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The Relationship of Breathlessness with Psychological Distress and Quality of Life in Adults with Advanced Disease

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List of abbreviations

6MWT	Six-Minutes-Walking-Test
ALS	Amyothrophic lateral sclerosis
AMOS	Analysis of a moment structures
ASI-3	Anxiety Sensitivity Index-3
BDI/TDI	Baseline and Transition Dyspnea Indexes
BMI	Body Mass Index
BTF	Breathing – Thinking - Functioning
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CES-D	Center for Epidemiological Studies Depression Scale
CFI	Comparative fit index
CHF	Congestive heart failure
CI	Confidence Interval
COAD	Chronic Obstructive Airways Disease
COPD	Chronic obstructive pulmonary disease
CRQ	Chronic Respiratory Disease Questionnaire
CRQ-D	Dyspnea domain of the CRQ
CRQ-M	Mastery domain of the CRQ
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders (4^{th} version)
DSMP	Dyspnea Self-Management Program
eDSMP	Internet-based DSMP
EFA	Exploratory factor analysis
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D-5L	EuroQol Five Dimension Scale
FACT-G	Functional Assessment of Cancer Therapy–General
fDSMP	Face-to-face DSMP
FEV_1	Forced Expiratory Volume in the first second
FEV_1 (%)	Percentage of predicted FEV_1 value
FVC	Forced Vital Capacity
GAD-7	Generalized Anxiety Disorder 7
GHQ	General Health Questionnaire
GI	GastroIntestinal cancer
GOLD	Global Initiative for Chronic Obstructive Lung Disesase

HADS	Hospital Anxiety and Depression Scale
HRSD	Hamilton Rating Scale for Depression
I^2	Statistical heterogeneity
IBM	International Business Machines
ILD	Interstitial lung disease
IPF	Idiopathic pulmonary fibrosis
IPOS	Integrated Palliative Care Outcome Scale
IQR	Interquartile range
KCCQ-12	Kansas City Cardiomyopathy Questionnaire-Short Form
LMU	Ludwig-Maximilians-Universität München
MAR	Missing at random
MD	Mean differences
MLHFQ	Minnesota Living with Heart Failure Questionnaire
mMRC	Modified MRC
MND	Motor neuron disease
MRC	Medical research council breathlessness scale
MSAS	Memorial Symptom Assessment Scale
NCT	National Clinical Trial
NMAR	Not missing at random
NR	Not Reported
NRS	Numerical Rating Scale
NSCLC	Non-Small Lung Cancer
NYHA	New York Heart Association
O_2	Oxygen
p	Probability value
PCA	Principal Components Analysis
PEF	Peak Expiratory Flow
PEG	Pain, Enjoyment and General Activity Scale
PFSDQ-M	Pulmonary Functional Status & Dyspnoea Questionnaire-modified
PHQ-8	Patient Health Questionnaire eight-item depression scale
PICOS	Population, intervention, comparator, outcome, study design
PR	Pulmonary rehabilitation
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QoL	Quality of Life

qRCT	quasi-RCT
r	Correlation coefficient
RCT	Randomised Controlled Trial
RevMan	Review Manager
RMSEA	Root-Mean-Square Error of Approximation
SCID	Structural Clinical Interview for DSM disorders
SD	Standard Deviation
SEM	Structural Equation Modelling
SF-36	36-Item Short Form Survey
SGRQ	St. George's Respiratory Questionnaire
SMD	Standard Mean Differences
SPACE	Self-management Programme of Activity Coping and Education
SPO_2	Peripheral Oxygen Saturation
SPPB	Short Physical Performance Battery
SPSS	Statistical Package for Social Sciences
SSAI/STAI	Spielberger State/Trait Anxiety Inventory
TAU	Treatment As Usual
TNM	Tumour, Nodes and Metastases
UCSD-SOBQ	The University of California, San Diego Shortness of Breath Questionnaire
USA	United States of America
VAS	Visual Analogue Scale
WHO	World Health Organisation
ZBI	Zarit Burden Interview

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Summary

Background: Breathlessness is one of the most common and burdensome symptoms in many advanced diseases, for example different types of cancer, respiratory diseases or neurological diseases. Besides breathlessness, anxiety and depression disorders are common symptoms in adults with advanced disease. The effects of sociodemographic or clinical characteristics on the relationships between breathlessness, psychological distress and quality of life is less investigated. Furthermore, the effects of different interventions targeting cognitive-emotional mechanisms of breathlessness are not fully understood.

The aim of the present dissertation was to investigate the complex symptom breathlessness in adults with advanced disease and to gain a better understanding of relationships between breathlessness, quality of life and psychological distress as well as the effects of cognitive-emotional interventions.

Methods: Secondary data analyses of cross-sectional data. Sociodemographic and clinical characteristics were analysed descriptively. Correlations between sociodemographic variables, breathlessness (MRC, IPOS, NRS and CRQ-M), psychological distress (HADS) and quality of life (EQ-VAS) were investigated. A structural equation model was built to analyse the relationships between the three constructs of interest.

Additionally, a Cochrane systematic literature review was conducted. Randomised controlled trials were included, if they determined the effects of cognitive-emotional interventions (‘counselling and support’, ‘meditative movements’, ‘psychotherapy’, ‘mindfulness-based stress reduction’ or ‘self-management)’ to active or inactive control for breathlessness in adults with advanced diseases and had at least one measure of breathlessness. Both active and inactive controls were allowed as comparators. Studies were eligible, if any measure of breathlessness were used (primary outcome). Secondary outcomes included psychological distress and quality of life.

The conduct of the review followed Cochrane guidelines, including screening of relevant publications and data extraction of included trials by two researchers individually.

Continuous data were analysed using mean differences (MD) or standardised mean differences (SMDs) with 95% CIs. Meta-analyses were only undertaken if studies were judged to be similar enough to give a clinically meaningful answer. Otherwise, a narrative summary of the results was reported. The risk of bias assessment was carried out using the Cochrane criteria.

Results: Descriptive analysis showed that subjective experience of breathlessness, psychological distress and quality of life did not correlate with underlying disease or age, but with marital status and educational level. The structural equation model showed significant relationships between the three constructs, and 79% of the variance in breathlessness could be explained with psychological distress and quality of life. The systematic literature review found significant differences or positive trends favouring cognitive-emotional interventions for all three outcomes of interest, when compared to inactive control groups. Narrative synthesis of the remaining data was inconclusive about possible effects.

Discussion: This dissertation presents evidence that breathlessness in adults with advanced disease is correlated with different sociodemographic variables and other constructs. The variance in breathlessness can largely be explained by psychological distress and quality of life. Furthermore, cognitive-emotional interventions may reduce breathlessness as well as psychological distress and improve quality of life. Missing standardization, different or no definitions and the complexity of the palliative situation is an ongoing issue in this research field. Causal relationships and specific factors of each construct that either affects or is affected by other constructs as well as patients' characteristics (such as educational level) and has an impact on the effects of cognitive-emotional interventions should be investigated further. However, in order to increase reproducible research and understand the 'vicious cycles', clear definitions and less generic, but setting-specific measurements of constructs should be developed.

German summary/Zusammenfassung

Der Zusammenhang von Atemnot mit psychischer Belastung und Lebensqualität bei Patienten mit fortgeschrittenen Erkrankungen

Hintergrund: Atemnot ist eines der häufigsten und belastendsten Symptome von Erwachsenen mit fortgeschrittenen Erkrankungen, z. B. verschiedene Krebserkrankungen, Atemwegserkrankungen oder neurologische Erkrankungen. Außerdem leiden schwer erkrankte Erwachsene mitunter an psychischer Belastung und geringer Lebensqualität. Die Effekte soziodemographischer und klinischer Variablen auf die Zusammenhänge zwischen Atemnot, psychischer Belastung und Lebensqualität sind noch wenig untersucht. Ebenfalls wenig untersucht ist die Wirksamkeit von kognitiv-emotionalen Interventionen für Atemnot bei schwererkrankten Erwachsenen.

Ziel dieser Arbeit war es, das komplexe Symptom Atemnot bei schwer erkrankten Erwachsenen zu untersuchen. Des Weiteren sollte ein besseres Verständnis zwischen den Zusammenhängen des Symptoms mit psychischer Belastung und Lebensqualität sowie die mögliche Wirksamkeit kognitiv-emotionaler Interventionen auf Atemnot entwickelt werden.

Methoden: Sekundärdatenanalysen von Querschnittsdaten. Soziodemographische und klinische Variablen wurden deskriptiv analysiert. Korrelationen wurden zwischen soziodemographischen Variablen, Atemnot (gemessen mit MRC, IPOS, NRS und CRQ-M), psychischer Belastung (gemessen mit HADS) und Lebensqualität (gemessen mit EQ-VAS) untersucht. Mit einem Strukturgleichungsmodell wurden im nächsten Schritt die Beziehungen aller drei Konstrukte Atemnot, psychische Belastung und Lebensqualität analysiert und explorativ die Abhängigkeit dieser Beziehungen von soziodemographischen Faktoren geprüft.

Zusätzliche wurde ein systematischer Literaturreview nach Cochrane durchgeführt. Randomisiert kontrollierte Studien mit schwer erkrankten Erwachsenen wurden eingeschlossen, wenn die Wirksamkeit kognitiv-emotionaler Interventionen untersucht wurde und Atemnot als Outcome definiert war. Sowohl aktive als auch inaktive Kontrollgruppen wurden akzeptiert. Es kamen Studien in Frage, welche Atemnot

gemessen haben (primäres Outcome). Sekundäre Outcomes waren psychische Belastung und Lebensqualität.

Gemäß den Richtlinien von Cochrane folgend, wurden alle relevanten Referenzen und die Datenerhebung von zwei Forschenden unabhängig durchgeführt. Kontinuierliche Daten wurden mittels (standardisierter) Mittelwertunterschiede und 95%-Konfidenzintervallen analysiert. Meta-Analysen wurden nur durchgeführt, falls eingeschlossene Studien als vergleichbar galten, um eine klinische relevante Antwort zu erhalten. Andernfalls wurden die Ergebnisse narrativ zusammengefasst. Die Risikobewertung der eingeschlossenen Studien erfolgte ebenfalls nach den Cochrane-Kriterien.

Ergebnisse: Deskriptive Analysen zeigten, dass die subjektive Empfindung von Atemnot, psychischer Belastung und Lebensqualität nicht mit der zugrunde liegenden Erkrankung oder dem Alter korrelierten, dafür aber mit dem Bildungslevel und dem Familienstand. Das Strukturgleichungsmodell ergab signifikante Zusammenhänge zwischen den drei Konstrukten. Dabei wurden 79% der Varianz der Atemnot durch psychologische Belastung und Lebensqualität erklärt. Der systematische Literaturreview lieferte Hinweise auf die Wirksamkeit kognitiv-emotionaler Interventionen. Die Meta-Analysen zeigten signifikante Ergebnisse bzw. Trends für die Wirksamkeit dieser Interventionen im Gegensatz zu den inaktiven Kontrollgruppen. Die narrativen Zusammenfassungen der übrigen Daten ergaben keine weiteren Hinweise.

Diskussion: In dieser Arbeit konnte nachgewiesen werden, dass Atemnot bei schwererkrankten Erwachsenen mit soziodemographischen Variablen und anderen Konstrukten korreliert. Die Varianz der Atemnot kann größtenteils durch psychische Belastung und Lebensqualität erklärt werden. Außerdem könnten kognitiv-emotionale Interventionen Atemnot bei schwererkrankten Erwachsenen verbessern. Fehlende Standardisierungen, unterschiedliche oder gar nicht vorhandene Definitionen sowie die insgesamt komplexe Situation in der Palliativmedizin sind andauernde Herausforderungen in diesem Forschungsgebiet. Kausale Beziehungen zwischen verschiedenen, zu spezifizierenden Faktoren jedes Konstrukts, das entweder andere Faktoren affiziert oder durch andere Faktoren sowie soziodemographische Daten wie

Bildungsniveau affiziert wird, sowie mögliche Auswirkungen auf die Wirksamkeit kognitiv-emotionaler Interventionen sollte weiter untersucht werden. Jedoch sollte für eine reproduzierbare Forschung und zum besseren Verständnis der ‚Teufelskreise' zwischen den Konstrukten klare Definitionen und weniger allgemeine, sondern an das Setting angepasste Messinstrumente entwickelt werden.

1. Background

Adults with advanced disease suffer from several symptoms, including pain, fatigue, breathlessness, anorexia, constipation, anxiety, and depression (Blinderman 2008, Elkington 2004, Janssen 2011, Lagman 2005, Potter 2003, Solano 2006). On average, these patients report eleven symptoms (Gift 2004, Walsh 2000). These symptoms may be related to the underlying disease, received treatments or due to the life-limiting situation (Koesel 2019, Ryan 2013, Sarna 1993).

1.1. Breathlessness

Breathlessness is one of the most common and burdensome symptoms in many advanced diseases, for example different types of cancer, respiratory diseases or neurological diseases (Bailey 2010, Booth 2008, Breaden 2011, Lansing 2009, Solano 2006). Reported prevalence numbers of patients experiencing breathlessness are high and range between 60% to 88% for heart disease, and between 90% to 95% in chronic obstructive pulmonary disease (COPD) (Solano 2006). Prevalence of breathlessness increases at the end of life, regardless of the underlying disease (Currow 2010).

A widely accepted definition of this complex symptom is suggested by the American Thoratic Society describing breathlessness as "*a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. The experience derives from interactions among multiple physiological, psychological, social, and environmental factors, and may induce secondary physiological and behavioral responses.*" (American Thoracic Society 1999).

Severity of breathlessness can have different causes. The breathing-thinking-functioning (BTF) model, presented in Figure 1, identifies three vicious cycles that are associated with breathlessness (Booth 2014):

- Breathing: Inefficient breathing and higher work of breathing based on dysfunctional breathing with increased breathing rate, and the need of accessory muscles.

- Thinking: Incorrect expectations and increased focus on the sensation of breathlessness (for example remembering past negative experiences) lead to anxiety, stress, panic attacks and thoughts about dying.
- Functioning: Severe breathlessness lead to a less active lifestyle, increasing social isolation and more need of assistance and deconditioning of respiratory muscles.

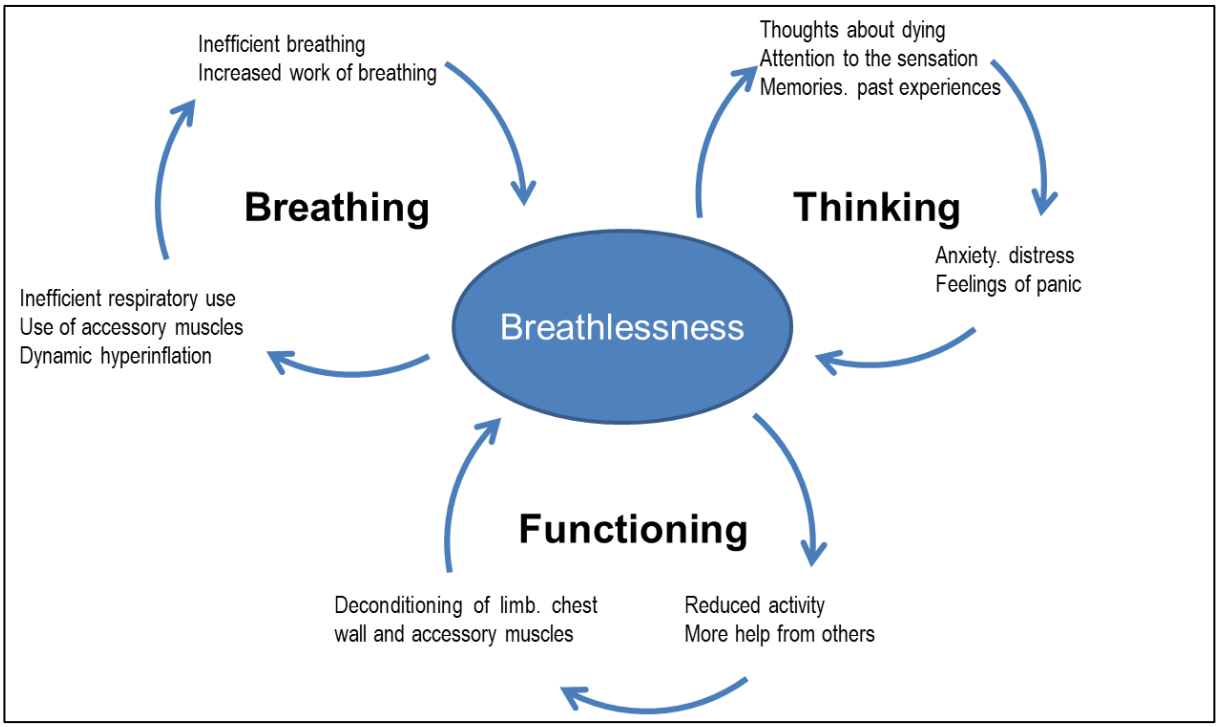


Figure 1 Breathing - Thinking - Functioning Model; adapted version based on Booth 2014

The measurement of breathlessness remains complicated due to the subjective experience of breathlessness and poor correlation with clinical parameters (Hajiro 1999, Wegner 1994, Wolkove 1989). In the last decades, a variety of uni- and multidimensional measures were developed with the focus on breathlessness itself (for example frequency or severity) or different dimensions (for example psychosocial or physical) (Bausewein 2008, Bausewein 2007, Dorman 2007). Both cited systematic literature reviews of Bausewein 2007 and Dorman 2007 identified more than 35 and 29 breathlessness measures, respectively, which shows the complexity of measuring breathlessness.

1.2. Psychological distress

Besides breathlessness, anxiety and depression are common symptoms in adults with advanced disease (Maurer 2008, Van Lancker 2014). Wide ranges for the prevalence of anxiety and depression can be found in the literature: Prevalence of depressive symptoms was between 0% - 58% in cancer patients (Massie 2004) with one study reporting a prevalence of depression symptoms for 87%-92% in cancer patients (Castelli 2009). A meta-analysis identified ranges between 1% - 49% for anxiety and 0% - 46% for depressive symptoms (van't Spijker 1997). Another review reported 1% - 76% prevalence of several psychological disorders (Crunkilton 2009). A review, amongst others investigating the variety of psychological disorders in common advanced diseases, presented wide prevalence ranges, regardless of the underlying disease (Moens 2014).

Several factors contribute to the variety in prevalence rates, for example demographic factors (for example age or education), stage of the underlying disease (for example cancer, CHF, etc.), uncontrolled symptoms (for example pain), or other domains of well-being (Brenes 2003, Ciaramella 2001, Hong 2014, King 2005, Spiegel 1994).

Another reason for wide prevalence estimates of anxiety and depression is the use of different assessment of these symptoms. A variety of in depth-interviews and self-reported measurements exist for different types of psychological distress, including anxiety and depressive symptoms (Maurer 2008). Even though diagnostic interviews are referred to as the ‘gold standard’ for the assessment of psychological disorders (Wing 1990), screening tools rather than a full diagnostic assessment are most often used in palliative care (Kelly 2006, Thekkumpurath 2008). Reasons for this development include critical discussions about the appropriateness of these interviews in the palliative care setting, especially because of the comprehensiveness and the related burden of administration for the palliative patient as well as possible misinterpretation of ‘depressive’ symptoms that are actually due to the underlying disease (Atkin 2017, Kaasa 2003, Kelly 2006).

However, even though screening tools can be very helpful as an indicator for the potential occurrence of these symptoms, these measurements should not be confused with the comprehensive assessment or manifest diagnosis (Thekkumpurath 2008, Zabora 2001).

In order to avoid confusion about terminology, the broader term ‘psychological distress’ is used in this dissertation. This term “*covers a wide spectrum, ranging from normal feelings of vulnerability, sadness, and fears to problems that can become disabling, such as depression, anxiety, extensive worries, negative thoughts, or social isolation.”* (Hardiess 2015)

1.3. Quality of life

‘Quality of life’ is a multidimensional construct, and several definitions and approaches exist for the term ‘quality of life’ (Thaniyath 2019). Following the suggestion of Post 2014 that a definition of ‘quality of life’ should be provided that fits the research topic, the term will be defined in more detail and discussed in the palliative care context next.

The definition for overall quality of life in this dissertation is based on the WHO definition, stating quality of life as “*an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, personal beliefs, social relationships and their relationship to salient features of their environment*” *(World Health Organisation 1993).*

The concept of quality of life in medicine is an ongoing topic of discussion but is most commonly described as health-related quality of life (Kaasa 2003). Health-related quality of life includes physical, functional, social and mental factors (Aaronson 1988, Kaasa 2003, Post 2014, Thaniyath 2019). However, in palliative care, the different objectives of the provided care due to the life-limiting situation should also be reflected in the concept of health-related quality of life (Kaasa 2003). Therefore, several domains can be identified, for example health, spiritual, coping and also the involvement of the family (Kaasa 2003, McCaffrey 2016). In this dissertation, the term quality of life will be used for health-related quality of life, but it is acknowledged that health is only one aspect of quality of life (Ferrans 1990, Post 2014).

Even though a variety of quality of life measurements exist, the adaption and validation for the palliative care context is challenging (Lundh Hagelin 2005). Multi-dimensional questionnaires are often too time-consuming and do not match the special situations of palliative care patients, for example preparation for death (McCaffrey 2016). Generic measurements can be used to compare the level of quality of life between groups (Megari 2013). For example, it was found that for patients with cancer, quality of life is low and does not depend on the type of cancer (Götze 2014). A study with severely ill haemodialysis patients in an outpatient clinic reported substantially low quality of life (Weisbord 2003). Similar results were found in a study comparing quality of life in patients with either end stage renal disease or cancer (Saini 2006).

1.4. Relationships between breathlessness, psychological distress and quality of life

Growing evidence indicates relationships between breathlessness, psychological distress and/or quality of life (Booth 2019, Faller 2009, Götze 2014, Gruenberger 2017, Hajiro 1999, Henoch 2008, Kim 2017, Paz-Díaz 2007, Skarstein 2000).

Breathlessness and psychological distress

Studies including adults with advanced or terminally ill cancer showed significant correlations between breathlessness and psychological distress (Chiu 2004, Montazeri 2003, Tanaka 2002). As the correlation is positive, higher psychological distress is associated with worse breathlessness. The relationship between both symptoms is incorporated in the BTF model (in form of the cognitive-emotional cycle) (Booth 2014, Spathis 2017). The investigation of causal relationships between psychological distress and breathlessness is challenging, as symptoms of the underlying disease overlap with psychological distress (Mitchell 2011). Even though underlying mechanisms are not fully understood, pathophysiological evidence supports the assumption that psychological distress causes breathlessness due to changing respiratory sensations and ventilation (O'Donnell 2007, Tselebis 2016). This causal relationship was also observed in a study including 515 adults from the general population (Neuman 2006).

Breathlessness and quality of life

Studies with COPD patients presented significant correlations between quality of life and breathlessness (Gruenberger 2017, Hajiro 1999). The negative correlation indicates that worse breathlessness is associated with lower quality of life (Currow 2017). As a side note, the study of Hajiro 1999 also reported that self-reported breathlessness correlates better with quality of life than clinical parameters. The evidence about the causal relationship between quality of life and breathlessness is less clear. In general, better quality of life leads to less severe symptoms (Megari 2013). The impact of low quality of life on breathlessness in adults with advanced disease has to be examined in more detail.

Psychological distress and quality of life

Worse psychological distress correlates with lower quality of life (Götze 2014, Kim 2017). Studies with palliative patients reported relationships between psychological distress and quality of life (Evangelista 2012, Pelletier 2002). There is evidence that worse psychological distress lowers quality of life (Akechi 2004, Brenes 2003, Miravitlles 2017).

Breathlessness, psychological distress and quality of life

Even though all three variables seem to be correlated, studies focused on the prevalence of breathlessness or psychological distress and the level of quality of life rather than the relationship between these variables (Götze 2014, Moens 2014, Solano 2006). A model for estimating the effects of both psychological distress and quality of life on breathlessness has yet to be developed.

1.5. Sociodemographic and clinical characteristics and its relationships with breathlessness, psychological distress and quality of life

Different clinical and sociodemographic characteristics, for example age, gender, disease severity, marital status and education level influence the severity of breathlessness, psychological distress and quality of life:

Age: Younger age correlates with worse breathlessness, worse psychological distress and lower quality of life (Borge 2010, Kim 2017, Lundh Hagelin 2005).

Gender: Women report worse breathlessness, lower quality of life and worse psychological distress (Hayen 2013, Laurin 2007, Walsh 2000).

Disease severity: Advanced stage of the underlying disease is associated with worse psychological distress (Cleland 2007, Degner 1995, Kim 2017).

Marital status: Marital status is associated with different levels of breathlessness, psychological distress and quality of life (Bowden 2011, Lundh Hagelin 2005, Tel 2013).

Education level: Lower levels of education are associated with worse breathlessness, worse psychological distress and lower quality of life (Borge 2010, Kim 2017, Moons 2004).

Due to many factors described above, as well as additional effects not discussed in more detail (for example different settings), the experience of palliative symptoms is dynamic,

and may therefore lead to different symptom clusters (Omran 2017). However, the relationships of sociodemographic or clinical characteristics and breathlessness, psychological distress and quality of life is less investigated. Age and gender influenced symptom patterns in a study with 1,358 cancer patients (Cheung 2011). Similar results were reported in a study with hospice patients (Omran 2017).

1.6. Cognitive-emotional interventions for breathlessness

Several interventions for breathlessness have been developed and investigated in the last decades. As the effects of pharmacological treatments is analysed in several current reviews (Ameer 2014, Barnes 2016, Cranston 2008, Mahler 2013, Sharp 2016, Simon 2016), non-pharmacological interventions for breathlessness will be the sole focus in this dissertation.

In more detail, different interventions targeting the cognitive-emotional cycle of breathlessness (see Figure 1) are of interest:

- **Counselling and support** includes interventions based on specific follow-up programs after treatment (including pulmonary rehabilitation), for example telephone-based follow-ups, support provided by nurse specialists, or counselling to increase physical activity (Burtin 2012, Faithfull 2001, Moore 2002).

- **Meditative movements**, combining body movements or positioning, and focusing on breathing and/or calm state of mind or cleared mind, aiming to achieve relaxation (Larkey 2009). The term “meditative movements” is used in this dissertation, but it is acknowledged that other definitions for these types of interventions exist, for example “mind-body therapies” (Pölönen 2019).

- **Mindfulness based stress reduction**, which are techniques based on relaxation and meditation mechanisms to create a level of stress relieve and relaxation by withdrawing surrounding distractions (Glanze 2012).

- **Psychotherapy**, for example cognitive behavioural therapy, is used to stop the avoidance of physical activity and to break the vicious cycle of breathlessness, which encompasses several components, for example problem-solving techniques (von Leupoldt 2012).

- **Self-management** includes a variety of interventions, which are defined as structured programs to increase coping abilities. There are a variety of techniques, for example teaching about the underlying disease and early recognition of breathlessness attacks, management of associated symptoms like anxiety, or the use of relaxation techniques (Gadoury 2005, Johnson-Warrington 2016, McGeoch 2006, Zwerink 2014) .

Reviews indicate effects of cognitive-emotional therapies, but most reviews did not focus on adults with advanced disease and/or did not have breathlessness as primary outcome of interest (Baraniak 2011). The impact of the effects of cognitive-emotional interventions for breathlessness on psychological distress and quality of life have yet to be investigated. Furthermore, it is unknown how the effects of these interventions relate to patients' characteristics.

Summary of the introduction

Adults with advanced disease suffer from several symptoms, including breathlessness and psychological distress, and have a lower quality of life when compared to the general population. Relationships between breathlessness, psychological distress and/or quality of life exist. However, relationships and the effects of sociodemographic factors on these relationships have yet to be investigated in more detail.

There are many pharmacological and non-pharmacological interventions for breathlessness in advanced disease. The effects of the non-pharmacological interventions, targeting cognitive-emotional mechanisms to relieve breathlessness are unclear. Furthermore, the interplay of the relationships between the three factors and patients' characteristics on the effects is not fully understood.

2. Aims and objectives

The aim of the present dissertation is to investigate the complex symptom breathlessness in adults with advanced disease and to gain a better understanding of relationships between breathlessness, quality of life and psychological distress as well as the effects of cognitive-emotional interventions.

The objectives are therefore:

(1) To describe sociodemographic and clinical characteristics regarding breathlessness, low quality of life and psychological distress of adults with advanced disease;
(2) To examine the relationships between breathlessness and psychological distress as well as quality of life;
(3) To assess the effects of interventions targeting cognition, emotion or both to relieve breathlessness in adults suffering from advanced disease as well as the effects of these interventions on quality of life and psychological distress.

3. Methods

This chapter will give a methodological overview as well as a detailed description of the research methods used for data collection and analysis.

Given the different levels of objectives, two different studies were conducted:

Study 1: Relationships between breathlessness, quality of life and psychological distress

The first study was a secondary data analysis of cross-sectional study baseline data of the BreathEase trial (NCT02622412) to determine objectives (1) and (2). The checklist "Gute Praxis Sekundärdatenanalyse" ["*good practice in secondary data analysis*"] as well as guidelines for reporting structural equation modelling were taken into account to ensure high scientific standards (Schreiber 2006, Swart 2014) .

Study 2: Effects of cognitive-emotional interventions for breathlessness

The second study, a systematic literature review, was conducted to examine objective (3). This systematic literature review is part of a series of Cochrane reviews and therefore following the Cochrane guidelines to ensure high scientific standards (Higgins 2011). In accordance to these guidelines, protocols were published prior to the conduct of the series (Bolzani 2017a, Bolzani 2017b, Bolzani 2017c). Wording of the protocols as well the methods section of this dissertation are based on Cochrane templates and published Cochrane guidelines (AUREF 2012, Higgins 2011). The protocol can be found in Appendix A. During the conduct of systematic reviews, protocols cannot always be followed due to necessary refinements of methods, specification of analyses, or other reasons. Differences between the published protocols and this dissertation are therefore summarized in Appendix B.

Cochrane systematic literature reviews cannot be conducted by an individual researcher, because several tasks should be individually undertaken by two researchers to improve the quality of the systematic literature review. Therefore, the responsibilities of each author of this series of Cochrane reviews are presented in Appendix C.

3.1. Study 1: Relationships between breathlessness, psychological distress and quality of life

3.1.1. Study design

Secondary data analyses of cross-sectional baseline data of a randomised controlled trial.

