BMJ Open

Effectiveness of the management of major depressive episodes/disorder in adults with comorbid chronic physical diseases: a protocol for a systematic review and meta-analysis

Pablo Martínez,[1,2,3,4] Ariel Castro,[5] Diego Alonso,[5] Paul A Vöhringer,[1,3,6] Graciela Rojas[1,3]

To cite: Martínez P, Castro A, Alonso D, *et al*. Effectiveness of the management of major depressive episodes/disorder in adults with comorbid chronic physical diseases: a protocol for a systematic review and meta-analysis. *BMJ Open* 2017;**7**:e011249. doi:10.1136/bmjopen-2016-011249

► Prepublication history and additional material are available. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2016-011249).

Received 22 January 2016
Revised 15 September 2016
Accepted 17 October 2016

For numbered affiliations see end of article.

Correspondence to
Mr. Pablo Martínez; pablo88.martinezdiaz@gmail.com

ABSTRACT

Introduction Depression is a global-scale public health problem, and a significant association has been established between depression and chronic physical diseases. This growing comorbidity poses a challenge to healthcare systems. We aim to assess the effectiveness of the management of major depressive episodes/disorder in adults with comorbid chronic physical diseases.

Methods and analysis We will conduct a systematic review and meta-analysis of randomised clinical trials. Two databases MEDLINE and Cochrane Library (Cochrane Database for Systematic Reviews and CENTRAL), as well as the reference lists of the included articles, will be searched for studies either in English or Spanish with published results within the 2005–2015 period. Studies must fulfil the following conditions: (1) participants aged 18 years or older, diagnosed as having a major depressive episodes/disorder according to standardised criteria and chronic physical diseases; (2)interventions (be it pharmacological, psychological, psychosocial or a combination) must be compared with control conditions (other 'active' intervention, treatment as usual, waiting list or placebo); (3)and must report reduction in depressive symptoms after treatment, response to treatment, remission of major depressive episodes/disorder and significant improvement in quality of life. Data extraction, risk of bias evaluation, results summarisation and quality of the evidence (GRADE) will be performed as recommended by the Cochrane Collaboration. A qualitative synthesis and a random effects meta-analysis will be carried out. Effect sizes will be calculated (relative risk and Cohen's d), I^2 and Q statistics will be employed to study heterogeneity and publication bias analysis will be performed. Subgroup analyses and meta-regression will be carried out.

Ethics and dissemination Results are expected to be published in specialised peer-reviewed journals (preferred topics: Mental Health, Psychology, Psychiatry and/or Systematic Reviews) and dissemination activities will be targeted to all the healthcare providers.

Trial registration number International Prospective Register of Systematic Reviews (CRD42016029166) submitted on 11 January 2016.

Strengths and limitations of this study

- The PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist was used for the publication of this protocol.
- A more stringent definition of depression will be employed (standardised diagnostic criteria).
- The Cochrane Handbook for Systematic Reviews of Interventions was used to assist the design of this systematic review.
- Subgroup analyses and meta-regression will be carried out to assess possible sources of heterogeneity.
- Effects of physical conditions will not be taken into account, possibly affecting the rates of depression and the estimation of treatment effect.

INTRODUCTION

Depression is a global-scale public health problem due to its frequency, associated disabilities and recurrence. At the start of the present decade, it was estimated that the world prevalence of major depressive disorder had reached 4.4%,[1] thus establishing itself as the main cause of years lived with disability (YLD), explaining 8.2% of the total YLDs in 2010.[2]

The lack of timely treatment for unipolar depression is a predictor of poorer response, lower likelihood of remission, higher recurrence and greater risk of chronicity.[3] This situation, in addition to inconsistencies in the management of the disease in real contexts and the insufficient resources assigned to mental health,[4 5] amplifies the impact of depression as a public health problem.

