sharing to ensure that future analyses have better access to data.

Another limitation of the study is that the evaluation of physical conditions was not pursued in an entirely consistent manner across trials. Most of the trials assessed the number of physical conditions using validated comorbidity indexes that contain extensive lists of physical conditions, but some trials used less-comprehensive lists of physical conditions that were empirically devised.[37] Although we separately examined the influence of 5 common physical conditions, participants could have more than 1 of these conditions. The experience and interactions of multiple concordant or discordant conditions[84] is another possible factor to recognize why people might respond differently to depression treatment.

The use of multiple mixed-effects regression analyses of IPD and controlling for covariates significantly reduces the possibility of bias present in aggregate data meta-analyses (eg, ecologic fallacy or Simpson paradox).[26,83,85-87] However, we recommend interpreting these findings cautiously since some of these biases might still operate.

Finally, there were important between-study variations, including intervention content (collaborative care is generally heterogeneous)[10] and depression measures. However, these study-level variations are unlikely to influence the participant-level analyses that showed that chronic physical conditions do not moderate the effectiveness of collaborative care. A post hoc sensitivity analysis indicated that the results were similar regardless of using self-reported or observer-rated measures for depression.

Comparison With Previous Systematic Reviews

Previous systematic reviews[12,16] have examined moderators of the effect of collaborative care on depression outcomes but were based on aggregate data and used meta-regressions. Improved depressive outcomes were predicted by the inclusion of psychological interventions, and the use of antidepressant medication was predicted by recruiting people with physical conditions.[12] Based on these findings, it was proposed[12] that patients with physical conditions may derive greater benefits from collaborative care compared with patients without physical conditions. As noted above, these analyses are a less-robust basis for decision making because they are insensitive to variation in physical conditions at the level of individual patients. In this IPD meta-analysis, we found no support for this hypothesis.

Implications for Clinicians, Policymakers, and Researchers

This study suggests that depressed patients with and without comorbid physical conditions gain important improvements in depression outcomes from collaborative care. As such, our findings do not support the recommendation by the National Institute for Health and Care Excellence that collaborative care should be considered only for people with depression and comorbid physical conditions with functional impairment.[15] Limiting collaborative care to people with depression and comorbid physical conditions does not appear to be a reasonable policy recommendation with important implications for patient benefit. Individual participant data meta-analyses are underused in the development of clinical guidelines, and the next iteration of guidelines for depression could be improved by using the most-reliable evidence available.[88]

Given that the effectiveness of collaborative care is confirmed, future research should focus on understanding how to optimize the delivery and outcomes of collaborative care. For instance, based on recent published evidence,[89] the systematic measurement and management of physical health outcomes along with mental health outcomes has the potential to boost the effectiveness of collaborative care in people with physical comorbidities. However, the overall treatment benefits associated with collaborative care are modest.[10] It is therefore legitimate to suggest that future treatment policy guidelines should also be grounded on the comparative cost-effectiveness of collaborative care to other types of interventions.

Conclusions

To our knowledge, this IPD meta-analysis represents the most rigorous and precise analysis to date on the extent to which physical conditions influence the effectiveness of collaborative care on depression outcomes. People with depression derive significant benefits from collaborative care regardless of the presence, number, or type of comorbid physical conditions. The core challenge now is to understand how to deliver these interventions at scale in routine settings and to better operationalize the treatment outcomes to maximize patient benefits.

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Acquisition, analysis, or interpretation of data: Panagioti, Bower, Kontopantelis, Lovell, Dickens, Simon, Huffman, Richards, van der Feltz-Cornelis, Adler, Bruce, Buszewicz, Cole, Davidson, de Jonge, Gensichen, Menchetti, Patel, Rollman, Shaffer, Coventry.
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