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

Maria Panagioti, PhD, NIHR School for Primary Care Research, Centre for Primary Care, Institute of Population Health, University of Manchester, M13 9PL, UK

Peter Bower, PhD, NIHR School for Primary Care Research, Centre for Primary Care, Institute of Population Health, University of Manchester, M13 9PL, UK

Evangelos Kontopantelis, PhD, NIHR School for Primary Care Research, Centre for Primary Care, Institute of Population Health, University of Manchester, M13 9PL, UK

Karina Lovell, PhD, School of Nursing, Midwifery & Social Work, University of Manchester, M13 9PL, UK

Simon Gilbody, DPhil, Mental Health and Addiction Research Group, Department of Health Sciences and Hull York Medical School, University of York, YO10 5DD, UK

Waquas Waheed, MD, NIHR School for Primary Care Research, Centre for Primary Care, Institute of Population Health, University of Manchester, M13 9PL, UK
Chris Dickens, PhD, Institute of Health Service Research and NIHR Collaboration for Leadership in Applied Health Research and Care for the South West Peninsula, University of Exeter, EX2 4SG, UK

Janine Archer, PhD, School of Nursing, Midwifery & Social Work, University of Manchester, M13 9PL, UK

Gregory Simon, MD, Group Health Research Institute, Seattle, 1730 Minor Ave, WA 98101, US

Kathleen Ell, PhD, Ethnicity, and Poverty, School of Social Work, MRF 214 (MC 0411), University of Southern California, Los Angeles, CA 90089-0411, USA

Jeff C. Huffman, MD, Harvard Medical School, General Hospital/Blake 11, 55 Fruit St, MA 02114 Boston, Massachusetts, USA

David A Richards, PhD, Institute of Health Research, University of Exeter Medical School, Exeter EX1 2LU, UK

Christina van der Feltz-Cornelis, MD, Department of Psychiatry and Behavioral Sciences, Faculty of Social and Behavioral Sciences, Box 356560, Tilburg University, The Netherlands
David A Adler, MD, Department of Psychiatry, Tufts Medical Center, 800 Washington Street, #345, Boston, MA 02111, USA

Martha Bruce, PhD, Department of Psychiatry, Weill Cornell Medical College, 21 Bloomingdale Rd, White Plains, NY 10605, USA

Marta Buszewicz, MD, Institute of Epidemiology & Health, Faculty of Population and Health Sciences, University College London, UK Royal Free Campus, Upper 3rd Floor, Rowland Hill Street, London, NW3 2PF

Martin G. Cole, MD, Department of Psychiatry, St. Mary’s Hospital Center, 3830 Avenue Lacombe, McGill University, Montreal, Quebec H3T 1M5, Canada

Karina W. Davidson, PhD, Center for Behavioral Cardiovascular Health, Department of Medicine, Columbia University, PH9West, New York, NY 10032, USA

Peter de Jonge, PhD, Interdisciplinary Center Psychopathology and Emotion regulation (ICPE), University Medical Center Groningen, CC72, Netherlands

Jochen Gensichen, MD, Institute of Psychosocial Medicine and Psychotherapy, University Hospital, Jena, Institute of General Practice & Family Medicine, Bachstraße 18, 07743 Jena, Germany
*Correspondence to*

Postal Address: Mental Health and Addiction Research Group, Department of Health Sciences, University of York, YO10 5DD, UK

e: peter.coventry@york.ac.uk

t: +44 (0) 1904 321528

This manuscript has not been presented at any academic meeting.

**Author Contributions**

The original idea for the research was developed by PC, PB, and EK. The database of individual patient data was developed by MP, and the analysis conducted by MP with input from EK, PC and PB. MP, PC conducted quality assessments and other data extraction. GES, KE, JCF, DAR, CFC, DAA, MC, MB, MGC, KWD, PDJ, JG, KH, MM, VP, BR, JS and MCV all supplied data and assisted with queries. MP, PC, PB and EK wrote the paper. All authors interpreted the findings and contributed to critical revision of the manuscript. PC is the guarantor. PC affirms that the manuscript is an honest, accurate, and transparent account of the research findings and no important aspects of the study have been omitted.

**Conflict of interests**

PB is a paid consultant to the British Association of Counselling and Psychotherapy, The author have been/are involved in the conduct of trials of collaborative care in the UK funded by the Medical Research Council and the National Institute for Health Res
All authors declare no conflict of interest

Word count (not including abstract, tables, acknowledgment, or references):

3,498
Abstract

IMPORTANCE: Collaborative care is an intensive care model involving a number of healthcare professionals working together, typically a medical doctor, 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: Medline, Embase, Pubmed, PsycINFO, Cinahl, and Central, and references from relevant systematic reviews.