In addition, a significant association has been established globally between depression and chronic diseases such as asthma, angina

and diabetes,[6] which illustrates the complex interaction between mental diseases —especially depression — and other health conditions, thus highlighting the notion that there can be no health without mental health[7] and stressing the need to develop responsive health services.[8]

It has also been documented that depression is a risk factor for chronic physical diseases[9–11] and that it significantly worsens the health[6 12 13] and the prognosis of its sufferers,[14–19] which results in a greater usage rate of healthcare services[20] and low treatment adherence[21]; likewise, poor health[22] and the presence of chronic diseases are risk factors for depression.[11 22 23]

The strong link between depression and chronic physical diseases signals the presence of complex underlying biological mechanisms.[24] Recent evidence strongly supports this notion: clear links have been observed between such pathologies, in the form of deregulations in the activity of the hypothalamic–pituitary–adrenal axis,[25 26] a rise in metabolic stress,[27 28] increased cellular ageing[29] and an alteration of innate inflammatory response.[30–33]

These shared biological pathways and lifestyle-associated factors may be the basis of morbimortality and disability in sufferers of these diseases,[16] rather than the specific mechanisms of each health condition, which stresses the need to approach these problems in an integrated fashion.[34] In this context, timely treatment for depression has been shown to have a major impact on the control of chronic diseases[35] and on the reduction of healthcare costs.[36 37]

The global health situation, characterised by a tendency towards ageing populations, along with a higher prevalence of chronic diseases and their increased degree of associated disability,[38] poses a challenge to healthcare systems, which will also need to deal with a greater number of mental patients.[39] In this context, the search for effective treatments for depression in people with comorbid chronic physical diseases gains relevance.

The most recent efforts made to summarise this evidence have been mainly limited by their use of studies that include subjects classed as depressed according to either validated questionnaires or standardised diagnostic criteria,[40–44] which constitutes a potential source of heterogeneity, and by their focus on depression in specific chronic diseases[40–42 44] or on a single type of therapeutic approach, such as psychoactive drugs.[43 45] In view of the aforementioned, the present systematic review is intended to assess the effectiveness of the management of major depressive episodes/disorder in adults with comorbid chronic physical diseases.

Objectives

The objective of this systematic review is to assess the effectiveness of the available treatments for major depressive episodes/disorder in adults who suffer from chronic physical diseases. In order to do this, the present systematic review and meta-analysis seek to answer the following questions:

1. Which treatments are effective in reducing depressive symptoms in adults with major depressive episodes/disorder and comorbid chronic physical diseases?
2. Which treatments for major depressive episodes/disorder in adults with comorbid chronic physical diseases are effective in achieving a response?
3. Which treatments are effective in achieving the remission of major depressive episodes/disorder in adults with comorbid chronic physical diseases?
4. Which treatments are effective in attaining a significant improvement in the quality of life of adults with major depressive episodes/disorder and comorbid chronic physical diseases?

METHODS AND ANALYSIS

The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols checklist[46] was used for the publication of the protocol of the present systematic review and meta-analysis.

Study eligibility criteria

Participants

1. *Participant characteristics*: Adults, aged 18 years or older, with no distinction of sex or ethnicity, diagnosed with major depressive episodes/disorder and one (or more) comorbid chronic physical disease(s).
2. *Diagnosis of major depression*: The review will only include studies whose participants were diagnosed with major depressive episodes/disorder using the following standardised criteria: ICD-9 (International Classification of Diseases, 9th Revision),[47] ICD-10 (International Classification of Diseases, 10th Revision),[48] DSM-III (Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition),[49] DSM-IV[50] or DSM-5.[51] The diagnosis must have been provided by a qualified individual, either a psychiatrist or another suitably trained health professional.
3. *Comorbidities*: Comorbid physical diseases are not the main concern of this review; however, they must be diagnosed using well-established standardised criteria applied by qualified health professionals. Patients with one or more of the following conditions will be included: diabetes, cancer, cardiovascular diseases, chronic respiratory diseases, HIV infection, rheumatic diseases and gastrointestinal disease.

