The Effect of Complex Interventions on Depression and Anxiety in Chronic Obstructive Pulmonary Disease: Systematic Review and Meta-Analysis

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Abstract

Background: Depression and anxiety are very common in people with chronic obstructive pulmonary disease (COPD) and are associated with excess morbidity and mortality. Patients prefer non-drug treatments and clinical guidelines promote non-pharmacological interventions as first line therapy for depression and anxiety in people with long term conditions. However the comparative effectiveness of psychological and lifestyle interventions among COPD patients is not known. We assessed whether complex psychological and/or lifestyle interventions are effective in reducing symptoms of anxiety and depression in patients with COPD. We then determined what types of psychological and lifestyle interventions are most effective.

Methods and Findings: Systematic review of randomised controlled trials of psychological and/or lifestyle interventions for adults with COPD that measured symptoms of depression and/or anxiety. CENTRAL, Medline, Embase, PsychINFO, CINAHL, ISI Web of Science and Scopus were searched up to April 2012. Meta-analyses using random effects models were undertaken to estimate the average effect of interventions on depression and anxiety. Thirty independent comparisons from 29 randomised controlled trials (n = 2063) were included in the meta-analysis. Overall, psychological and/or lifestyle interventions were associated with small reductions in symptoms of depression (standardised mean difference \(-0.28, 95\%\) confidence interval \(-0.41 to \(-0.14\)) and anxiety (standardised mean difference \(-0.23, 95\%\) confidence interval \(-0.38 to \(-0.09\)). Multi-component exercise training was the only intervention subgroup associated with significant treatment effects for depression (standardised mean difference \(-0.47, 95\%\) confidence interval \(-0.66 to \(-0.28\)), and for anxiety (standardised mean difference \(-0.45, 95\%\) confidence interval \(-0.71 to \(-0.18\)).

Conclusions: Complex psychological and/or lifestyle interventions that include an exercise component significantly improve symptoms of depression and anxiety in people with COPD. Furthermore, multi-component exercise training effectively reduces symptoms of anxiety and depression in all people with COPD regardless of severity of depression or anxiety, highlighting the importance of promoting physical activity in this population.

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Introduction

One in four patients with chronic obstructive pulmonary disease (COPD) will have clinically significant depression, which is twice the prevalence observed in people without COPD [1]. Similarly, compared with matched controls, people with COPD are at least twice as likely to experience anxiety [2]. Inflammatory and physiologic changes associated with COPD have been implicated in the onset of depression and anxiety [3], although there is strong evidence to suggest that subjective health status is a better predictor of depression in COPD than biological or physiological markers [4]. Irrespective of cause, depression and anxiety have profound consequences for the health of patients with COPD. Depression is
associated with increased mortality, impaired health related quality of life and longer hospital stay after acute exacerbation [5], increased risk of exacerbation and hospital admission [6], hospital readmission [7], and poorer exercise performance [8]. Equally, anxiety is associated with increased risk of exacerbations, poorer health related quality of life and worse exercise performance [2], relapse within one-month of receiving emergency treatment [9], and hospital readmission [10].

In the UK, the National Institute for Health and Clinical Excellence have published guidelines for treating depression and anxiety in people with long term conditions [11]. Treatments include psychological therapies with or without antidepressant medication. Importantly the National Institute for Health and Clinical Excellence guideline for COPD emphasises offering patients psychological and psychosocial interventions, including behaviour approaches such as pulmonary rehabilitation, before considering antidepressants [12].

However, the comparative effects of different psychological interventions remains uncertain in long term conditions, and the relevance of systematic review data is largely confined to treatment of depression rather than both depression and anxiety, which commonly coexist in people with long term conditions [11]. Moreover, the evidence for using psychological interventions in COPD patients is equivocal. While there is some support for treating depression and anxiety in COPD using cognitive and behavioural therapy (CBT), (with or without exercise or education), evidence is largely derived from either small randomised controlled trials or uncontrolled and non-randomised studies [13,14]. Whereas Rose et al found insufficient evidence to support the use of psychologically-based treatments to reduce anxiety [15], a more recent meta-analysis of eight psychotherapeutic and one relaxation intervention reported a small but significant effect on anxiety (r = -0.27, 95% confidence interval −0.41 to −0.14), but not depression [16]. Previous reviews of pulmonary rehabilitation have indicated that 4-week programmes can improve fatigue and emotional function, but these reviews either included trials that did not specifically address effects on anxiety and depression [17], or included non-randomised trials known to be affected by selection bias [18].

Attempts to systematically review and quantify the effectiveness of a more broad range of complex, non-pharmacological interventions, including psycho-educational and lifestyle interventions, on mental health in COPD have similarly been confounded by methodologically heterogeneous approaches [19,20], leading to uncertainty about which interventions to use in this population. We have therefore conducted a systematic review and meta-analysis of randomised controlled trials of complex psychological and/or lifestyle interventions for managing COPD. Our first objective was to assess whether complex interventions that incorporate psychological and/or lifestyle components are effective in reducing symptoms of anxiety and depression in patients with COPD. Secondly, we determined what types of complex psychological and/or lifestyle interventions are most effective.

Methods

This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (Appendix S1) [21]. No formal protocol was published.

Information Sources and Search Strategy

The following electronic databases were searched: Cochrane Central Register of Controlled Trials (CENTRAL, issue 10, 2010), Medline In-Process and Other Non-Indexed Citations (Ovid) and Medline (Ovid) from inception to January 2011, Embase (Ovid) from inception to January 2011, PsycINFO (Ovid) from inception to January 2011, Cinahl (Ovid), 1981 to January 2011, ISI Web of Science 1945 to January 2011, and Scopus. In addition we searched reference lists of included studies and of three reviews of psychological management of COPD that were not identified in the electronic search [22–24]. All searches were carried out between October 2010 and January 2011 and updated in April 2012. Non-English publications were translated. The full search strategy for each database is available in Appendix S2.