STUDY SELECTION: Randomized controlled trials that compared the effectiveness of collaborative care with usual care in adults with depression. Measured change in depression severity symptoms at 4 to 6 months post-randomization.

DATA EXTRACTION AND SYNTHESIS: Individual participant data on baseline demographics and chronic physical conditions and 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 MEASURE: Continuous outcomes of depression severity symptoms measured using self-reported or observer-rated measures.
RESULTS: Datasets from 31 randomized controlled trials including 36 independent comparisons (n= 10,962 participants) were analyzed. At study-level, trials which explicitly identified participants with chronic physical conditions produced larger treatment effects compared with trials which did not explicitly identify participants with chronic physical conditions (interaction coefficient -0.12, 95% CI= -0.23 to -0.02). When individual participant data analyses, which are more powerful, were performed, no significant interaction effects were found 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.

CONCLUSION: There is compelling 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.
Background

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

A promising intervention for depression in primary care is ‘collaborative care’,\textsuperscript{9} which involves the use of a case manager (usually non-medical but also medical e.g. clinical social workers) working with primary care professionals, often supervised by a mental health specialist and supported by care management systems. A Cochrane review showed that collaborative care is more effective than usual care for depression.\textsuperscript{10}

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.\textsuperscript{11,12} In the United States the Community Preventive Services Task Force 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.\textsuperscript{13,14} In the UK, the English organization responsible for clinical guidelines (National Institute for Health and Care Excellence - NICE) 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 two sets of trials – collaborative care for patients with depression, and collaborative care for patients with depression and physical conditions.\textsuperscript{15} Although these recommendations were based on the best available evidence at the time, conducting two separate meta-analyses means that any differences in effectiveness may be confounded by differences between the trials (e.g. location, quality, intervention format) and may not be due physical conditions.\textsuperscript{16} Additionally, some collaborative care trials that recruited people with depression would not necessarily have excluded those with physical conditions, especially trials conducted in older populations where such conditions are highly prevalent.\textsuperscript{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 modelling treatment effects than aggregate data meta-analyses.\textsuperscript{26} IPD meta-analysis is more precise because it involves the application of standardized analyses across multiple datasets, overcomes sample size and reporting issues, and allows more sophisticated modelling of moderator effects.\textsuperscript{26-28} In this context, IPD allows for more accurate coding of comorbidity based on actual patient health.

In this 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 which recruited participants with physical conditions as part of inclusion criteria demonstrated greater effect of collaborative care on depression outcomes (i.e. 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 (i.e. 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

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

We used the published Cochrane review10 of collaborative care to identify eligible randomized controlled trials (RCTs). The Cochrane review searches were updated in March 2014 (MEDLINE, EMBASE, PsycINFO, CENTRAL and CINAHL) but search and collection of eligible studies was ongoing until May 2015. The reference lists of reports of all included studies were screened for reports of additional studies. We also asked authors of studies identified from the published reviews to identify additional published studies and other trials in progress.

Eligibility criteria
We used the same inclusion criteria reported by the Cochrane review, except we excluded studies conducted in adolescents and studies that did not report a depression outcome (see study protocol in eMethods 1):

1) Population: Adults ≥18 years with depression or mixed anxiety and depressive disorder

2) Intervention: Collaborative care interventions: i. a multi-professional approach to patient care; ii. a structured management plan; iii. scheduled patient follow-ups; and iv. enhanced inter-professional communication

3) Comparison: Usual or enhanced usual care

4) Outcome: Continuous depression scores

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\(^\text{33}\) the Center for Epidemiologic Studies Depression Scale,\(^\text{34}\) the Hamilton Rating Scale for Depression\(^\text{35}\) and the Patient Health Questionnaire.\(^\text{36}\) We focused on short-term depression outcomes reported between 4 and 6 months post-randomization. Depression scores were standardized within each study, using the baseline standard deviation and the follow-up mean score.

At study-level, nine of the 36 comparisons recruited participants with a physical condition. 30 of the 36 comparisons reported data on the presence and number of...
physical conditions at individual participant-level. Of these, the majority of the
comparisons (n=21) used validated comorbidity indices such as the Charlson Index\(^{37}\)
while six used empirical lists of physical conditions. 17 comparisons identified the type of
physical conditions among participants. Based on these data, we were able to create five
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 datasets for the following data:
treatment group, age, gender, baseline and follow-up depression scores and number and
types of physical conditions (see eTable 2). 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 by the original study. We also extracted data from
the published reports of all the eligible studies using a standardized Excel data extraction
form. We extracted data on populations, interventions, chronic conditions (used as
moderator in the analyses), risk of bias, and outcome effect sizes. We compared studies
which made data available to us with studies with unavailable data in terms of outcome
effect sizes and moderator analyses.