Interventions

1. *Pharmacological treatment*: Involving the use of tricyclic antidepressants (eg, amitriptyline), selective serotonin reuptake inhibitors (eg, fluoxetine), monoamine oxidase inhibitors (eg, phenelzine), serotonin and norepinephrine reuptake inhibitors (eg, venlafaxine), non-classified antidepressants (eg, bupropion) and/or any new antidepressant agents.[52]
2. *Psychological therapy*: Any standardised treatment method with a well-defined psychotherapeutic content in which a collaborative bond is established between

a patient and a provider (a psychologist or a suitably trained health professional), aimed at reducing the gravity of the symptoms of major depressive episodes/disorder and attaining a better level of functioning.[53] Treatments can be intended for individuals, families or groups, in either a face-to-face or distance format, through the use of information and communication technologies. Examples of psychological therapies that may be included are: behavioural, cognitive, interpersonal, among others.

3. *Psychosocial interventions*: Treatments intended to supply help, education or orientation to patients concerning major depression episode/disorder. These can include psychoeducational strategies, self-help groups, psychosocial rehabilitation strategies, support for reintegration to society or the workplace and monitoring, among others.[54]
4. Any combination of points 1, 2 and 3.

Comparators

1. Comparison between one or more treatments labelled 'interventions' by the researchers and which are consistent with the previous section (Interventions).[55]
2. Treatment as usual/standard treatment for the management of the disease, established according to current norms or according to the criterion of the clinician at the relevant level of healthcare, conducted naturalistically.[55]
3. Waiting list in which patients are temporarily assigned to the *treatment as usual/standard treatment* condition until treatment and follow-up have been completed for those in the intervention group.[55]
4. Placebo: any control condition defined by the researchers as lacking an active component.[55]

Outcomes

Studies must specify the following outcomes: reduction in depressive symptoms after treatment, response to treatment, remission of major depressive episodes/disorder and significant improvement in quality of life.

Further details are included in the Outcomes and prioritisation section.

Study design

Randomised clinical trials, systematic reviews or meta-analyses published in the databases defined for the searches.

Context

There is no restriction of setting; that is, patients can come from the primary, secondary or tertiary healthcare levels, from any healthcare system and from any country. The population included must be receiving treatment at a healthcare facility.

Report eligibility criteria

Studies must have been published in English or Spanish. Publications must have an abstract available which includes its results. Study protocols will be excluded. Studies must have been published within the last 10 years, from 30 August 2005 to 30 August 2015.

Information sources

The databases defined as information sources were MEDLINE and Cochrane Library (Cochrane Database for Systematic Reviews and CENTRAL). The search strategy for both sources is described in the relevant section.

In addition, the researchers reviewed the reference lists of the articles included in order to facilitate the identification of relevant studies.

Search strategy

Table 1 includes the search strategies for each information source.

Table 1 Search strategies

Search strategies	
MEDLINE	1. Depression[Mesh] OR (depress*[Title/Abstract] AND care[Title/Abstract] AND manag*[Title/Abstract]) OR (depress*[Title/Abstract] AND (therapy[Title/Abstract] OR treatment[Title/Abstract] OR psychotherapy[Title/Abstract] OR counseling[Title/Abstract] OR antidepress*[Title/Abstract]) 2. Chronic Disease[Mesh] OR Diabetes Mellitus[Mesh]) OR Chronic Obstructive Pulmonary Disease[Mesh] OR Chronic Respiratory Disease[Title/Abstract] OR Ashtma[Title/Abstract] OR Neoplasms[Mesh] OR Cancer[Title/Abstract] OR Cardiovascular Diseases[Mesh] OR HIV Infections[Mesh] OR Rheumatic Diseases[Mesh] OR Gastrointestinal Diseases[Mesh] 3. Randomized Controlled Trial[Publication type] OR Controlled Clinical Trial[Publication Type] OR Random Allocation[Mesh] OR Placebos[Mesh] OR Control Groups[Mesh] OR Clinical Trials As A Topic[Mesh] OR Meta-Analysis[Publication Type] OR Systematic Review[Title/Abstract] 4. #1 AND #2 AND #3
Cochrane Library*	1. [mh 'Depression'] OR [mh 'Depressive Disorder'] OR ((depress*:ti,ab) AND (care OR manag*):ti,ab) OR ((depress*:ti,ab) AND (therapy OR treatment OR psychotherapy OR counseling OR antidepress*):ti,ab) 2. [mh 'Chronic Disease'] OR [mh 'Diabetes Mellitus'] OR [mh 'Chronic Obstructive Pulmonary Disease'] OR ('Chronic Respiratory Disease':ti,ab) OR (Asthma:ti,ab) OR [mh Neoplasms] OR (Cancer:ti,ab) OR [mh 'Cardiovascular Diseases'] OR [mh 'HIV Infections'] OR [mh 'Rheumatic Diseases'] OR [mh 'Gastrointestinal Diseases'] 3. #1 AND #2