Eligibility Criteria

Studies were eligible for inclusion in this review if they met the following criteria:

- Study design: cluster or individual randomised controlled trials.
- Population: individuals with chronic obstructive pulmonary disease confirmed by post-bronchodilator spirometry of forced expiratory volume in 1 second/forced vital capacity ratio of <70% and a forced expiratory volume in 1 second of <30%.
- Intervention: single or multiple component interventions that include psychological and/or lifestyle components to change knowledge, attitudes, beliefs, emotions, skills and/or behaviour in people with COPD. Studies that included patients treated for depression and/or anxiety with psychotropic medications were excluded. Interventions were classified based on an updated taxonomy of behaviour change techniques [25] (Table 1).

| Table 1. Classification of intervention components. |
|---------------------------------------------------|
| **Type of intervention** | **Description** | **Components** |
| **Lifestyle** | General education | Basic provision of information, commonly using didactic techniques |
| | General discussion | Discussions facilitated by a professional or lay leader |
| | Exercise training | Illness-specific exercise |
| | Skills and self-management training | Teaching of practical skills to improve illness |
| | Behaviour therapy | Use of behavioural techniques, such as goal setting, to improve illness |
| | Relapse prevention | Discussion of how to maintain positive change and prevent future relapse |
| **Psychological** | Problem-solving techniques | Identification of problems/barrriers to behaviour change and techniques to overcome them |
| | Cognitive behavioural therapy | Use or teaching of cognitive and behavioural techniques to invoke positive psychological change |
| | Social support | Use of teaching of techniques to improve social support |
| | Relaxation | Practice of relaxation techniques, including imagery and distraction |
| | Biofeedback | Biological feedback to support relaxation |
| | Miscellaneous | Mental health interventions lacking detailed description e.g. stress management |

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Table 2. Characteristics of the study populations.

| Study | Sample size | Mean age | Males (%) | COPD severity (GOLD stage) | Where recruited | Depressed at baseline? | Anxious at baseline? | Depression assessment | Anxiety assessment | Baseline mean (SD) depression score | Baseline mean (SD) anxiety score |
|-------|-------------|----------|-----------|-----------------------------|-----------------|-----------------------|----------------------|---------------------|-------------------|-----------------------------------|-------------------------------|
| Blumenthal et al 2006 | 158 | 50 | 44 | Severe (stage 3) | Secondary care | No | No | BDI | STAI | I = 13.4 (8.3); C = 10.9 (7.4) | I = 40.3 (12.6); C = 35.6 (11.3) |
| Bucknall et al 2012 | 464 | 69.1 | 37 | I = severe (stage 3); C = severe (stage 3) | Secondary care | Yes | Yes | HADS | HADS | I = 8.5 (3.9); C = 8.3 (4.1) | I = 10 (4.5); C = 9.3 (4.6) |
| de Blok et al 2006 | 21 | 64.1 | 43 | I = moderate (stage 2); C = severe (stage 3) | Tertiary care | No | No | BDI | N/A | I = 12.6 (95% CI 7.5–17.7); C = 12.9 (95% CI 8.5–17.2) | N/A |
| de Godoy and de Godoy 2003 | 30 | 60.5 | 73 | Severe (stage 3) | Secondary care | Yes | Yes | BDI | BAI | I = 137 (8.9); C = 149 (11.5) | I = 129 (6.9); C = 109 (9.8) |
| Donesky-Cuenco et al 2009 | 41 | 70 | 28 | I = moderate (stage 2); C = severe (stage 3) | Primary care | No | No | CES-D | STAI | I = 9.5 (4.5); C = 12.6 (9.4) | I = 30.2 (8); C = 33.8 (9) |
| Effing et al 2009 | 142 | 63.4 | 59 | I = moderate (stage 2); C = severe (stage 3) | Secondary care | No | No | HADS | HADS | I = 4.4 (3.5); C = 4.6 (4) | I = 4.6 (3.3); C = 4.8 (4) |
| Elçi et al 2008 | 78 | 58.9 | 85 | Severe (stage 3) | Tertiary care | No | No | HADS | HADS | Not reported | Not reported |
| Emery et al 1998 | 79 | 66.6 | 47 | Severe (stage 3) | Primary care | No | No | SCL -Depression | SCL-Anxiety | I (a) = 59.2 (7.6); I (b) = 55.5 (5.3); C = 60 (7.7) | I (a) = 54.3 (7.2); I (b) = 54.0 (5.3); C = 53.4 (4.5) |
| Gift et al 1992 | 26 | 68.5 | 31 | Moderate (stage 2) | Primary care | No | No | N/A | STAI | I = 7.3 (3.2); C = 7.5 (4.3) | I = 4.6 (4.7); C = 8.9 (4.3) |
| Griffiths et al 2000 | 200 | 68.3 | 60 | Severe (stage 3) | Primary care and secondary care | No | No | HADS | HADS | I = 4.4 (3.5); C = 4.6 (4) | I = 4.6 (3.3); C = 4.8 (4) |
| Güell et al 2006 | 40 | 67 | 94 | Severe (stage 3) | Tertiary care | No | No | SCL-90-R | SCL-9-R | I = 1.3 (0.8); C = 0.6 (0.6) | I = 1.0 (0.5); C = 0.6 (0.7) |
| Hospes et al 2009 | 39 | 62.2 | 60 | Moderate (stage 2) | Secondary care | No | No | BDI | N/A | I = 8.4 (5.2); C = 9.1 (8.3) | N/A |
| Hyyninen et al 2010 | 51 | 61 | 49 | Moderate (stage 2) | Secondary care | Yes | Yes | BDI-II | BAI | I = 20.7 (8.6); C = 20.5 (9.7) | I = 17.5 (7.3); C = 17.5 (9.5) |
| Kapella et al 2011 | 23 | 63 | 83 | I = moderate (stage 2); C = moderate (stage 2) | Community Unknown | Unknown | Unknown | POMS-D | POMS-A | I = 9.9 (10.3); C = 10.4 (8.2) | I = 9.4 (8.2); C = 8.6 (3.7) |
| Kayahan et al 2006 | 45 | 66 | 87 | Moderate (stage 2) | Tertiary care | No | No | HAM-D | HAM-A | I = 5.43 (4.8); C = 7.18 (6.5) | I = 8.91 (6.9); C = 7.91 (6.6) |
| Kunik et al 2001 | 53 | 71.3 | 83 | Severe (stage 3) | Secondary care | No | No | GDS | BAI | I = 11.5 (33); C = 7.7 (5.4) | I = 15.3 (9.2); C = 10 (6.8) |
| Kunik et al 2008 | 238 | 66.3 | 97 | Severe (stage 3) | Primary care | Yes | Yes | BDI-II | BAI | I = 23.4 (12.5); C = 21.1 (12) | I = 22.67 (14.2); C = 23 (13.9) |
| Lamers et al 2010 | 187 | 71 | 60 | Mild to moderate (stage 1 to 2) | Primary care | Yes | No | BDI-II | SCL | I = 17.1 (6.5); C = 18.3 (7.2) | I = 20.6 (6.2); C = 20.4 (7.3) |
| Livermore et al 2010 | 41 | 73.4 | 44 | Moderate (stage 2) | Secondary care | No | No | HADS | HADS | I = 3.9 (2.1); C = 4.1 (2.8) | I = 5.2 (2.9); C = 5.9 (2.7) |
Table 2. Cont.