Missing data
We used multiple imputation techniques to obtain more complete datasets 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 14) using Markov Chain Monte Carlo. This process produces several datasets, each of which is analyzed separately using the pre-specified model; the results are then combined together using Rubin’s rules which accounts for uncertainty in imputed values. 1000 new datasets with the observed and the imputed scores for age and depression at follow-up were generated based on values 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. 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 differences were detected in any of the reported results.

**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 modelling of covariates (age, sex and baseline depression scores in this study). A one step IPD meta-analysis constructs a model for the hypothesized treatment-covariate relationships across all
individual participant datasets whilst statistically accounting for clustering at the level of each included dataset.\textsuperscript{45,46}

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 and within-study variances and the effects of covariates.\textsuperscript{47} Clustered RCTs were statistically accounted for in the model by adhering to Sutton et al’s\textsuperscript{48} methodological recommendations. The \textit{Stata v14} command \textit{mixed} was used through the \textit{ipdforest} command, to summarize the evidence by study and obtain forest plots.\textsuperscript{49,50} A one-stage meta-analysis variant of the $I^2$ statistic was used to assess heterogeneity.\textsuperscript{51} We examined the impact of covariates separately, building a model based on both statistical and theoretical criteria. Where 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, funnel plots were constructed to assess the potential for publication bias.\textsuperscript{52}

A number of pre-specified 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; 0=absent), number (continuous variable), and types of physical conditions (binary variables for each condition; present=1; 0=absent).
We conducted two secondary analyses to examine the robustness of the results. We 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. 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 (n=22,284) RCTs 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's regression test intercept = -0.54, SE= 0.42, P=0.21, eFigure 1). We collected data from 32 (n=11531; 52% of total number of participants) trials that included 37 comparisons (see reference list in eResults 1). One RCT (a pilot study based on 49 participants) was excluded from the analyses because it did not include data on age and gender, leaving a total of 36 comparisons. 569 (5%) individual cases were excluded from the analyses because of missing baseline values on depression or age leaving 10,962 unique cases (of which n=1819; 16% were imputed using multiple imputations).

**Baseline characteristics and comparisons between available and unavailable data**
18 studies were conducted in the US, 11 were conducted in Europe, 1 in Canada and 1 in India. The majority of the participants were women (77%) with a mean age of 51 (SD=15; range 17-97). Over three quarters of participants (78%) had at least one physical condition with a mean of 2.5 conditions (SD=2.3). No important issues were identified while checking the IPD data (see details about the characteristics of the studies in eTable 3 and 4).

Available and non-available 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 two previous reviews which applied meta-regression analyses to identify moderators of the main effect of collaborative care interventions. As shown in Table 1, none of the differences identified were statistically significant except for the intervention content - a larger proportion of trials which incorporated psychological interventions made data available.

**What are the effects of collaborative care on depressive symptoms at 4-6 months follow-up?**

Collaborative care is associated with a small but significant effect on depression outcomes compared with usual care (SMD =-0.22, 95% CI -0.25 to −0.18; I²=0.8%, 0.3% to 3.5%; see eFigure 2) equal to a drop of around 2-points on PHQ9 over and above the change in the controls. This effect size is smaller but not significantly different from the Cochrane review (-0.28, 95% CI -0.31 to -0.25; p=0.227 in Table 1).
Is the effect of collaborative care on depression scores different in RCTs in which participants with physical conditions were part of the inclusion criteria?

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). RCTs 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).

Is the effect of collaborative care on depression moderated by the presence of physical conditions in patients?

When we compared the effects of collaborative care in participants with and without physical conditions, the interaction term with the treatment effect was non-significant (interaction coefficient = 0.02, 95% CI = -0.10 to 0.13; Figure 3). 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 SMD = -0.23, 95% CI -0.32 to -0.12).
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).

Is the effect of collaborative care on depression scores moderated by the number of physical conditions?

The interaction term between number of physical conditions and treatment effect was non-significant (interaction coefficient = 0.01, 95% CI = -0.01 to 0.02; Figure 4). This finding suggests that the improvement of depression scores at follow-up does not differ according to numbers of physical conditions.

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).