This study is a secondary-data analysis using individual-patient data from the BreathEase trial (NCT02622412), an evaluation study of the breathlessness service offered at the Department of Palliative Medicine, University Hospital, LMU Munich (ClinicalTrials.gov 2020). The Research Ethics Committee of Ludwig-Maximilians-Universitaet Munich (reference number 523-14) approved the trial.

3.1.2. Description of data source

3.1.2.1. Inclusion and exclusion criteria

Inclusion and exclusion criteria are presented in Table 1 (shortened and adapted version from ClinicalTrials.gov).

Table 1 Inclusion and exclusion criteria of BreathEase (adapted from ClinicalTrials.gov)

Inclusion criteria	Exclusion criteria
Adults with breathlessness due to advanced disease	Adults with breathlessness due to asthma, chronic hyperventilation syndrome, or any unknown reasons
Patients able (cognitive and functional) to carry out all parts of the intervention, including visits to outpatient clinic, physiotherapy visits and self-management	Patients currently receiving initial or full dose systemic treatment or radiotherapy due to cancer (except maintenance therapy)
Patients with acute exacerbations due to underlying conditions were put on a waiting list for two to four weeks before entering the trial	Trial activities targeting underlying conditions/ illness

3.1.2.2. Outcome measures

A variety of data were collected at baseline and at the end of the 8-week intervention with follow-up measurements at 16 and 24 weeks. Only outcomes relevant for this study are described in detail below. For completeness, a list of all collected outcome data during the trial is presented in Appendix D.

Sociodemographic data included age and sex, underlying disease characteristics focused on type and stage of the condition. Breathlessness was assessed with several uni- and multi-dimensional self-reported measures. Three questions about the severity of breathlessness were asked: (1) severity of breathlessness in the last 24 hours (on average), (2) maximum of breathlessness experienced during resting phases in the last 24 hours and (3) maximum of breathlessness experienced during activity in the last 24 hours. Answers were given on an adapted Numerical Rating Scale (NRS) from 1 (no breathlessness) to 10 (worst breathlessness possible), using verbal anchors on each side (Gift 1998). Mastery of breathlessness was assessed with the mastery domain of the German Chronic Respiratory Disease Questionnaire (CRQ) (Guyatt 1987, Puhan 2004). Answers are provided on a 7-point Likert scale with 1 (extreme shortness of breath) to 7 (no shortness of breath at all). How severe the subjects were affected by breathlessness was assessed by one item of the Integrated Palliative Care Outcome Scale (IPOS) (Murtagh 2019, Schildmann 2016). A 5-point Likert scale was used, ranging from 0 (not at all) to 4 (overwhelmingly).

Psychological distress was assessed with the Hospital Anxiety and Depression Scale (HADS), a 14-item questionnaire using a 4-point Likert scale, ranging from 0 to 3 with higher values indicating better health (Petermann 2015, Zigmond 1983). A cut-off score of 8 on the anxiety or depression subscale was used to indicate psychological distress (Bjelland 2002).

Quality of life was measured with the generic health-related quality of life (EQ-5D-5L) questionnaire (Herdman 2011). It consists of five items, which are scored on a 5-point Likert scale with 1 (no problems) to 5 (extreme problems). Additionally, a Visual Analogue Scale (VAS) ranging from 0 (worst health) to 100 (best health) is part of the EQ-5D-5L to rate the overall health of today (EUROQOL 2020).

All baseline data were collected by a study nurse in patients' homes.

3.1.3. Analysis

3.1.3.1. Descriptive data analysis

Sociodemographic and clinical characteristics were analysed descriptively for the total sample as well as subgroups based on the underlying disease (COPD or other disease). These included variables regarding age, sex and disease as well as characteristics of breathlessness, quality of life and psychological distress. Continuous, normally distributed data are represented as mean and standard deviation, non-normally distributed data by median and IQR. Dichotomous data are presented in frequencies and percentages. Differences in sociodemographic and clinical characteristics between subgroups were analysed with the χ^2-test (categorical data) or t-test (continuous data).

Additional descriptive analyses were undertaken as preliminary steps of structural equation modelling. Besides normal distribution, additional distribution parameters, that is skewness and kurtosis, of individual items were examined. Skewness and kurtosis values < 1.0 or > -1.0 were considered to be skewed (Hair 2016). Non-normal distributions were investigated further to check for potential outliers. Outliers were defined as all scores 1.5 x interquartile range (IQR) higher than the third quartile/ lower than the first quartile (IBM Corporation 2019). Based on these analyses, item parcels were created, as explained in more detail in chapter 3.1.3.3.

As a side note, missing data would have been investigated further to understand if data were missing at random (MAR) or not missing at random (NMAR). In case of MAR, values would have been imputed with maximum likelihood with the EM-algorithm as suggested in Weiber 2014. In case of NMAR, it was planned to check for systematic bias and exclude variables. However, no MAR and NMAR cases were identified, as there were no missing data in all relevant variables (all data collected by trained study nurse).

3.1.3.2. Relationships between variables

In the next step, correlations between sociodemographic variables (age, education level and COPD stage), breathlessness (MRC, IPOS, NRS 1-3 and CRQ-M), psychological distress (HADS) and quality of life (EQ-VAS) were investigated. Correlations coefficients (r) were interpreted as follows (Weiber 2014):

- $0.00 \leq r \leq 0.2$ or $-0.2 \leq r \leq 0.0$ (very weak correlation)
- $0.20 < r \leq 0.50$ or $-0.50 < r \leq -0.20$ (weak correlation)
- $0.50 < r \leq 0.70$ or $-0.70 < r \leq -0.50$ (moderate correlation)
- $0.70 < r \leq 0.90$ or $-0.90 < r \leq -0.70$ (high correlation)
- $0.90 < r$ or $r \leq -0.90$ (very high correlation).

Analysis of variances (ANOVA) was conducted to investigate the relationships between categorical sociodemographic characteristics (marital status and residence), COPD (yes/no) groups and latent variables.

3.1.3.3. Structural equation modelling

Structural equation modelling (SEM) is a technique for second generation data analysis, that is analysis used to confirm hypothetical theories (Fornell 1985). SEM is used to model dependent and independent relationships between constructs simultaneously (Anderson 1988). These models are more suitable to characterize real-word processes than simple correlation-based models (Gefen 2000). The different analytical steps of SEM, including theoretical considerations and terminology used in this dissertation are described below (adapted from Gefen 2000, and Weiber 2014).

Step I: Identifying latent variables

Latent variables, also known as *constructs*, cannot directly be measured but are estimated with functions including observable data (Bollen 2002). By contrast, *manifest* variables, also known as *observed* variables, can be measured directly at an empirical level, for example blood pressure (Weiber 2014) SEM can be used to analyse relationships between latent variables, which is a major advantage over other analysis types, for example regression analysis (Weiber 2014) and one of the main reasons that SEM is the method of choice in this study. In this dissertation, three latent variables were of interest: breathlessness, quality of life, and psychological distress. None of these variables can be observed directly. However, a variety of instruments (manifest variables) exist to estimate these variables. For example, a systematic review identified 35 different instruments to measure breathlessness (Bausewein 2007).

Step II: Formulating hypotheses

Once the latent variables are identified, the expected interaction between them are described further. Different types of relationships between the three latent variables breathlessness, quality of life, and psychological distress are described in the literature. Quality of life and psychological distress are correlated, and both may affect breathlessness. For this study, two hypotheses were formulated:

H_1: Psychological distress affects breathlessness.
H_2: Quality of life affects breathlessness.

A path diagram illustrating the relationships between the three latent variables breathlessness, psychological burden and quality of life is presented in Figure 2. Latent variables are presented with ellipses, and predictive relationships are indicated with straight arrows, leading from the exogeneous to the endogenous variable (Tabachnick 2012), for example from quality of life to breathlessness. The correlation between both exogeneous variables is indicated with the double-sided, curved arrow (Tabachnick 2012).

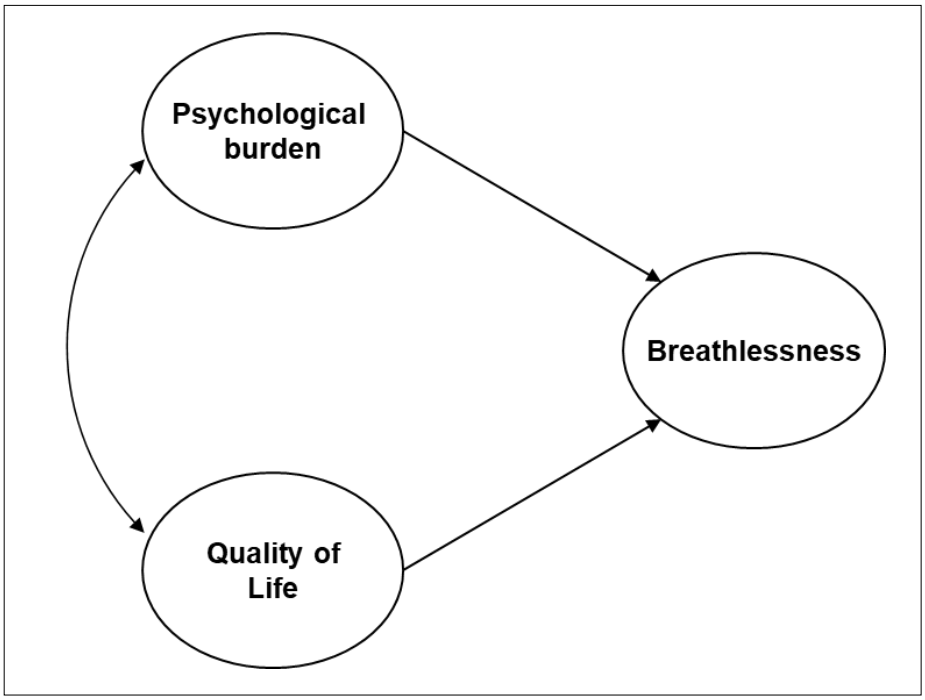


Figure 2: Assumed relationships between latent variables breathlessness, quality of life and psychological burden

Looking at the different types of relationships, the concept of dependent and independent variables comes to mind. However, as several latent variables might be independent and dependent variables in SEM, the terms endogenous and exogeneous variables are used instead (Bollen 2011). *Endogenous* variables depend on at least one other latent variable whereas *exogeneous* variables are not affected by the endogenous variables (Bollen 2011, Weiber 2014). The terms refer to predictive effects only, and do not consider correlation. In this example, breathlessness can be described as an endogenous variable, and both psychological burden as well as quality of life are exogeneous variables.

Step III: Developing measurement models

After identifying the structure between all latent variables, measurement models for each of these variables were developed. The manifest variables were included as rectangles in the model (Weiber 2014), which is presented in Figure 3. Furthermore, measurement errors for each item and endogenous variables should be considered. These error terms (indicated with letters d, e, and g) are also shown in Figure 3, represented as circles.

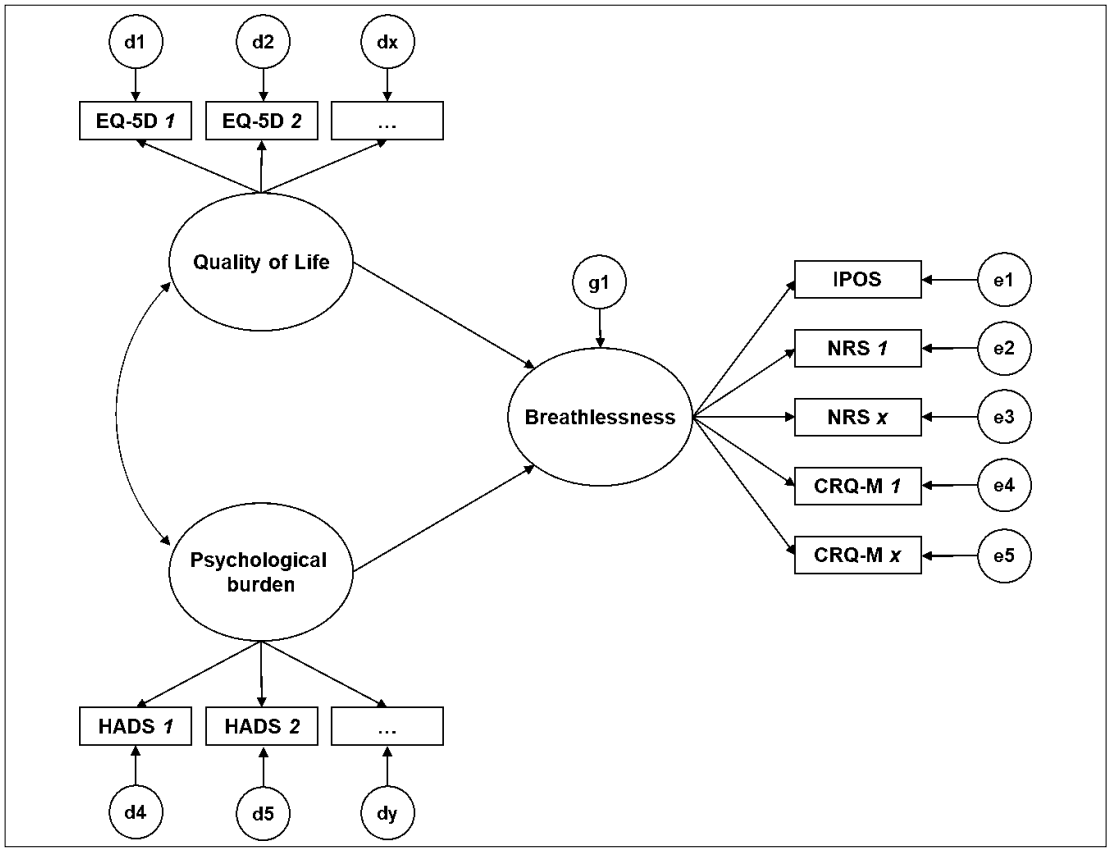


Figure 3: Model with latent and manifest variables

For the development of the measurement model in this study, data needed to be transformed first. Data measured with questionnaires of different directions indicating better or worse health were transformed, for example on the EQ-VAS high values indicate better quality of life, whereas higher values on the HADS indicate more psychological distress. For this study, outcome measures were transformed in a way that higher values indicated worse health. Additionally, the outcome measure with a broad scale, that is the EQ-VAS, was z-transformed in order to allow for more balanced

effects of the distinct manifest variables indicating the overarching construct of breathlessness.

After data transformation, measurement models for all latent variables were built. For this step, item parcels instead of single items were used for several reasons. Firstly, reliability can be increased, if items are combined in parcels, rather than using each item individually, leading to stronger factor loadings (Coffman 2005, Little 2013). Secondly, following the rule of thumb, the sample size should be the size of 5 to 10 subjects for each estimated parameter (Bentler 1987). This includes all free parameters, for example paths, endogenous variances and correlations. Therefore, a totally disaggregated model (that is a model, in which all items are direct indicators for constructs; Coffman 2005) would not have been feasible in this study. Item parcels were therefore used to minimise the number of parameters needed to be estimated (Coffman 2005). Different approaches exist to appropriately split items in different parcels, which is why three different approaches were considered (Coffman 2005, Little 2013, Matsunaga 2008).

Latent variables were estimated with several instruments: homogeneous parcels based on the mean of each measure across several items were constructed (Coffman 2005).

Latent constructs estimated with items of a singular instrument: In case of non-normally distributed data, skewness or kurtosis was used to combine items of opposite directions to even out imbalances (Matsunaga 2008). Otherwise, exploratory factor analysis (EFA) was conducted to combine items loading on the same factor (Lewith 2004). Principal components analysis (PCA) for factor extraction in combination with orthogonal rotation (Varimax) was used.

Step IV: Estimating the structural model

In the last step, the validity of the complete structural model was examined. Real-life data are tested against the theoretical model. The model fit can be assessed with a variety of parameters (Hu 1999, Schermelleh-Engel 2003, Schreiber 2006, Weiber 2014). Differences between the theoretical and the empirical variance-covariance-matrix can be examined with the χ^2-test. If significant ($p \leq 0.05$), differences between the theoretical model and the observed data are assumed, and therefore, the model is

rejected (Weiber 2014). However, the χ^2-test should be interpreted carefully, the assumptions of the test are normally not met with real-world data (Schermelleh-Engel 2003). As an alternative, the χ/df is proposed, as it takes the degrees of freedom into account. A good model fit is assumed if the ratio is less than 2 (Schermelleh-Engel 2003). The root-mean-square error of approximation (RMSEA), assessing how well the model approximately fits the observed data, is a more sensitive test criteria for real-world data (Browne 1993). RMSEA was investigated using the following cut-offs as an orientation about the model fit: RMSEA ≤ 0.05 (close model fit), RMSEA ≤ 0.08 (reasonable model fit) and RMSEA ≥ 0.10 (inacceptable model fit) (Browne 1993, Weiber 2014). Additionally, the standardised root-mean-square residual (SRMR) was used with a cut-off ≤ 0.10 indicating a good model fit (Weiber 2014). Furthermore, the Comparative Fit Index (CFI) was used to examine the model of fit (Weiber 2014). CFI-values ≥ 0.9 describe a 'good' model fit (Weiber 2014). As a side note: strict cut-off values for model fit are a topic of critical discussion, especially for psychological questionnaires, not only the cut-off values themselves but also the general use of it (Marsh 2004, Weiber 2014). Therefore, the criteria presented here are reported, but discussed with these critical considerations in mind.

Exploratory subgroup analyses were planned based on sociodemographic or clinical characteristics that correlated significantly with latent constructs. As the sample size was considered too small, the model fit of the group-specific SEM was not judged and the results were only summarized narratively.

IBM SPSS Statistics, version 25, and AMOS, version 25 (Arbuckle 2017, IBM Corporation 2017) were used for all analyses.

3.2. Study 2: Effects of cognitive-emotional interventions for breathlessness

3.2.1. Study design

Cochrane systematic literature review.

As mentioned above, this dissertation is part of a series of Cochrane reviews to determine the effects and safety of non-pharmacological interventions for breathlessness in adults with advanced disease. The series consists of four reviews based on the theoretical concept explained in chapter 1.1 including one review for each mechanism (respiratory, physical, and cognitive-emotional) and one for interventions targeting several mechanisms simultaneously (multi-dimensional). Due to different intervention categories used in the series, this dissertation combines parts of the cognitive-emotional and the multi-dimensional reviews.

3.2.2. Inclusion and exclusion criteria

An established way of identifying and describing inclusion and exclusion criteria of systematic literature reviews is PICOS, an acronym based on all important categories that should be specified before the conduct of the review: population, intervention, control, outcomes, and study design, adapted from Higgins 2011.

The inclusion and exclusion criteria for this systematic literature review are summarized in Table 2 and described in more detail in the following subsections.

Table 2: Inclusion criteria of the systematic literature review

PICOS	Inclusion criteria
Population	Adults suffering from advanced disease
Intervention	Non-pharmacological; targeting cognition, emotion or both either with or without additional movement
Control	No treatment, attention control, standard care, or different kind of therapy
Outcomes	Primary outcome: Breathlessness Secondary outcomes: psychological distress; quality of life
Study design	RCT's; cluster RCT's; qRCT's

RCT: Randomised controlled trial; qRCT: quasi-RCT

Population

Studies were included, if subjects were adults suffering from advanced disease with a high prevalence of breathlessness. The majority (≥ 50%) of participants had to meet one of the following criteria:

- Cancer: TNM Classification of Malignant Tumours state ≥ T3 or N ≥ 1 or M ≥ 1.
- Chronic obstructive lung disease (COPD): forced expiratory volume in one second (FEV_1) predicted of < 50%.
- Pulmonary hypertension: a WHO class level ≥ III, defined by (Barst 2004).
- Chronic heart failure (CHF): New York Heart Association (NYHA) stage III or IV.
- Interstitial lung disease (ILD) or idiopathic pulmonary fibrosis (IPF): all studies were included as breathlessness is the predominant symptom and there are hardly any disease-specific treatment options.
- Neuromuscular diseases (Motor neuron diseases (MND), Amyotrophic lateral sclerosis (ALS)): all studies were included as advanced disease is marked by the occurrence of breathlessness.

Patients in all settings were considered for this systematic literature review. Patients with any condition not regarded as advanced and life-limiting and this disease being the primary cause for breathlessness (for example acute or chronic asthma) were excluded. If severity of disease was unclear, an experienced physician (CB) included or excluded studies based on other clinical variables reported.

Intervention

Interventions targeting cognition, emotion or both to relieve breathlessness according to the following categories were included:

- Psychological therapy (e.g. cognitive behavioural therapy)
- Self-management
- Counselling and support
- Meditative movements
- Mindfulness-based stress reduction

The judgement for inclusion was based on the study authors' description of the intervention. There were no restrictions for the setting, in which these interventions were provided.

Comparator

The comparator might have been any treatment, with the exception of additional pharmacological treatments not received in the intervention group (for example cognitive intervention (intervention) compared to additional morphine (control) would not have been considered for this review). Control groups were categorised into *active controls* or *inactive controls* based on the description of the comparison group. Active controls were defined as additional therapies not received in the intervention group. The definition of inactive controls was adapted from (Bahar-Fuchs 2019) and included both usual treatment and no treatment, defined as:

- **Standard treatment/treatment as usual (TAU)**: treatment that would normally be provided for patients with breathlessness at the study location, and was not administered in the study. It may include all standard treatments except specific breathlessness interventions.
- **No treatment:** If study authors did not report details of the comparison treatment, or described it as 'no treatment', TAU was assumed and not withholding of treatment, unless specifically stated otherwise.

If study participants received concomitant interventions, especially pharmacological treatment, it was only accepted, if both the intervention and the control groups received it the same way.

Outcome measures

Studies were eligible, if any measure of breathlessness was used. The following primary and secondary outcomes were considered (if they were measured with reliable and validated measures).

Primary outcomes

Breathlessness, measured by self-reported instruments (for example Borg Scale (Borg 1970), Chronic Respiratory Disease Questionnaire (CRQ) (Guyatt 1987, Puhan 2004), or Medical Research Council (MRC) Breathlessness Scale (Fletcher 1960)). Other terms for breathlessness, for example dyspnoea or difficult breathing, were also accepted in this review.

Secondary outcomes

- Psychological distress (e.g. Hospital Anxiety and Depression Scale (HADS) (Zigmond 1983)).
- Quality of life (e.g. 36-Item Short Form Health Survey (SF-36) (Ware Jr 2000)).

Study design

Randomised controlled trials (RCTs), cluster RCTs, and quasi-RCTs (qRCTs) were included. The definition of quasi-randomisation followed the Cochrane definition, that is some pseudo-random method of allocation such as alternation, date of birth, case record number or date of presentation (Higgins 2011). In case of cross-over studies, data had to be reported separately for both time frames and only data of the first period for analysis were used to avoid carry-over effects. Full journal publication was required, unless sufficient data were presented in conference abstracts or summary reports.

3.2.3. Literature search

Electronic searches

The following databases were searched from their inception to July 2017, without date or language restrictions.

- Cochrane Database of Systematic Reviews (CDSR), the Cochrane Library to July 2017.
- Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Library to July 2017.
- MEDLINE (OVID) 1946 to July (week 1) 2017.
- Embase (OVID) 1974 to July 2017.
- PsycINFO (OVID) 1806 to July (week 1) 2017.
- LILACS (Bireme) 1967 to July 2017.
- CINAHL (EBESCO) 1982 to July 2017.

MEDLINE and Embase were searched using both controlled vocabulary (namely, MeSH in MEDLINE and EMTREE in Embase) and a wide range of free-text terms (see *Appendix E* for details). A search filter for RCTs based on the Cochrane Highly Sensitive Search Strategy for MEDLINE was used (Higgins 2011).

Searching other resources

Study authors were contacted where necessary for additional information, when the study was published in 2002 or after. Citation searches of included studies as well as reference lists of reviews were checked for additional studies of interest. The search was conducted in collaboration with the Information Specialist of the Pain and Palliative Support Cochrane Group.

3.2.4. Data extraction and management

Selection of studies

After the identification of relevant studies by the search strategy, two authors (AB, SR or PS) independently screened the titles and abstracts. Studies that did not meet the inclusion criteria were excluded, all other publications were checked in full text. Again, two authors (AB, SR or PS) individually read these full texts to select all studies that met the inclusion criteria. A third author (CB) resolved any disagreements and unclear decisions.

Data extraction and management

Based on a Cochrane template, a data collection form was developed (Cochrane Effective Practice and Organisation of Care 2017). Two review authors (AB, AH, SB or PS) independently extracted data and solved any disagreement. If disagreements could not be solved, a third author (CB) was consulted to resolve differences. Information about the variables regarding participant characteristics, details of intervention, study design, methods, outcomes and context were extracted (see *Appendix F* for a full list of variables). For data management, Excel and the Cochrane software Review Manager (RevMan) were used (RevMan 2014).

In case of multiple publications of the same trial, data were extracted from the main publication and checked for differences between the other reports. The software 'DigitizeIt' was used for data only presented in 2D figures (Bormann 2016).

3.2.5. Analysis

3.2.5.1. Data synthesis

Measures of treatment effect

Continuous data were analysed using mean differences (MD) or standardised mean differences (SMDs) with 95% CIs. Standard deviations were calculated, if not reported, using the methods described in the Cochrane Handbook (Higgins 2011). SMD effect sizes were interpreted as follows: 0.2 (small effect), 0.5 (moderate effect), and 0.8 (large effect) (Higgins 2011).

Study authors were contacted (AB) if additional analysis could not be conducted due to missing data. If possible, missing data was imputed based on the methods described in the Cochrane Handbook (Higgins 2011).

Assessment of heterogeneity

As many different interventions, settings, and participants were of interest for this systematic literature review, large heterogeneity was expected throughout all comparison categories. Methodological heterogeneity was analysed based on differences in PICOS, especially intervention deliveries, its components, and the characteristics of the providers (see Appendix F for more details). Statistical heterogeneity was assessed with the I^2 statistic, with I^2 value greater than 50% indicating substantial statistical heterogeneity. I^2 values were documented, but did not have any direct consequences for analyses, as large methodological heterogeneity was assumed regardless of the statistical heterogeneity. Statistical heterogeneity was calculated in Review Manager 5.3 (RevMan 2014).

Data synthesis

Studies comparing the same intervention and comparator categories assessing the same outcome were pooled in a meta-analysis using Review Manager 5.3 (RevMan 2014). Due to the assumption of large methodological heterogeneity, a random-effects model was chosen throughout the review. The analyses of the primary outcome breathlessness were divided into uni- and multidimensional measures.

Meta-analyses were only undertaken if studies were judged to be similar enough to give a clinically meaningful answer. Otherwise, a narrative summary of the results was reported. In case of skewed data, results of the according studies were summarised narratively, as the planned log transformation of these data were not feasible. The narrative summary includes within the intervention group and between group effects as well as the measure(s) used in each trial that reported the relevant outcome.

3.2.5.2. Sensitivity analysis

Sensitivity analysis were conducted, if possible, to test the robustness of the estimated effects. Sensitivity analysis included analyses including different outcome measures and interventions with different duration.

3.2.6. Bias

The risk of bias assessment was carried out using the Cochrane criteria (Higgins 2011).

Two authors (AB, AH, SB or PS) independently assessed risk of bias for each study, using adapted Cochrane criteria (Cochrane Pregnancy and Childbirth Group 2017, Higgins 2011). Discrepancy between two assessments were solved by a third author (AB or CB). Five different bias categories were assessed: selection bias, detection bias, attrition bias, reporting bias, and bias due to sample size. The details of the judgment for bias followed the recommendation by Cochrane and are presented in Table 3. The Review Manager tool were used to complete a 'Risk of bias' table (RevMan 2014).

Table 3: Criteria for the risk of bias assessment

Bias category	Judgement
Selection bias	
Random sequence generation	• **Low risk:** 'true' random process, for example random number table • **Unclear risk:** insufficient details reported • **High risk:** non-random process, for example date of recruitment
Allocation concealment	• **Low risk:** intervention allocation was unknown prior to the assignment, for example numbered sealed opaque envelopes • **Unclear risk:** insufficient details reported • **High risk:** not concealed allocation, for example open lists
Detection bias	
Blinding of participants and personnel	• **Low risk:** participants and personnel were blinded and methods described • **Unclear risk:** blinding of participants and personnel stated, but insufficient details reported • **High risk:** no or incomplete blinding
Blinding of outcome assessors	• **Low risk:** outcome assessors were blinded and methods described • **Unclear risk:** blinding of outcome assessors stated, but insufficient details reported • **High risk:** no or incomplete blinding
Attrition bias	
Incomplete outcome data	• **Low risk:** missing data have been imputed with appropriate methods and/or less than 10% drop-out rates • **Unclear risk:** insufficient details reported • **High risk:** complete-case analysis and ≥ 10% drop-out rates
Reporting bias	
Selective outcome reporting	• **Low risk:** all prespecified outcomes were reported • **Unclear risk:** insufficient details reported • **High risk:** not all prespecified outcomes were reported
Bias due to sample size	
Sample size	• **Low risk:** ≥ 200 participants per group • **Unclear risk:** 50 to 199 participants per group • **High risk:** < 50 participants per group
Other bias	
Other bias	• **Low risk:** No indication for additional bias. • **Unclear risk:** Conference abstract • **High risk:** Indication for additional bias.

4. Results

4.1. Study 1: Relationships between breathlessness, psychological distress and quality of life

4.1.1. Sample characteristics

183 participants were included in the BreathEase trial between March 2015 and October 2018. Baseline characteristics are presented in Table 4. 93 (50.8%)[1] of these participants were female, 73.4 (8.5) years, and suffered from COPD (115 (62.8%)), CHF (14 (7.7%)), cancer (13 (7.1%)), or other diseases (41 (22.4%)). Around a quarter of the participants (48 (26.2%)) had a university or high school degree, and all other participants had a degree from other school types. Half of the participants (97 (53.0%)) were married, the other part was either single, widowed, or divorced (25 (13.7%), 30 (16.4%), and 31 (16.9%), respectively).

Breathlessness

Disability due to breathlessness, measured with MRC[2], was rated as grade 2/3/4/5 by 16/68/93/6 participants. More than a third of the participants (70 (38.3%)) were severely or very severely affected by breathlessness in the last week (breathlessness IPOS item). The average severity of breathlessness (NRS scale) in the last 24 hours was 5.4 (1.8). Average scoring for mastery of breathlessness (CRQ-M) was 3.9 (1.2).