Study records

All the records yielded by the database search will be compiled and duplicates will be removed. Two authors (DA and PM) will review all the titles and abstracts independently and in duplicate to assess the eligibility of the publications. The results of this phase will be discussed within the group (AC, DA and PM), which will make it possible to estimate the degree of agreement reached. AC will provide his assistance to solve any disagreements that may arise.

Publications selected after reviewing their title and abstract, as well as those whose inclusion is in doubt, will be evaluated in full by three of the authors (AC, DA and PM). Disagreements will be solved through discussion and with the assistance of a fourth author (GR) whenever necessary.

Multiple publications of a single study will be grouped together to avoid repeating the same data. This is how the final list of studies included in the review will be defined.

To extract data from the studies selected and to present their characteristics, the format recommended in the Cochrane Handbook for Systematic Reviews of Interventions will be used.[56]

To follow this format, a piloting process will be conducted that will make it possible to estimate the degree of agreement reached. Three studies will be randomly selected and the authors (AC, DA and PM), independently and in duplicate, will extract information from them. The results obtained will be compared within the group, disagreements will be resolved through discussion and the consensual criteria for extracting information will be refined.

After this piloting process, the authors (AC, DA and PM) will divide the studies among themselves to extract data independently and will meet periodically to evaluate the fidelity of the process. The assistance provided by a fourth author (GR) will be used to solve substantial disagreements and to randomly evaluate the correspondence between the data reported by the studies and those extracted for the review.

Data items

Using the extraction format specified in the previous section,[56] the data included will concern: the study (author, year), details about its design and the duration of the follow-up process, participant characteristics (setting, sex, age, type of chronic physical diseases (if specified), major depressive episodes/disorder, gravity of the symptoms (if specified) and any specific characteristics of the sample which are relevant to the clinical trial), intervention specifications (active and control groups) and the main results of the study that are relevant to the review.

Outcomes and prioritisation

Primary outcomes

1. *Effectiveness in the reduction of depressive symptoms*: Significant differences between the intervention and control groups in terms of depressive symptomatology after treatment, measured using validated questionnaires for depression: the Beck Depression Inventory,[57] the Hamilton Depression Rating Scale,[58] the Patient Health Questionnaire[59] or the Montgomery-Åsberg Depression Scale,[60] among others. *Timing*: not specified. At least two follow-up measures.
2. *Treatment response*: According to standard definition,[61] a change of over 50% in depression scores on validated questionnaires, compared with baseline scores. *Timing*: not specified. At least two follow-up measures.
3. *Remission of major depressive episodes/disorder*: Absence of clinical depression after treatment completion, according to depression scores on validated questionnaires. *Timing*: not specified. At least two follow-up measures.

Secondary outcomes

1. Significant improvement in quality of life, evaluated through validated instruments, such as the SF-36 Health Survey[62] or the WHO Quality of Life-BREF instrument.[63]

Timing: not specified. At least two follow-up measures.

Risk of bias: individual studies

Risk of bias will be assessed with the Cochrane Risk of Bias Tool, as per the Cochrane Handbook for Systematic Reviews of Interventions.[56] This tool includes an assessment of six well-defined bias sources: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective reporting. Each of these sources is associated with specific criteria for classifying the risk of bias as high, low or unclear.

Usually, in randomised clinical trials of psychological interventions, it is not possible to blind the participants and providers.[64] Even though this aspect will be considered and discussed as a plausible source of bias, it will not be prioritised in the evaluation compared with other potential sources of bias in studies of psychological interventions.