Is the effect of collaborative care on depressive symptoms moderated by different types of physical conditions in patients?

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

**Discussion**

Analyzing data from 36 comparisons of collaborative care and nearly 11,000 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 which only recruited participants with comorbid physical conditions were associated with larger treatment effects compared with trials which did not, confirming previous findings. However, when a more accurate analysis at 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 only be considered 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**
This study is the most methodologically rigorous test of the influence of physical conditions on the effects of collaborative care on depression outcomes.\textsuperscript{26,57} However, there are a number of limitations. IPD meta-analysis remains vulnerable to important sources of bias including publication, study/reviewer selection and data availability bias.\textsuperscript{52} No funnel plot asymmetry was detected suggesting that publication bias is not likely to be present in the overall dataset. Study selection bias was minimized by including studies through multiple sources (i.e. an existing gold standard Cochrane review, top-up database searches, and author requests) using strict pre-specification of trial eligibility criteria. These efforts facilitated access to data from approximately half of participants included in published RCTs of collaborative care for depression, which is below the recommended recruitment target (80\% of data requested).\textsuperscript{52} We observed some differences between available and non-available studies, but these differences rarely reached statistical significance. For example, the overall effect size was smaller than that found in the previous Cochrane review. 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 were generally larger than trials 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 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 indices which contain extensive lists of physical conditions, but some trials used less comprehensive lists of physical conditions.
which were empirically devised.\textsuperscript{37} Although we separately examined the influence of 5 common physical conditions, participants could have more than one of these conditions. The experience and interactions of multiple concordant or discordant conditions\textsuperscript{58} is another factor that might differentiate why people might respond differently to depression treatment.

The use of multiple mixed-effects regression analyses of individual patient data and controlling for covariates significantly reduces the possibility of bias present in aggregate data meta-analyses (e.g. ecological fallacy or Simpson paradox).\textsuperscript{26,57,59-61} However, we recommend interpreting these findings cautiously as some of these biases might still operate.

Finally, there were important between-study variations including intervention content (collaborative care is generally heterogeneous)\textsuperscript{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 irrespective of using self-reported or observer-rated measures for depression.

**Comparison of this study with previous systematic reviews**

Previous systematic reviews have examined moderators of the effect of collaborative care on depression outcomes but were based on aggregate data and used meta-regressions.\textsuperscript{12,16} Improved depressive outcomes were predicted by inclusion of
psychological interventions and the use of antidepressant medication was predicted by recruiting people with physical conditions in trials. Based on these findings it was proposed that patients with physical conditions may derive greater benefits from collaborative care compared with patients without physical conditions. As noted earlier, 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. Indeed, in this IPD meta-analysis, we found no support for this hypothesis.

**Implications for clinicians, policymakers and researchers**

This study suggests that 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 NICE that collaborative care should only be considered for people with depression and comorbid physical conditions with functional impairment. 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. IPD meta-analyses are under-used in clinical guidelines and the next iteration of guidelines for depression could be improved by using the most reliable evidence available.

Given that the effectiveness of collaborative care is confirmed, future research should focus on understanding how to optimize the delivery and the outcomes of collaborative care. For instance, based on recent evidence, 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. On the other hand, the overall treatment benefits associated with collaborative care are modest. 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.

**Conclusion**

This IPD meta-analysis represents the most rigorous and precise analysis to date about 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.

**Acknowledgments**

This study was funded by the UK National Institute of Health Research (NIHR) School for Primary Care Research. The research team members were independent from the funding agency. The views expressed in this publication are those of the authors and not necessarily those of the National Health Service, the NIHR, or the Department of Health. The funders had no role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; and the preparation, review, or approval of the manuscript.
Dr Peter Coventry had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

We would like to acknowledge the important contribution of Professor Wayne Katon (passed away in March 2015 before approving this manuscript), who provided us access to six datasets of collaborative care trials. We also thank Professor Harm van Marwijk and Dr. Penny Bee for commenting on drafts of this manuscript.
References

diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the

attributable to mental and substance use disorders: findings from the Global

3. Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V, Ustun B. Depression,
chronic diseases, and decrements in health: results from the World Health

4. Freedland KE, Carney RM. Depression as a risk factor for adverse outcomes in


in Primary Care: A Systematic Review and Meta-Analysis. PloS One.
2015;10(8):e0135947.

urgent and unscheduled care by people with long term conditions? A systematic

conditions and mental health. The cost of co-morbidities. London: King’s Fund and
Centre for Mental Health;2012.