Psychological distress

114 (62.9%) of included participants had HADS scores ≥ 8 on anxiety or depression scores. In more detail, almost half of the participants (78; 42.6%) had scores ≥ 8 on the anxiety subscale, and more than half (96; 52.5%) had scores ≥ 8 on the depression subscale. 60 (32.8%) participants had ≥ 8 on both subscales.

[1] All data presented as mean (SD) or n (%)
[2] Higher scores indicate worse breathlessness

Quality of life

The overall health was rated as 46.2 (18.0) on the VAS. Most participants rated all items of the EQ-5D as having no or little problems/symptoms (mean range: 66.1% - 80.9%).

Subgroups

Most adults with COPD had a stage IV diagnosis (43; 37.4%), followed by stage III and stage II (34; 29.6% and 33; 28.7%, respectively) and five (4.3%) participants had a stage I diagnosis. Due to the underlying disease, FEV_1 (%) values significantly differed between adults with COPD (40.1 (18.0)) and adults with other diseases (62.7 (24.0)). There were no differences in demographic characteristics between these two groups (Table 4). Scores in one NRS scale (maximum during resting phase in the last 24 hours) were significantly different between subgroups. All other measures of latent variables were similar between adults with and without COPD.

Table 4 Baseline characteristics with subgroups COPD yes/no

		All		COPD		Other	
N		**n = 183**		**n = 115**		**n = 68**	
Gender	Male	90	49.2 %	52	45.2 %	38	55.9 %
	Female	93	50.8 %	63	54.8 %	30	44.1 %
Age (years)	Total	71.3	8.6	70.7	7.8	72.2	9.8
	< 65	35	19.1 %	22	19.1 %	13	19.1 %
	≥ 65	148	80.9 %	93	80.9 %	55	80.9 %
Education	No degree	0	0.0 %	0	0.0 %	0	0.0 %
	2nd general school	69	37.7 %	48	41.7 %	21	30.9 %
	Interm. 2nd school	66	36.1 %	40	34.8 %	26	38.2 %
	High school/ university	48	26.2 %	27	23.5 %	21	30.9 %
Marital status	Married	97	53.0 %	54	47.0 %	43	63.2 %
	Single	25	13.7 %	16	13.9 %	9	13.2 %
	Widowed	30	16.4 %	22	19.1 %	8	11.8 %
	Divorced	31	16.9 %	23	20.0 %	8	11.8 %
Residence	Living alone	71	38.8 %	48	41.7 %	23	33.8 %
	Living with partner	112	61.2 %	67	58.3 %	45	66.2 %
	Unknown	0	0.0 %	0	0.0 %	0	0.0 %
COPD	I	5	2.7 %	5	4.3 %	-	-
	II	33	18.0 %	33	28.7 %	-	-
	III	34	18.6 %	34	29.6 %	-	-
	IV	43	23.5 %	43	37.4 %	-	-
Primary tumour	Lung	8	4.4 %	-	-	8	11.8 %
	Cervical	1	0.5 %	-	-	1	1.5 %
	Bladder	1	0.5 %	-	-	1	1.5 %
	Other	3	1.6 %	-	-	3	4.4 %
Heart failure	NYHA I	1	0.5 %	-	-	1	7.1 %
	NYHA II	5	2.7 %	-	-	5	35.7 %
	NYHA III	7	3.8 %	-	-	7	50.0 %
	NYHA IV	1	0.5 %	-	-	1	7.1 %
*FEV_1 (%)**		48.5	23.0	40.1	18.0	62.7	24.0
MRC	1	16	8.7 %	10	8.7 %	6	8.8 %
	2	68	37.2 %	44	38.3 %	24	35.3 %
	3	93	50.8 %	58	50.4 %	35	51.5 %
	4	6	3.3 %	3	2.6 %	3	4.4 %
CRQ-M		3.9	1.2	3.9	1.2	3.9	1.2
IPOS		3.3	0.7	3.4	0.7	3.2	0.7
NRS	Average last 24 h	5.4	1.8	5.5	1.8	5.2	1.8
	Max during resting*	2.8	1.7	3.0	1.7	2.4	1.7
	Max during activity	7.4	1.9	7.6	1.7	7.2	2.1
HADS	Total	14.9	7.4	15.3	7.3	14.2	7.6
	Anxiety	6.9	3.8	7.1	3.8	6.7	3.9
	Depression	7.9	4.2	8.2	4.2	7.5	4.3
EQ-VAS		53.8	18.0	54.6	16.7	52.5	20.0

**Significant differences between subgroups ($p < 0.05$); Data presented as mean SD or n %*

Relationships within and between measures of breathlessness, psychological distress and quality of life

Measurements of breathlessness demonstrated weak to moderate correlations with each other (Table 5). Furthermore, these measurements showed weak (MRC score) to high (CRQ-M) significant correlations with psychological distress (Table 5). Significant negative correlations were weak to moderate between breathlessness measurements and measurements of quality of life. The only exception was the non-significant weak correlation with the MRC score. Correlations between other EQ-5D measures and breathlessness were slightly higher (data for correlations between EQ-5D items and other measures not shown for better readability). A significant weak to moderate negative correlation was found between measures for psychological distress and quality of life.

Table 5 Correlations between measures for breathlessness, psychological distress and quality of life

		MRC	IPOS	NRS 1	NRS 2	NRS 3	CRQ-M	HADS total	EQ-VAS
MRC	Pearson Corr.	1	**,335****	**,233****	**,198****	**,159***	**,182***	**,165***	-,131
	Sig. (2-tailed)		,000	0,001	0,007	0,032	,014	,026	,076
	N	183	183	183	183	183	183	183	183
IPOS	Pearson Corr.	**,335****	1	**,489****	**,354****	**,420****	**,447****	**,385****	**-,156***
	Sig. (2-tailed)	,000		0,000	0,000	0,000	,000	,000	,036
	N	183	183	183	183	183	183	183	183
NRS 1	Pearson Corr.	**,233****	**,489****	1	**,591****	**,647****	**,338****	**,354****	**-,183***
	Sig. (2-tailed)	0,001	0,000		0,000	0,000	0,000	0,000	0,013
	N	183	183	183	183	183	183	183	183
NRS 2	Pearson Corr.	**,198****	**,354****	**,591****	1	**,261****	**,378****	**,393****	**-,179***
	Sig. (2-tailed)	0,007	0,000	0,000		0,000	0,000	0,000	0,015
	N	183	183	183	183	183	183	183	183
NRS 3	Pearson Corr.	**,159***	**,420****	**,647****	**,261****	1	**,237****	**,240****	-0,108
	Sig. (2-tailed)	0,032	0,000	0,000	0,000		0,001	0,001	0,146
	N	183	183	183	183	183	183	183	183
CRQ-M	Pearson Corr.	**,182***	**,447****	**,338****	**,378****	**,237****	1	**,614****	**-,321****
	Sig. (2-tailed)	,014	,000	0,000	0,000	0,001		,000	,000
	N	183	183	183	183	183	183	183	183
HADS total	Pearson Corr.	**,165***	**,385****	**,354****	**,393****	**,240****	**,614****	1	**-,363****
	Sig. (2-tailed)	,026	,000	0,000	0,000	0,001	,000		,000
	N	183	183	183	183	183	183	183	183
EQ-VAS	Pearson Corr.	-,131	**-,156***	**-,183***	**-,179***	-0,108	**-,321****	**-,363****	1
	Sig. (2-tailed)	,076	,036	0,013	0,015	0,146	,000	,000	
	N	183	183	183	183	183	183	183	183

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Relationships between measures and sociodemographic factors

No significant correlations between age and measures of breathlessness, psychological distress and QoL were identified (Table 6). Education level showed (significant) negative weak correlations with breathlessness measures and psychological distress but not with quality of life. ANOVA results showed no significant differences between COPD subgroups for measures of breathlessness, psychological distress and quality of life (see Appendix G for more details). Significant between-group differences were identified for marital status and residence.

Table 6 Correlations between measures for breathlessness, psychological distress and quality of life, and sociodemographic factors

		Age	Education	COPD stage
MRC	Pearson Corr.	0,042	-0,126	**,331****
	Sig. (2-tailed)	0,572	0,089	0,000
	N	183	183	115
Impact	Pearson Corr.	-0,014	**-,155***	0,106
	Sig. (2-tailed)	0,852	0,036	0,259
	N	183	183	115
NRS1	Pearson Corr.	-0,123	**-,184***	0,054
	Sig. (2-tailed)	0,096	0,013	0,567
	N	183	183	115
NRS2	Pearson Corr.	**-,159***	**-,200****	0,061
	Sig. (2-tailed)	0,032	0,007	0,520
	N	183	183	115
NRS3	Pearson Corr.	-0,026	**-,160***	0,066
	Sig. (2-tailed)	0,724	0,030	0,485
	N	183	183	115
CRQ-M	Pearson Corr.	-0,030	-0,061	0,051
	Sig. (2-tailed)	0,685	0,413	0,588
	N	183	183	115
HADS total	Pearson Corr.	-0,068	**-,174***	0,004
	Sig. (2-tailed)	0,362	0,019	0,967
	N	183	183	115
EQ-VAS	Pearson Corr.	-0,079	-0,017	-0,076
	Sig. (2-tailed)	0,288	0,824	0,418
	N	183	183	115

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

4.1.2. Exploratory factor analysis

Breathlessness

The available measurements for different dimensions of breathlessness, i.e. the average score of the CRQ mastery domain, the MRC score, the breathlessness item of IPOS and the average of the three NRS were combined in four parcels in order to indicate the latent construct “breathlessness” in a balanced way (Figure 4).

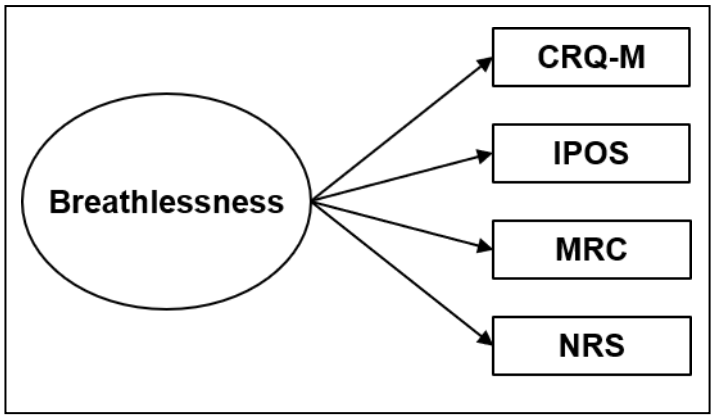


Figure 4 Latent construct breathlessness with four parcels

Psychological distress

Psychological distress was assessed with the HADS. Factor analysis (PCA with Varimax rotation) suggested that the items load on three factors (Figure 5), therefore three different item parcels were constructed (see Appendix H for scree plot and the final item parcels). Names of item parcels were developed based on the content of the included items.

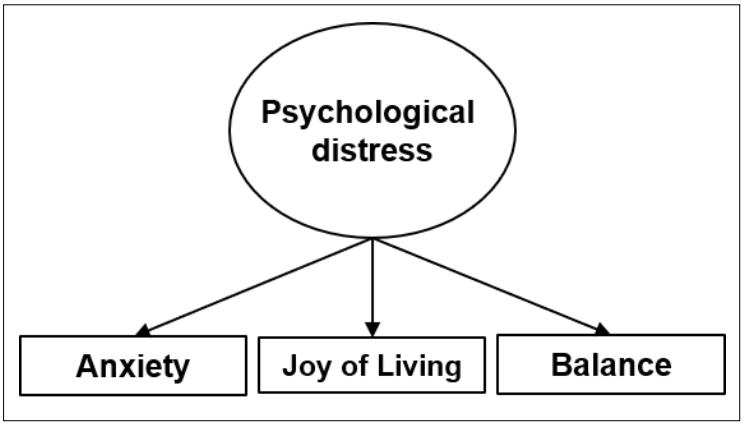


Figure 5 Latent construct psychological distress with three parcels

Quality of life

Quality of life was measured with the EQ-5D. As global health in the EQ-5D was measured with a different scale, one item parcel was created with the VAS. As the other five items of the questionnaire were skewed, two other parcels were constructed based on the direction of the distribution (explained in more detail in 3.1.3.3). The final construct is shown in Figure 6.

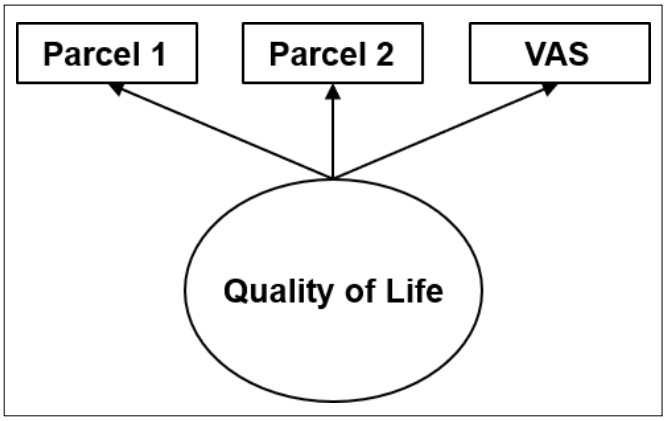


Figure 6 Latent construct quality of life with three parcels

4.1.3. Structural equation modelling

Relationships between breathlessness, psychological distress and quality of life

The final model including three latent constructs, that is breathlessness (four item parcels), psychological distress (three item parcels) and quality of life (three item parcels) is shown in Figure 7. The model fits indicate a reasonable to good fit with RMSEA = 0.086 (95% CI: 0.056; 0.115), SRMR = 0.061, and CFI = 0.941. The only exception was the significant χ^2 test with χ^2 = 56.009, p < 0.001. However, the alternative, which takes the degrees of freedom into account, indicated a good fit: χ/df = 2.334.

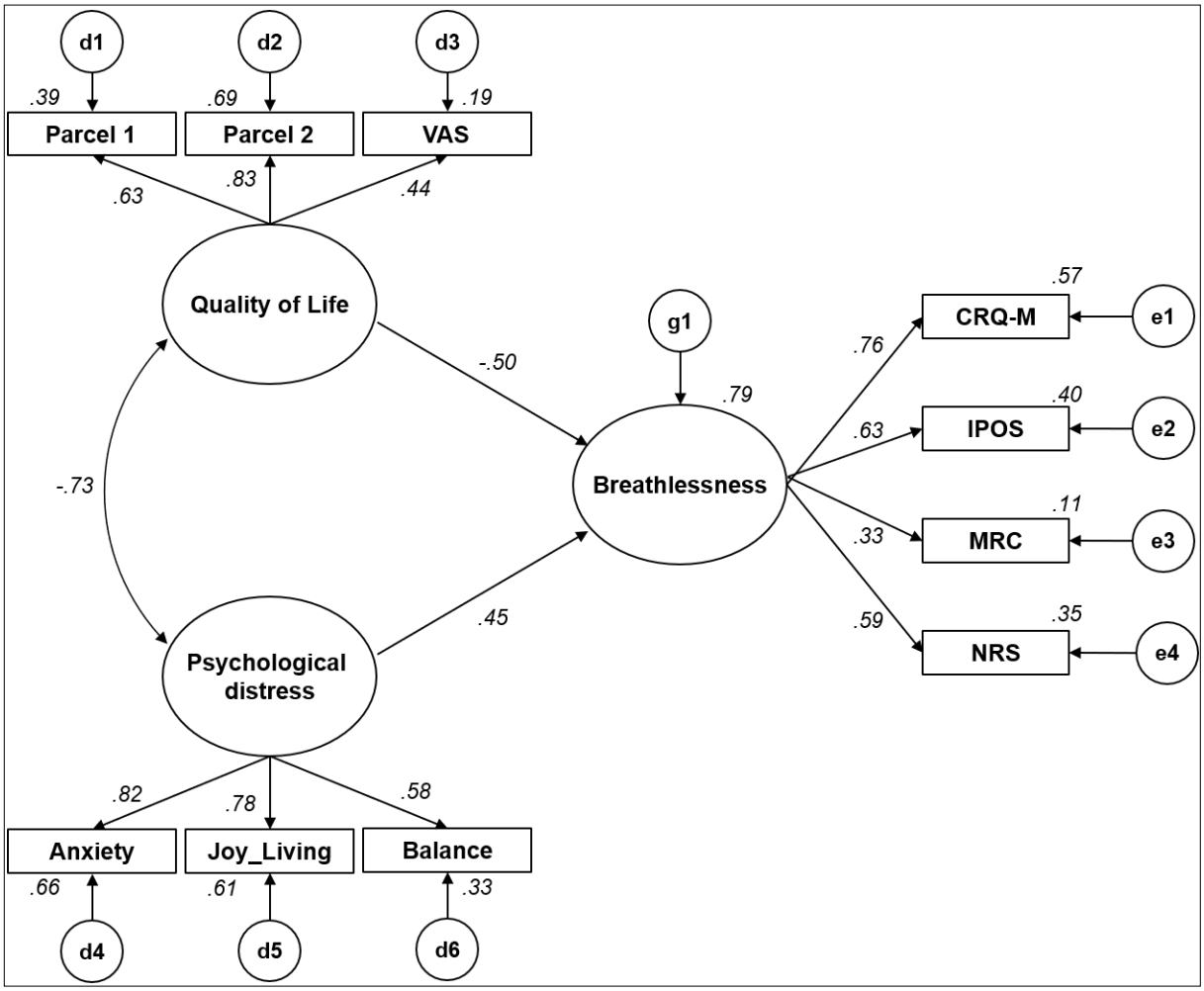


Figure 7 Structural equation model with standardised covariance coefficients (next to arrows), within group variances (next to item parcels) and overall variance explained (next to endogenous variable breathlessness)

Psychological distress was most strongly explained by the item parcel ‘anxiety’, indicated by the highest covariance coefficient of 0.82, followed by the parcel ‘joy_living’ (0.78) and ‘balance’ (0.58). Variances within parcels were similar between ‘anxiety’ and ‘joy_living’, and smaller for ‘balance’. Quality of life was most strongly explained by the two parcels of the EQ-5D items (0.83, and 0.63, respectively), and less strongly by the VAS (0.44). Variances within parcels were different between all three parcels. The exogenous variables quality of life and psychological distress are highly correlated (0.73).

Breathlessness was most strongly indicated by the CRQ-M (0.76), followed by IPOS and NRS (0.63, and 0.59, respectively). MRC only had a lower effect of 0.33, which is due to the small variance within the parcel. Variances within other parcels were similar between IPOS and NRS, and higher in the CRQ-M. Regression coefficients between both exogeneous variables and breathlessness were of similar strength and significant. The final model explained 79% of the variance in breathlessness.

Comparative analyses identified less explained variance when only analysing the relationship between psychological distress and breathlessness (explained variance: 69%) and even less explained variance by analysing the relationship between quality of life and breathlessness (explained variance: 68%; data not shown).

Subgroup analysis

As presented above, marital status and education level showed significant correlations with breathlessness, psychological distress and/or quality of life. Due to the limited number of participants, only exploratory analysis for the differences in the relationship between latent constructs based on the education level was possible. SEM showed similar results between adults with a 2nd general school degree (group 1) and adults with an intermediate 2nd school degree (group 2), explaining 82% and 80% of variance in breathlessness. Different to the main model, the variance was explained most by quality of life (standardised regression coefficient of -0.64 (group 1), and -0.70 (group 2)). The standardised regression coefficients of psychological distress were 0.30 (group 1) and 0.26 (group 2). In contrast, these coefficients switched for the subgroup with the highest education level, with a regression coefficient of 0.-36 for quality of life and 0.59 for psychological distress, explaining 75% of the variance in breathlessness.

4.2. Study 2: Effects of cognitive-emotional interventions for breathlessness

4.2.1. Results of the search

A PRISMA flow diagram of the search results is shown in Figure 8 (Moher 2009). From 20,444 citations, 14,853 records were screened after the removal of duplicates. 15,197 references during the title and abstract screening were not relevant, and therefore 656 full text publications were checked in more detail. A total of 26 RCTs (presented in 39 publications) were included in this review.

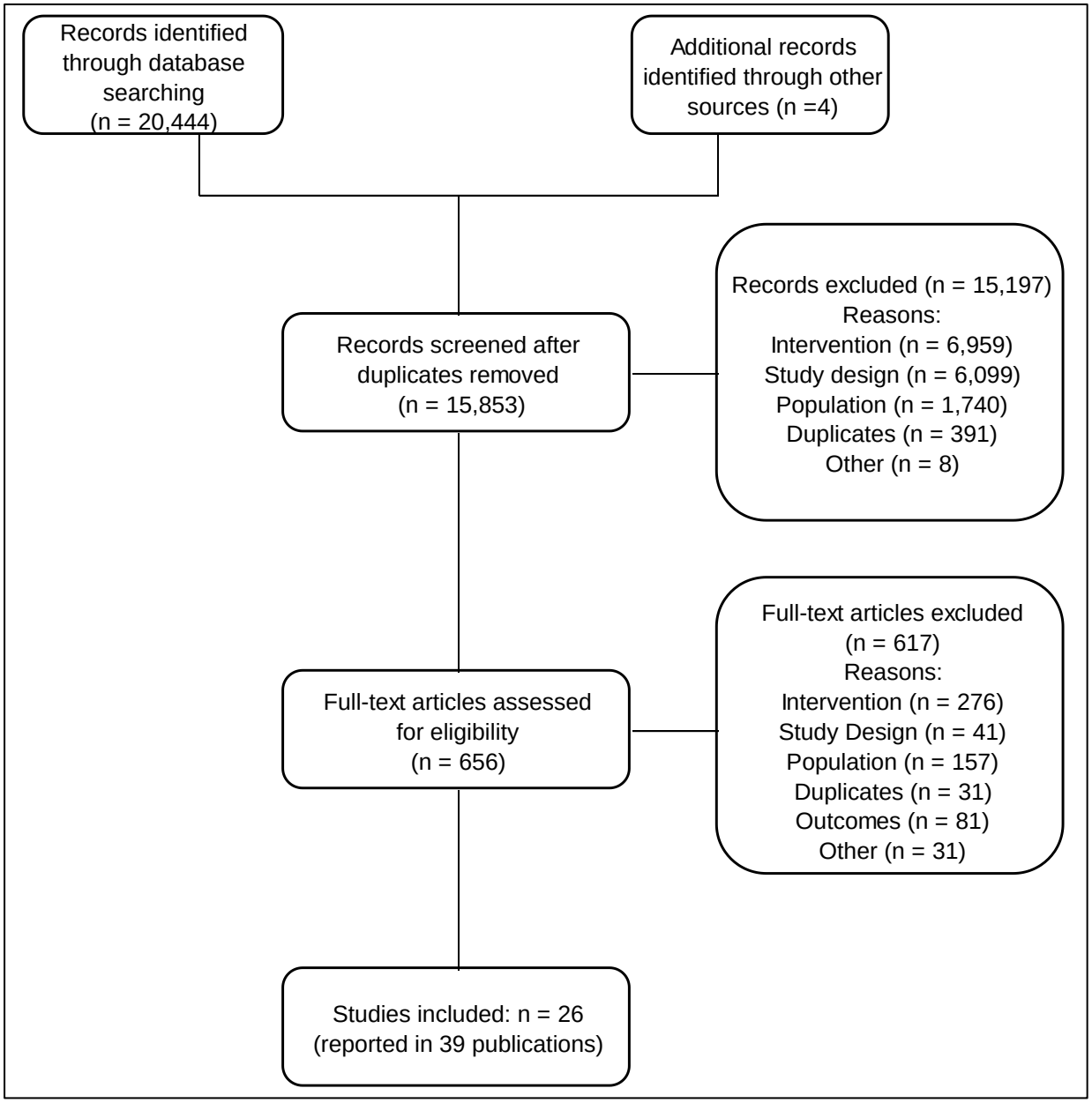


Figure 8: Flow chart diagram

4.2.2. Included studies

A summary about the participants, interventions and outcomes of the included studies is presented below. More details about each trial are presented in Appendix I.

Participants

Twenty studies included subjects with COPD, including 3,005 participants in total. Four studies analysed a total of 484 advanced lung cancer patients. One study included 314 patients with congestive heart failure. One study included 112 patients with different diseases, that is COPD and heart failure. A total of four studies were including patients with a specific disease but also on having symptoms of anxiety and/or depression (Alexopoulos 2013, Bove 2016, Kunik 2008, Mosher 2016).

The mean (standard deviation (SD)) age of participants ranged from 59.8 (6.4) (Heidari 2015) to 73.5 (7.9) years (Soler 2006) and more male than female patients (M: 1,902/F: 1,003)[3] were included. In studies with COPD patients only, the mean (SD) FEV1 (%) values at baseline ranged from 34.0% (13.2) to 49.6% (17.0).

Interventions

The interventions were divided into the following categories:

Counselling and support (seven studies, 1,228 participants): All seven studies that were identified in this category compared the intervention to an inactive control group (Bekelman 2017, Benzo 2016, Burtin 2012, Moore 2002, Ries 2003, Scalvini 2016, Wilson 2015). Bekelman 2017 investigated the effects of collaborative care to manage symptoms compared to usual care (*inactive control*) for 24 weeks. Benzo 2016 provided a health care intervention or usual care (*inactive control*) for a year. Burtin 2012 compared an activity counselling programme to usual care (*inactive control*) for 24 weeks. Moore 2002 investigated the effect of a nurse led follow up compared to usual care (*inactive control*) for a year. Ries 2003 and Scalvini 2016 compared a telephone maintenance programme against usual care (*inactive control*) for twelve weeks (Scalvini

[3] *Total number of included patients and sex distribution differs, because of missing data in the studies.*

2016) or a year (Ries 2003). Wilson 2016 compared education session to usual care (*inactive control*) for a year.

Meditative movements (four studies, 244 participants): Two studies in this category compared meditative movements against inactive control, and two other studies compared the intervention against active control (Chan 2015, Donesky-Cuenco 2009, Vanderbyl 2017, Xiao 2015). Three studies investigated the effects of Qi-Gong: Chan 2015 and compared it to usual care (*inactive control*) for eight weeks (Chan 2015); Vanderbyl 2017 to endurance and strength training (*active control*) for six weeks; and Xiao 2015 to walking and other training sessions (*active control*) for 24 weeks. Donesky-Cuenco 2009 provided either yoga or usual care (*inactive control*) for twelve weeks.

Mindfulness-based stress reduction (one study, 86 participants): one study in this category was identified, which compared mindfulness-based stress reduction against support groups (*active control*) for eight weeks (Mularski 2009).

Psychotherapy (six studies, 678 participants): four studies compared the intervention against inactive control, one study used an active control group, and one study had both active and inactive control groups (Alexopoulos 2013, Bove 2016, Chan 2011, Kunik 2008, Livermore 2015, Rosser 1983). Alexopoulos 2013 compared a personalised intervention for depression and COPD against usual care (*inactive control*) for 26 weeks. Bove 2016 provided psycho-educative intervention or usual care (*inactive control*). Chan 2011 tested the combination of psychotherapy and progressive muscle relaxation against usual care for three weeks (with a 12-week follow-up). Kunik 2008 and Livermore compared cognitive behavioural therapy with COPD education (*active control*) for eight weeks (Kunik 2008) or usual care (*inactive control*) for eight weeks with a 24-weeks follow-up (Livermore 2015). Rosser 1983 compared different types of psychotherapy for eight weeks. The trial consisted of an analytical group (intervention), supportive group (*active control*), or a nurse group (*active control*). The control group was without any psychotherapeutic treatment (*inactive control*).

Self-management (eight studies, 769 participants): Six studies in this group compared the intervention against inactive control, whereas the other two studies used an active control group (Boesch 2007, Coultas 2016, Garcia-Aymerich 2007, Heidari 2015,

Johnson-Warrington 2016, Mosher 2016, Nguyen 2008, Soler 2006). Boesch 2007 and Soler 2006 investigated the effects of an education programme against usual care (*inactive control*) for twelve months. Coultas 2016 compared physical activity self-management against usual care (*inactive control*) for twenty weeks with a one-year follow-up. Garcia-Aymerich 2007 provided an integrated care intervention or usual care only (*inactive control*) for twelve months. Heidari 2014 compared self-management to usual care (*inactive control*) for twelve weeks. Johnson-Warrington 2016 compared a self-management programme of activity coping and education (SPACE) for COPD to usual care (*inactive control*) for twelve weeks. Mosher 2016 investigated the effects of telephone/based management and compared it to an education and support group (*active control*) for four weeks and a six-week follow-up. Nguyen 2008 provided either an internet-based dyspnoea self-management programme (intervention) or a face-to-face programme (*active control*) for 24 weeks.

Outcomes

Details of the measures used in the included studies for the primary outcome breathlessness are presented in Table 7. A short overview for each outcome of interest is presented below.

Breathlessness

All included studies assessed breathlessness by utilising various measurements. Uni-dimensional measures (Borg, NRS, and VAS) were used in eight studies, results for breathlessness-specific scales (Fletcher Scale, MRC) were presented in one study, and multi-dimensional measures (CRQ-D, CRQ-M, PFSDQ-M, BDI/TDI, UCSD-SOBQ, Bode, and MSAS) were used in 17 studies.

Table 7: Reported outcome measures by intervention categories

Study ID and intervention category	BDI/TDI	Bode	Borg	CRQ-M	MRC	MSAS	NRS	PEG (m)	PFSDQ-M	SOBQ	SOB	VAS
Counselling and support vs active control												
No studies identified.												
Counselling and support vs inactive control												
Bekelman 2017								X				
Benzo 2016				X								
Burtin 2012												
Moore 2002												
Ries 2003	X			X						X		
Scalvini 2016			X									
Wilson 2015				X								
Meditative movements vs active control												
Vanderbyl 2017							X					
Xiao 2015				X								
Meditative movements vs inactive control												
Chan 2015				X								
Donesky-Cuenco 2009			X	X								
Mindfulness-based stress reduction vs active control												
Mularski 2009			X									X
Mindfulness-based stress reduction vs inactive control												
No studies identified.												
Psychotherapy vs active control												
Kunik 2008				X								
Rosser 1983												X
Psychotherapy vs inactive control												
Alexopoulos 2013										X		
Bove 2015				X								
Chan 2011												X
Livermore 2015			X									
Rosser 1983												X
Self-management vs active control												
Mosher 2016						X						
Ngyuen 2008				X								
Self-management vs inactive control												
Boesch 2007		X			X							
Coultas 2016				X	X							
Garcia-Aymerich 2007					X							
Heidari 2014			X									
Johnson-Warrington 2016				X								
Soler 2006					X							

Psychological distress

Twelve studies assessed psychological distress with a variety of instruments. Most commonly used were HADS (five studies) and the state-trait anxiety inventory (two studies).