| Study                      | Sample size | Mean age | COPD severity (GOLD stage) | Where recruited | Baseline mean (SD) depression score | Baseline mean (SD) anxiety score |
|----------------------------|-------------|----------|----------------------------|-----------------|------------------------------------|----------------------------------|
| Lolak et al 2008           | 83          | 67.7     | Severe (stage 3)           | Secondary care  | No                                 | HADS I = 6.6 (4); C = 4.9 (3)   |
| Lord et al 2010            | 28          | 67.4     | Not stated                 | Secondary care  | No                                 | HADS I = 5.7 (2.8); C = 5.8 (3) |
| McGeoch et al 2006         | 159         | 71.5     | Moderate (stage 2)         | Primary care    | No                                 | HADS I = 4.6 (3.7); C = 4.1 (2.9) |
| Øzdemir et al 2010         | 50          | 62.5     | Moderate (stage 2)         | Secondary care  | No                                 | HADS I = 6.8 (3.2); C = 7.1 (2.3) |
| Paz-Díaz et al 2007        | 24          | 64.5     | Severe (stage 3)           | Primary care    | No                                 | BDI I = 14 (8); C = 14 (6.8)     |
| Ries et al 1995            | 119         | 62.6     | Moderate (stage 2)         | Primary care    | No                                 | CES-D I = 153 (10)               |
| Sassi-Dambron et al 1995   | 89          | 67.4     | Moderate (stage 2)         | Secondary care  | No                                 | STAI I = 14 (10.2); C = 119 (7.6) |
| Spencer et al 2010         | 59          | 69.5     | Moderate (stage 2)         | Primary care    | No                                 | HADS I = 6.8 (3.2); C = 7.1 (2.3) |
| Taylor et al 2009          | 116         | 69.5     | Moderate (stage 2)         | Secondary care  | No                                 | HADS I = 6.8 (3.2); C = 7.1 (2.3) |
| Yeh et al 2010             | 10          | 65.5     | Moderate (stage 2)         | Secondary care  | No                                 | N/A                              |

BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; CES-D = Center for Epidemiologic Studies Depression Scale; C = Control group; GOLD = Global initiative for chronic Obstructive Lung Disease; HADS = Hospital Anxiety and Depression Scale; I = Intervention group; N/A = not applicable; POMA = Profile of Mood States Anxiety scale; POMS-S = Profile of Mood States Depression scale; SCL-90 = Symptom Checklist-90; SD = Standard deviation; STAI = State Trait Anxiety Inventory.
| Author                        | Intervention                                                                 | Control group                                                                 | Delivery method                                      | Delivery method                                      | Follow-up |
|-------------------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------------|-----------------------------------------------------|-----------------------------------------------------|-----------|
| Blumenthal et al 2006         | Telephone-based coping skill training                                         | Usual medical care including clinic visits with the pulmonologists and regular contact with the nurse | Individual, face-to-face and remote.                | Respiratory nurse                                    | 12 weeks  |
|                                |                                                                              |                                                                               |                                                     |                                                     | 52 weeks  |
| Bucknall et al 2012           | Supported self-management                                                    | Usual medical care from GP and hospital based specialists (including out of hospital based emergency care) | Individual, face-to-face                           | Respiratory physicians                               | 12 weeks  |
| de Blok et al 2006            | PR plus physical activity counselling                                       | PR plus physical activity counselling                                         | Group and individual, face-to-face                 | Group, face-to-face                                   | 28 weeks  |
| de Godoy and de Godoy 2003    | CBT, physiotherapy, exercise and education                                    | Physiotherapy, exercise and education                                         | Group, face-to-face                                   | Group, face-to-face                                   | 26 weeks  |
| Donesky-Cuenco et al 2009     | Yoga training                                                                | Yoga training                                                                 | Group, face-to-face                                   | Group, face-to-face                                   | 9 weeks   |
| Effing et al 2011             | Psycho-therapeutic exercise; self-management education                       | Self-management education                                                     | Group, face-to-face                                   | Group, face-to-face                                   | 12 weeks  |
| Epig et al 2008               | PR                                                                           | Standard medical care including instructions on the use of respiratory medication | Individual, face-to-face and remote.                | Individual, face-to-face and remote.                | 4 weeks   |