15. NICE. Depression in Adults with a Chronic Physical Health Problem: Treatment and Management. Leicester: British Psychological Society; 2010.


detection and multidisciplinary care of depression in older medical inpatients: a

test the feasibility of a collaborative care model for the management of

Statistical analysis of individual participant data meta-analyses: a comparison of

27. Clarke MJ, Stewart LA. Obtaining data from randomised controlled trials: how
much do we need for reliable and informative meta-analyses? *BMJ.*

28. Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data:
rationale, conduct, and reporting. *BMJ.* 2010;340:c221.

effects of depression and multimorbidity on the effectiveness of a chronic disease

30. Fried TR, O'Leary J, Towle V, Goldstein MK, Trentelange M, Martin DK. The
effects of comorbidity on the benefits and harms of treatment for chronic

Review and Meta-Analyses of individual participant data: the PRISMA-IPD


43. Stewart LA, Parmar MK. Meta-analysis of the literature or of individual patient data: is there a difference? Lancet. 1993;341(8842):418-422.


Figure 1: PRISMA flowchart

Figure legend: Flowchart of the inclusion of studies in the review

Figure 2: Study-level analysis examining the effect of the presence chronic physical conditions on the effectiveness of collaborative care

Figure legend: Meta-analysis forest plot of study-level data and pooled effects across 36 comparisons. 2a: Studies which did not explicitly recruit patients with chronic physical conditions. 2b: Studies which explicitly recruited patients with chronic physical conditions (2b) Mixed effects model used. 95% CI = 95% confidence intervals

Figure 3: Individual participant-level analysis examining the effect of the presence of chronic physical conditions on the effectiveness of collaborative care.

Figure legend: Meta-analysis forest plot of individual participant data and pooled effects across 30 comparisons. 3a: Studies in which participants did not have a chronic physical condition. 3b: Studies in which participants had a chronic physical condition. Mixed effects model used. 95% CI = 95% confidence intervals

Figure 4: Individual participant-level analysis examining the effect of the number of chronic physical conditions on the effectiveness of collaborative care

Figure legend: Meta-analysis forest plot of individual participant data and pooled effects across 30 comparisons. 4a: Main effect of the individual participant data analysis. 4b: Interaction effect of the study group and the number of physical chronic conditions. Mixed effects model used. 95% CI = 95% confidence intervals
Table 1. Comparison of studies providing data for the IPD analyses and those not providing data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unavailable (n=49)</th>
<th>Available (36)</th>
<th>Statistical test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country (US)</td>
<td>36 (78)</td>
<td>23 (62)</td>
<td>$\chi^2 (1, 85) = 3.17, P=0.08$</td>
</tr>
<tr>
<td>Publication date</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>2006 (4.03)</td>
<td>2007 (5.29)</td>
<td>$t(83)=1.01, P=0.32$</td>
</tr>
<tr>
<td>Recruitment method</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systematic n (%)</td>
<td>41 (84)</td>
<td>31 (84)</td>
<td>$\chi^2 (1, 85) = 0.01, P=0.98$</td>
</tr>
<tr>
<td>Chronic physical condition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present n (%)</td>
<td>12 (24)</td>
<td>9 (24)</td>
<td>$\chi^2 (1, 85) = 0.01, P=0.97$</td>
</tr>
<tr>
<td>Intervention content</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychological or both n (%)</td>
<td>20 (41)</td>
<td>28 (76)</td>
<td>$\chi^2 (1, 85) = 12.79, P&lt;0.01$</td>
</tr>
<tr>
<td>Supervision frequency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scheduled mean (SD)</td>
<td>1.64 (0.82)</td>
<td>1.76 (0.91)</td>
<td>$t(83)=0.65, P=0.52$</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>low risk n (%)</td>
<td>30 (61)</td>
<td>18 (49)</td>
<td>$\chi^2 (1, 85) = 3.17, P=0.24$</td>
</tr>
<tr>
<td>Sample size</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>220 (305)</td>
<td>292 (192)</td>
<td>$t(83)=1.63, P=0.11$</td>
</tr>
<tr>
<td>Median (range)</td>
<td>165 (23 to 1570)</td>
<td>227 (64 to 783)</td>
<td></td>
</tr>
<tr>
<td>Effect size; SMD (SE)</td>
<td>-0.32 (0.31)</td>
<td>-0.24 (0.30)</td>
<td>$t(83)=1.22, P=0.23$</td>
</tr>
<tr>
<td></td>
<td>(95%CI -0.40 to -0.23)</td>
<td>(95%CI -0.29 to -0.10)</td>
<td></td>
</tr>
</tbody>
</table>