Quality of life

Sixteen studies measured quality of life eight instruments, most commonly SF-36 (six studies), SGRQ (four studies) and CRQ total score (four studies).

Risk of bias

The quality of publications varied widely, and in many cases, insufficient information was presented for an informed judgement. A summary of the overall risk of bias is given below and presented in Figure 9 and Figure 10. Additional details and reasons for the assessed risk of bias are presented in Appendix I.

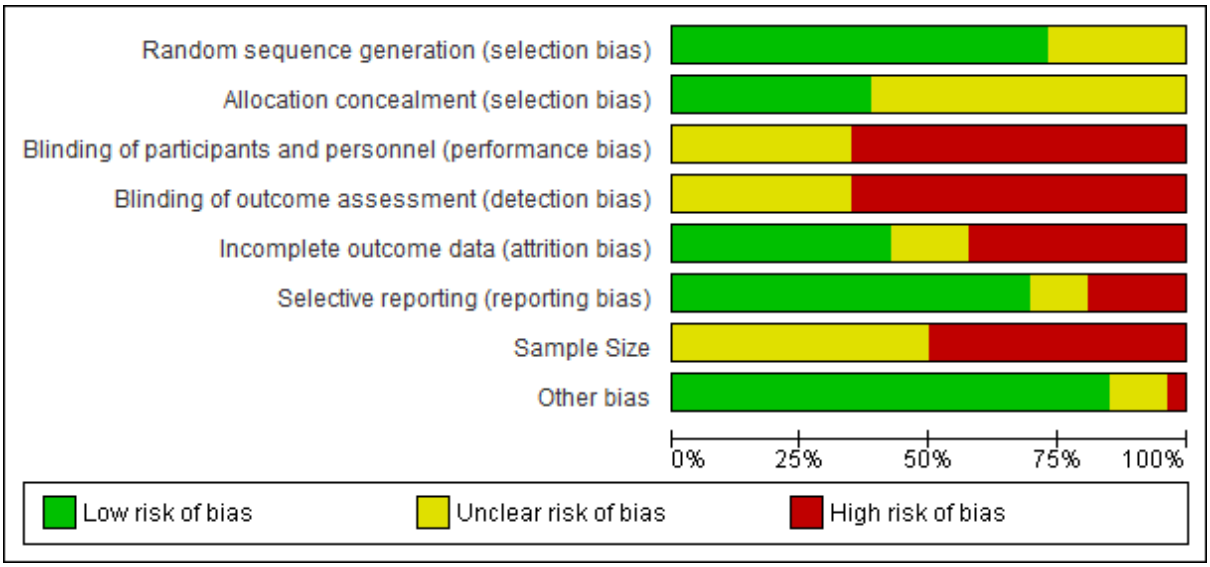


Figure 9: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 10: Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Allocation (selection bias)

Random sequence generation (selection bias)

The risk of bias in 19 studies was as 'low', and as 'unclear' in the other seven trials, due to insufficient details for a judgement.

Allocation concealment (selection bias)

Ten studies were rated as a 'low' risk of bias for allocation concealment. The other sixteen trials did not describe the allocation concealment and were rated as 'unclear' risk.

Blinding (performance bias and detection bias)

17 studies were rated as ‘high’ risk of bias, because participants and/or were not blinded. The other nine studies were assessed as ‘unclear’ risk of bias due to insufficient details reported.

The assessment of outcomes was rated 'high' in 19 studies due to self-reported outcome measures and unblinded patients. The other seven studies did not report details on the assessment of outcomes were therefore rated as 'unclear'.

Incomplete outcome data (attrition bias)

Eleven studies were judged as ‘low’ risk of bias because either the statistical analysis seemed appropriate or the drop-out rate was < 10%. The risk of bias was judged as ‘high’ in elven other studies, due to high drop-out rates and complete-case analysis. The other four trials did not provide enough information for an informed judgement and the risk was therefore rated as ‘unclear’.

Selective reporting (reporting bias)

Eighteen studies reported all outcomes that were stated in the methods sections and therefore judged as 'low'. Five studies reported only parts of the expected results and/or did not present results of all measures and were consequently judged as 'high' risk of

bias. The three conference abstracts did not provide sufficient details for informed judgement and were therefore rated as ‘unclear’ risk.

Study size

Half of the studies included less than 50 patients in the trial and were judged as ‘high’ risk. The other thirteen studies included between 50 and 199 participants and were judged as ‘unclear’ risk.

Other bias

There was no indication for additional bias in 21 studies, and as a result were judged as ‘low’ risk. The risk of bias was assessed as ‘high’ in two studies, due to stopping early because of technical issues with the intervention (Nguyen 2008), and significant different baseline values for outcomes of interest between groups (Rosser 1983). Three conference abstracts were rated as ‘unclear’ risk of bias.

4.2.3. Effects of interventions

Due to the high number of intervention and comparison groups as well as the outcomes that were of interest in this systematic literature review, multiple data were identified. For better clarity, the effects on each symptom are presented separately, and the interventions, divided by comparisons with inactive or active control, are reported for each symptom.

As a side note, trial authors reported study data in various ways and the planned data synthesis (described in 3.2.5.1) turned out to be challenging. To report the full evidence, results of data synthesis for each of the comparisons is presented as follows: first, the number of studies in the corresponding category that reported the outcome is presented in combination with the outcome measure used. Second, if meta-analysis was feasible, the results are presented. If sensitivity analysis were feasible, the results are reported next. Reasons for studies that reported relevant data but could not be included in the meta-analysis are stated as well. Last, a narrative synthesis of the remaining studies that were not included in quantitative analysis is given (for more details see 3.2.5.1).

4.2.3.1. Breathlessness

Counselling and support vs active control

No studies in this comparison category were identified.

Counselling and support vs inactive control

Uni-dimensional measures

Two studies measured breathlessness with uni-dimensional instruments, measuring breathlessness at rest with a Borg scale (Scalvini 2016) and a modified PEG for breathlessness (Bekelman 2017). Data could not be pooled due to different presentation of results. Scalvini 2016 presenting change from baseline values reported significant differences between groups, favouring counselling and support, whereas Bekelman 2017 did not identify differences between groups.

Multi-dimensional measures

Four of the five studies measuring breathlessness with multi-dimensional instruments, that is CRQ-M and the EORTC, provided sufficient data for meta-analysis (Benzo 2016, Burtin 2012, Ries 2003, Wilson 2015). Significant differences between groups were found, favouring counselling (SMD -0.28, 95% CI -0.54 to -0.02; I^2 = 57%; see Table 8, page 50). The SMD indicates a small effect size. In a sensitivity analysis with results of trials with a one year duration, the effects were not significant (SMD -0.14, 95% CI -0.34 to 0.06; I^2 = 1%; see Table 9, page 50).

One study could not be included in the analysis due to only reporting change from baseline data (Scalvini 2016). Using the MRC scale, no significant differences within groups were identified *(no data for between group analysis provided).*

Table 8 Counselling vs inactive control; outcome breathlessness: multi-dimensional measures

	Counselling			Inactive Control				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Benzo 2016	4.9	1.3	74	5.1	1.3	70	25.9%	-0.15 [-0.48, 0.17]
Moore 2002	25	18.5	76	33.3	2.7	74	25.8%	-0.62 [-0.95, -0.29]
Ries 2003	45.9	20.4	74	46.5	22.9	64	25.4%	-0.03 [-0.36, 0.31]
Wilson 2015	4.4	1.4512	53	4.9	1.5213	58	22.9%	-0.33 [-0.71, 0.04]
Total (95% CI)			**277**			**266**	**100.0%**	**-0.28 [-0.54, -0.02]**

Heterogeneity: Tau² = 0.04; Chi² = 6.99, df = 3 (P = 0.07); I² = 57%
Test for overall effect: Z = 2.14 (P = 0.03)

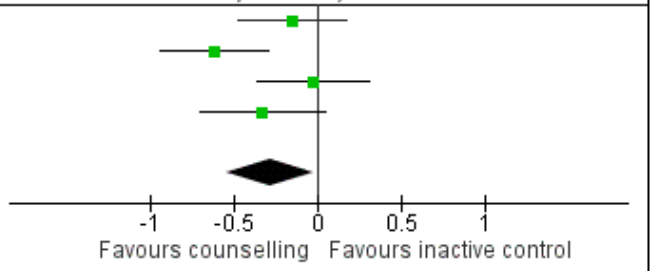
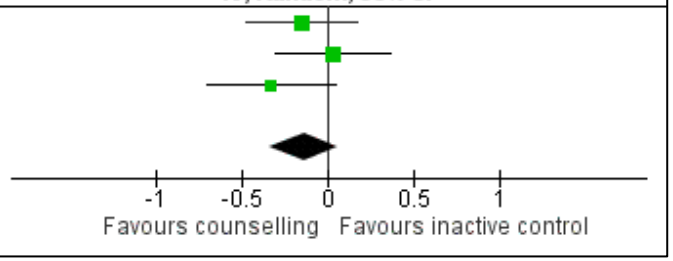


Table 9 Counselling vs inactive control; outcome breathlessness: multi-dimensional measures (sensitivity analysis with one-year data)

	Counselling			Inactive Control				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Benzo 2016	4.9	1.3	74	5.1	1.3	70	36.8%	-0.15 [-0.48, 0.17]
Ries 2003	51.1	23.4	74	50.4	23.7	64	35.2%	0.03 [-0.31, 0.36]
Wilson 2015	4.4	1.4512	53	4.9	1.5213	58	28.0%	-0.33 [-0.71, 0.04]
Total (95% CI)			**201**			**192**	**100.0%**	**-0.14 [-0.34, 0.06]**

Heterogeneity: Tau² = 0.00; Chi² = 2.02, df = 2 (P = 0.36); I² = 1%
Test for overall effect: Z = 1.37 (P = 0.17)



Mindfulness-based stress reduction vs active control

Uni-dimensional measures

The one study in this category measured breathlessness on a Borg scale after a 6MWT and in addition reported the average VAS over the study period (Mularski 2009). No between or within group differences were reported for either instrument.

Multi-dimensional measures

No studies using this outcome measure were identified in this comparison category.

Mindfulness-based stress reduction vs inactive control

No studies in this comparison category were identified.

Meditative movements vs active control

Uni-dimensional measures

One study measured breathlessness with a uni-dimensional scale (NRS) and reported no differences within or between groups (Vanderbyl 2017).

Multi-dimensional measures

One study, using CRQ-M, reported significant differences between groups, favouring the group with meditative movements (Xiao 2015).

Meditative movements vs inactive control

Uni-dimensional measures

One study measured breathlessness with a uni-dimensional scale (Borg) and reported no differences between or within groups (Donesky-Cuenco 2009).

Multi-dimensional measures

Two studies used the CRQ-M and provided sufficient data for analysis (Chan 2015, Donesky-Cuenco 2009). Significant differences between groups were found, favouring meditative movements (SMD 0.74, 95% CI 0.24 to 1.24; I^2 = 0%; see Table 10, page 55). The SMD indicates a large effect size.

Psychotherapy vs active control

Uni-dimensional measures

One study measured breathlessness with the VAS and reported no differences within or between groups (Rosser 1983).

Multi-dimensional measures

Two studies used a multi-dimensional measure for breathlessness, but due to missing data, a pooled effect could not be estimated (Kunik 2008, Rosser 1983). Kunik 2008, using the CRQ-M, reported significant change from baseline improvements within but not between groups. Rosser 1983, using the Fletcher scale, did not identify any differences within or between groups.

Psychotherapy vs inactive control

Uni-dimensional measures

Three studies used a uni-dimensional measure for breathlessness, that is VAS (Chan 2011, Rosser 1983) or Borg (Livermore 2015). Due to different ways of presenting results or missing information, no overall effect estimate could be calculated. One study reported no differences within or between groups (Rosser 1983), one study reported significant differences between groups, favouring psychotherapy, but found no significant differences within the intervention group (Chan 2011) and one study reported significant differences between groups for change from baseline values, favouring psychotherapy (Livermore 2015).

Multi-dimensional measures

Three studies measured breathlessness, each of them using a different multi-dimensional scale (Alexopoulos 2013, Bove 2016, Rosser 1983). Pooled effects could not be calculated due to insufficient data provided. Alexopoulos 2013 reported significant differences between groups. Measured with the Pulmonary Functional Status and Dyspnea Questionnaire (PFSDQ-M), Bove 2016, using CRQ-M, reported significant differences between groups at the end of the study, favouring psychotherapy. Rosser 1983 reported no significant differences based on the Fletcher scale.

Self-Management vs active control

Uni-dimensional measures

The MSAS was used in one study, reporting no differences within or between groups (Mosher 2016).

Multi-dimensional measures

One study, using CRQ-M, reported significant differences within both groups but not between groups (Nguyen 2008).

Self-Management vs inactive control

Uni-dimensional measures

One study used a uni-dimensional measure for breathlessness, reporting significant differences between groups, favouring self-management (Heidari 2015).

Multi-dimensional measures

Two of the five studies provided sufficient data for meta-analysis, both used the MRC (Boesch 2007, Soler 2006). Due to insufficient information presented, the other three trials could not be included in the quantitative analysis (Coultas 2016, Garcia-Aymerich 2007, Johnson-Warrington 2016). Significant differences between groups were found, favouring self-management (MD -0.96, 95% CI -1.81 to -0.12; I^2 = 59%; Table 11, page 55).

Coultas 2016, using CRQ-D, reported no significant differences within or between groups. Johnson-Warrington 2016, presenting data for both the CRQ-D and the CRQ-M, observed significant improvements in both groups, but not between groups. Garcia-Aymerich 2007, using MRC, did not find any within or between group differences.

Table 10: Meditative movements vs inactive control; outcome breathlessness: multi-dimensional measures

Study or Subgroup	Meditative movements Mean	SD	Total	Inactive control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Chan 2015	5.47	1.25	16	4.31	1.36	22	55.0%	0.86 [0.19, 1.54]
Donesky-Cuenco 2009	22.3	4	14	19.4	5.3	15	45.0%	0.60 [-0.15, 1.34]
Total (95% CI)			**30**			**37**	**100.0%**	**0.74 [0.24, 1.24]**

Heterogeneity: Tau² = 0.00; Chi² = 0.27, df = 1 (P = 0.60); I² = 0%
Test for overall effect: Z = 2.91 (P = 0.004)

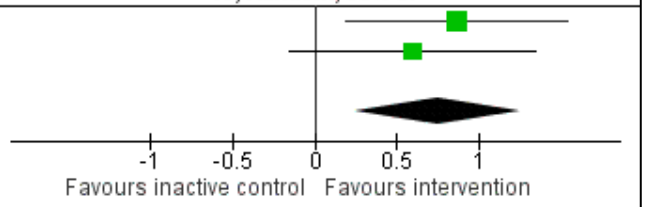
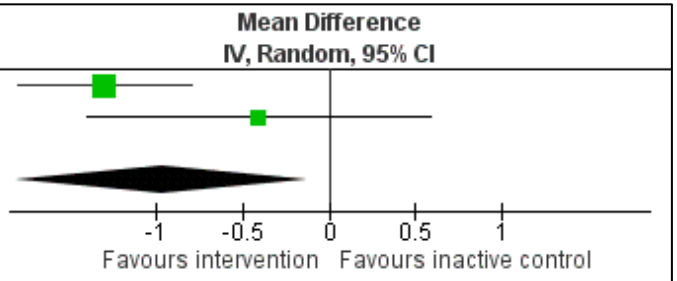


Table 11 Self-management vs inactive control; outcome breathlessness: multi-dimensional

Study or Subgroup	Favours intervention Mean	SD	Total	Inactive control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Boesch 2007	1.1	0.8	30	2.4	0.7	11	62.0%	-1.30 [-1.80, -0.80]
Soler 2006	1.89	1.16	13	2.3	1.41	13	38.0%	-0.41 [-1.40, 0.58]
Total (95% CI)			**43**			**24**	**100.0%**	**-0.96 [-1.81, -0.12]**

Heterogeneity: Tau² = 0.23; Chi² = 2.46, df = 1 (P = 0.12); I² = 59%
Test for overall effect: Z = 2.23 (P = 0.03)



4.2.3.2. Psychological distress

Counselling and support vs active control

No studies in this comparison category were identified.

Counselling and support vs inactive control

Three studies reported psychological distress but did not provide sufficient data for analysis (Bekelman 2017, Ries 2003, Wilson 2015). Two studies, using CES-D or HADS, did not find significant differences between groups (Ries 2003, Wilson 2015), whereas one study found significant differences between groups (Bekelman 2017).

Mindfulness-based stress reduction vs active control

No studies measuring this symptom were identified in this comparison category.

Mindfulness-based stress reduction vs inactive control

No studies in this comparison category were identified.

Meditative movements vs active control

One study measured psychological distress with HADS, reporting no differences within or between groups (Vanderbyl 2017).

Meditative movements vs inactive control

One study measured psychological distress with both the Spielberger State Anxiety Inventory (SSAI) and the CES-D questionnaire, reporting no significant differences within or between groups for both measures (Donesky-Cuenco 2009).

Psychotherapy vs active control

Both studies in this category measured psychological distress, either with Beck or VAS measures for anxiety and depression (Kunik 2008, Rosser 1983). Kunik 2008 found significant differences between but not within groups, Rosser 1983 reported no significant differences between groups, but significant worsening within the control group (VAS depression) and within the intervention group (VAS anxiety).

Psychotherapy vs inactive control

Four of the five studies using measures for psychological distress reported sufficient data for meta-analysis (Alexopoulos 2013, Bove 2016, Chan 2011, Livermore 2015). Significant differences between groups were found, favouring psychotherapy (SMD -0.37, 95% CI -0.63 to -0.12; I^2 = 16%; see Table 12, page 59). SMD indicates a small to moderate effect size.

One study reported VAS measures for anxiety and depression, respectively, but could not be included in the quantitative analysis due to missing information (Rosser 1983). In this study, no differences between groups and significant improvements in the control group were identified.

Self-Management vs active control

One study in this category measured psychological distress, using GAD-7, and did not find significant differences within or between groups (Mosher 2016).

Self-Management vs inactive control

One study used the HADS to measure psychological distress and did not find any differences within or between groups (Johnson-Warrington 2016).

4.2.3.3. Quality of life

Counselling and support vs active control

No studies in this comparison category were identified.

Counselling and support vs inactive control

Three of the five studies measuring quality of life reported sufficient data for meta-analysis (Bekelman 2017, Moore 2002, Ries 2003). No significant differences between groups were found (SMD -0.36, 95% CI -0.91 to 0.20; I^2 = 90%; see Table 13, page 59). The other two studies could not be included in the analysis due to modified subscales or missing information (Benzo 2016, Wilson 2015).

One study, reporting combined CRQ scores for physical function (dyspnea and fatigue domain) and emotional function (mastery and emotion domain), found significant differences between groups and within the intervention group for both scores (Benzo 2016). One study reported change from baseline results measured with the EQ-5D and did not find significant differences within or between groups (Wilson 2015).

Table 12 Psychotherapy vs inactive control; outcome breathlessness: multi-dimensional

Study or Subgroup	Psychotherapy Mean	SD	Total	Inactive control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Alexopoulos 2013	9.2	5.7	38	12.4	6	46	27.5%	-0.54 [-0.98, -0.10]
Bove 2015	8.24	3.3743	30	10.4	3.2494	28	20.0%	-0.64 [-1.17, -0.11]
Chan 2011	42.13	11.52	69	43.62	11.76	66	41.0%	-0.13 [-0.47, 0.21]
Livermore 2015	3.4	2.7	18	4.5	2.8	13	11.5%	-0.39 [-1.11, 0.33]
Total (95% CI)			**155**			**153**	**100.0%**	**-0.37 [-0.63, -0.12]**

Heterogeneity: Tau² = 0.01; Chi² = 3.58, df = 3 (P = 0.31); I² = 16%
Test for overall effect: Z = 2.88 (P = 0.004)

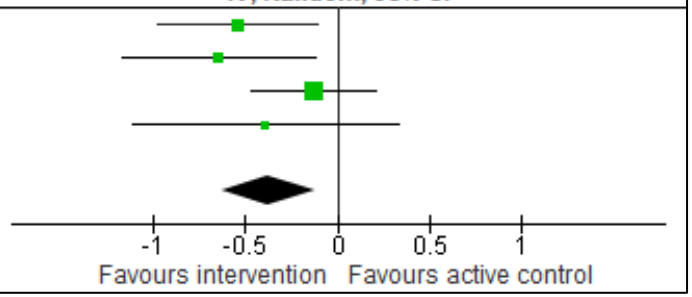
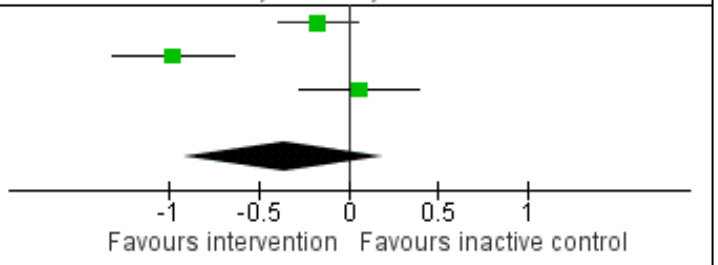


Table 13 Counselling and support vs inactive control; outcome quality of life

Study or Subgroup	Counselling Mean	SD	Total	Inactive Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bekelman 2017	-48.6	17.4	157	-45.3	21	157	34.9%	-0.17 [-0.39, 0.05]
Moore 2002	25	7.2	76	33.3	9.6	74	32.5%	-0.98 [-1.31, -0.64]
Ries 2003	-99.6	19.8	74	-100.8	19.6	64	32.6%	0.06 [-0.27, 0.40]
Total (95% CI)			**307**			**295**	**100.0%**	**-0.36 [-0.91, 0.20]**

Heterogeneity: Tau² = 0.22; Chi² = 20.99, df = 2 (P < 0.0001); I² = 90%
Test for overall effect: Z = 1.26 (P = 0.21)



Mindfulness-based stress reduction vs active control

The one study in this category used both the SGRQ and SF-36 to measure quality of life (Mularski 2009). QoL worsened significantly within the intervention group, and showed significant differences between groups, favouring the control group.

Mindfulness-based stress reduction vs inactive control

No studies in this comparison category were identified.

Meditative movements vs active control

The two studies in this category reported data for quality of life, measured with the SF-36 or the FACT-G, but quantitative analysis was not possible due to missing information (Vanderbyl 2017, Xiao 2015). Both studies did not find significant differences between groups. One study analysed within group differences and found significant improvements within the intervention group (Xiao 2015).

Meditative movements vs inactive control

One study in this category measured quality of life, using SF-36, and did not find differences within or between groups (Donesky-Cuenco 2009).

Psychotherapy vs active control

One study in this category measured quality of life, using SF-36, and significant improvement within both groups, no significant differences between groups (Kunik 2008).

Psychotherapy vs inactive control

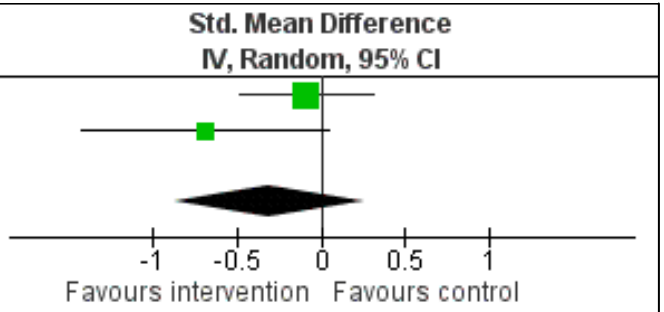
Two studies in this category measured quality of life, using SF-36 or SGRQ and provided sufficient data for quantitative analysis (Chan 2011, Livermore 2015). No significant differences, but a trend, favouring psychotherapy, was found (SMD -0.31; 95% CI -0.81 to 0.26; I^2 = 49%; see Table 14, page 61).

Table 14 Psychotherapy vs inactive control; outcome quality of life

Study or Subgroup	Intervention Mean	SD	Total	Active control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Chan 2011	-56.4	31.5	62	-53.5	33.1	40	63.9%	-0.09 [-0.49, 0.31]
Livermore 2015	33.8	11.4	18	44.2	18.4	13	36.1%	-0.69 [-1.43, 0.05]
Total (95% CI)			**80**			**53**	**100.0%**	**-0.31 [-0.87, 0.26]**

Heterogeneity: Tau² = 0.09; Chi² = 1.97, df = 1 (P = 0.16); I² = 49%

Test for overall effect: Z = 1.06 (P = 0.29)



Self-Management vs active control

One study in this category measured quality of life, using both CRQ and SF-36, and reported significant differences within both groups but not between groups (Nguyen 2008).

Self-Management vs inactive control

Two studies in this category measured quality of life, using SGRQ and/or EQ-5D (Garcia-Aymerich 2007, Soler 2006). One study reported no significant differences within or between groups (Soler 2006), and one study reported significant differences within both groups but not between groups (Garcia-Aymerich 2007).

5. Discussion

5.1. Summary of results

Individual patient data of adults with advanced disease as well as aggregated data investigating the effects of cognitive-emotional interventions were analysed to gain a better understanding about the complex symptom breathlessness.

Descriptive analysis showed that subjective experience of breathlessness, psychological distress and quality of life did not correlate with underlying disease or age. However, relationships with marital status and educational level were identified. The structural equation model showed significant relationships between the three constructs, and 79% of the variance in breathlessness could be explained with psychological distress and quality of life.

Aggregated data with sufficient information were included in meta-analyses, which found significant differences or positive trends favouring cognitive-emotional interventions for all three outcomes of interest, when compared to inactive control groups. Narrative synthesis of the remaining data was inconclusive about possible effects.

5.2. Interpretation of results

Prevalence and severity of breathlessness, psychological distress and quality of life

Participants of the BreathEase trial reported average CRQ-M values when compared to other studies determining the effects of breathlessness services for adults with advanced disease (Farquhar 2014, Farquhar 2016, Higginson 2014, Johnson 2015). Other scores, for example NRS, could not be compared across most studies due to different or unclear focus of questions (Bredin 1999, Farquhar 2016, Vanderbyl 2017). However, in the ones that were identified, average scores were similar to the BreathEase trial. For example, the average NRS for average breathlessness in the last 24h scores were between 5.3 and 5.9 (Higginson 2014, Johnson 2015, Yorke 2015). When compared with studies included in the systematic review, breathlessness scores (measured with CRQ-M) were

within that range. Five trials investigating different interventions and included in study 2 showed mainly higher CRQ-M scores (Benzo 2016, Chan 2015, Wilson 2015, Xiao 2015), three trials reported lower (Bove 2016, Johnson-Warrington 2016) or identical scores (Kunik 2008). These findings suggest that even though no clear definition of 'adults with advanced disease', 'palliative population' or similar exist (King 2005), the subjective experience of breathlessness seems to be similar in this undefined population. The use of the large variety of measurements should be questioned as well as whether these measurements take different dimensions of breathlessness into account or are too general to clearly identify these dimensions. Given the specific situation of adults with advanced disease, e.g. limited time and low health resources, it may not be feasible to interview patients in detail (similar to in-depth interviews for the assessment of anxiety or depression disorders). Therefore, screening tools should focus on key dimensions of breathlessness, that is impact or burden, sensory-perceptual experience and the associated distress (Leitlinienprogramm Onkologie 2019, Parshall 2012). Defining standard measurements of breathlessness in clinical trials could also help to deeper investigate effects of interventions as more data of different studies could be pooled and analysed (see discussion in more detail below).

Based on HADS, participants in the BreathEase trial showed similar prevalence of psychological distress as other studies determining the effects of similar interventions. However, in contrast to BreathEase and Higginson 2014, most trials reported higher scores on the anxiety than the depression subscale as well as more patients with scores ≥ 8 on the anxiety scale (Farquhar 2014, Farquhar 2016, Johnson 2015). For example, one study that compared a breathlessness intervention service to usual care, reported that 53% of participants had HADS values ≥ 8 on the anxiety subscale and 45% had ≥ 8 on the depression subscale (Farquhar 2016). For the comparison of psychological distress of BreathEase participants and trials in study 2, it was necessary to take inclusion criteria of each trial into account because some studies included only patients with HADS ≥ 8 (Alexopoulos 2013, Bove 2016). BreathEase participants were within the range of the anxiety subscale compared to three remaining studies with sufficient data but had the highest average on the depression subscale (Johnson-Warrington 2016, Livermore 2015, Vanderbyl 2017). These findings are in line with the current evidence about the prevalence of psychological distress, where BreathEase is within the higher

end of these ranges. Including data of potentially higher depressed patients in the SEM in study 2 may limit the generalisability of results for less depressed patients.

The same challenges that were described for the other two constructs were identified for quality of life. Comparing data across studies has proven to be limited due to the use of different disease-specific or generic measurements. One study that presented EQ-VAS values reported very similar values as the BreathEase data (Higginson 2014). No studies included in the systematic literature review reported any EQ-VAS values. The lack of data may be related to different definitions of quality of life as well as the dependence on different settings (McCaffrey 2016).

Significant differences between COPD and non-COPD participants in FEV_1(%) values are explainable by the normal progression of COPD with worsening FEV_1(%) (Pauwels 2001). Otherwise, both subgroups were similar, which confirms that in adults with advanced disease, the experience of breathlessness, psychological distress and the general level of quality of life is not necessarily related to the underlying disease. Instead, it is a complex construct, depending on many different variables, for example sociodemographic characteristics.

Relationships between constructs (breathlessness, psychological distress and quality of life) and sociodemographic factors

As expected, breathlessness and psychological distress showed positive correlations, whereas both breathlessness and psychological distress had negative correlations with quality of life. Educational level and marital status showed significant relationships with all three constructs. Results show that adults with advanced disease suffer from different symptoms that are influenced again by other factors. In line with the holistic approach of palliative care (World Health Organisation 2013), the study demonstrated that a variety of factors related to the patient and his or her situation should be considered to understand and relieve the experienced symptoms.