### Table 3. Characteristics of the interventions.

| Author                        | Intervention                                                                 | Control group                                                                 | No. Sessions | Session length  | Delivered by                          |
|-------------------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------------|--------------|-----------------|---------------------------------------|
| Blumenthal et al 2006         | Telephone-based coping skill training                                         | Usual medical care including clinic visits with the pulmonologists and regular contact with the nurse | 12           | 30              | Clinical psychologists, social workers |
| Bucknall et al 2012           | Supported self-management                                                    | Usual medical care from GP and hospital based specialists (including out of hospital based emergency care) | 22           | 40              | Physical therapists                   |
| de Blok et al 2006            | PR plus physical activity counselling                                       | PR plus physical activity counselling                                         | 4            | 30              | Physical therapists                   |
| de Godoy and de Godoy 2003    | CBT, physiotherapy, exercise and education                                    | Physiotherapy, exercise and education                                         |              |                 |                                       |
| Donesky-Cuenco et al 2009     | Yoga training                                                                | Yoga training                                                                 |              |                 |                                       |
| Effing et al 2011             | Psycho-therapeutic exercise; self-management education                       | Self-management education                                                     |              |                 |                                       |
| Epig et al 2008               | PR                                                                           | Standard medical care including instructions on the use of respiratory medication |              |                 |                                       |
| Author          | Intervention                               | Control group                  | Lifestyle components                                                                 | Psychological components                                                                 | No. Sessions | Session length (minutes) | Delivered by                                      | Delivery method                        | Follow-up |
|-----------------|--------------------------------------------|--------------------------------|--------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|--------------|-------------------------|-----------------------------------------------|------------------------------------------|-----------|
| Emery et al 1998 | Treatment (a) = Exercise, education and stress management Treatment (b) = education and stress management | Waiting list control          | General education; Group discussion; Exercise                                         | CBT; Relaxation; Miscellaneous (stress management)                                       | 37           | 240 (all modules)       | Respiratory specialists and clinical psychologist | Group, face-to-face                        | 10 weeks  |
| Gift et al 1992  | Progressive muscle relaxation with pre-recorded tapes | Participants instructed to sit quietly for 20 minutes | N/A                                                                                 | Relaxation (Bernstein and Borkovec method)                                                | 4            | 20                      | Primary care practitioners                      | Individual, face-to-face                 | 4 weeks   |
| Griffiths et al 2000 | Multi-disciplinary PR                     | Standard medical management | General education; Exercise; Skills training                                          | Relaxation; Miscellaneous (stress management to promote mastery and control over illness) | 18           | 120                     | Occupational therapist physiotherapist, dietetic staff, specialist respiratory nurse and a smoking-cessation counsellor. | Group, face-to-face                        | 6 weeks   |
| Güell et al 2006 | PR including breathing training and exercise | Usual care                    | General education; Exercise; Skills training                                          | Relaxation                                      | Phase 1 = 16 sessions; Phase 2 = 40 sessions | 30           | Not reported            | Group, face-to-face                        | 16 weeks                                |           |
| Hospes et al 2009 | Pedometer-based exercise counselling programme | Usual care                    | Exercise                                                                             | Biofeedback; Problem-solving techniques; Exercise counselling; Motivational interviewing | 5            | 30                      | Trained exercise counsellor                    | Individual, face-to-face                 | 12 weeks  |
| Hynninen et al 2010 | CBT                                       | Enhanced standard care for COPD | N/A                                                                                 | CBT                                         | 7            | 60                      | Masters level psychology student               | Group, face-to-face                        | 4 weeks   |
| Kapella et al 2011 | CBT                                       | COPD education                 | N/A                                                                                 | CBT                                         | 6            | Not reported            | Nurse behavioural sleep medicine specialist    | Group, face-to-face                        | 6 weeks   |
| Kayahan et al 2006 | PR                                        | Usual care                    | General education; Exercise; Skills training                                          | Relaxation                                      | 24           | 150                     | Not reported                                      | Individual and group, face-to-face        | 8 weeks   |
| Kunik et al 2001  | CBT                                       | COPD education                 | N/A                                                                                 | CBT                                         | 1 (+6 phone calls) | 120                     | Board-certified gero-psychiatrist              | Group, face-to-face and individual, remote | 6 weeks   |
| Author                | Intervention                          | Control group                        | Lifestyle components       | Psychological components                                                                 | No. Sessions | Session length (minutes) | Delivered by                  | Delivery method   | Follow-up |
|-----------------------|---------------------------------------|--------------------------------------|---------------------------|----------------------------------------------------------------------------------------|--------------|--------------------------|------------------------------|------------------|-----------|
| Kunik et al 2008      | CBT group treatment intervention      | COPD education                       | N/A                       | CBT                                                                                    | 8            | 60                       | Psychology interns and postdoctoral fellows | Group, face-to-face | 4 weeks   |
| Lamers et al 2010     | Minimal psychological intervention    | Usual care                           | Skills training           | Problem-solving techniques; CBT                                                         | Average of 4 contacts | 60                       | Primary care nurses          | Individual, face-to-face | 12 weeks  |
| Livemore et al 2010   | CBT                                   | Routine care (including PR)          | N/A                       | CBT                                                                                    | 4            | 60                       | Clinical psychologist        | Individual, face-to-face | 6 weeks   |
| Lolak et al 2008      | Progressive muscle relaxation and PR  | Exercise training                    | General education;       | Relaxation (Bernstein and Borkovec method)                                             | 12           | 60                       | Multi-disciplinary PR team   | Group, face-to-face          | 8 weeks   |
| Lord et al 2010       | Singing teaching                      | Usual care                           | Skills training           | Relaxation                                                                              | 12           | 60                       | Singing teacher              | Group, face-to-face          | 7 weeks   |
| McGeoch et al 2006    | Usual care and education on the use of a written self-management plan. | Usual GP care                       | General education;       | N/A                                                                                    | 1            | 60                       | Practice nurse or respiratory educator in association with GP | Individual, face-to-face | 24 weeks  |
| Özdemir et al 2010    | Water-based PR                        | Usual care                           | Exercise                  | N/A                                                                                    | 12           | 35                       | Physio-therapist and chest physician. | Group, face-to-face          | 4 weeks   |
| Paz-Díaz et al 2007   | Exercise rehabilitation programme     | Usual care                           | Exercise; Skills training | Miscellaneous (relaxation techniques)                                                   | 24           | 85                       | Not reported                 | Group, face-to-face          | 8 weeks   |
| Ries 1995             | Pulmonary rehabilitation              | Education (videotapes, lectures, and discussions but no individual instruction or exercise training) | General education;       | Relaxation; Miscellaneous (psychological support)                                      | 12           | 240                      | Not reported                 | Group, face-to-face          | 8 weeks   |
| Sass-Dambronz et al 1995 | Dyspnoea self-management training     | General health education.            | General education; Group discussion; Skills training | Relaxation (progressive muscle relaxation); Miscellaneous (self-talk and panic control) | 6            | not reported             | Graduate student in psychology and a clinical nurse | Group, face-to-face          | 6 weeks   |
| Spencer et al 1995    | Supervised outpatient-based exercise plus unsupervised home exercise | Exercise                           | N/A                       | Exercise                                                                              | 52           | 50                       | Physio-therapist             | Group, face-to-face          | 12 weeks  |
### Table 3. Cont.

| Author          | Intervention                                      | Control group | Lifestyle components | Psychological components                                      | No. Sessions | Session length (minutes) | Delivered by                           | Delivery method | Follow-up |
|-----------------|---------------------------------------------------|----------------|----------------------|-------------------------------------------------------------|--------------|--------------------------|-----------------------------------------|----------------|-----------|
| Taylor et al 2009 | Disease-specific self-management programme        | Usual care     | Skills training       | Miscellaneous (Self-management using social cognitive self-efficacy theory) | 7            | 150                      | Lay trainer and respiratory physician   | Group, face-to-face | 8 weeks   |
| Yeh et al 2010   | Tai Chi classes                                   | Usual care     | Exercise             | Relaxation; Miscellaneous (meditation and mindfulness)      | 24           | 60                       | Tai Chi instructor                      | Group, face-to-face | 12 weeks  |

CBT = Cognitive and Behavioural Therapy; GP = General Practitioner; N/A = Not applicable; PR = Pulmonary rehabilitation.