The same piloting process used for extracting data from the studies included will be carried out. AC, DA and PM will participate directly, while GR will supervise the process, providing her assistance to solve substantial disagreements and to randomly evaluate the fidelity of the data extracted vis-à-vis the original material.

No studies will be excluded from later analyses, regardless of the assessment of their risk of bias; however, this issue will be taken into account when discussing the effects of the studies on treatment effectiveness outcomes.

Data synthesis

In this stage, all the authors (AC, DA, GR, PM and PV) will work together.

A qualitative synthesis of all the studies included will be conducted in order to provide an overview of the

effectiveness of treatments for major depressive episodes/disorder in adults with chronic physical diseases.

A meta-analytic methodology will be applied, including a random effects model of the studies with relatively similar characteristics, since it is assumed that multiple sources of heterogeneity will exist (the studies are not identical).[65]

As effect size measures, in each of the selected studies, relative risk will be calculated for dichotomous outcomes, while the standardised mean difference (Cohen's d) between treatment groups will be calculated for continuous data.[66]

In general, the treatments described in the intervention section will be compared with the control condition selected for each study in order to assess their effect on the primary and secondary outcome measures relevant to the present review.

Heterogeneity between randomised clinical trials will be studied by visually inspecting the resulting forest plots and by employing the I^2 and Q statistics.[67]

Results will be summarised using the Summary of Findings table recommended in the Cochrane Handbook for Systematic Reviews of Interventions.[56] This table will include:

A. Reduction in depressive symptoms achieved by the treatments, reported as a continuous outcome measure.
B. Response to treatments for major depressive episodes/disorder, reported as a dichotomous outcome measure.
C. Remission of major depressive episodes/disorder achieved by the treatments, reported as a dichotomous outcome measure.
D. Significant improvement in the quality of life of adults with major depressive episodes/disorder and chronic physical diseases achieved by the treatments, reported as a continuous outcome measure.

Subgroup analyses will be conducted by ethnicity, setting, type of physical chronic condition, psychiatric comorbidities and treatment type.

In addition, a meta-regression will be carried out. In order to do this, the sample will be stratified according to the initial severity of the major depressive episodes/disorder, which will make it possible to assess the potential differential effect of a treatment in connection with the severity of the disorder.

Meta-bias (ES)

Funnel plots and Egger's test will be used to assess potential publication biases.[68]

Confidence in cumulative evidence

After presenting this summary of findings, the quality of the whole set of tests for each individual result will be assessed using the GRADE approach, as recommended in the Cochrane Handbook for Systematic Reviews of Interventions.[56] This approach considers the following aspects: within-study risk of bias, directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias. This approach specifies four levels of quality (high, moderate, low and very low).

Author affiliations
[1]Department of Psychiatry and Mental Health, Clinical Hospital, Universidad de Chile, Santiago de Chile, Chile
[2]Information Technology Innovation Centre for Social Applications (CITIAPS), Universidad de Santiago de Chile, Santiago, Chile
[3]Millennium Institute for Depression and Personality Research (MIDAP), Santiago, Chile
[4]School of Psychology, Faculty of Humanities, Universidad de Santiago de Chile, Santiago, Chile
[5]School of Medicine, Faculty of Medicine, Universidad de Chile, Santiago, Chile
[6]Mood Disorders Program, Tufts Medical Center, Tufts University, Boston, Massachusetts, USA

Contributors GR is in charge of the review, of supervising the process and of providing her expert opinion on the subject. DA, AC and PM made contributions to the development of the selection criteria and the search strategy and will be tasked with extracting the data and evaluating the risk of bias. PV provided his statistical and clinical expertise and will help to supervise the process. All the authors contributed equally to the study design and edited, modified and approved the final version of the manuscript.