The SEM showed clear relationships between the constructs of interest. Due to generic measurements and broad definitions of the constructs, the question remains which underlying factors of each construct are relevant for these relationships. For example,

the model showed that psychological distress had an effect on breathlessness, but as it is measured with the non-specific measurement HADS, it is unclear, what type of psychological distress is the reason for this relationship. Again, the question about the use of screening tools only instead of in-depth measurements should be raised. In the SEM, the balance between the regression coefficients could be balanced with more specific indicators of constructs. Even though the situation in palliative care is challenging, without precise tools the factors that contribute to the relationships across different constructs may not be identified. As a consequence, developing individually targeted interventions remains challenging as long as it is unclear, which mechanisms should be the focus of these interventions. For example, one study reported the relationship between anxiety and breathlessness through the mediator dyspnoea-related fear (Janssens 2011). Study authors suggest exercise for patients with higher dyspnoea-related fear in order to adapt to situations with different breathing patterns. Another study found no correlation of anxiety and dyspnoea-related fear (Carrieri-Kohlman 1996), and therefore a reduction in dyspnea-related fear would probably not lead to a general decrease of anxiety (Scano 2013). Herigstad 2017 and von Leupoldt 2017 emphasised the importance of treating (among other) psychological symptoms such as anxiety and depression in COPD patients to reduce the dyspnoea-related fear, which may then alleviate the overall experience of breathlessness. Underlying neural mechanisms are still poorly understood but understanding those is a promising key for patient stratification in order to offer individualised treatment options (Herigstad 2017, von Leupoldt 2017).

Quality of life and psychological distress largely explained the variance in breathlessness. Results also showed higher explained variance when all three constructs where part of the model instead of only one endogenous variable predicting breathlessness. The overall model itself showed moderate to good fit. These results suggest that all three constructs should be considered together instead of focusing on one construct or relationship at a time. Studies with all three constructs are sparse but confirm the findings of this dissertation. A study with COPD patients showed that psychological distress is associated with the effect of respiratory symptoms on quality of life (Ng 2007). Another study, again with COPD patients, demonstrated the impact of anxiety on quality of life, including mastery of breathlessness (Cully 2006).

Analysis stratified by the educational level revealed interesting differences in the magnitude of explanation of each exogeneous variable. For the highest educational level, psychological distress played a much larger role in the explanation for the variance in breathlessness than in the other two groups. This might be due to a more differentiated perception of the concepts ‘psychological distress’ and ‘quality of life’ as well as more reflective answers in the questionnaires. However, these results should be interpreted carefully, as the sample size within each subgroup was very small. Nonetheless, it highlights the importance of considering that sociodemographic factors do not only affect the constructs but also the relationship between different constructs. Even though these findings are in line with current research confirming that different sociodemographic factors and the latent constructs correlate with each other (Borge 2010, Kim 2017), research in palliative care about the effects of the sociodemographic factors on the relationship between these constructs is sparse. One study with oesophageal cancer patients showed that the severity of symptom clusters depended on cancer stage, gender and resilience, and the clusters showed a weak to moderate correlation with quality of life (Guo 2019). In agreement with different systematic reviews, the results suggest that future research for symptom clusters in cancer patients should also evaluate the role of sociodemographic characteristics (Miaskowski 2016, Ward-Sullivan 2018). A deeper understanding of the complex situation is necessary for the development of targeted interventions (Gift 2004). As this is not only challenging in the context of breathlessness, but across palliative care, for example missing definitions for ‘palliative patient’, first projects are now conducted to define the complexity in more detail, for example COMPANION, a study to develop a patient centred classification system for the complexity of the adult palliative patient, based on resources and patients’ needs (G-BA Innovationsausschuss 2019).

During the development of the measurement model, exploratory factor analysis (PCA) was conducted to inform item parcelling for the HADS items. Even though HADS is constructed as a two-factor measurement, exploratory factor analysis identified three factors. The differentiation between anxiety and depression subscales could not be confirmed. This finding is in line with a systematic review that out of 50 included studies, only half of them could confirm the two-factor structure (Cosco 2012). Therefore, HADS

may not be appropriate to identify anxiety or depression disorders but serve as a generic measurement of psychological distress (Cosco 2012, Martin 2008).

Effects of interventions

The identified studies revealed large differences in all PICOS criteria except study design:

Population: Even though only trials with adults with advanced disease were included, inclusion criteria had varied substantially, for example hospital vs. outpatient, after acute exacerbation vs. stable over a specific time period or additional comorbidities like major depression. Additionally, trials included most often adults with advanced COPD, followed by trials with cancer patients. The generalizability of the analysed data is therefore limited but indicate significant effects of cognitive-emotional interventions for breathlessness in adults with advanced disease.

Intervention: Cognitive-emotional interventions exist in many different types and categories. Included interventions were provided in different settings (for example at home or in the hospital), varied between a few days up to one year, and differed in other categories as well, for example providers and delivery type. Either the intervention was defined differently in each study or not at all. Again, generalizability of the data is limited. However, the results are consistent across different intervention groups and suggest that cognitive-emotional interventions may relieve breathlessness.

Comparators: Interventions were compared to active and inactive controls, but again, definitions of the controls differed, due to the nature of ‘usual care’ with its dependence on setting, country and population. As quantitative analyses were only possible with inactive control groups, the effects between different intervention types (that is cognitive-emotional interventions compared to other interventions) cannot be investigated further.

Outcomes: As expected, there was a large variety in outcome measurements. In the 26 included trials, more than 40 (modified) measurements of breathlessness, psychological distress and quality of life were identified. As many of these scales do not have valid clinical mean differences, no conclusions can be drawn about the importance of the identified effects in clinical practice.

Besides PICOS, one of the major issues when interpreting the results of this systematic literature review are the generally high risk of bias judgements of included studies. All studies had at least one high risk of bias and several unclear risk of bias categories, and most trials had at least two high risk of bias categories. The risk of bias assessment that is recommended by Cochrane, may not fit well for the assessment in RCTs with non-pharmacological interventions in palliative care, especially with blinding (which is challenging to impossible with cognitive-emotional interventions) and sample size. Nonetheless, the quality of reporting evidence in palliative care needs to follow guidelines, for example the CONSORT statement (Schulz 2010). Additional research is needed on how to appropriately judge the risk of bias in small size trials with non-pharmacological interventions.

In general, reviews about the impact of cognitive-emotional interventions focusing on breathlessness in advanced disease are sparse. Nevertheless, the results of the review in this dissertation agree with the conclusions of published reviews, and also confirm the limitation of low quality of evidence and/or insufficient number of trials: Cognitive-emotional interventions were described as promising for the reduction of breathlessness in one review that only included a limited number of studies (Baraniak 2011). However, this review focused on anxiety as the primary outcome of interest and included trials with other study designs than RCTs as well. Other reviews that investigated the effects of cognitive-emotional interventions, for example meditation, did not focus on adults with advanced disease or had different primary outcomes of interest (Usmani 2017, Volpato 2015). Systematic literature reviews that included only specific types of cognitive-emotional interventions reported similar issues and results as well. A review including 18 studies found short-term effects of cognitive-behavioural therapy for COPD patients in the reduction of both breathlessness and anxiety (Yohannes 2017). Another review that was conducted to determine the effects of self-management interventions for breathlessness in adults with COPD stated that even though breathlessness is common among COPD patients, the evaluation of self-management interventions does not take this outcome into account most of the time (Bentsen 2012). Meditative movements were found to reduce breathlessness in COPD patients, but only included two studies (Wu 2018). Furthermore, data of the CRQ-M score presented in this review did not confirm this conclusion.

Similar to the findings in this dissertation, systematic literature reviews determining the effects of mindfulness-based stress reduction or counselling and support did not identify sufficient data for analysis (Bausewein 2013, Brick 2012, Crowe 2016, Harrison 2016).

The German guidelines “Leitlinienprogramm Onkologie for Palliative Care for Patients with Incurable Cancer” as well as the ESMO Clinical Practice Guidelines suggest including non-pharmacological therapies in the treatment of palliative patients with breathlessness (Kloke 2015, Leitlinienprogramm Onkologie 2019). In contrast to the German Guidelines, which do not specifically state the use of cognitive-emotional interventions, it is mentioned in the ESMO guidelines that psychological training may reduce panic during breathlessness, which should also reduce the perceived breathlessness.

5.3. Strengths and limitations

Missing standardization, different or no definitions and the complexity of the palliative situation is an ongoing issue in this research field, which had a substantial impact on this dissertation and is explained in more detail below.

The development of the measurement models for the latent constructs itself was complicated and followed theoretical considerations as far as possible. However, it has to be noted that some multi-dimensional measurements are constructed in a way that not only different dimensions of one construct but also across different constructs are of interest. For example, CRQ total scores can be used to measure quality of life, whereas the mastery subscale estimates the mastery of breathlessness, and the dyspnoea subscale takes activities that are affected by breathlessness into account. As a modified version of the CRQ was used in the BreathEase trial (individual CRQ dyspnoea subscale instead of standardised subscale), scores for both the CRQ dyspnoea subscale as well as the total CRQ score would have been depended on number of items chosen by the participants instead of standardised ranges (Pearson 2008). Therefore, the CRQ-M was chosen to inform the latent construct breathlessness, and no additional data could be used to inform quality of life to avoid double-counting. Due to the missing standardisation, results of the CRQ dyspnoea subscales could not be included in the meta-analyses of the systematic review neither.

An important strength of the systematic literature review was the conduct following Cochrane guidelines. This approach ensured high quality of this systematic review, for example because of the publication of a protocol and independent screening and data extraction by two researchers for reduction of random errors. Methodological limitations of any systematic literature review include publication bias and the analysis on secondary-data level only (Egger 2001), which was taken into account during the risk of bias assessment.

An additional strength of the systematic literature review was the broad search strategy. In order to identify all relevant references for the review, the search strategy was not limited to specific interventions, as study authors may have used different names or descriptions. Furthermore, the search strategy had no limitations in relation to language or date. All studies that included a measurement of breathlessness were of interest, regardless of the presentation of the results. However, limiting the search strategy to the population of interest remained challenging as the term ‘adults with advanced disease’ is too unspecific. Therefore, the search included a section about advanced or terminal stages, which may have missed the identification of few trials, for example studies including COPD patients with FEV1(%) < 50% may not be described as patients with advanced disease or palliative. Reference lists of included studies, trial registries, and other reviews were searched to control for this possible bias.

Pooling and analysing data of the identified studies was challenging, due to the reasons explained above. Therefore, a conservative approach with a random-effects model for meta-analysis was chosen. Even though, in cases where meta-analyses were possible, clear trends or significant effects were seen for all three outcomes, always favouring cognitive-emotional interventions compared to inactive control groups. Furthermore, due to small sample size and inconsistent reporting, subgroup analyses based on different levels of any variable could not be conducted. Therefore, this systematic literature review could not be analysed subgroups based on patient characteristics as planned.

Besides the challenges of the research field, additional strengths and limitations regarding theoretical and methodological decisions should be noted. Structural equation modelling is used to explain the variance of the endogenous variable in this dissertation breathlessness. Therefore, it was assumed that psychological distress and quality of life affect breathlessness. As the relationships between the three constructs of interest are complex, there may not be 'one-way' but rather reciprocal relationships (Bentsen 2012, Scano 2013). Furthermore, in the SEM it was assumed, that, due to the evidence of psychological distress affecting breathlessness as well as correlating with quality of life, quality of life also affects breathlessness. Additional research about the causality of relationships is needed but was not possible in this dissertation (due to cross-sectional nature of the data). However, the SEM showed moderate good model fit and explained a large amount of the variance in breathlessness.

An additional limitation in both studies was the sample size. Even though the BreathEase trial can be considered as a large trial in palliative care (n=183), the sample size was rather low in the context of SEM (Weiber 2014). Therefore, the number of parameters that needed to be estimated was reduced with item parcelling. In the systematic literature review, all included studies were rated as high or unclear risk due to sample size (median n = 96). Pooling data was one way of increasing the power of the analysis. However, due to lack of standardisation and missing information in the publications, data could not be combined very often, or meta-analyses had to be conducted with less than 50% of included participants. The remaining data was therefore summarized narratively, which could not pool data accordingly.

Furthermore, it has to be noted that the literature search was run in July 2017. It can be assumed that additional trials would have been identified with a search update. However, the issues described above would have remained unsolved, regardless of the possible inclusion of additional trials. It is recommended to update the search, when, among others, substantial changes in the research field can be expected, which is most often the case after five years (Cumpston 2019, Garner 2016). Therefore, it can be assumed that the results of this review are up to date.

5.4. Conclusion

This dissertation presents evidence that breathlessness in adults with advanced disease is correlated with educational level and marital status, as well as with psychological distress and quality of life. The variance in breathlessness can largely be explained by psychological distress and quality of life. Furthermore, the relationship between breathlessness and the other two constructs may be affected by the educational level of the patient. Causal relationships and specific factors of each construct that either affects or is affected by other constructs and the possible impact on the effects of cognitive-emotional interventions should be investigated further. However, in order to increase reproducible research and understand the 'vicious cycles' of breathlessness with psychological distress and quality of life, clear definitions and less generic, but setting-specific measurements of constructs should be developed and used.

Furthermore, cognitive-emotional interventions may reduce breathlessness as well as psychological distress and improve quality of life. There was limited evidence for patients with other advanced diseases than COPD, as less than 20% of studies included adults with other diseases (lung cancer or CHF).

Besides missing definitions of cognitive-emotional interventions and standard care, comparators may also play an important role to understand the effects of these interventions. The context in which these interventions should be used has to be investigated further.

The review confirms the gap in evidence already noticed in other reviews. Based on the current evidence, not only more studies are needed, but also multi-centre studies to power studies sufficiently for the outcomes of interest. Current studies suffer from small sample sizes that limit the generalization of their results due to lack of power. Additionally, huge variety in outcome measures limits the possibility of combining data across studies. Cross-mapping of different measurements and defining gold standards may help to better understand the complex situation of breathlessness.

With the current guidelines about risk of bias assessment most studies in this research field, regardless of the quality of the publication, would normally be rated as high risk of bias due to the very limited possibility of blinding and the above mentioned issue with small sample sizes. This may indicate the need for different guidelines for non-pharmacological interventions. Even though possible high risks of bias due to unblinded trials and small sample sizes should be considered, adequate differentiation between high- and low-quality studies is currently challenging.

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Appendices

Appendix A. Publication of the protocol

Cognitive-emotional interventions for breathlessness in adults with advanced diseases (Protocol)

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A B S T R A C T

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effects and safety of interventions targeting cognition, emotion or both as the predominant underlying mechanism of effect to relieve breathlessness in adults suffering from advanced diseases.

B A C K G R O U N D

This protocol is partly based on suggested wording from the Cochrane Pain, Palliative and Supportive Care Review Group (PaPaS CRG). Some wording is used from the original review (Bausewein 2008), which this new review will update and replace.

Description of the condition

Breathlessness or dyspnoea is defined as "subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity" (Meek 1999). The term 'breathlessness' reflects the patients' perspective based on the daily experience whereas the medical term 'dyspnoea' focuses more on the clinical sign of an underlying condition (Johnson 2014). "The experience derives from interactions among multiple physiological, psychological, social, and environmental factors, and may include secondary physiological and behavioural responses" (Meek 1999). Since this definition was adopted, new evidence has led to better understanding of the mainly sensory and affective components and that dyspnoea "must generally be distinguished from signs that clinicians typically invoke as evidence of respiratory distress, such as tachypn(o)ea, use of accessory muscles, and intercostal retractions."

(Parshall 2012). Many patients with different conditions including primary and secondary cancer, lung diseases (e.g. chronic obstructive pulmonary disease (COPD), pulmonary hypertension, cystic fibrosis, interstitial lung disease (ILD)), chronic heart failure (CHF) or motor neuron disease/amyotrophic lateral sclerosis (MND/ALS) suffer from this distressing symptom (Bailey 2010; Booth 2008; Breaden 2011; Lansing 2009; Solano 2006). Breathlessness is a multifactorial and complex symptom and an experience unique to the individual (Booth 2008). It is often expressed as air hunger, work of breathing, laboured breathing, awareness of respiratory distress, and shortness of breath or chest tightness (Barnes 2016; Parshall 2012). Breathing discomfort is described by such phrases as 'could not breathe fast or deep enough' or 'could not get enough air' or 'suffocating' (Guz 1997). Breathlessness is one of the most prevalent and distressing symptoms in advanced stages of malignant and non-malignant diseases. Up to 95% of patients with advanced chronic pulmonary disease, 88% with advanced heart disease, and 70% with end stage cancer experience breathlessness in their last year of life (Graham 2010; Lansing 2009; Moens 2014; Solano 2006; Teunissen 2007). The frequency and severity of breathlessness increase during the course of the disease until death (Bailey 2010; Breaden 2011). It is an extremely distressing symptom for the patient but also for the accompanying family and professional carers (Booth 2008). Overall, breathlessness is still difficult to palliate.

Description of the intervention

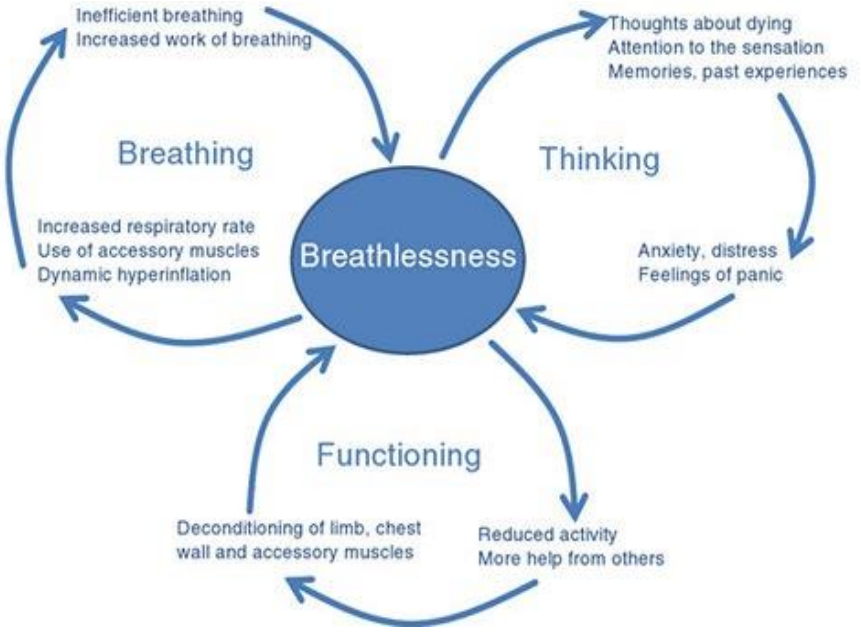
Management of breathlessness

Appropriate management to relieve breathlessness in advanced diseases requires both pharmacological and non-pharmacological interventions. Different systematic reviews and meta-analyses were published in recent years and analysed the effects of pharmacological interventions such as opioids (Barnes 2016;Mahler2013),benzodiazepines (Simon 2016), and oxygen (Ameer 2014; Cranston 2008; Sharp 2016) for breathlessness in adult patients. However, the use of drugs to treat breathlessness is sometimes limited as they entail adverse effects and doses need to be titrated carefully. Therefore, non-pharmacological interventions are an important part of the treatment of breathlessness. As mentioned above, many systematic reviews analysed the effects of pharmacological treatments, which is why we are focusing solely on non-pharmacological interventions in this review.

Non-pharmacological

Many non-pharmacological interventions for the relief of breathlessness have been developed and evaluated in recent years. For better clarity, we therefore categorise the interventions based on a theoretical concept developed by Booth 2014, Chin 2016 and Spathis 2017. This concept builds on the effect breathlessness has on patients (Figure 1).

Figure 1. Perpetuation of breathlessness by vicious cycles (Booth 2014)

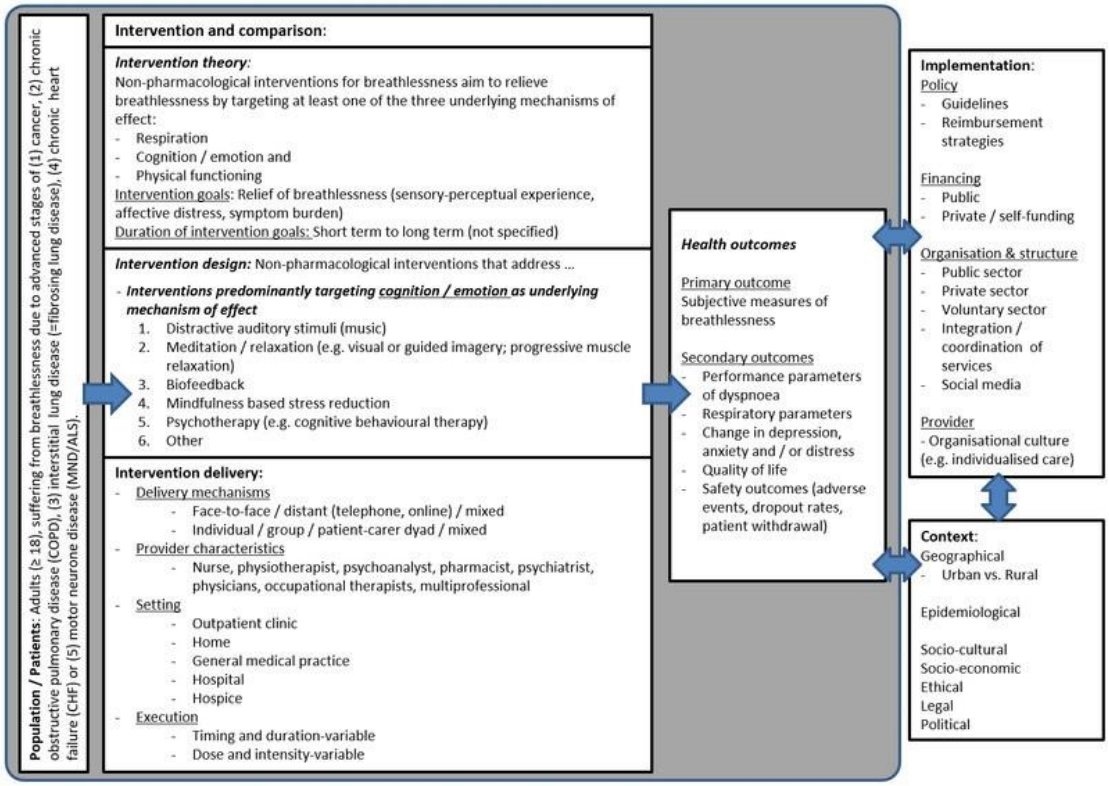


interventions

- Respiratory: Inefficient breathing and increased work of breathing can be observed due to dysfunctional breathing patterns with an increased respiratory rate, the need for the use of accessory muscles, and dynamic hyperinflation.
- Cognitive-emotional: Misconceptions and paying too much attention to the sensation of breathlessness such as memories of past or negative experiences lead to anxiety, distress, feelings of panic, and thoughts about dying.
- Physical: Persons suffering from severe breathlessness show reduced physical activity with a tendency to self-isolation and the need for more help from others. This leads to We expect a huge number of studies and categories of interventions to be included. Therefore, three different reviews, based on the theoretical concept, will be conducted. An additional review is planned, focusing on interventions targeting more than one underlying mechanism as described above.

In this review, we will analyse non-pharmacological interventions targeting primarily cognition and/or emotion to relieve breathlessness in patients suffering from advanced stages of disease, for example distractive auditory stimuli (music), meditation/relaxation(e.g.visualorguidedimagery;progressivemusclerelaxation), biofeedback, mindfulness-based stress reduction, and psychological therapy (e.g. cognitive behavioural therapy). These interventions may take place in a variety of settings, and can, with guidance of healthcare professionals, mostly be carried out by patients themselves (Figure 2).

Figure 2. System-based logic model on cognitive-emotional interventions for breathlessness in patients with advanced diseases



Invasive interventions could also be classified as non-pharmacological but they will not be the focus in this review. Therefore, we will exclude surgical procedures such as drainage, tapping, endoscopy, ventilation and catheterisation. We will also exclude the following non-pharmacological interventions as there have been recent Cochrane Reviews: (McCarthy 2015), and nutrition (Ferreira 2012).

How the intervention might work

All interventions that will be subsumed in this review aim to address and modify behaviour, mood, emotional state and cognition. This may help people suffering from advanced diseases to better cope with their breathlessness. Cognitive-emotional interventions target the training of coping strategies, the reduction of fear and stress relating to breathlessness or the enhancement of positive thinking. Different types of cognitive-emotional techniques are of interest in this review.

Psychological therapy, for example cognitive behavioural therapy, aims to help patients to break through the vicious cycle of breathlessness and activity avoidance, by providing, among others, behavioural activation, and problem-solving techniques (von Leupoldt 2012).

Relaxation and meditative techniques aim to produce a stage of relaxation and stress relief through elimination of environmental distractions (Glanze 2012).

Distractive auditory stimuli (music) with and without exercise are supposed to reduce the intensity of symptoms, e.g. breathlessness, through drawing the attention away from the symptoms (Lee 2015).

Based on a template byRohwer 2017 we developeda system-based logic model in which we show how non-pharmacological interventions for breathlessness, with a focus on interventions predominantly targeting cognition and/or emotion, are implemented in the healthcare system (Figure 2).

Why it is important to do this review

Non-pharmacological interventions can complement pharmacological interventions and may offer alternative treatment options in the management of breathlessness occurring in advanced illness. As research into this challenging, poorly managed and burdensome symptom is rapidly evolving, there is a need to synthesise the most recent evidence to inform practice and research. Our review aim is to aid health professionals in the treatment of breathlessness with palliative intent and to inform patients and carers about the evidence of non-pharmacological interventions targeting cognition, emotion or both to relieve breathlessness.

This is an update of a Cochrane review on non-pharmacological interventions for the relief of breathlessness in advanced disease (Bausewein 2008). The former review showed effectiveness of neuromuscular electrical stimulation, chest wall vibration, walking aids, and breathing training. The review included 47 studies that were categorised in different intervention groups (e.g. walking aids, acupuncture, breathing training, psychological therapy). Since its publication, many randomised controlled studies on non-pharmacological interventions have been published, including new intervention groups (e.g. breathlessness services). Therefore, although necessary, a single review as an update of the earlier review seemed infeasible. Based on the interventions used to target breathlessness, we decided to assess the interventions in different reviews.

O B J E C T I V E S

To assess the effects and safety of interventions targeting cognition, emotion or both as the predominant underlying mechanism of effect to relieve breathlessness in adults suffering from advanced diseases.

M E T H O D S

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs), cluster RCTs, and quasi-RCTs (QRCTs). Quasi-randomisation is defined as some pseudo-random method of allocation such as alternation, date of birth, case record number or date of presentation (Higgins 2011). We will include cross-over studies, if separate data for both time periods are presented. We will only use the data of the first period for analysis to avoid carry-over effects. We will require full journal publication. Where full journal publication is not available, we will try to obtain data by contacting the trial authors unless sufficient data for analyses are provided in online clinical trial results, summaries of otherwise unpublished clinical trials, or conference abstracts. QRCTs will be included in order to obtain the full breadth of

relevant trials, in particular as we expect to find a small number of RCTs for some of the intervention categories; we are aware of the higher risk of bias in these studies and will account for this in the analysis.

Types of participants

Adult patients aged 18 years and above, suffering from advanced diseases with a high prevalence of breathlessness. We will include studies if the majority (≥ 50%) of participants meet the following criteria.

- Patients suffering from cancer should have advanced local or metastatic disease (e.g. TNM Classification of Malignant Tumours (TNM) state ≥ T3 or N ≥ 1 or M ≥ 1).
- Patients with severe COPD should have a forced expiratory volume in one second (FEV1) predicted of < 50%.
- Patients with pulmonary hypertension will be included if they reach a WHO class level ≥ III, defined by Barst 2004.
- Patients suffering from CHF should have New York Heart Association (NYHA) stage III or IV.
- Patients with ILD or idiopathic pulmonary fibrosis (IPF) : all studies will be included as breathlessness is the predominant symptom and there are hardly any disease-specific treatment options.
- Patients with neuromuscular diseases (MND, ALS): all studies will be included as advanced disease is marked by the occurrence of breathlessness.

If groups for the inclusion criteria mentioned above were stratified, we will only include the subgroups of interest. We will document difficult decisions in the review. Sensitivity analysis can assess the impact of these decisions on the review's result. Patients included in the studies can be in any setting. We will exclude studies of patients with any condition not regarded as advanced and life limiting such as acute or chronic asthma, or with pre-existing diagnosis of acute asthma or acute cardiac condition as a primary cause of breathlessness.

Types of interventions

We will include interventions targeting cognition-emotion or both to relieve breathlessness according to the following prespecified categories.

- Distractive auditory stimuli (music).
- Meditation/relaxation (e.g. visual/guided imagery; progressive muscle relaxation).
- Biofeedback.
- Mindfulness-based stress reduction.
- Psychological therapy (e.g. cognitive behavioural therapy).

If we find interventions of interest that do not fit in the above categories, we will define an additional category 'Other' or add new categories if there is a sufficient number of studies. The judgement for inclusion will be based on the study authors' description of the intervention; any deviation from this will be explicitly mentioned.
Interventions may take place in any setting, e.g. outpatient clinic, home, hospital, hospice, general medical practice. The comparator may be no treatment, placebo, attention control, standard care, or a different kind of therapy. We will categorise the control groups into 'active controls' or 'other' based on the description of the comparison group. We will focus on active controls as comparison group in our primary analysis. Concomitant interventions, especially pharmacological treatment, will be accepted, if administered in the same way in both the control and the treatment groups. If these interventions are suspected to have some relevant influence on our outcomes we will consider this in subgroup analysis.

Types of outcome measures

We anticipate that studies will use a variety of outcome measures. To be included, a study must have any measure of breathlessness. Adverse effects of cognitive-emotional interventions will be measured as absent or present and a narrative description of these effects will be given when reported. We will consider all reliable and validated measures for the following outcomes.

Primary outcomes

Breathlessness, measured by self-reported instruments with a focus on breathlessness or mastery of breathlessness (e.g. Baseline Dyspnoea Index (BDI), Borg Dyspnoea Scale (BDS), Medical Research Council (MRC) Breathlessness Scale, or Chronic Respiratory Disease Questionnaire (CRQ)). Other terms for breathlessness such as dyspnoea, shortness of breath, and difficulty breathing will also be accepted.