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Comparators: any control (e.g. waiting list, usual care, attention or active control).

Outcomes: standardised measure of depression and/or anxiety.

We excluded studies and reports not published in peer reviewed journals, editorials, opinions and commentaries.

Study Selection

Titles and abstracts were independently screened by four reviewers, and full papers of potentially relevant abstracts were retrieved. Full text versions of abstracts were independently screened and final decisions about eligibility were made at a consensus meeting with all review authors. Research staff with relevant language skills translated and interpreted non-English publications.

Data Extraction

Data were extracted and cross-checked by pairs of reviewers using a standardised data extraction form used in a similar review of psychological interventions in diabetes [26]. Disagreements were resolved by discussion with two other reviewers (PC and CD). We contacted study authors to retrieve data not available in published study reports. Data were extracted on patient characteristics including age, gender, severity of COPD (classified according to the Global Initiative for Chronic Obstructive Lung Disease staging) [27], depression and anxiety severity at baseline, and whether patients were recruited on the basis of identified depression and/or anxiety. Data extracted on interventions included intensity (duration, number, and length of sessions), setting (e.g. primary care, community centre), mode of delivery.
(e.g. individual or group, face to face or remote delivery), and the professionals involved (e.g. mental health professional, respiratory nurse). Data on outcomes relevant to the review (post-treatment depression and anxiety symptoms), comparator, and risk of bias were also extracted. Where studies combined COPD data with data for other respiratory disorders we wrote to authors to obtain separate data relevant to COPD patients.

### Risk of Bias

Risk of bias assessments were conducted independently for all included studies by two reviewers (CG and JK) using the Cochrane Collaboration tool [28]; discrepancies were resolved by discussion with a third reviewer (PC). Specifically, assessments were made that relate to: randomisation sequence generation, allocation bias, blinding of outcome assessment, losses to follow-up, incomplete outcome data (adequate statistical handling of missing data), and intention-to-treat. Evaluations of risk of bias associated with blinding of outcome assessments and incomplete outcome data were restricted to depression and anxiety outcomes.

### Data Analysis and Synthesis

For each study that included continuous outcomes for depression and anxiety, a standardised mean difference (SMD) was calculated by taking the mean of the intervention group minus the mean of the control group, divided by the pooled standard deviation (SD). If there were several follow-ups we used the outcome data closest to post-treatment. Effect sizes expressed as SMDs are a useful method to compare the effect of an intervention across studies when different measures (such as different depression scales) are used. In keeping with established cut-offs of effect in behavioural medicine, effect sizes of 0.56 to 1.2 were categorised as large; effect sizes of 0.33 to 0.55 as moderate, and effect sizes 0.32 as small [30]. In this review, negative effect sizes indicated that the intervention improved depression and anxiety; statements about significance refer to statistical significance within 95% confidence intervals. Where exact means and SDs were missing from published reports or not provided by the authors (k=4) we estimated effect sizes using conventional methods [31], from exact P values [32,33], and from a figure shown in the articles reviewed [34,35]. If an SD was missing (k=2) [36,37] we...
imputed SDs from a comparable study in the meta-analysis that used the same measure [38]. Where trials reported two intervention groups and a single control group, separate SMDs were calculated for each intervention group but in the pooled analyses the sample size of the control group was halved to avoid double counting.

Meta-analyses using random effects models were undertaken to estimate the average effect of interventions on symptoms of depression and anxiety. Heterogeneity was analysed with the $I^2$ index which represents the percentage of the total variability in a set of effect sizes due to between-study variability, rather than sampling error alone [39]; and by using Cochran’s $Q$ test, which is calculated as the weighted sum of squared differences between individual study effects and the pooled effect across studies. The $Q$ statistic follows a $\chi^2$ distribution with $k-1$ degrees of freedom, where $k$ is equal to the number of studies contributing to the meta-analysis [31]; $Q > k - 1$ suggests statistical heterogeneity with a cut-off value of 0.10.

Figure 4. Funnel plot of effect size versus standard error for depression outcomes.
doi:10.1371/journal.pone.0060532.g004

Figure 5. Funnel plot of effect size versus standard error for anxiety outcomes.
doi:10.1371/journal.pone.0060532.g005
The possibility of small publication bias (owing to the chance that significant studies are selectively published and not representative of all completed studies) was examined visually by scrutinising funnel plots and statistically using Egger’s test [40].

Meta-analysis and tests for small study bias were performed using Stata version 12 (Stata Corp. College Station, TX).

Sensitivity and Subgroup Analysis

We carried out a pre-specified sensitivity analysis by removing studies where allocation concealment was either inadequate or not known from the overall pooled analysis to evaluate the effect of risk of bias; trials in which randomisation is inadequately concealed or inadequately reported are known to be empirically associated with exaggerated treatment effects [41]. In addition, we also tested, post-hoc, whether missing data impacted on the size and direction of effect sizes by running a sensitivity analysis that excluded studies...
that reported losses of >20% at follow-up or where losses to follow-up were unknown, and studies that either did not report using intention-to-treat, or where it was not possible to judge if intention-to-treat had been used.

We undertook a subgroup analysis to investigate treatment effects within four separate groups of interventions: cognitive and behaviour therapy (CBT), multi-component exercise training, self-management education, and relaxation. To determine whether severity of depression and/or anxiety were associated with the effectiveness of interventions, we investigated treatment effects in two population subgroups: 1) studies that included confirmed depressed and/or anxious samples or above threshold samples; and 2) studies where depression and/or anxiety severity was unknown at baseline.

In addition, we undertook, post-hoc, sub-group analysis to determine the effects of all non-exercise based interventions to enable comparison with effect sizes for the overall pooled analyses for both depression and anxiety.