Funding This systematic review was financed by the Chilean National Fund for Scientific and Technological Development (FONDECYT), project no 1130230; the Fund for Innovation and Competitiveness (FIC) of the Chilean Ministry of Economy, Development, and Tourism, through the Millennium Scientific Initiative, grant no IS130005 and the Program for Institutional Improvement – Universidad de Santiago de Chile (PMI USA 1204) of the Ministry of Education, through the Information Technology Innovation Centre for Social Applications (CITIAPS). Financial backers are not involved in any other aspect of the project.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

REFERENCES

1. Ferrari AJ, Charlson FJ, Norman RE, *et al*. The epidemiological modelling of major depressive disorder: application for the global burden of disease study 2010. *PLoS One* 2013;8:e69637.
2. Ferrari AJ, Charlson FJ, Norman RE, *et al*. Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. *PLoS Med* 2013;10:e1001547.
3. Ghio L, Gotelli S, Marcenaro M, *et al*. Duration of untreated illness and outcomes in unipolar depression: a systematic review and meta-analysis. *J Affect Disord* 2014;152-154:45–51.
4. Saxena S, Thornicroft G, Knapp M, *et al*. Resources for mental health: scarcity, inequity, and inefficiency. *Lancet* 2007;370:878–89.
5. Mitchell AJ, Vaze A, Rao S. Clinical diagnosis of depression in primary care: a meta-analysis. *The Lancet* 2009;374:609–19.
6. Moussavi S, Chatterji S, Verdes E, *et al*. Depression, chronic diseases, and decrements in health: results from the World Health surveys. *Lancet* 2007;370:851–8.
7. Prince M, Patel V, Saxena S, *et al*. Global Mental Health 1: no health without mental health. *Lancet* 2007;370:859–77.
8. World Health Organization. *Mental health action plan 2013–2020*. Geneva: World Health Organization, 2013.