Secondary outcomes

- Performance parameters (e.g. walking tests, International Physical Activity Questionnaire (IPAQ)).
- Respiratory parameters (e.g. change in FEV1(%)).
- Change in depression, anxiety and/or distress (e.g. Hospital Anxiety and Depression Scale (HADS)).
- Quality of life (e.g. 36-Item Short Form Health Survey (SF-36)).
- Safety outcomes:

◦ Adverse events (measured as absent or present);
◦ Dropout rates; and
◦ Patient withdrawal from the trial, due to any reason (if mentioned).

Search methods for identification of studies

Electronic searches

We will search the following databases from their inception to the present, without date or language restrictions.

- Cochrane Database of Systematic Reviews (CDSR), the Cochrane Library.
- Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Library.
- MEDLINE (Ovid).
- Embase (Ovid).
- PsycINFO (Ovid).
- LILACS (Bireme) • CINAHL (Ebsco).

We will search MEDLINE and Embase using both controlled vocabulary (namely, MeSH in MEDLINE and EMTREE in Embase) and a wide range of free-text terms. To detect all RCTs we will perform the search on MEDLINE using the Cochrane Highly Sensitive Search Strategy, sensitivity-maximising version (Higgins 2011).
The search strategy for MEDLINE is in Appendix 1.

Searching other resources

We will search the meta-register of controlled trials (mRCT) (www.controlled-trials.com/mrct), clinicaltrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/) for ongoing trials. In addition, we will check reference lists of reviews and retrieved articles for additional studies, and we will perform citation searches on key articles. We will contact experts in the field for unpublished and ongoing trials. We will contact study authors where necessary for additional information. We will perform the search in collaboration with the Information Specialist of the Cochrane Pain, Palliative and Supportive Care Group.

Data collection and analysis

Selection of studies

Two review authors (AB, SR) will independently screen all titles and abstracts retrieved by the search to identify all trials that may be eligible and for which the full paper should be obtained. Independent review authors will eliminate studies that clearly do not satisfy inclusion criteria, and obtain full copies of the remaining studies. Two review authors (AB, SR) will read these studies independently to select relevant studies, and in the event of disagreement or unclear

decision to include, we will resolve disagreement with a third author (MM or CB, depending on the topic). We will not anonymise the studies in any way before assessment. We will include a PRISMA flow chart in the full review which will show the status of identified studies (Moher 2009) as recommended in Part 2, Section 11.2.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will include studies in the review irrespective of whether measured outcome data are reported in a 'usable' way.

Data extraction and management

Two review authors (SR, AB, AH or MM) will independently extract data using a data collection form based on a standard form released by the Cochrane Effective Practice and Organisation of Care Group (EPOC) and check for agreement before entry into Review Manager (RevMan 2014). Where there is disagreement, a third author (CB or SB) will be consulted to resolve differences. We will include information about the following.

Participant characteristics

- Demographic characteristics (age, gender, nationality).
- Underlying disease characteristics (type and stage of condition).

Intervention

- Intervention theory
- Type of intervention (description of intervention, frequency, duration (total and per session)).
- Types of control condition (control intervention, control group).
- Type of delivery (delivery mechanisms such as face-to-face, distant; group, individual; provider characteristics such as nurses, physicians, multi-professional; setting such as outpatient clinic, home, hospital).

Methods

- Study design.
- Size of intervention and control group at baseline and follow-up.
- Study duration and follow-up.
- Sources of bias (sequence generation, allocation sequence concealment, blinding, incomplete outcome data, selective reporting, other concerns about bias).

Outcomes

- Key outcomes with measurement instruments.
- Timing, duration and frequency of follow-up.
- Adverse events.
- Number of withdrawals and dropouts.

Context

- Country of origin.

In case multiple reports of the same study are found, we will extract data of all these reports independently of each other and compare; if data differ between reports, all authors will make a decision how to treat this study and this will be documented in the review. We will collate multiple reports of the same study, so that each study rather than each report is the unit of interest in the review. We will collect characteristics of the included studies in sufficient detail to populate a table of 'Characteristics of included studies' in the full review. Review authors will not be involved in the data extraction of studies they authored or co-authored.

Assessment of risk of bias in included studies

Two authors (AB, AH) will independently assess risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and adapted from those used by the Cochrane Pregnancy and Childbirth Group.
We will assess the following for each study.

- Random sequence generation (checking for possible selection bias). We will assess the method used to generate the allocation sequence as: low risk of bias (any truly random process, e.g. random number table; computer random number generator); unclear risk of bias (method used to generate sequence not clearly stated). Studies using a non-random process (e.g. odd or even date of birth; hospital or clinic record number) will be assessed as high risk of bias.
- Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions prior to assignment determines whether intervention allocation could have been foreseen in advance of, or during, recruitment, or changed after assignment. We will assess the methods as: low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes); high risk of bias (studies that do not conceal allocation (e.g. open list); unclear risk of bias (method not clearly stated).
- Blinding of outcome assessment (checking for possible detection bias). We will assess the methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received. We will assess the methods as: low risk of bias (study states that it was blinded and describes the method used to achieve blinding); high risk of bias (no or incomplete blinding); unclear risk of bias (study states that it was blinded but does not provide an adequate description of how it was achieved). We will also report if study participants are asked about their expectations of benefit of intervention/control if blinding is not feasible.
- Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data). We will assess the methods used to deal with incomplete data as: low risk (< 10% of participants did not complete the study and/or data have been imputed using appropriate methods); high risk of bias (used 'completer' analysis); unclear risk of bias (insufficient information for low/ high risk of bias category).
- Selective reporting (checking for reporting bias). We will assess the methods as: low risk of bias (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported); high risk of bias (where not all the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported); unclear risk of bias (insufficient information for low/high risk of bias category).
- Other bias (e.g. checking for possible biases confounded by small size. We will assess studies as being at low risk of bias (≥ 200 participants per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm); high risk of bias (< 50 participants per treatment arm)).

We will use the Review Manager tool to complete a 'Risk of bias' table (RevMan 2014). Any discrepancy between the two authors will be resolved by discussion involving a third author (CB).

Measures of treatment effect

We will analyse dichotomous outcomes using risk ratios (RRs) with 95% confidence intervals (CIs). We will recategorise any categorical outcomes with more than two categories into two groups. We will analyse continuous data using standardised mean differences (SMDs) with 95% CIs. We will calculate standard deviations, if not reported, using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We plan to report the proportion of participants experiencing any adverse effects of cognitive-emotional interventions, and combine studies using RRs with 95% CIs.

Unit of analysis issues

We will reanalyse data, if possible, for cluster trials which have not taken clustering into account in their analysis. We will calculate effective sample sizes and adjusted standard errors using the design effect method. We will try to obtain estimates for intracluster correlation coefficients from study authors or will use external estimates obtained from comparable studies, as recommended by Cochrane guidelines (Higgins 2011). We will document if reanalysis is not feasible.

In studies with more than two arms, we will consistently choose the active control arms in the main analysis, and, if possible, do a sensitivity analysis, in which we will choose the other control arm. We will combine individually randomised controlled trials and cluster RCTs in the same meta-analyses or harvest plots, but these will be clearly identified (Higgins 2011).

Dealing with missing data

We will contact study authors if missing data on study characteristics or outcome measures precludes study inclusion or limits use of a study at further stages of the review. If studies do not report outcomes based on intention-to-treat analyses this will be considered as a source of bias during 'Risk of bias' assessment. We will try to calculate effect measures or CIs wherever possible from available data, if we get no response.

Assessment of heterogeneity

We will assess methodological and clinical heterogeneity with tables documenting the following characteristics of the included studies.

- Intervention components (e.g. music, meditation/ relaxation, biofeedback, psychological therapy).
- Intervention delivery mechanism (e.g. face-to-face, distant).
- Provider characteristics (e.g. nurses, physiotherapists, physicians).
- Setting (e.g. outpatient clinic, hospice, home).
- Patients (e.g. COPD, cancer, fibrosing lung disease).
- Methods (outcome measures, outcome assessment).

For those studies assessing the impacts of a given intervention category on comparable outcomes, thus making pooling through meta-analysis feasible, we will assess statistical heterogeneity graphically with a forest plot by examining the extent to which CIs overlap, and statistically with the I^2 statistic. We will consider an I^2 value greater than 50% to indicate substantial statistical heterogeneity, and will consider it statistically significant if the P-value for the Chi^2 test is < 0.1. We will document statistical heterogeneity but this will not have any direct consequences for meta-analysis (see below). We will create forest plots and I^2 calculations using Review Manager 5.3 (RevMan 2014).

Assessment of reporting biases

We will try to minimise publication bias by searching trials registers for projected and registered studies that have never been published. We will contact the authors to get unpublished information if there are such studies registered or some relevant information is missing and can therefore narrow the risk of reporting bias. We will assess the possibility that publication bias affects the review using funnel plots when at least 10 studies are available for meta-analysis.

Data synthesis

We will attempt to pool all studies within a given intervention category assessing the same outcome by conducting a meta-analysis using Review Manager 5.3 (RevMan 2014). We will use the random-effects model due to the expected large heterogeneity in delivery mechanisms, provider characteristics, setting and study population.
We will report results as RRs for dichotomous outcomes and SMDs for continuous outcomes. We will undertake meta-analysis only if studies are judged to be similar enough to give a clinically meaningful answer. We will provide an outcome table and summarise the results narratively if meta-analysis is not possible. In the case of skewed data, we will log transform these data for our analysis or, if that approach is not feasible, summarise them narratively.

'Summary of findings' table

We will include a 'Summary of findings' table using the GRADE profiler software (GRADEpro GDT 2015) as set out in the PaPaS author guide (AUREF 2012) and recommended in the *Cochrane Handbook for Systematic Reviews of Interventions,* Chapter 4.6.6 (Higgins 2011) to evaluate the quality of evidence in our review. The 'Summary of findings' table will include outcomes of: a) change of breathlessness, b) objective parameters of breathlessness, c) quality of life indicators, d) change of depression or anxiety,
e) adverse events, f) characteristics of the patient population that benefits most.

Quality of the evidence

This section is taken from the Cochrane Drugs and Alcohol Group recommended text. The overall quality of the evidence for each outcome in our review will be assessed using the GRADE system (GRADEpro GDT 2015) and presented in the 'Summary of findings' tables, to present the main findings of a review in a transparent and simple tabular format. In particular, we will include key information concerning the quality of evidence, the magnitude of effect of the interventions examined, and the sum of available data on the main outcomes.
The GRADE system uses the following criteria for assigning grade of evidence.

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
- Low: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- Very low: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

We will decrease grade rating by one(-1)or two(- 2) if we identify:

- serious (-1) or very serious (-2) limitation to study quality;
- important inconsistency (-1);
- some (-1) or major (-2) uncertainty about directness;
- imprecise or sparse data (-1); or • high probability of reporting bias (-1).

Subgroup analysis and investigation of heterogeneity

We will undertake subgroup analysis for the primary outcomes to examine factors that may explain variation in the effectiveness, if numbers are sufficiently large. We will perform stratification as follows.

- Type of intervention.
- Intervention delivery (delivery mechanisms such as face-to-face, distant; group, individual; provider characteristics such as nurses, physicians, multi-professional; setting such as outpatient clinic, home, hospital).
- Patient characteristics (underlying disease, disease stage, age, gender).
- Underlying therapy

Sensitivity analysis

We will conduct sensitivity analysis where possible, to test the effect of different methodological decisions made throughout the review process on the primary outcome. We will test the robustness of the results by removing from the pooled effect estimate:

- studies with a high risk of bias for two or more key domains;
- quasi-randomised clinical trials;
- outcome measures; and
- intervention of varying duration.

A C K N O W L E D G E M E N T S

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Appendix B. Changes between protocol and dissertation

Data extraction

Instead of independent data extraction of several reports on the same trial, the main publication was extracted, and additional data identified in subsequent publications were added in the same sheet.

Missing data

Study authors were only contacted if studies were published in or after 2002, mostly because of missing contact information and retired study authors.

Data presented in 2D-figures were extracted with a specialised software (DigitizeIt).

Intervention categories

Interventions targeting cognitive-emotional mechanisms were included in this dissertation, even though additional mechanisms may have been targeted as well (for example meditative movements were included in this dissertation, which targets the cognitive-emotional cycle as well as the physical cycle).

Measures of secondary outcomes

For this dissertation, the secondary outcomes of interest were limited to the topic and therefore included breathlessness, psychological distress and quality of life.

Main analyses

Originally, main analyses were planned to include comparisons with active controls only. As several intervention groups were included in this dissertation, the focus of only one comparison might have been an unrealistic representation of the research field.

Additional assessments and summary of finding tables

As this systematic literature review was one part of the dissertation only, it was decided that GRADE, summary of finding tables and additional analyses were outside of the scope of this dissertation and are therefore not presented here.

Appendix C. Responsibilities of the author team

Project lead of the series of Cochrane reviews	CB
Project coordination of the series of Cochrane reviews	AB
Drafted the protocol	AB, HK, SR, CB, MM, ER, SB, IJH, MG, AH
Developed and ran the search strategy	SR (except LILACS data base: AB); PaPaS Information Specialist provided support.
Obtained copies of studies	AB
Contacted study authors	AB
Selected which studies to include (2 people)	AB, SR, PS
Dissolving disagreements	AB, CB
Extracted data from studies (2 people)	AB, AH, SB, PS
Entered data into RevMan*	AB, AH, PS
Risk of bias assessment	AB (with support of AH, SB, and PS)
Classification of intervention types	CB, AH, AB
Carried out the analysis*	AB
Interpreted the analysis*	AB

**Analysis and data that were included in this dissertation (study 2)*

Appendix D. Variables collected in the BreathEase trial

One-time data collection

Sociodemographic and clinical characteristics

- Demographic variables: age, education, marital status, nationality, place of residence (aggregated), date of birth
- Living situation
- Diseases and comorbidities; Clinical characteristics of disease
- Medical history and treatment
- Charlson index
- Lung function: Height; Weight; FEV1L; FEV1 (%); FVCL; FVC (%); FEV1/FVC; FEV1/FVC (%); PEF; PEF (%); SpO2; O2; O2 flow; SpO2 flow; BMI; Tiff Index
- Additional data of relatives/ carer

Adverse events: Time; Description; Action; Serious adverse event (yes/no)

Survival data

Multiple data collection

Patients

- Australian Karnofsky Index
- Health status: infection, weight change, anaemia, derailed blood pressure, allergic reaction, reduced mobility, accident, other information
- CRQ; NRS; IPOS; HADS; EQ-5D; Medication; SPPB; Lung function

Relatives: ZBI, EQ-5D, sleep

Health-economic data

- Visits to specialists; Number of visits
- Official grading of the need for care
- Medical aids

Additional data

- Hospitalisation; Medication: number of drugs, number of prescription drugs, names, administration form, doses, intake, taken since

Appendix E. Search strategies

CENTRAL and CDSR (Cochrane Library)

Number	Search details
# 1	MeSH descriptor: [Dyspnea] explode all trees
# 2	dyspn?ea:ti,ab,kw (Word variations have been searched)
# 3	(short* near/2 breath):ti,ab,kw (Word variations have been searched)
# 4	(urge* near/2 breath*):ti,ab,kw (Word variations have been searched)
# 5	((labo?red or difficult* or small) near/3 breath*):ti,ab,kw (Word variations have been searched)
# 6	((respirat* or breath*) near/3 (distress* or comfort* or discomfort*)):ti,ab,kw (Word variations have been searched)
# 7	(air near/3 (hunger or starve* or need* or gasp* or pant*)):ti,ab,kw (Word variations have been searched)
# 8	suffocat* or breathless*:ti,ab,kw (Word variations have been searched)
# 9	unsatisf* inspiration:ti,ab,kw (Word variations have been searched)
# 10	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9
# 11	MeSH descriptor: [Neoplasms] this term only
# 12	MeSH descriptor: [Lung Neoplasms] this term only
# 13	((lung* or bronchi* or pulmo*) near/3 (neoplasm* or cancer* or tumo?r* or metasta* or malignan*)):ti,ab,kw (Word variations have been searched)
# 14	MeSH descriptor: [Lung Diseases] this term only
# 15	MeSH descriptor: [Pulmonary Disease, Chronic Obstructive] explode all trees
# 16	(COPD or COAD):ti,ab,kw (Word variations have been searched)
# 17	MeSH descriptor: [Lung Diseases, Obstructive] this term only
# 18	(obstruct* near/3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)):ti,ab,kw Word variations have been searched)
# 19	MeSH descriptor: [Hypertension, Pulmonary] this term only
# 20	#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19
# 21	MeSH descriptor: [Heart Failure] explode all trees
# 22	((heart or cardia* or myocard*) near/2 (fail* or insufficienc*)):ti,ab,kw (Word variations have been searched)
# 23	(decompensat* near/2 (heart* or cardia*)):ti,ab,kw (Word variations have been searched)
# 24	decompensatio cordis:ti,ab,kw (Word variations have been searched)
# 25	insufficientia cardis:ti,ab,kw (Word variations have been searched)
# 26	((cardiac or heart) near/2 incompetenc*):ti,ab,kw (Word variations have been searched)
# 27	cardiac stand still:ti,ab,kw (Word variations have been searched)
# 28	#21 or #22 or #23 or #24 or #25 or #26 or #27
# 29	MeSH descriptor: [Lung Diseases, Interstitial] explode all trees
# 30	(interstitial near/3 (disease* or pneumoni* or fibrosis)):ti,ab,kw (Word variations have been searched)
# 31	pulmonary fibrosis:ti,ab,kw (Word variations have been searched)
# 32	fibrosing alveolitis:ti,ab,kw (Word variations have been searched)
# 33	MeSH descriptor: [Cystic Fibrosis] this term only
# 34	(cystic fibrosis or mucoviscidosis):ti,ab,kw (Word variations have been searched)
# 35	#29 or #30 or #31 or #32 or #33 or #34
# 36	MeSH descriptor: [Motor Neuron Disease] explode all trees
# 37	(MND or ALS):ti,ab,kw (Word variations have been searched)
# 38	motor neuron disease*:ti,ab,kw (Word variations have been searched)

Number	Search details
# 39	sclerosis:ti,ab,kw (Word variations have been searched)
# 40	MeSH descriptor: [Amyotrophic Lateral Sclerosis] this term only
# 41	charcot disease*:ti,ab,kw (Word variations have been searched)
# 42	lou gehrig disease*:ti,ab,kw (Word variations have been searched)
# 43	encephalomyelitis disseminate:ti,ab,kw (Word variations have been searched)
# 44	#36 or #37 or #38 or #39 or #40 or #41 or #42 or #43
# 45	#44 or #35 or #28 or #20
# 46	((end stage or advanc* or final or terminal* or limit*) near/3 (disease* or illness*)):ti,ab,kw (Word variations have been searched)
# 47	MeSH descriptor: [Terminally Ill] this term only
# 48	MeSH descriptor: [Terminal Care] this term only
# 49	MeSH descriptor: [Palliative Care] this term only
# 50	MeSH descriptor: [Prognosis] this term only
# 51	((advanc* or terminal or limit*) near/3 (prognos* or prospect* or prediction*)):ti,ab,kw (Word variations have been searched)
# 52	MeSH descriptor: [Disease Progression] this term only
# 53	((incurable or worsen* or chronic) near/3 (illness* or disease*)):ti,ab,kw (Word variations have been searched)
# 54	#46 or #47 or #48 or #49 or #50 or #51 or #52 or #53
# 55	#54 or #45
# 56	#10 and #55

MEDLINE (OVID)

Number	Search details
# 1	exp Dyspnea/
# 2	dyspn?ea.tw.
# 3	(short* adj2 breath).tw.
# 4	(urge* adj2 breath*).tw.
# 5	breathless*.tw.
# 6	((labo?red or difficult* or small) adj3 breath*).tw.
# 7	((respirat* or breath*) adj3 (distress* or comfort* or discomfort*)).tw.
# 8	(air adj3 (hunger or starve* or need* or gasp* or pant*)).tw.
# 9	suffocat*.tw.
# 10	unsatisf* inspiration.tw.
# 11	or/1-10
# 12	Neoplasms/ or Lung Neoplasms/
# 13	((lung* or bronchi* or pulmo*) adj3 (neoplasm* or cancer* or tumo?r* or metasta* or malignan*)).mp.
# 14	Lung diseases/
# 15	exp Pulmonary Disease, Chronic Obstructive/
# 16	(COPD or COAD).tw.
# 17	Lung Diseases, Obstructive/
# 18	(obstruct* adj3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)).tw.
# 19	hypertension, pulmonary/
# 20	or/12-19
# 21	exp Heart Failure/

Number	Search details
# 22	((heart or cardia* or myocard*) adj2 (fail* or insufficienc*)).tw.
# 23	(decompensat* adj2 (heart* or cardia*)).tw.
# 24	decompensatio cordis.tw.
# 25	insufficientia cardis.tw.
# 26	((cardiac or heart) adj2 incompetenc*).tw.
# 27	cardiac stand still.tw.
# 28	or/21-27
# 29	exp Lung Diseases, Interstitial/
# 30	(interstitial adj3 (disease* or pneumoni* or fibrosis)).tw.
# 31	pulmonary fibrosis.tw.
# 32	fibrosing alveolitis.tw.
# 33	Cystic Fibrosis/
# 34	(cystic fibrosis or mucoviscidosis).tw.
# 35	or/29-34
# 36	exp Motor Neuron Disease/
# 37	(MND or ALS).tw.
# 38	motor neuron disease*.tw.
# 39	sclerosis.tw.
# 40	Amyotrophic Lateral Sclerosis/
# 41	charcot disease*.tw.
# 42	lou gehrig disease*.tw.
# 43	encephalomyelitis disseminate.mp.
# 44	or/36-43
# 45	20 or 28 or 35 or 44
# 46	((end stage or advanc* or final or terminal* or limit*) adj3 (disease* or illness*)).tw.
# 47	Terminally Ill/
# 48	Terminal Care/
# 49	Palliative Care/
# 50	Prognosis/
# 51	((advanc* or terminal or limit*) adj3 (prognos* or prospect* or prediction*)).tw.
# 52	disease progression/
# 53	((incurable or worsen* or chronic) adj3 (illness* or disease*)).tw.
# 54	or/46-53
# 55	45 or 54
# 56	randomized controlled trial.pt.
# 57	controlled clinical trial.pt.
# 58	randomized.ab.
# 59	placebo.ab.
# 60	drug therapy.fs.
# 61	randomly.ab.
# 62	trial.ab.
# 63	groups.ab.
# 64	56 or 57 or 58 or 59 or 60 or 61 or 62 or 63
# 65	exp animals/ not humans.sh.
# 66	64 not 65

Number	Search details
# 67	11 and 55
# 68	66 and 67

Embase (OVID)

Number	Search details
# 1	exp Dyspnea/
# 2	dyspn?ea.tw.
# 3	(short* adj2 breath).tw.
# 4	(urge* adj2 breath*).tw.
# 5	breathless*.tw.
# 6	((labo?red or difficult* or small) adj3 breath*).tw.
# 7	((respirat* or breath*) adj3 (distress* or comfort* or discomfort*)).tw.
# 8	(air adj3 (hunger or starve* or need* or gasp* or pant*)).tw.
# 9	suffocat*.tw.
# 10	unsatisf* inspiration.tw.
# 11	or/1-10
# 12	Neoplasms/ or Lung Neoplasms/
# 13	((lung* or bronchi* or pulmo*) adj3 (neoplasm* or cancer* or tumo?r* or metasta* or malignan*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
# 14	Lung diseases/
# 15	exp Pulmonary Disease, Chronic Obstructive/
# 16	(COPD or COAD).tw.
# 17	Lung Diseases, Obstructive/
# 18	(obstruct* adj3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)).tw.
# 19	hypertension, pulmonary/
# 20	or/12-19
# 21	exp Heart Failure/
# 22	((heart or cardia* or myocard*) adj2 (fail* or insufficienc*)).tw.
# 23	(decompensat* adj2 (heart* or cardia*)).tw.
# 24	decompensatio cordis.tw.
# 25	insufficientia cardis.tw.
# 26	((cardiac or heart) adj2 incompetenc*).tw.
# 27	cardiac stand still.tw.
# 28	or/21-27
# 29	exp Lung Diseases, Interstitial/
# 30	(interstitial adj3 (disease* or pneumoni* or fibrosis)).tw.
# 31	pulmonary fibrosis.tw.
# 32	fibrosing alveolitis.tw.
# 33	Cystic Fibrosis/
# 34	(cystic fibrosis or mucoviscidosis).tw.
# 35	or/29-34
# 36	exp Motor Neuron Disease/
# 37	(MND or ALS).tw.
# 38	motor neuron disease*.tw.

Number	Search details
# 39	sclerosis.tw.
# 40	Amyotrophic Lateral Sclerosis/
# 41	charcot disease*.tw.
# 42	lou gehrig disease*.tw.
# 43	encephalomyelitis disseminate.mp.
# 44	or/36-43
# 45	20 or 28 or 35 or 44
# 46	((end stage or advanc* or final or terminal* or limit*) adj3 (disease* or illness*)).tw.
# 47	Terminally Ill/
# 48	Terminal Care/
# 49	Palliative Care/
# 50	Prognosis/
# 51	((advanc* or terminal or limit*) adj3 (prognos* or prospect* or prediction*)).tw.
# 52	disease progression/
# 53	((incurable or worsen* or chronic) adj3 (illness* or disease*)).tw.
# 54	or/46-53
# 55	45 or 54
# 56	random$.tw.
# 57	factorial$.tw.
# 58	crossover$.tw.
# 59	cross over$.tw.
# 60	cross-over$.tw.
# 61	placebo$.tw.
# 62	(doubl$ adj blind$).tw.
# 63	(singl$ adj blind$).tw.
# 64	assign$.tw.
# 65	allocat$.tw.
# 66	volunteer$.tw.
# 67	Crossover Procedure/
# 68	double-blind procedure.tw.
# 69	Randomized Controlled Trial/
# 70	Single Blind Procedure/
# 71	or/56-70
# 72	(animal/ or nonhuman/) not human/
# 73	71 not 72
# 74	11 and 55
# 75	73 and 74
# 76	limit 75 to embase

PsycINFO (OVID)

Number	Search details
# 1	exp Dyspnea/
# 2	dyspn?ea.tw.
# 3	(short* adj2 breath).tw.
# 4	(urge* adj2 breath*).tw.
# 5	breathless*.tw.
# 6	((labo?red or difficult* or small) adj3 breath*).tw.
# 7	((respirat* or breath*) adj3 (distress* or comfort* or discomfort*)).tw.
# 8	(air adj3 (hunger or starve* or need* or gasp* or pant*)).tw.
# 9	suffocat*.tw.
# 10	unsatisf* inspiration.tw.
# 11	or/1-10
# 12	Neoplasms/ or Lung Neoplasms/
# 13	((lung* or bronchi* or pulmo*) adj3 (neoplasm* or cancer* or tumo?r* or metasta* or malignan*)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
# 14	Lung diseases/
# 15	exp Chronic Obstructive Pulmonary Disease/
# 16	(COPD or COAD).tw.
# 17	Lung Diseases, Obstructive/
# 18	(obstruct* adj3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)).tw.
# 19	hypertension, pulmonary/
# 20	or/12-19
# 21	((heart or cardia* or myocard*) adj2 (fail* or insufficienc*)).tw.
# 22	(decompensat* adj2 (heart* or cardia*)).tw.
# 23	decompensatio cordis.tw.
# 24	insufficientia cardis.tw.
# 25	((cardiac or heart) adj2 incompetenc*).tw.
# 26	cardiac stand still.tw.
# 27	or/21-26
# 28	(interstitial adj3 (disease* or pneumoni* or fibrosis)).tw.
# 29	pulmonary fibrosis.tw.
# 30	fibrosing alveolitis.tw.
# 31	Cystic Fibrosis/
# 32	(cystic fibrosis or mucoviscidosis).tw.
# 33	or/28-32
# 34	(MND or ALS).tw.
# 35	motor neuron disease*.tw.
# 36	sclerosis.tw.
# 37	Amyotrophic Lateral Sclerosis/
# 38	charcot disease*.tw.
# 39	lou gehrig disease*.tw.
# 40	encephalomyelitis disseminate.mp.
# 41	or/34-40
# 42	20 or 27 or 33 or 41

Number	Search details
# 43	((end stage or advanc* or final or terminal* or limit*) adj3 (disease* or illness*)).tw.
# 44	Terminally Ill/
# 45	Palliative Care/
# 46	Prognosis/
# 47	((advanc* or terminal or limit*) adj3 (prognos* or prospect* or prediction*)).tw.
# 48	disease course/
# 49	((incurable or worsen* or chronic) adj3 (illness* or disease*)).tw.
# 50	44 or 45 or 46 or 47 or 48 or 49
# 51	42 or 50
# 52	51 and 11
# 53	clinical trials/
# 54	(randomis* or randomiz*).tw.
# 55	(random$ adj3 (allocat$ or assign$)).tw.
# 56	((clinic$ or control$) adj trial$).tw.
# 57	((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
# 58	(crossover$ or "cross over$").tw.
# 59	random sampling/
# 60	Experiment Controls/
# 61	Placebo/
# 62	placebo$.tw.
# 63	exp program evaluation/
# 64	treatment effectiveness evaluation/
# 65	((effectiveness or evaluat$) adj3 (stud$ or research$)).tw.
# 66	or/53-65
# 67	52 and 66

CINAHL (EBSCO)

Number	Search details
S67	S65 AND S66
S66	S11 AND S56
S65	S57 OR S58 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64
S64	(allocat* random*)
S63	(MH "Quantitative Studies")
S62	(MH "Placebos")
S61	placebo*
S60	(random* allocat*)
S59	(MH "Random Assignment")
S58	(Randomi?ed control* trial*)
S57	(singl* blind*) or (doubl* blind*) or (tripl* blind*) or (trebl* blind*) or (trebl* mask*) or (tripl* mask*) or (doubl* mask*) or (singl* mask*)
S56	S46 OR S55
S55	S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54
S54	((incurable or worsen* or chronic) N3 (illness* or disease*))
S53	(MH "Disease Progression")
S52	((advanc* or terminal or limit*) N3 (prognos* or prospect* or prediction*))