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**Figure 7. Effects of complex interventions by sub-group on self-reported symptoms of anxiety at post-treatment.** Note: Random effects model used. 95% CI = 95% confidence interval; SMD = standardised mean difference. doi:10.1371/journal.pone.0060532.g007
Results

Characteristics of Populations

Thirty two studies met the inclusion criteria, and included 35 relevant comparisons, of which 30 (n = 2063) could be included in the meta-analysis (Figure S1). All included studies were individually randomised controlled trials. The COPD patients had a median age of 66.3 years; one study recruited a male only sample (median 59% male). The majority of studies recruited patients with moderate [33–36,42–48] or severe COPD [38,49–60]; one study recruited patients with mild to moderate COPD [37], and in three studies patients in the intervention group had milder disease than patients in the control group, but this did result in baseline imbalance [32,61,62]. Only a minority of studies (k = 5) recruited patients with identified depression and anxiety [37,44,50,51,56]. In addition, using established cut-offs, seven studies reported baseline mean scores indicative of mild depression and four studies reported baseline mean scores indicative of mild anxiety. The average length of follow-up at post-treatment was 10.5 weeks (range 4 to 52 weeks). See Table 2 for population characteristics.

Characteristics of Interventions

The content, duration, intensity and delivery of the interventions varied considerably between the included trials. Over half (65%) of the interventions included both psychological and lifestyle components, while six included only psychological components [35,42,44,45,55,56], and four focused on lifestyle alone [34,38,46,48]. The most common psychological components were cognitive and behavioural interventions, problem solving techniques, relaxation and miscellaneous stress management interventions. The most common lifestyle components were structured exercise training, skills training, and education, typically as part of a pulmonary rehabilitation programme. The average number of treatment contacts (including remote contacts) was 18 (range 1 to 63), and the length of treatment sessions ranged from 30 to 240 minutes (mean 81.5 hours). Mean length of interventions was 11 weeks. A wide range of professionals and para-professionals (e.g. lay trainers) delivered the interventions, with the majority delivered face to face, either in groups or to individuals (see Table 3 for characteristics of interventions).
Risk of Bias
Seventeen (59%) of the 29 trials described an adequate method of random sequence generation, but only nine reported adequate methods of allocation concealment; the method of allocation concealment was unclear in 19 (65%) trials, and one trial did not conceal treatment allocation (Figure 1). Blinding of outcome assessors for anxiety and depression outcomes was reported in ten trials (34%). Losses to follow-up of >20% occurred in nine (31%) trials but only two of these reported using statistical methods (full information maximum likelihood method and substitution of baseline scores) to replace missing values at follow-up. Thirteen (45%) trials stated that an intention-to-treat approach was used.

Meta-analysis
Are psychological and lifestyle interventions effective in reducing symptoms of anxiety and depression in patients with COPD? Depression was reported in 29 trials and anxiety was reported in 26 trials. Interventions were associated with small, significant improvements in depression (SMD $-0.28$, 93% confidence interval $-0.41$ to $-0.14$, $I^2 = 47.5\%$, $P = 0.003$; Figure 2) and in anxiety (SMD $-0.24$, 95% confidence interval $-0.39$ to $-0.09$, $I^2 = 56.4\%$, $P = 0.000$; Figure 3).

Small Study Bias
We found no evidence of funnel plot asymmetry for either depression (Egger test $P = 0.413$; Figure 4) or anxiety (Egger test $P = 0.295$; Figure 5).

Sensitivity Analysis
Does risk of bias impact the size and direction of treatment effects? We removed from the pooled analyses for depression and anxiety studies in which the method of allocation concealment was either not reported or was inadequate. For depression, nine studies remained in the meta-analysis; the magnitude of the effect size increased marginally compared with the larger pooled analysis (SMD $-0.32$, 95% confidence interval $-0.56$ to $-0.08$, $I^2 = 59\%$, $P = 0.01$). For anxiety, eight studies remained in the meta-analysis, resulting in a small reduction of the effect size compared with the larger pooled analysis (SMD $-0.21$, 95% confidence interval $-0.40$ to $-0.02$, $I^2 = 33\%$, $P = 0.16$).

In a separate sensitivity analysis we also removed from the pooled analyses for depression and anxiety studies which reported losses of >20% at follow-up or where losses to follow-up were unknown, and studies that either did not report using intention-to-treat, or where it was not possible to judge if intention-to-treat had
been used. For depression, 17 studies remained in the meta-analysis resulting in a small reduction in the effect size, and lower but still significant heterogeneity compared with the larger pooled analysis (SMD $\pm 0.26$, 95% confidence interval $-0.41$ to $-0.12$, $I^2 = 39.3\%$, $P = 0.049$). For anxiety, 11 studies remained in the meta-analysis, resulting in a small reduction in the effect size and non-significant heterogeneity compared with the larger pooled analysis (SMD $\pm 0.20$, 95% confidence interval $-0.35$ to $-0.05$, $I^2 = 21.2\%$, $P = 0.242$).

**Subgroup Analyses**

**What types of psychological and lifestyle interventions are most effective?** The direction and magnitude of effect sizes were similar across the four intervention subgroups for both depression and anxiety outcomes (Figure 6 and Figure 7). The subgroup of trials that used multi-component exercise training [32,34,43,45,48,51–54,57,59,60,62] were associated with moderate to substantial heterogeneity (for depression $I^2 = 43.9\%$, $P = 0.040$; for anxiety $I^2 = 63.3\%$, $P = 0.002$). Small but non-significant effects were observed in the subgroup of trials that tested relaxation techniques [33,42,58,61]. Similarly, the subgroup of trials that tested CBT [35,37,44,49,55,56,63] were associated with the small, non-significant treatment effects. The subgroup that tested self-management education [36,46,47,50,52] were associated with no treatment differences between intervention and control groups for either depression or anxiety.

When studies that only tested non-exercise based complex interventions were pooled in a sub-group the overall results for depression ($k = 17$) and for anxiety ($k = 11$) favoured the intervention, but were non-significant (Figure 8 and Figure 9).