9. Dong J-Y, Zhang Y-H, Tong J, *et al*. Depression and risk of stroke. *Stroke* 2012;43:32–7.
10. Pan A, Sun Q, Okereke OI, *et al*. Depression and risk of stroke morbidity and mortality: a meta-analysis and systematic review. *JAMA* 2011;306:1241–9.
11 Lloyd CE, Roy T, Nouwen A, *et al*. Epidemiology of depression in diabetes: international and cross-cultural issues. *J Affect Disord* 2012;142(Suppl):S22–S29.
12. Ayerbe L, Ayis S, Wolfe CD, *et al*. Natural history, predictors and outcomes of depression after stroke: systematic review and meta-analysis. *Br J Psychiatry* 2013;202:14–21.
13. Blakemore A, Dickens C, Guthrie E, *et al*. Depression and anxiety predict health-related quality of life in chronic obstructive pulmonary disease: systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis* 2014;9:501–12.
14. Meijer A, Conradi HJ, Bos EH, *et al*. Adjusted prognostic association of depression following myocardial infarction with mortality and cardiovascular events: individual patient data meta-analysis. *Br J Psychiatry* 2013;203:90–102.
15. Lichtman JH, Froelicher ES, Blumenthal JA, *et al*. Depression as a risk factor for poor prognosis among patients with acute coronary syndrome: systematic review and recommendations: a scientific statement from the American Heart Association. *Circulation* 2014;129:1350–69.
16. Cuijpers P, Vogelzangs N, Twisk J, *et al*. Comprehensive meta-analysis of excess mortality in depression in the general community versus patients with specific illnesses. *Am J Psychiatry* 2014;171:453–62.
17. Pinquart M, Duberstein PR. Depression and cancer mortality: a meta-analysis. *Psychol Med* 2010;40:1797–810.
18. Hofmann M, Köhler B, Leichsenring F, *et al*. Depression as a risk factor for mortality in individuals with diabetes: a meta-analysis of prospective studies. *PLoS One* 2013;8:e79809.
19. van Dooren FE, Nefs G, Schram MT, *et al*. Depression and risk of mortality in people with diabetes mellitus: a systematic review and meta-analysis. *PLoS One* 2013;8:e57058.
20. Dickens C, Katon W, Blakemore A, *et al*. Does depression predict the use of urgent and unscheduled care by people with long term conditions? A systematic review with meta-analysis. *J Psychosom Res* 2012;73:334–42.
21. Grenard JL, Munjas BA, Adams JL, *et al*. Depression and medication adherence in the treatment of chronic diseases in the United States: a meta-analysis. *J Gen Intern Med* 2011;26:1175–82.
22. Chang-Quan H, Xue-Mei Z, Bi-Rong D, *et al*. Health status and risk for depression among the elderly: a meta-analysis of published literature. *Age Ageing* 2010;39:23–30.
23. Zhang MW, Ho RC, Cheung MW, *et al*. Prevalence of depressive symptoms in patients with chronic obstructive pulmonary disease: a systematic review, meta-analysis and meta-regression. *Gen Hosp Psychiatry* 2011;33:217–23.
24. Penninx BW, Milaneschi Y, Lamers F, *et al*. Understanding the somatic consequences of depression: biological mechanisms and the role of depression symptom profile. *BMC Med* 2013;11:129.
25. Stetler C, Miller GE, . Depression and hypothalamic–pituitary–adrenal activation: a quantitative summary of four decades of research. *Psychosom Med* 2011;73:114–26.
26. Belvederi Murri M, Pariante C, Mondelli V, *et al*. HPA Axis and aging in depression: systematic review and meta-analysis. *Psychoneuroendocrinology* 2014;41:46–62.
27. Black CN, Bot M, Scheffer PG, *et al*. Is depression associated with increased oxidative stress? A systematic review and meta-analysis. *Psychoneuroendocrinology* 2015;51:164–75.
28. Palta P, Samuel LJ, Miller ER, *et al*. Depression and oxidative stress: results from a meta-analysis of observational studies. *Psychosom Med* 2014;76:12–19.
29. Verhoeven JE, Révész D, Epel ES, *et al*. Major depressive disorder and accelerated cellular aging: results from a large psychiatric cohort study. *Mol Psychiatry* 2014;19:895–901.
30. Jiang M, Qin P, Yang X. Comorbidity between depression and asthma via immune-inflammatory pathways: a meta-analysis. *J Affect Disord* 2014;166:22–9.
31. Sperner-Unterweger B, Kohl C, Fuchs D. Immune changes and neurotransmitters: possible interactions in depression? *Prog Neuropsychopharmacol Biol Psychiatry* 2014;48:268–76.
32. Haapakoski R, Mathieu J, Ebmeier KP, *et al*. Cumulative meta-analysis of interleukins 6 and 1β, tumour necrosis factor α and C-reactive protein in patients with major depressive disorder. *Brain Behav Immun* 2015;49:206–15.
33. Mazereeuw G, Herrmann N, Bennett SA, *et al*. Platelet activating factors in depression and coronary artery disease: a potential biomarker related to inflammatory mechanisms and neurodegeneration. *Neurosci Biobehav Rev* 2013;37:1611–21.
34. Charlson FJ, Moran AE, Freedman G, *et al*. The contribution of major depression to the global burden of ischemic heart disease: a comparative risk assessment. *BMC Med* 2013;11:250.
35. Schmittdiel JA, Dyer W, Uratsu C, *et al*. Initial persistence with antihypertensive therapies is associated with depression treatment persistence, but not depression. *J Clin Hypertens* 2014;16:412–7.