Number	Search details
S51	(MH "Prognosis")
S50	(MH "Palliative Care")
S49	(MH "Terminal Care")
S48	(MH "Terminally Ill Patients")
S47	((end stage or advanc* or final or terminal* or limit*) N3 (disease* or illness*))
S46	S21 OR S29 OR S36 OR S45
S45	S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44
S44	encephalomyelitis disseminate
S43	lou gehrig disease*
S42	charcot disease*
S41	(MH "Amyotrophic Lateral Sclerosis")
S40	sclerosis
S39	motor neuron disease*
S38	(MND or ALS)
S37	(MH "Motor Neuron Diseases+")
S36	S30 OR S31 OR S32 OR S33 OR S34 OR S35
S35	(cystic fibrosis or mucoviscidosis)
S34	(MH "Cystic Fibrosis")
S33	fibrosing alveolitis
S32	pulmonary fibrosis
S31	(interstitial N3 (disease* or pneumoni* or fibrosis))
S30	(MH "Lung Diseases, Interstitial+")
S29	S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28
S28	cardiac stand still
S27	((cardiac or heart) N2 incompetenc*)
S26	insufficientia cardis
S25	decompensatio cordis
S24	(decompensat* N2 (heart* or cardia*))
S23	((heart or cardia* or myocard*) N2 (fail* or insufficienc*))
S22	(MH "Heart Failure+") Search modes - Boolean/Phrase
S21	S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20
S20	(MH "Hypertension, Pulmonary")
S19	(obstruct* N3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)) Search modes - Boolean/Phrase
S18	(MH "Lung Diseases, Obstructive")
S17	(COPD or COAD)
S16	(MH "Pulmonary Disease, Chronic Obstructive+")
S15	(MH "Lung Diseases")
S14	((lung* or bronchi* or pulmo*) N3 (neoplasm* or cancer* or tumo?r* or metasta* or malignan*))
S13	(MH "Lung Neoplasms")
S12	(MH "Neoplasms")
S11	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10
S10	unsatisf* inspiration Search modes - Boolean/Phrase
S9	suffocat* Search modes - Boolean/Phrase
S8	(air N3 (hunger or starve* or need* or gasp* or pant*))

Number	Search details
S7	((respirat* or breath*) N3 (distress* or comfort* or discomfort*))
S6	((labo?red or difficult* or small) N3 breath*)
S5	breathless*
S4	(urge* N2 breath*)
S3	(short* N2 breath)
S2	dyspn?ea
S1	(MH "Dyspnea+")

LILACS (Bireme)

"NEOPLASM" or "NEOPLASM METASTASIS/" or "TUMOR" or "TUMOUR" or "TUMOUR'" or "TUMOUR'S" or "METASTASIS" or "METASTASIS/" or "METASTASIS.." or "CANCER" or "LUNG CANCER/" or "LUNG DISEASES" or "LUNG DISEASES, INTERSTITIAL" or "LUNG DISEASES, INTERSTITIAL/" or "LUNG DISEASES, OBSTRUCTIVE" or "LUNG DISEASES, OBSTRUCTIVE/" or "LUNG DISEASES/" or "LUNG NEOPLASMS/" or "PULMONAR-FIBROSIS" or "PULMONAR.." or "PULMONAR/" or "PULMONAR/PULMONARY" or "PULMONARY CANCER/" or "PULMONARY DISEASE, CHRONIC OBSTRUCTIVE" or "PULMONARY DISEASE, CHRONIC OBSTRUCTIVE/" or "PULMONARY FIBROSIS" or "PULMONARY FIBROSIS/" or "PULMONARY HEART DISEASE" or "PULMONARY HEART DISEASE/" or "PULMONARY HYPERTENSION" or "HEART DECOMPENSATION" or "HEART FAILURE" or "HEART FAILURE, CONGESTIVE" or "HEART FAILURE/" or "CARDIAC FAILURE" or "CARDIAC FAILURE/" or "CARDIAC-RESPIRATORY" or "CYSTIC FIBROSIS" or "MUCOVISCIDOSE" or "MUCOVISCIDOSE/" or "MOTOR NEURON DISEASE" or "MOTOR NEURON DISEASE, AMYOTROPHIC LATERAL SCLEROSIS" or "MOTOR NEURON DISEASE, AMYOTROPHIC LATERAL SCLEROSIS/" or "MOTOR NEURON DISEASE/" or "SCLEROSIS" or "FIBROSING/" or "FIBROSIS" or "TERMINAL CARE/" or "TERMINALLY ILL/" or "END-STAGE" or "ADVANCED-STAGE" or "ADVANCED-STAGED" or "INCURABLE/" or "PALLIATIVE CARE/" or "PALLIATIVE CARE NURSING/" or "PALLIATIVE TREATMENT/" or "PALLIATIVE-CARE"

AND

"RANDOMISED" or "RANDOMISED-CONTROLLED" or "RCT" or "RCT'S" or "RANDOMIZATION" or "RANDOMIZED CONTROLLED CLINICAL TRIAL" or "RANDOMIZED CONTROLLED TRIAL" or "RANDOMIZED CONTROLLED TRIALS AS TOPIC/" or "RANDOMIZED PLACEBO-CONTROLLED" or "PLACEBO-CONTROLLED" or "RANDOMLY"

AND

"DYSPNEA" or "DYSPNEA.." or "DYSPNEA/" or "DYSPNOE" or "DYSPNOEA" or "DYSPNEIC" or "BREATHLESS" or "BREATHLESSNESS" or "SHORTPNEA" or "BREATHING" or "BREATHING EXERCISES/" or "BREATHING.." or "BREATHLESSNESS"

Results filtered by „LILACS" and „Controlled Clinical Trial"

Appendix F. Template for data extraction

Participant characteristics

- Demographic characteristics (age, gender, nationality).
- Underlying disease characteristics (type and stage of condition).

Intervention

- Intervention theory.
- Type of intervention (description of intervention, frequency, duration (total and per session)).
- Types of control condition (control intervention, control group).
- Type of delivery (delivery mechanisms such as face-to-face, distant; group, individual; provider characteristics such as nurses, physicians, multiprofessional; setting such as outpatient clinic, home, hospital).

Methods

- Study design.
- Size of intervention and control group at baseline and follow-up.
- Study duration and follow-up.
- Sources of bias (sequence generation, allocation sequence concealment, blinding, incomplete outcome data, selective reporting, and other concerns about bias).

Outcomes

- Key outcomes with measurement instruments.
- Timing, duration and frequency of follow-up.

Context

- Country of origin.

Appendix G. ANOVA results of baseline differences

Between group differences based on marital status

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
NRS 1	Between Groups	29,421	3	9,807	3,166	**,026***
	Within Groups	554,492	179	3,098		
	Total	583,913	182			
NRS 2	Between Groups	7,736	3	2,579	,854	,466
	Within Groups	540,570	179	3,020		
	Total	548,306	182			
NRS 3	Between Groups	29,737	3	9,912	2,915	**,036***
	Within Groups	608,700	179	3,401		
	Total	638,437	182			
MRC	Between Groups	1,591	3	,530	1,077	,360
	Within Groups	88,125	179	,492		
	Total	89,716	182			
CRQ-M	Between Groups	14,532	3	4,844	3,483	**,017**
	Within Groups	248,944	179	1,391		
	Total	263,476	182			
IPOS	Between Groups	1,475	3	,492	,948	,419
	Within Groups	92,853	179	,519		
	Total	94,328	182			
HADS total	Between Groups	508,475	3	169,492	3,197	**,025***
	Within Groups	9490,541	179	53,020		
	Total	9999,016	182			
EQ-VAS	Between Groups	1834,816	3	611,605	1,927	,127
	Within Groups	56826,868	179	317,469		
	Total	58661,683	182			

*. Correlation is significant at the 0.05 level (2-tailed).

Between group differences based on residence

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
NRS 1	Between Groups	,034	1	,034	,011	,918
	Within Groups	583,878	181	3,226		
	Total	583,913	182			
NRS 2	Between Groups	7,809	1	7,809	2,615	,108
	Within Groups	540,497	181	2,986		
	Total	548,306	182			
NRS 3	Between Groups	7,865	1	7,865	2,257	,135
	Within Groups	630,573	181	3,484		
	Total	638,437	182			
MRC	Between Groups	,147	1	,147	,298	,586
	Within Groups	89,569	181	,495		
	Total	89,716	182			
CRQ-M	Between Groups	3,716	1	3,716	2,589	,109
	Within Groups	259,760	181	1,435		
	Total	263,476	182			
IPOS	Between Groups	,012	1	,012	,023	,880
	Within Groups	94,316	181	,521		
	Total	94,328	182			
HADS total	Between Groups	134,592	1	134,592	2,470	,118
	Within Groups	9864,425	181	54,500		
	Total	9999,016	182			
EQ-VAS	Between Groups	38,325	1	38,325	,118	,731
	Within Groups	58623,358	181	323,886		
	Total	58661,683	182			

*. Correlation is significant at the 0.05 level (2-tailed).

Between group differences based on COPD (yes/no)

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
NRS 1	Between Groups	2,911	1	2,911	,907	,342
	Within Groups	581,002	181	3,210		
	Total	583,913	182			
NRS 2	Between Groups	14,620	1	14,620	4,958	**,027**
	Within Groups	533,686	181	2,949		
	Total	548,306	182			
NRS 3	Between Groups	6,956	1	6,956	1,994	,160
	Within Groups	631,481	181	3,489		
	Total	638,437	182			
MRC	Between Groups	,087	1	,087	,176	,675
	Within Groups	89,629	181	,495		
	Total	89,716	182			
CRQ-M	Between Groups	,296	1	,296	,203	,653
	Within Groups	263,180	181	1,454		
	Total	263,476	182			
IPOS	Between Groups	,927	1	,927	1,797	,182
	Within Groups	93,401	181	,516		
	Total	94,328	182			
HADS total	Between Groups	51,622	1	51,622	,939	,334
	Within Groups	9947,395	181	54,958		
	Total	9999,016	182			
EQ-VAS	Between Groups	186,892	1	186,892	,578	,448
	Within Groups	58474,791	181	323,065		
	Total	58661,683	182			

*. Correlation is significant at the 0.05 level (2-tailed).

Appendix H. Results for item parcelling

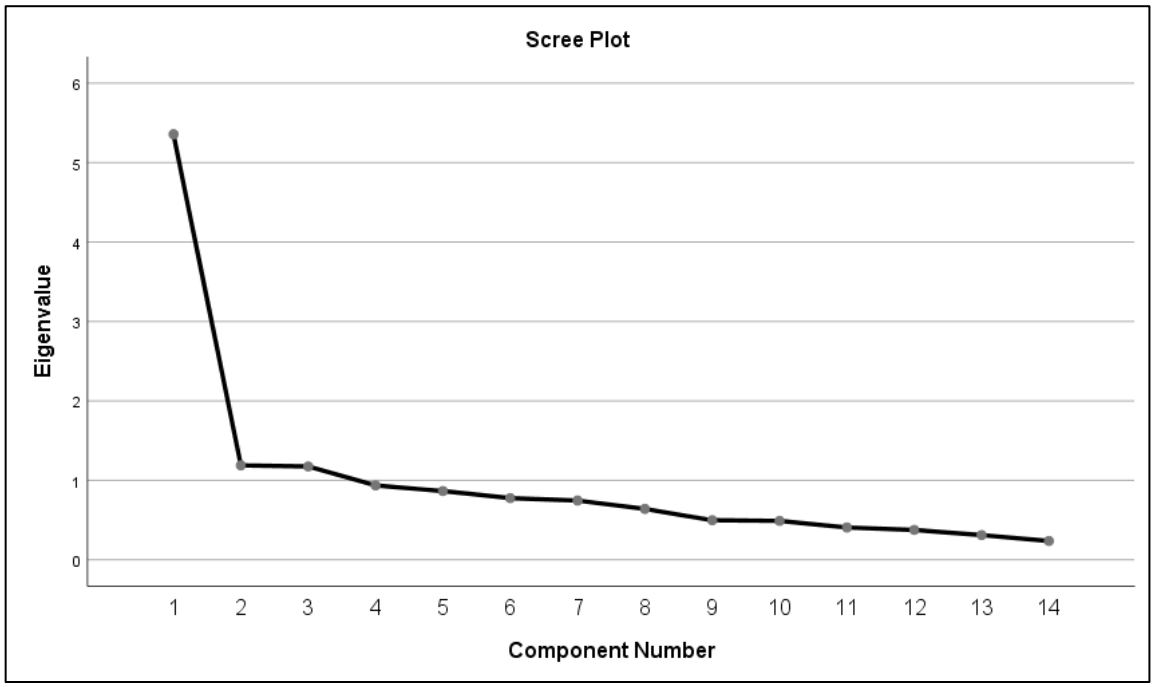

Figure H.1: Scree Plot for HADS factors

Table H.1: Factor analysis for HADS items; items of each factor in bold

Rotated Component Matrix[a]

	Component		
	1	2	3
Tenseness	,464	**,588**	
Current enjoyment	**,772**		
Frightened		**,670**	
Laughter	**,812**		
Worry	,463	**,590**	
Cheerfulness	**,770**		
Relaxed	,584		**,528**
Reduced energy	**,384**		-,364
Nervousness		**,625**	
Loss of interest in self	**,363**		
Restlessness			**,718**
Future enjoyment	**,738**		
Panic		**,801**	
Leisure time enjoyment	,409		**,495**

Extraction Method: Principal Component Analysis.

Rotation Method: Varimax with Kaiser Normalization.

[a] Rotation converged in 6 iterations.

Note: for better readability, factor loadings < 0.3 are not shown

Appendix I. Characteristics of included studies

Alexopoulos 2013

Methods	**Publication type:** Short report; **Design**: RCT (NCT00151372)
Participants	**Inclusion criteria:** Age 50 to 95 yrs, COPD, unipolar major depression (SCID/DSM-IV); Hamilton score ≥ 14 **Exclusion criteria**: Other psychiatric conditions except anxiety or severe cognitive impairment (mini-mental score < 20) **Patient characteristics:** *presented in mean (SD) or n (%)* Age: 71.0 (8.1) Gender: 91 (65.9%) female; 47 (34.1%) male FEV_1 % pred: 36.5 (15.2) **Number of participants**: *Randomised*: 138; *Analysed*: 67/71 (Intervention/Control) **Setting:** Home; USA
Interventions	**Duration:** 26 weeks **Intervention:** *(category psychotherapy)* Personalized Intervention for Depression and COPD focused on mobilizing the patient to participate in the care of both conditions; frequency: bi-weekly to once a month; duration: 30 minutes; delivery: face-to-face; providers: social workers **Comparison:** *(category inactive control)* Usual care
Outcomes	**Assessment:** Baseline, 14 weeks, 28 weeks **Breathlessness measures:** PFSDQ-M **Other measures:** Hamilton Rating Scale for Depression (HRSD)
Funding	NIMH R01 HLB071992, P30 MH068638, P30 MH085943 and the Sanchez Foundation. R.S.N. partially supported by a grant from the Will Rogers Institute.
Declaration of interest	First author has received grant support from Forest Pharmaceuticals; has consulted to Hoffman-LaRoche, Lilly, Pfizer and Otsuka; and has served on speakers bureaux of AstraZeneca, Avenir, Forest, Merck, Novartis and Sunovion.
Notes	Intervention started at discharge of acute in-patient PR unit.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"At the end of hospitalization, participants were randomized (1:1) into PID-C or UC in blocks of 5 using random numbers provided by our Biostatistics Unit"
Allocation concealment (selection bias)	Unclear risk	No details reported.
Blinding of participants and personnel (performance bias)	High risk	Open-label study.
Blinding of outcome assessment (detection bias)	High risk	Self-reported outcome measures of participants not blinded to the intervention.
Incomplete outcome data (attrition bias)	Low risk	"All participants who completed baseline assessments were included in intent-to-treat analyses"
Selective reporting (reporting bias)	High risk	Outcomes measured at different time points only selectively reported, for example PFSDQ-M at 52 weeks not reported
Sample Size	Unclear risk	138 patients randomised.
Other bias	Low risk	No indication for additional bias.

Bekelman 2017

Methods	**Publication type:** Abstract; **Design:** RCT
Participants	**Inclusion criteria:** Congestive heart failure; Prior diagnosis of heart failure; Kansas City Cardiomyopathy Questionnaire-Short From (KCCQ-12) score of less than or equal to 70 **Exclusion criteria:** Diagnosis of dementia, bipolar disorder or schizophrenia; Prior heart transplant recipient **Patient characteristics:** *presented in mean (SD) or n (%)* Age: 65.5 (NR) Gender: 72 (23%) female; 242 (77%) male Illness severity: NYHA III: 150 (47.8 %); IV: 44 (14.0%) **Number of participants:** Randomised: 314 Analysed: Intervention: 157, Control: 157 **Setting:** Outpatient; USA
Interventions	**Duration:** 24 weeks **Intervention:** *(category counselling and support)* Collaborative care to manage symptoms; frequency: weekly reviews; duration; unclear; delivery; face-to-face; providers: nurse; social workers; and specialist team **Comparison:** *(category inactive control)* Usual care
Outcomes	**Assessment:** Baseline and 24 weeks **Breathlessness measures:** PEG pain measure adapted for breathlessness **Other measures:** Kansas City Cardiomyopathy Questionnaire; PHQ-9; General Symptom Distress Scale
Funding	National Institute of Nursing Research
Declaration of interest	The authors declare there are no conflicts of interest to report
Notes	Published and published data included.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The random allocation sequence is computer generated using block sizes of 2-4, an allocation ratio of 1:1, and stratification by recruitment health system."
Allocation concealment (selection bias)	Low risk	"The allocation sequence will be concealed until after the last subject has completed the 12-month follow up and all of the data have been entered, checked, and finalized."
Blinding of participants and personnel (performance bias)	High risk	Open-label study.
Blinding of outcome assessment (detection bias)	High risk	Self-reported outcome measures of participants not blinded to the intervention.
Incomplete outcome data (attrition bias)	Low risk	Intent-to-treat analysis
Selective reporting (reporting bias)	Unclear risk	Insufficient information (conference abstract)
Sample Size	Unclear risk	314 participants randomised
Other bias	Unclear risk	Insufficient information (conference abstract)

Benzo 2016

Methods	**Publication type:** Full report; **Design:** RCT (NCT01058486)
Participants	**Inclusion criteria:** COPD; > 40 years old **Exclusion criteria:** patients receiving hospice care **Patient characteristics:** *presented in mean (SD) or n (%)* Age: mean (SD) 68.0 (9.5) Gender: 118 (54.7%) female; 97 (45.3%) male FEV_1 % pred: 40.3 (17.2) **Number of participants:** Randomised: 215 Analysed: Intervention: 108, Control: 107 **Setting:** Outpatient; USA
Interventions	**Duration:** 48 weeks **Intervention:** *(category counselling and support)* Health coaching intervention; delivery: face-to-face; providers: registered nurse or respiratory therapist **Comparison:** *(category inactive control)* Usual care
Outcomes	**Assessment:** baseline and 48 weeks **Breathlessness measure:** CRQ-D; CRQ-M **Other measures:** CRQ total
Funding	Supported by NHLBI grant R01 HL09468 (R.B., principal investigator) from the National Institutes of Health
Declaration of interest	K Lorig received consulting fees received to help develop the intervention as part of the NIH grant and the royalties from Bull Publishing Company as disclosed above
Notes	Intervention started at discharge after acute exacerbation.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"We randomly assigned subjects using an online, computer-generated, simple binomial randomization program to one of the two groups, stratified by center."
Allocation concealment (selection bias)	Unclear risk	No details reported.
Blinding of participants and personnel (performance bias)	High risk	Open-label study.
Blinding of outcome assessment (detection bias)	High risk	Self-reported outcome measures of participants not blinded to the intervention.
Incomplete outcome data (attrition bias)	High risk	"Patients with missing or unknown outcomes were excluded from this analysis." complete-case analysis
Selective reporting (reporting bias)	Low risk	Results of all outcomes described in the methods section were presented.
Sample Size	Unclear risk	215 subjects randomised.
Other bias	Low risk	No indication for additional bias.

Boesch 2007

Methods	**Publication type:** Full report; **Design:** RCT
Participants	**Inclusion criteria:** COPD; FEV_1/VC_{max} of < 70% **Exclusion criteria:** Relevant co-morbidity affecting symptoms, endurance or lung function **Patient characteristics:** *presented in mean (SD) or n (%)* Age: mean (SD) 64.0 (7.9) Gender: 15 (36.6%) female; 26 (63.4%) male FEV_1 % pred: 46.4 (17.2) **Number of participants:** *Randomised*: 50; *Analysed*: 30/11 (Intervention/Control) **Setting:** Outpatient; Germany
Interventions	**Duration:** 6 weeks **Intervention:** *(category self-management)* Education programme; delivery: face-to-face, group sessions; providers: trained nurses **Comparison:** *(category inactive control)* Usual care
Outcomes	**Assessment:** Baseline, 6 weeks and 52 weeks **Breathlessness measure:** Bode-Index; MRC **Other measures:** not applicable
Funding	NR
Declaration of interest	NR
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not enough details about randomisation process provided.
Allocation concealment (selection bias)	Unclear risk	No details reported.
Blinding of participants and personnel (performance bias)	Unclear risk	No details reported.
Blinding of outcome assessment (detection bias)	Unclear risk	No details reported.
Incomplete outcome data (attrition bias)	High risk	Complete-case analysis
Selective reporting (reporting bias)	Low risk	Results of all outcomes described in the methods section were presented.
Sample Size	High risk	50 participants randomised.
Other bias	Low risk	No indication for additional bias.

Bove 2016

Methods	**Publication type:** Full report; **Design:** RCT (NCT02366390)
Participants	**Inclusion criteria:** COPD classified category C or D according to GOLD; HADS subscale for anxiety score ≥ 8 **Exclusion criteria:** psychiatric diagnosis or pulmonary cancer **Patient characteristics:** *presented in mean (SD) or n (%)* Age**:** 70.2 (8.5) Gender: female 44 (67%), male 22 (33%) FEV1 % pred: 34.0 (13.2) **Number of participants**: *Randomised*: 66; *Analysed*: 33/33 (Intervention/Control) **Setting:** Outpatient; Denmark
Interventions	**Duration:** 2 weeks **Intervention:** *(category psychotherapy)* Psycho-educative plus usual care; delivery: face-to-face at home and phone: trained nurse **Comparison:** *(category inactive control)* Usual care
Outcomes	**Assessment:** Baseline, 4 weeks, 16 weeks **Breathlessness measures:** CRQ-M; CRQ-D **Other measures:** HADS
Funding	Supported by a grant from TrygFonden [109444]. The project also received funding from the Novo Nordisk Foundation [11781] and Sister Marie Dalgaard's Foundation.
Declaration of interest	The authors have no conflicts of interest.
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Random allocation is conducted by using a system of sequentially numbered opaque sealed envelopes. Two employees, who are not involved in the research project or linked to the PI, place 33 notes stamped ‘intervention group’ and 33 stamped ‘control group’ in 66 identical envelopes. Subsequently, the envelopes are shuffled and numbered from 1 to 66. The envelopes are stored in a locked cabinet in a locked office in the central research unit."
Allocation concealment (selection bias)	Low risk	"Random allocation is conducted by using a system of sequentially numbered opaque sealed envelopes."
Blinding of participants and personnel (performance bias)	High risk	Open-label study
Blinding of outcome assessment (detection bias)	High risk	Self-reported measures of unblinded patients.
Incomplete outcome data (attrition bias)	Unclear risk	No details reported.
Selective reporting (reporting bias)	High risk	Not all outcome measures described in the protocol were presented.
Sample Size	High risk	66 participants randomised.
Other bias	Low risk	No indication for additional bias.

Burtin 2012

Methods	**Publication type:** Abstract; **Design:** RCT
Participants	**Inclusion criteria:** COPD **Exclusion criteria:** No additional information reported. **Patient characteristics:** *presented in mean (SD) or n (%)* Age: 66 (6) Gender:14 (21%) female; 52 (79%) male FEV_1 % pred: NR **Number of participants:** *Randomised*: 65; *Analysed*: 23/16 (Intervention/Control) **Setting:** Clinic; Belgium
Interventions	**Duration:** 24 weeks **Intervention:** *(category counselling & support)* Activity counselling program (face-to-face) to agreed individualized action plan; duration: 30 minutes; delivery: face-to-face, individual sessions **Comparison:** *(category inactive control)* Usual care
Outcomes	**Assessment:** Baseline, 24 weeks and 52 weeks **Breathlessness measures:** CRQ-D **Other measures:** 6-MWT
Funding	Research Foundation - Flanders
Declaration of interest	NR
Notes	Trial conducted with patients currently enrolled in pulmonary rehabilitation.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details reported.
Allocation concealment (selection bias)	Unclear risk	No details reported.
Blinding of participants and personnel (performance bias)	Unclear risk	No details reported.
Blinding of outcome assessment (detection bias)	Unclear risk	No details reported.
Incomplete outcome data (attrition bias)	Unclear risk	Complete-case analysis (>10% drop-out)
Selective reporting (reporting bias)	Unclear risk	Insufficient information (conference abstract)
Sample Size	High risk	65 participants in total
Other bias	Unclear risk	Insufficient information (conference abstract)

Chan 2011

Methods	**Publication type:** Full report; **Design**: RCT
Participants	**Inclusion criteria:** ≥16 years; stage 3 or 4 lung cancer; scheduled to receive palliative RT; A Karnofsky Performance Status score of ≥ 60% **Exclusion criteria:** Known psychiatric morbidity and/or involvement in other clinical trials. **Patient characteristics:** *presented in mean (SD) or n (%)* Age: NR Gender: 24 (17%) female; 1160(83%) male **Number of participants**: *Randomised*: 140; *Analysed*: 70/70 (intervention/Control) **Setting:** Outpatient; Hong Kong
Interventions	**Duration:** 12 weeks **Intervention:** *(category psychotherapy; category meditative movements)* Psychotherapy + Meditation/relaxation; frequency: 1 week before and 3 weeks after radiotherapy; delivery: mixed; providers: Nurses **Comparison:** *(category inactive contol)* Usual care
Outcomes	**Assessment:** Baseline, 3 weeks, 6 weeks and 12 weeks **Breathlessness measures:** VAS **Other measures:** SF-36, STAI: State anxiety items
Funding	The project was supported by the Hong Kong Health Service Research Fund.
Declaration of interest	The authors declare no conflicts of interest.
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomized by lucky draw method to either an intervention group or control group."
Allocation concealment (selection bias)	Unclear risk	No details reported.
Blinding of participants and personnel (performance bias)	High risk	Open-label study.
Blinding of outcome assessment (detection bias)	High risk	Self-reported outcome measures of participants not blinded to the intervention.
Incomplete outcome data (attrition bias)	Low risk	"Missing data at T1, T2, and T3 were imputed by a carry-forward method based on intention to- treat analysis"
Selective reporting (reporting bias)	Low risk	Results of all outcomes described in the methods section were presented
Sample Size	Unclear risk	140 participants randomised.
Other bias	Low risk	No indication for additional bias.

Chan 2015

Methods	**Publication type:** Full report **Design:** RCT
Participants	**Inclusion criteria:** ≥ 40 years; COPD; having reliable transportation **Exclusion criteria:** Presence of any active lung disease other than COPD **Patient characteristics:** *presented in mean (SD) or n (%)* Age: 69.5 (7.9) Gender: 27 (65.9%) female; 14 (34.1%) male GOLD stage: III: 19 (47%); IV 8 (20%) **Number of participants:** *Randomised*: 41; *Analysed*: 16/22 (Intervention/Control) **Setting:** USA
Interventions	**Duration:** 8 weeks **Intervention:** *(category meditative movements)* Qi-Gong; frequency: weekly; duration: 1 hour **Comparison:** *(category meditative movements)* Usual care
Outcomes	**Assessment:** Baseline and 8 weeks **Breathlessness measures:** CRQ-DM; CRQ-M **Other measures:** ASI-3
Funding	NIH grant
Declaration of interest	This current paper includes some work submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy (Nursing) at the University of Michigan in 2013 by Roxane Raffin Chan as per website. The authors report no other conflicts of interest in this work.
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Stratified randomization was conducted using baseline measures of spirometry to assure participant balance in disease severity. The participant identification number, and forced end expiratory pressure in 1 second percent of predicted normal value (FEV1%) results were sent to an independent researcher, who assigned participants to groups by using a list of randomly generated numbers and by blocking on the FEV1%"
Allocation concealment (selection bias)	Unclear risk	No details reported.
Blinding of participants and personnel (performance bias)	High risk	Open-label study.
Blinding of outcome assessment (detection bias)	High risk	Self-reported outcome measures of participants not blinded to the intervention.
Incomplete outcome data (attrition bias)	Unclear risk	No details reported.
Selective reporting (reporting bias)	High risk	Missing results for some outcomes and different baseline data between publications.
Sample Size	High risk	41 participants randomised.
Other bias	Low risk	No indication for additional bias.

Coultas 2016

Methods	**Publication type:** Full report **Design:** RCT
Participants	**Inclusion criteria:** COPD; age > 45 years; FEV_1/FVCa < 70% and FEV_1 < 70%; MMRC+ dyspnoea score ≥ 2; ≥ 110 meters during 6-MWT **Exclusion criteria:** Inability to speak/read English **Patient characteristics:** *presented in mean (SD) or n (%)* Age: 70.3 (9.5) Gender: 154 (50.5%) female, 151 (49.5%) male FEV_1 % pred: 46.45 (13.1) **Number of participants:** *Randomised*: 305; *Analysed*: 149/156 (Intervention/Control) **Setting:** Outpatient; USA
Interventions	**Duration:** 68 weeks (20 weeks + 48 weeks maintenance) **Intervention:** *(category self-management)* Physical activity self-management **Comparison:** *(category inactive control)* Usual care
Outcomes	**Assessment:** baseline and 72 weeks **Breathlessness measure:** CRQ-D; CRQ-M; MRC **Other measures:** CRQ total; SF-12
Funding	Funded by National Heart, Lung, and Blood Institute grant R18 HL092955 from the National Institutes of Health
Declaration of interest	NR
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"list of randomized unique patient identification numbers with group assignment was completed before patient enrolment by the data coordinating center"
Allocation concealment (selection bias)	Low risk	"Patients were sequentially assigned unique patient identification numbers at the time of enrolment but group assignment is provided only to the study coordinator (RR) and concealed from other study personnel and patients"
Blinding of participants and personnel (performance bias)	High risk	"Group assignment was provided only to the study coordinator at enrolment." - However, only blinded during run-in period
Blinding of outcome assessment (detection bias)	High risk	Participants were not blinded after the run-in period.
Incomplete outcome data (attrition bias)	Low risk	Intent-to-treat analysis
Selective reporting (reporting bias)	High risk	No secondary outcomes of this study have been reported; t1; t2 missing
Sample Size	Unclear risk	305 participants randomised.
Other bias	Low risk	No indication for additional bias.