**Do these effects vary by patient population?** In the subgroup of studies ($k = 13$) that included confirmed depressed or above threshold samples the effects were very similar to the pooled effects from the larger group of treatment comparisons, (SMD $\pm 0.29$, 95% confidence interval $-0.49$ to $-0.10$, $I^2 = 54.6\%$, $P = 0.007$) (Figure 10). The effects of the subgroup of studies ($k = 8$) that included samples of confirmed anxious and above threshold samples were, like the pooled effects from the larger group of comparisons, small, but significant (SMD $\pm 0.21$, 95% confidence interval $-0.36$ to $-0.03$, $I^2 = 4.4\%$, $P = 0.398$) (Figure 11). Small, significant treatment effects were also observed for depression outcomes (SMD $\pm 0.24$, 95% confidence interval $-0.41$ to $-0.08$, $I^2 = 39.6\%$, $P = 0.052$) and anxiety outcomes (SMD $\pm 0.27$, 95% confidence interval $-0.49$ to $-0.05$, $I^2 = 67.3\%$, $P = 0.000$) in the

**Figure 10.** Effects on self-reported symptoms of depression in trials that included confirmed depressed samples or above threshold samples. Note: Random effects model used. 95% CI = 95% confidence intervals; SMD = standardised mean difference. doi:10.1371/journal.pone.0060532.g010
subgroup of studies that included samples where depression ($k = 16$) and anxiety ($k = 17$) severity was unknown at baseline (Figure 12 and Figure 13).

Discussion

Main Findings

This meta-analysis of 29 trials (30 comparisons) shows that complex psychological and/or lifestyle interventions that include exercise components are associated with moderate and significant treatment effects over the short term compared with usual care or active control groups. Small, non-significant treatment effects were found for the subgroups of trials that tested CBT and relaxation techniques. No significant difference in treatment effects were found for trials that compared self-management education with a control group. Overall, treatment effects were not substantially different in the subgroup of studies that included confirmed depressed and/or anxious samples or above threshold samples, and the subgroup of studies that included samples where severity of depression and/or anxiety was unknown.

Strengths and Limitations

This systematic review used rigorous search methods to identify all randomised controlled trials of complex interventions that included psychological and/or lifestyle components and measured depression and/or anxiety across a broad range of severity in people with COPD. Included trials differed significantly in terms of interventions, patient populations, study quality and follow-up times, which limits the extent to which broad conclusions can be made about the overall effectiveness of complex interventions for depression and anxiety in COPD populations.

However, we increased homogeneity by standardising follow-up times across outcomes and estimates of heterogeneity in the pooled analyses were moderate by conventional thresholds [39]. Moreover, there is a strong argument for avoiding narrow approaches to meta-analysis and to instead adopt broad and inclusive approaches that maximise power and allow exploratory (subgroup) analyses – meta-analyses can tolerate substantial clinical and methodological heterogeneity and publication bias and study quality may be a more important threats to validity of results [64]. We therefore tested for publication bias and investigated whether selection bias owing to inadequate allocation concealment exaggerated treatment effects for both outcomes. In addition we undertook a small series of pre-planned subgroup analyses to determine the relative effects of different interventions. While this approach might provide more useful data to support design and delivery of the most effective interventions for managing depression and anxiety in COPD, such subgroup analyses should be interpreted cautiously because other, unanalysed differences between studies might account for the results [65].

The optimal strategy to explore heterogeneity is to therefore use meta-regression which investigates whether particular covariates

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**Figure 11. Effects on self-reported symptoms of anxiety in trials that included confirmed anxious samples or above threshold samples.** Note: Random effects model used. 95% CI = 95% confidence intervals; SMD = standardised mean difference. doi:10.1371/journal.pone.0060532.g011
(potential ‘effect modifiers’) explain any of the heterogeneity of treatment effects between studies [66]. However, the results of meta-regression only represent observational not causal associations and lack power in the presence of small sample sizes. In addition, because the vast majority of complex intervention trials are still not designed, conducted or reported in line with the UK Medical Research Council Framework [67] it is difficult to isolate the active ingredients of interventions such as those included in this review using meta-regression, leading to calls to strengthen and improve the reliability of specifications of characteristics of behaviour change interventions [68].

It is plausible that the small effects of the overall pooled analyses reflect that only a subset of trials included in this review recruited patients with confirmed depression and/or anxiety. However, compared with the larger pooled analyses, treatment effects were not substantially larger in the subgroup of trials that included samples of confirmed depressed and/or anxious patients or above threshold samples. Furthermore, small, significant treatment effects were associated with the subgroup of trials that included samples where the severity of depression and/or anxiety status was not known. These results suggest that all trials in this review will have included patients with symptoms of depression and/or anxiety, including sub-threshold symptoms, which are known to affect health outcomes in long term conditions and should be proactively managed [69].

Finally, because the meta-analysis was based on post-intervention sample sizes it is possible that the results do not reflect intention-to-treat analyses but rather available case analyses. Even in those studies that imputed missing data using conventional methods, the final sample sizes may not truly reflect intention-to-treat analyses [70]. However, in the absence of raw individual patient data the meta-analyst is therefore reliant on using data from participants whose results are known and should instead address the potential impact of missing data through risk of bias assessments [65]. We followed this advice by performing a sensitivity analysis to exclude studies where intention-to-treat was not used or reported and where losses to follow up exceeded 20%. While there appeared to be no clinically relevant differences in observed effect sizes between this sensitivity analysis and the overall pooled analysis the presence or absence of an intention-to-treat approach and losses to follow-up may well account for significant amounts of heterogeneity, as indicated by the changes we observed in the significance tests for heterogeneity.

Figure 12. Effects on self-reported symptoms of depression in trials where severity of depression was unknown at baseline. Note: Random effects model used. 95% CI = 95% confidence intervals; SMD = standardised mean difference. doi:10.1371/journal.pone.0060532.g012
Additionally, three of the eligible studies did not contain meta-analysable data and attempts to contact study authors failed to recover usable data [71–73].

Implications for Research and Practice
The overall results of this review are in-keeping with those of comparable comprehensive reviews of the effectiveness of complex psychological and lifestyle interventions on depression in people with diabetes [26] and coronary heart disease [74]. All three reviews have shown that overall, complex psychological and/or lifestyle intervention reduce depression but the effects are small. However, our review differs from those by Harkness et al and Dickens et al because we have shown that the small but significant effects observed for the pooled analyses for both depression and anxiety outcomes is largely driven by the inclusion of positive trials that tested exercise interventions. Indeed, multi-component exercise training with or without psychological components, and ordinarily given as part of pulmonary rehabilitation, were the only sub-group of interventions that significantly reduce both depression and anxiety; this remained true even when outliers were removed from the analyses [38,59]. When expressed as a binomial effect the estimate of effect of multi-component exercise training on depression is equivalent to a clinical effect of 22% beyond chance, potentially benefiting 193 of the 878 patients included in this subgroup of trials in this review. In terms of absolute risk reduction, this is equivalent to a number needed to treat of 5–reductions in symptoms of depression would be expected in 1 in 5 (95% confidence interval 3.5 to 6.4) patients exposed to multi-component exercise training.