36. Haschke A, Hutter N, Baumeister H. Indirect costs in patients with coronary artery disease and mental disorders: a systematic review and meta-analysis. *Int J Occup Med Environ Health* 2012;25:319–29.
37. Hutter N, Knecht A, Baumeister H. Health care costs in persons with asthma and comorbid mental disorders: a systematic review. *Gen Hosp Psychiatry* 2011;33:443–53.
38. Vos T, Barber RM, Bell B, *et al*. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the global burden of disease study 2013. *Lancet* 2015;386:743–800.
39. Whiteford HA, Degenhardt L, Rehm J, *et al*. Global burden of disease attributable to mental and substance use disorders: findings from the global burden of disease study 2010. *The Lancet* 2013;382:1575–86.
40. Callari A, Mauri M, Miniati M, *et al*. Treatment of depression in patients with breast cancer: a critical review. *Tumori* 2013;99:623–33.
41. Huang Y, Wei X, Wu T, *et al*. Collaborative care for patients with depression and diabetes mellitus: a systematic review and meta-analysis. *BMC Psychiatry* 2013;13:260.
42. van der Feltz-Cornelis CM, Nuyen J, Stoop C, *et al*. Effect of interventions for major depressive disorder and significant depressive symptoms in patients with diabetes mellitus: a systematic review and meta-analysis. *Gen Hosp Psychiatry* 2010;32:380–95.
43. Taylor D, Meader N, Bird V, *et al*. Pharmacological interventions for people with depression and chronic physical health problems: systematic review and meta-analyses of safety and efficacy. *Br J Psychiatry* 2011;198:179–88.
44. Baumeister H, Hutter N, Bengel J. Psychological and pharmacological interventions for depression in patients with coronary artery disease. *Cochrane Database Syst Rev* 2011;9:CD008012.
45. Iovieno N, Tedeschini E, Ameral VE, *et al*. Antidepressants for major depressive disorder in patients with a co-morbid axis-III disorder: a meta-analysis of patient characteristics and placebo response rates in randomized controlled trials. *Int Clin Psychopharmacol* 2011;26:69–74.
46. Shamseer L, Moher D, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;349:g7647.
47. World Health Organization. *International classification of diseases, Ninth Revision (ICD-9): Mental disorders: glossary and Guide to their classification*. Geneva: World Health Organization, 1978.
48. World Health Organization. *The ICD-10 classification of mental and behavioral disorders: clinical descriptions and diagnostic guidelines*. Geneva: World Health Organization, 1992.
49. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. Third Edition (DSM-III). Washington, DC: American Psychiatric Association, 1980.
50. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. Fourth Edition (DSM-IV). Washington, DC: American Psychiatric Association, 1994.
51. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. Fifth Edition (DSM-5). Washington, DC: American Psychiatric Association, 2013.
52. Food and Drug Administration (FDA). *Understanding antidepressant medications. FDA Consumer Health Information/U.S*: Food and Drug Administration, 2009. http://www.fda.gov/downloads/ForConsumers/ConsumerUpdates/UCM095990.pdf
53. American Psychological Association. *Recognition of Psychotherapy Effectiveness*: Council Policy Manual, 2012. http://www.apa.org/about/policy/resolution-psychotherapy.aspx
54. Ruddy R, House A. Psychosocial interventions for conversion disorder. *Cochrane Database Syst Rev* 2005;19:CD005331.
55. In: Nezu AM, Nezu CM, eds. *Evidence-based outcome research: a practical guide to conducting randomized controlled trials for psychosocial interventions*. New York, NY: Oxford University Press, 2008.
56. In: Higgin JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011*: The Cochrane Collaboration, 2011. www.cochrane-handbook.org
57. Beck AT, WARD CH, MENDELSON M, *et al*. An inventory for measuring depression. *Arch Gen Psychiatry* 1961;4:561–71.

58. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960;23:56–62.
59. Spitzer RL, Kroenke K, Williams JBW. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. *JAMA* 1999;282:1737–44.
60. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry* 1979;134:382–9.
61. Trivedi MH, Kleiber B, Greer TL. Remission and recovery in depression treatment. *Drug Dev Res* 2005;65:335–43.
62. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473–83.
63. Skevington SM, Lotfy M, O'Connell KA, *et al*. The World Health Organization's WHOQOL-BREF quality of life assessment: psychometric properties and results of the international field trial. A report from the WHOQOL group. *Qual Life Res* 2004;13:299–310.
64. Mayo-Wilson E, Grant S, Hopewell S, *et al*. Developing a reporting guideline for social and psychological intervention trials. *Trials* 2013;14:242.
65. Berkey CS, Hoaglin DC, Mosteller F, *et al*. A random-effects regression model for meta-analysis. *Stat Med* 1995;14:395–411.
66. McGough JJ, Faraone S. Estimating the size of treatment effects. *Psychiatry* 2009;6:21–9.
67. Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, *et al*. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? *Psychol Methods* 2006;11:193–206.
68. Egger M, Davey Smith G, Schneider M, *et al*. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.