When expressed as a binomial effect, the effect of multi-component exercise training on anxiety is less than for depression, equivalent to a clinical effect of 9.8% beyond chance, potentially benefiting 73 of the 719 patients in this subgroup of trials included in this review. This equates to a number needed to treat of 11–reductions in symptoms of anxiety would be expected in 1 in 11 (95% confidence interval 5.8 to 38.5) patients exposed to multi-component exercise training.

Exercise may offer patients an alternative and effective approach to managing depression, especially for those with physical comorbidities who have concerns about the antagonistic effects and burden of multiple medications [75]. However the science underpinning the use of exercise to treat depression is...
uncertain and even less robust in relation to anxiety. Based on high quality trials alone a Cochrane review has shown that exercise can improve depression in adults without long term conditions, and is as effective as cognitive therapy, but the effects are small [76]. By comparison two large meta-analyses concluded that exercise training, undertaken for 30 minutes for 3 to 12 weeks has positive effects on depression and anxiety in people with long term conditions [77,78]. While novel in their insights about the efficacy of exercise for depression and anxiety in chronically ill populations, the reviews by Herring et al only included a small number of COPD trials and did not look at the comparative effectiveness of other psychological or lifestyle interventions. By contrast our review is the first to specifically demonstrate that structured exercise training significantly reduces both symptoms of depression and anxiety in people with COPD. Furthermore we have showed that structured exercise training is more effective than other, complex psychological behavioural and lifestyle interventions previously thought to improve mental health in people with COPD.

While this review therefore represents a considerable advance on understanding the positive role exercise training can play in managing depression and anxiety in COPD, its main finding appears at odds with the results of a facilitated exercise intervention which increased physical activity but did not reduce depression or use of anti-depressants over 12 months in primary care patients with recognised depression [79]. However, the negative and controversial results of the trial by Chalder et al can be partly be explained by the fact that patients in the two arms engaged in very similar levels of exercise. Additionally, it is likely that the overall effect size of this trial was diluted by heterogeneity of response among individuals and we do not fully understand the factors that relate to this heterogeneity [80]. Moreover, outside of the context of pulmonary rehabilitation, increasing physical activity in sedentary and depressed and/or anxious COPD patients remains a challenge. This is especially true in primary care, but advice and counselling are effective methods to promote increased physical activity for people with and without long term conditions [81], whereas the cost-benefits of exercise referral schemes are uncertain [82].

The finding that CBT is not as effective as exercise training for depression or anxiety in COPD is inconsistent with clinical guidelines that recommend using low intensity psychological interventions as first line therapy for treating depression and anxiety in people with long term conditions [11]. CBT has a similar efficacy profile to antidepressants for managing depression and anxiety disorders [83], but in this review we found that the effectiveness of CBT is possibly reduced in the presence of COPD. Methodological parameters might partly account for this finding as a number of included trials in this subgroup compared CBT with active controls [55,56,63]. Alternatively, compared with exercise, CBT places relatively high cognitive demands on patients and treatment response to this form of psychological therapy may be compromised among older adults with cognitive impairments in memory, attention, and executive function. Patients in the CBT trials included in this review were generally over 60 years old and their engagement with CBT could have thus been affected by the presence of cognitive impairments. In addition, there is consistent evidence that COPD, in both non-hypoxic and hypoxic individuals, is associated with cognitive dysfunction not ordinarily associated with other comorbidities [84], further suggesting that CBT may not be appropriate for COPD patients with significant cognitive impairments.

The negative results for the CBT sub-group in this review may also owe to the fact that CBT, which centres on challenging thoughts and setting behavioural goals, is difficult to accommodate by people with COPD whose ruminative thinking and avoidance behaviours are associated with real and meaningful symptoms, especially dyspnoea. While there is growing evidence that CBT can improve generalised anxiety disorder and global mental health in older adults with medical diagnoses [93], psychological interventions that promote an ‘accepting mode of response’ such as mindfulness might be more appropriate and effective for managing psychological distress in COPD patients, especially breathing related anxiety. Mindfulness based interventions are associated with longer term benefits on psychological health than stand alone relaxation interventions [86], but their usefulness in COPD is yet to be established [87].

The least effective interventions in this review were self-management education programmes with or without action plans, and case management. Self-management education in COPD can prevent hospital admissions but they have little effect on other important outcomes such as exacerbations, respiratory symptoms, medication use and exercise capacity [88], and their effect on anxiety and depression has not been specifically assessed. By contrast, case management approaches that draw on integrated and collaborative approaches such as the chronic care model have been shown to reduce depression and improve physical health in people with diabetes and coronary heart disease [89], but their effectiveness and safety in COPD is unknown [90]. Developing integrated and collaborative care models that enhance opportunities for therapeutic synergies between mental and physical health is a major priority of advanced health systems confronted with increased prevalence and burden of multimorbidity [91]. There is then scope to explore the effectiveness of collaborative care models in the management of COPD, specifically testing whether the integration of exercise training in such models can confer physical and mental health benefits in people with COPD.

Conclusion

Complex psychological and/or lifestyle interventions that include exercise training reduce symptoms of depression and anxiety in people with COPD over the short term. Additionally, complex interventions that included exercise training, with or without psychological components, were associated with the largest treatment effects in people with COPD across a range of disease severity when compared with usual care or active control groups. We were not able to determine the optimal dose of exercise training but the most effective interventions in this subgroup typically comprised 3 to 12 weeks of ≥30 minute sessions of group based exercise training in the context of pulmonary rehabilitation. No other intervention subgroups, including CBT, were associated with significant treatment effects. Treatment effects were no larger in trials that included confirmed depressed and/or anxious samples or above threshold samples, than in trials where severity of depression and anxiety was unknown at baseline. In conclusion, exercise training can have adventitiously positive effects on psychological health in all COPD patients, even among those with sub-threshold levels of depression and anxiety.

Supporting Information

Figure S1  PRISMA flowchart. 
(TIF)

Appendix S1  PRISMA checklist. 
(DOC)

Appendix S2  Search strategies. 
(DOC)
Conducted data search: JK CG C. Keyworth C. Kenning. Extracted data: PC JK CG C. Keyworth C. Kenning. Conceived and designed the experiments: PC. Performed the experiments: PC CD PB. Analyzed the data: PC CD PB. Wrote the paper: PC PB JK DH AM.

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