Donesky-Cuenco 2009

Methods	**Publication type:** Full report; **Design:** RCT
Participants	**Inclusion criteria:** > 40 years of age, ADL limited by dyspnoea from COPD. Patients receiving supplemental oxygen were included if their oxygen saturation could be maintained > 80% in 6-MWT **Exclusion criteria:** Patients with active symptomatic disease (e.g. ischemic heart disease, neuromuscular disease, and psychiatric illness); pulmonary rehabilitation, yoga or exercise training program in the last 6 months **Patient characteristics:** *presented in mean (SD) or n (%)* Age: 69.9 (9.5); Gender: 21 (72.4%) female; 8 (27.6%) male FEV_1 % pred: 47.7 (15.6) **Number of participants:** *Randomised*: 41; *Analysed*: 14/15 (Intervention/Control) **Setting:** USA
Interventions	**Duration:** 12 weeks **Intervention:** *(category meditative movements)* Yoga asanas (poses) interspersed with visama vritti pranayama (timed breathing); Patients were given a videotape of one yoga class and were strongly encouraged to practice daily at home; frequency: twice weekly; delivery: face-to-face; duration: 60 minutes; providers: yoga teachers **Comparison:** *(category inactive control)* Educational pamphlet (Living with COPD) and offered yoga program at end of 12 weeks
Outcomes	**Assessment:** Baseline, 12 weeks **Breathlessness measures:** (modified) Borg; CRQ-D; CRQ-M **Other measures:** SF-36; STAI-S; CES-D; modified Borg Distress with dyspnoea at end of 6-MWT
Funding	This study was funded by grant No. R21 AT01168-03 from the National Center for Complementary and Alternative Medicine, National Institutes of Health (NIH), and grant No. 1KL2RR025015-01 from the National Center for Research Resources (NCRR), a component of the NIH and NIH Roadmap for Medical Research.
Declaration of interest	
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details reported.
Allocation concealment (selection bias)	Unclear risk	No details reported.
Blinding of participants and personnel (performance bias)	Unclear risk	No details reported.
Blinding of outcome assessment (detection bias)	Unclear risk	No details reported.
Incomplete outcome data (attrition bias)	Low risk	Intent-to-treat analysis.
Selective reporting (reporting bias)	Low risk	Results of all outcomes described in the methods section were presented.
Sample Size	High risk	41 participants randomised.
Other bias	Low risk	No indication for additional bias.

Garcia-Aymerich 2007

Methods	**Publication type:** Full report; **Design:** RCT
Participants	**Inclusion criteria:** COPD; Admitted to hospital because of an acute exacerbation requiring hospitalisation for more than 48 hours **Exclusion criteria:** Not living in the healthcare area or living in a nursing home; Lung cancer or other advanced malignancies; logistic limitations; Extremely severe neurological or cardiovascular comorbidities **Patient characteristics:** *presented in mean (SD) or n (%)* Age: 73 (8) Gender: 16 (14.2%) female; 54 (85.8%) male Illness severity: NR **Number of participants:** *Randomised*: 113; *Analysed*: 21/41 (Intervention/Control) **Setting:** Outpatient; Spain
Interventions	**Duration:** Baseline and 52 weeks **Intervention:** *(category self-management)* Integrated care intervention including education, coordination among levels of care, and improved accessibility; delivery: face-to-face; providers: specialist nurse **Comparison:** *(category inactive control)* Usual care
Outcomes	**Assessment:** Baseline, 24 and 52 weeks **Breathlessness measure:** MRC **Other measures:** SGRQ; EQ-5D
Funding	Linkcare grant from EU, Comissionat per a Universitats i recerca de la generalitat de Catalunya, two other ISCII registered grants
Declaration of interest	NR
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	“computer generated random numbers”
Allocation concealment (selection bias)	Unclear risk	No details reported.
Blinding of participants and personnel (performance bias)	Unclear risk	patients were blindly assigned; no information about personnel.
Blinding of outcome assessment (detection bias)	Unclear risk	No details reported.
Incomplete outcome data (attrition bias)	High risk	Complete-case analysis; > 10% drop-outs
Selective reporting (reporting bias)	High risk	No results for t1 reported/discussed.
Sample Size	Unclear risk	113 participants randomised.
Other bias	Low risk	No indication for additional bias.

Heidari 2014

Methods	**Publication type:** Full report; **Design:** RCT
Participants	**Inclusion criteria:** COPD with moderate or severe level; 45-70 years old; Having literacy, lack of major psychological disorder, lack of serious and restrictive diseases; Being on a constant medicine regime **Exclusion criteria:** Hospitalization during the study; Required oxygen or spray during the sixminute walking test; Absence in 1 education session **Patient characteristics:** *presented in mean (SD) or n (%)* Age: 59.8 (6.4) Gender: 6 (14.6%) female; 35 (85.4%) male COPD severity: moderate 20 (48.8%); severe 21 (51.2%) **Number of participants:** *Randomised*: 50: *Analysed*: 22/19 (Intervention/Control) **Setting:** Outpatient; Iran
Interventions	**Duration:** 12 weeks **Intervention:** *(category self-management)* Self-management; delivery: face-to-face **Comparison:** *(category inactive control)* Usual care
Outcomes	**Assessment:** Baseline and 12 weeks **Breathlessness measure:** modified Borg **Other measures:** not applicable
Funding	This article is the outcome of a MS thesis that approved and supported by Ahvaz Jundishapur University of Medical Sciences
Declaration of interest	NR
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details reported.
Allocation concealment (selection bias)	Unclear risk	No details reported.
Blinding of participants and personnel (performance bias)	High risk	Open-label study.
Blinding of outcome assessment (detection bias)	High risk	Self-reported outcome measures of participants not blinded to the intervention.
Incomplete outcome data (attrition bias)	High risk	Complete-case analysis; > 10% drop-out
Selective reporting (reporting bias)	Low risk	Results of all outcomes described in the methods section were presented.
Sample Size	High risk	41 participants randomised.
Other bias	Low risk	No indication of additional bias.

Johnson-Warrington 2016

Methods	**Publication type:** Full report; **Design:** RCT
Participants	**Inclusion criteria:** COPD; Grade 2-5 dyspnoea **Exclusion criteria:** Not acute exacerbation of COPD; four or more admissions in the previous 12 months **Patient characteristics:** *presented in mean (SD) or n (%)* Age: 68.0 (8.1) Gender: 50 (64.1%) female; 28 (35%) male FEV_1 % pred: 41.5 (13.8) **Number of participants:** *Randomised*: 78; *Analysed*: 39/39 (Intervention/Control) **Setting:** Home care; United Kingdom
Interventions	**Duration:** 12 weeks **Intervention:** *(category self-management)* SPACE for COPD: written educational information and a home-based exercise program; delivery: face-to-face; providers: physiotherapist **Comparison:** *(category inactive control)* Usual care
Outcomes	**Assessment:** Baseline and 12 weeks **Breathlessness measure:** CRQ-D; CRQ-M **Other measures:** HADS: anxiety: 8.7 (4.2); depression: 7.1 (3.7)
Funding	British Lung Foundation
Declaration of interest	The authors report no conflicts of interest in this work.
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"via a web-based, concealed allocation program (www.sealedenvelope.com) using simple random permuted block 1:1 randomization by VJ-W"
Allocation concealment (selection bias)	Low risk	"via a web-based, concealed allocation program (www.sealedenvelope.com) using simple random permuted block 1:1 randomization by VJ-W"
Blinding of participants and personnel (performance bias)	High risk	Open-label study.
Blinding of outcome assessment (detection bias)	High risk	Self-reported outcome measures of participants not blinded to the intervention.
Incomplete outcome data (attrition bias)	Low risk	"Analysis was conducted on an intention-to-treat basis"
Selective reporting (reporting bias)	Low risk	Results of all outcomes described in the methods section were presented.
Sample Size	High risk	78 participants randomised.
Other bias	Low risk	No indication of additional bias.

Kunik 2008

Methods	**Publication type:** Full report; **Design**: RCT
Participants	**Inclusion criteria:** COPD; moderate anxiety and/or moderate depression; and treatment by a primary care provider or pulmonologist **Exclusion criteria:** Cognitive disorder, evidenced by a score of 23 or less on the Mini-Mental State Examination; a psychotic disorder; or current non-nicotine substance abuse or dependence; psychotic and non-nicotine substance use disorders **Patient characteristics:** *presented in mean (SD) or n (%)* Age: 66.3 (10.2) Gender: 9 (3.8%) female; 226 (96.2%) male FEV_1 % pred: 46.0 (17.1) **Number of participants**: *Randomised*: 238; *Analysed*: 118/120 (Intervention/Control) **Setting:** Outpatient; USA
Interventions	**Duration:** 8 weeks **Intervention:** *(category psychotherapy)* Cognitive behavioural therapy; frequency: weekly; duration: 1 hour; delivery: face-to-face **Comparison:** *(category active control)* COPD education; frequency: weekly; duration: 1 hour; delivery: face-to-face
Outcomes	**Assessment:** Baseline, 4 weeks, 8 weeks, 4 months, 8 months and 12 months **Breathlessness measures:** CRQ-D, CRQ-M **Other measures:** SF-36, BDI, Beck anxiety inventory
Funding	This study was supported by Grant No. IIR 00-097 from the Department of Veterans Affairs, Veterans Health Administration and in part by the Houston Center for Quality of Care and Utilization Studies
Declaration of interest	None.
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"We used the Statistical Analysis Systems PLAN procedure (SAS Institute, Inc., Cary, NC, USA) to create the randomization list, with blocks of size 2 to provide approximately equal numbers per class."; "The instructor assigned the treatment to the code initially by flipping a coin."
Allocation concealment (selection bias)	Unclear risk	No details reported.
Blinding of participants and personnel (performance bias)	Unclear risk	No details reported.
Blinding of outcome assessment (detection bias)	Unclear risk	No details reported.
Incomplete outcome data (attrition bias)	High risk	Intent-to-treat analysis stated, but drop-out > 50%
Selective reporting (reporting bias)	Low risk	Results of all outcomes described in the methods section were presented
Sample Size	Unclear risk	138 participants randomised.
Other bias	Low risk	No indication for additional bias.

Livermore 2015

Methods	**Publication type:** Full report; **Design**: RCT
Participants	**Inclusion criteria:** being treated with a combination of long-acting 2 agonist/inhaled corticosteroid and a long-acting anticholinergic, lung function that corresponded to GOLD stages II or III with FEV in 1 s post-bronchodilator < 60% predicted and $FEV_1/FVC < 0.7$ **Exclusion criteria:** Being treated with high dose oral corticosteroids **Patient characteristics:** *presented in mean (SD) or n (%)* Age: 72 (6) Gender: 11 (35.5%) female; 18 (58.1%) male FEV_1 % pred: NR **Number of participants**: *Randomised*: 31; *Analysed*: 18/13 (Intervention/Control) **Setting:** Australia
Interventions	**Duration:** 24 weeks **Intervention:** *(category psychotherapy)* cognitive behaviour therapy; frequency: 4 weekly sessions; duration: one hour; delivery: face-to-face; providers: clinical psychologist **Comparison:** *(category inactive control)* Usual care
Outcomes	**Assessment:** Baseline and 24 weeks **Breathlessness measures:** Borg **Other measures:** HADS: anxiety 5.5 (2.8), depression 4.1 (2.3), SGRQ
Funding	National Health and Medical Research Council of Australia
Declaration of interest	NR
Notes	Participants received ongoing outpatient treatment.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details reported.
Allocation concealment (selection bias)	Unclear risk	No details reported.
Blinding of participants and personnel (performance bias)	Unclear risk	No details reported.
Blinding of outcome assessment (detection bias)	Unclear risk	No details reported.
Incomplete outcome data (attrition bias)	Unclear risk	No details reported.
Selective reporting (reporting bias)	Low risk	Results of all outcomes described in the methods section were presented.
Sample Size	High risk	31 participants randomised.
Other bias	Low risk	No indication for additional bias.

Moore 2002

Methods	**Publication type:** Full report; **Design:** RCT
Participants	**Inclusion criteria:** Patients with lung cancer who had completed their initial anticancer treatment and were expected to survive for at least three months **Exclusion criteria:** receiving cancer treatment, were having close medical supervision, or had a poor prognosis or performance status **Patient characteristics:** *presented in mean (SD) or n (%)* Age: 67 (8.8) Gender: 63 (31.0%) female; 140 (69.0%) male Tumor stage: IIIa/b: 21/64 (40.1%); IV: 38 (17.9%) **Number of participants:** *Randomised*: 203; *Analysed*: 76/74 (Intervention/Control) **Setting:** Outpatient; United Kingdom
Interventions	**Duration:** 48 weeks **Intervention:** *(category counselling and suport)* Nurse led follow up, providing information, support and coordinating input from other agencies or services; delivery: face-to-face, phone; providers: nurse specialists **Comparison:** *(category inactive control)* Usual care
Outcomes	**Assessment:** Baseline, 12 and 24 weeks **Breathlessness measures:** EORTC core questionnaire - Dyspnoea **Other measures:** Global health status or quality of life
Funding	NHS Research and Development National Cancer Programme funded the study; Macmillan Cancer Relief funded one of the nurse specialists in lung cancer's posts
Decl of interest	JC is a member of the board of trustees for Macmillan Cancer Relief
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"An independent trials office was responsible for randomisation of patients. For randomisation, patients were stratified according to hospital and treatment intent. An independent data monitoring committee advised on the conduct of the study."
Allocation concealment (selection bias)	Unclear risk	No details reported.
Blinding of participants and personnel (performance bias)	Unclear risk	No details reported.
Blinding of outcome assessment (detection bias)	Unclear risk	No details reported.
Incomplete outcome data (attrition bias)	High risk	Complete-case analysis and > 10% drop-out
Selective reporting (reporting bias)	Low risk	Results of all outcomes described in the methods section were presented.
Sample Size	Unclear risk	203 participants randomised.
Other bias	Low risk	No indication for additional bias.

Mosher 2016

Methods	**Publication type:** Full report; **Design:** RCT (NCT01993550)
Participants	**Inclusion criteria:** small-cell or non-small-cell lung cancer; at least one symptom of moderate severity; anxiety; pain; fatigue; or breathlessness; consenting family caregiver. **Exclusion criteria:** severe cognitive impairment; receiving hospice care **Patient characteristics:** *presented in mean (SD) or n (%)* Age: 63.7 (7.9) Gender: 56 (53%) female; 50 (47%) male Tumour stage: IIIa/b: 14/18; IV: 43 **Number of participants:** *Randomised*: 106; *Analysed*: 51/55 (Intervention/Control) **Setting:** Patient's Home; USA
Interventions	**Duration:** 10 weeks (4 weeks intervention + 6 weeks follow up) **Intervention:** *(category self-management)* Telephone-based management; frequency: weekly; duration: 45 minutes; delivery: face-to-face, phone; providers: clinical social worker **Comparison:** *(category active control)* Education/support condition; frequency: weekly; duration: 45 minutes; delivery: face-to-face, phone; providers: psychologist
Outcomes	**Assessment:** Baseline, 6 and 10 weeks **Breathlessness measures:**Memorial Symptom Assessment Scale **Other measures:** GAD-7 (Anxiety); PHQ-8
Funding	grant PEP-13-236-01-PCSM from the American Cancer Society, an Vol. 52 No. 4 October 2016 Telephone Symptom Management in Lung Cancer 479 American Cancer Society Institutional Research grant, and K07CA168883 and K05CA175048 from the National Cancer Institute
Declaration of interest	The authors declare no conflicts of interest
Notes	Published and unpublished data used.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization assignments were generated by a person who was not a study interviewer or therapist using a SAS procedure."
Allocation concealment (selection bias)	Unclear risk	No details reported.
Blinding of participants and personnel (performance bias)	High risk	Open-label study.
Blinding of outcome assessment (detection bias)	High risk	Self-reported outcome measures of participants not blinded to the intervention.
Incomplete outcome data (attrition bias)	Low risk	Intent-to-treat analysis
Selective reporting (reporting bias)	Low risk	Results of all outcomes described in the methods section were presented.
Sample Size	Unclear risk	106 participants randomised.
Other bias	Low risk	No indication for additional bias.

Mularski 2009

Methods	**Publication type:** Full report; **Design**: RCT
Participants	**Inclusion criteria:** COPD; self-reported dyspnoea at any time in the prior 4 weeks **Exclusion criteria:** Cognitive impairment **Patient characteristics:** *presented in mean (SD) or n (%)* Age**:** 67.4 (2.2) Gender: 42 (1.2%) female; 43 (98.8%) male Post FEV_1 < 50%: GOLD 3-4, n (%): 53 (64%) **Number of participants**: *Randomised*: 86; *Analysed*: 44/42 (Intervention/Control) **Setting:** Outpatient; USA
Interventions	**Duration:** 8 weeks **Intervention:** *(category mindfulness-based stress reduction)* Mindfulness-based stress reduction in form of breathing training; frequency: once weekly; delivery: face-to-face, group; providers: interventionalists **Comparison:** *(category inactive control)* Usual care
Outcomes	**Assessment:** Baseline, 8 weeks **Breathlessness measures:** Borg, VAS **Other measures:** SGRQ, SF-36
Funding	This study was supported by the VET-HEAL program, cooperation between the Veterans Health Administration and the Samueli Institute of Information Biology. Dr. Karl Lorenz was supported by a VA HSR&D Career Development Award.
Declaration of interest	No competing financial interests exist.
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Assignments generated by a random-number-generating program to achieve an equal number of assignments across four waves of groups."
Allocation concealment (selection bias)	Low risk	"Participants were randomized at completion of pretesting battery to intervention or control arms using preprinted sealed assignments [...]. Concealment was maintained until after completion of screening and baseline measures."
Blinding of participants and personnel (performance bias)	High risk	Open-label study.
Blinding of outcome assessment (detection bias)	High risk	Self-reported outcome measures of participants not blinded to the intervention.
Incomplete outcome data (attrition bias)	High risk	No differences between complete-case and intent-to-treat analysis.
Selective reporting (reporting bias)	Low risk	Results of all outcomes described in the methods section were presented.
Sample Size	High risk	86 participants randomised.
Other bias	Low risk	No indication for additional bias.

Nguyen 2008

Methods	**Publication type:** Full report; **Design:** RCT
Participants	**Inclusion criteria: C**OPD, clinically stable for 1 month; FEV_1/FVC < 70% and FEV_1 < 80%; ADL limited by dyspnoea **Exclusion criteria:** Any other symptomatic illness, participated in PR in last year, currently I > 2days of supervised maintenance exercise **Patient characteristics:** *presented in mean (SD) or n (%)* Age: 69.5 (8.5) Gender: 17 (43.6%) female; 22 (56.4%) male FEV_1 % pred: 49.6 (17.0) **Number of participants:** *Randomised*: 50; *Analysed*: 26/24 (Intervention/Control) **Setting:** Outpatient; USA
Interventions	**Duration:** 24 weeks **Intervention:** *(category self-management)* Internet-based dyspnoea self-management programs; providers: practice nurse **Comparison:** *(category active control)* dyspnoea self-management program; delivery: face-to-face
Outcomes	**Assessment:** Baseline, 12 and 24 weeks **Breathlessness measure:** CRQ-D; CRQ-M **other measures:** CRQ total; SF 36
Funding	This study was supported in part by Robert Wood Johnson Health e-Technologies Initiative grant RWJ49153 to Dr. Carrieri-Kohlman, General Clinical Research Centers at the University of Washington (MO1-RR-000037) and UC San Francisco (MO1-RR-00079) and Grant Number 1KL2RR025015-01 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH) and NIH Roadmap for Medical Research
Declaration of interest	None declared
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"An investigator who was not involved in the day-to-day study operations generated the randomization sequence using the SPSS version 14.0 (SPSS Inc, Chicago, IL, USA) random sequence generator feature"
Allocation concealment (selection bias)	Low risk	randomization was placed in "separate sealed opaque envelope"
Blinding of participants and personnel (performance bias)	High risk	Open-label study.
Blinding of outcome assessment (detection bias)	High risk	Self-reported outcome measures of participants not blinded to the intervention.
Incomplete outcome data (attrition bias)	Low risk	Intent-to-treat analysis
Selective reporting (reporting bias)	Low risk	Results of all outcomes described in the methods section were presented.
Sample Size	High risk	50 participants randomised.
Other bias	High risk	"The study was stopped early due to multiple technical challenges with the eDSMP"

Ries 2003

Methods	**Publication type:** Full report; **Design:** RCT
Participants	**Inclusion criteria:** COPD; chronic symptoms and perceived disability from disease; stable on an acceptable medical regimen under the care of a primary care physician; No other significant medical or psychiatric conditions **Exclusion criteria:** *not applicable* **Patient characteristics:** *presented in mean (SD) or n (%)* Age: 67.1 (8.2) Gender: 75 (45.7%) female; 89 (54.3%) male FEV1 % pred: 45 (NR) **Number of participants:** *Randomised*: 172; *Analysed*: 83/81 (Intervention/Control) **Setting:** Outpatient; USA
Interventions	**Duration:** 52 weeks **Intervention:** *(category counselling and support)* Telephone maintenance programme **Comparison:** *(category inactive control)* Usual care
Outcomes	**assessment:** Baseline, 24, 52 and 104 weeks **breathlessness measure:** BDI; CRQ-D; CRQ-M; UCSD **Other measures:** CRQ total; CES-D
Funding	Supported by National Institutes of Health grant R01 HD/HL 30912
Declaration of interest	NR
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Random allocation was accomplished using the Moses-Oakford assignment algorithm with an allocation ratio of 1:1. (E1) The required sequence of random numbers was produced using a QBASIC random number generator."
Allocation concealment (selection bias)	Low risk	"Assignments were sealed in sequentially numbered identical opaque envelopes and stored in a safe deposit box with access limited to the principal investigator and data coordinator."
Blinding of participants and personnel (performance bias)	High risk	Open-label study.
Blinding of outcome assessment (detection bias)	High risk	Self-reported outcome measures of participants not blinded to the intervention.
Incomplete outcome data (attrition bias)	High risk	Complete-case analysis and > 10% drop-out
Selective reporting (reporting bias)	Low risk	Results of all outcomes described in the methods section were presented.
Sample Size	Unclear risk	Intervention: 74 Control: 64
Other bias	Low risk	No indication of additional bias.

Rosser 1983

Methods	**Publication type:** Full report; **Design**: RCT
Participants	**Inclusion criteria:** Dyspnea due to COAD **Exclusion criteria:** Presence of another severe illness or a cause of dyspnoea other than COAD, dementia, and other conditions which were a contra-indication to psychotherapy **Patient characteristics:** *presented in mean (SD) or n (%)* Age**:** 65 (9) Gender 22 (33.8%) female; 43 (66.2%) male FEV1 % pred: NR **Number of participants**: *Randomised*: 65; *Analysed*: 16/16/16/17 (intervention/other intervention/other intervention/control) **Setting:** UK
Interventions	**Duration:** 8 weeks **Intervention:** *(category psychotherapy)* Analytic psychotherapy; frequency: weekly; duration: 45 minutes; delivery: face-to-face, group; providers: psychoanalysts **Comparison 1:** *(category active control)* Other intervention in form of supportive psychotherapy **Comparison 2:** *(category active control)* Psychotherapy provided by nurses **Comparison 3:** *(category inactive control)* Usual care
Outcomes	**Assessment:** Baseline, 8 weeks, 24 weeks **Breathlessness measures:** VAS, Fletcher Scale **Other measures:** GHQ, Visual Analogue ratings of depression, Visual Analogue ratings of anxiety
Funding	NR
Declaration of interest	NR
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Each batch contained a balanced allocation of subjects between all 4 groups, to control for seasonal and other effects on breathing."
Allocation concealment (selection bias)	Low risk	"Allocation was carried out by labelling all slots for male and female patients for each batch, sealing the labels and assigning them randomly to the subjects who were drawn from the waiting list for each batch."
Blinding of participants and personnel (performance bias)	High risk	Open-label study.
Blinding of outcome assessment (detection bias)	High risk	Self-reported outcome measures of participants not blinded to the intervention.
Incomplete outcome data (attrition bias)	Low risk	No drop-outs.
Selective reporting (reporting bias)	Low risk	Results of all outcomes described in the methods section were presented.
Sample Size	High risk	65 participants randomised.
Other bias	High risk	Described randomisation process not successful (severity of anxiety and depression significantly different between groups at baseline).

Scalvini 2016

Methods	**Publication type:** Abstract **Design:** RCT (NCT02269618)
Participants	**Inclusion criteria:** Age > 18 years; COPD (GOLD classification B, C and D); CHF (NYHA class II-IV); At least one hospitalization or visit due to HF or COPD exacerbation in last 12 months **Exclusion criteria:** limited life expectancy; physical activity limitations due ot noncardiac and/or pulmonary conditions **Patient characteristics:** *presented in mean (SD) or n (%)* Age: 70.5 (9.2) Gender: 20 (17.9%) female; 92 (82.1%) male FEV_1 % pred: 79.9 (17.9) NYHA: III: 41 (%); IV: 17 (%) **Number of participants:** *Randomised*: 112; *Analysed*: 56/56 (Intervention/Control) **Setting:** Home care; Italy
Interventions	**Duration:** 16 weeks **Intervention:** *(category counselling and support)* Telehealth support; frequency: weekly; delivery: face-to-face and phone; providers: nurse **Comparison:** *(category inactive control)* Usual care
Outcomes	**Assessment:** Baseline, 16 and 24 weeks **Breathlessness measure:** modified BDS **other measures:** MRC; MLHFQ
Funding	The work was financially supported by the Italian Ministry of Health (CCM 2011, project n. 14)
Declaration of interest	The authors declare that they have no competing interests
Notes	Intervention started after inpatient rehabilitation.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Consenting eligible patients were randomized to either an intervention or a control group (1:1). A computer generated tables to allocate patients in fixed blocks of 4."
Allocation concealment (selection bias)	Low risk	"In order to prevent selection bias, the allocation sequence was concealed from the investigators enrolling and assessing patients, in sequentially numbered, opaque, sealed envelopes."
Blinding of participants and personnel (performance bias)	High risk	"Due to the nature of the intervention, neither the patients nor the physicians were blinded to patients' group allocation"
Blinding of outcome assessment (detection bias)	High risk	Self-reported outcome measures of participants not blinded to the intervention.
Incomplete outcome data (attrition bias)	Unclear risk	Insufficient information.
Selective reporting (reporting bias)	Unclear risk	Borg scores only presented in the conference abstract; but not reported in fulltext
Sample Size	Unclear risk	112 participants randomised.
Other bias	Low risk	No indication for additional bias.

Soler 2006

Methods	**Publication type:** Full report; **Design:** RCT
Participants	**Inclusion criteria:** COPD;history of multiple exacerbations (3 or more in the last year); tabacco history of at least 20 package-years; $FEV_1/FVC < 70$ after bronchodilation **Exclusion criteria:** asthma; cystic fibrosis; upper airway obstruction; disease-related systemic bronchiolitis **Patient characteristics:** *presented in mean (SD) or n (%)* Age: 73.5 (7.9) Gender: 0 (0%) female; 26 (100%) male FEV_1 % pred: 42.8 (15.3) **Number of participants:** *Randomised*: 26; *Analysed*: 13/13 (intervention/control) **Setting:** Outpatient; Spain
Interventions	**Duration:** 48 weeks **Intervention:** *(category self-management)* Specific program with educational session; delivery: face-to-face; providers: nurse **Comparison:** *(category inactive control)* Usual care
Outcomes	**Assessment:** Baseline and 48 weeks **Breathlessness measure:** MRC **Other measures:** SGRQ
Funding	NR
Declaration of interest	NR
Notes	Publication in Spanish

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details reported.
Allocation concealment (selection bias)	Unclear risk	No details reported.
Blinding of participants and personnel (performance bias)	Unclear risk	No details reported.
Blinding of outcome assessment (detection bias)	Unclear risk	No details reported.
Incomplete outcome data (attrition bias)	High risk	Complete-case analysis.
Selective reporting (reporting bias)	Low risk	Results of all outcomes described in the methods section were presented.
Sample Size	High risk	26 participants randomised.
Other bias	Unclear risk	Only male patients; no explanation or discussion reported.

Vanderbyl 2017

Methods	**Publication type:** Full report; **Design:** cross-over RCT
Participants	**Inclusion criteria:** > 18 years; pathologically confirmed diagnosis of advanced stage (3 or 4) NSCLC or GI; life expectancy estimated at > 4 months **Exclusion criteria:** if exercise was contraindicated as determined by the treating oncology team; active psychiatric conditions; simultaneous participation in interventions to address anxiety or depressive symptoms, history of severe cardiac, neuromuscular or skeletal disease or brain metastases **Patient characteristics:** *presented in mean (SD) or n (%)* Age: 65.0 (9.9) Gender: 10 (41.7%) female; 14 (58.3%) male Tumour stage III: 8 (33.3%); IV: 16 (66.7%) **Number of participants:** *Randomised*: 36; *Analysed*: 11/13 (intervention/control) **Setting:** Outpatient; Canada
Interventions	**Duration:** 10 weeks (6 weeks intervention) **Intervention:** *(category meditative movements)* Medical Qigong intervention; frequency: twice weekly; duration: 45 minutes; delivery: face-to-face; providers: physiotherapist **Comparison:** *(category active control)* Endurance and strength training intervention
Outcomes	**Assessment:** 6 weeks **Breathlessness measures:** NRS: 2.5 (3.5) **Other measures:** HADS: anxiety: mean 5.5 (3.5); depression 5.6 (3.0); FACT-G
Funding	AT Tran and RT Jagoe received salary support from the Peter Brojde Lung Cancer Centre and RT Jagoe received salary support from the Backler Foundation, Jewish General Hospital Foundation. The McGill Cancer Nutrition Rehabilitation Clinic at the Jewish General Hospital received financial support from funds raised by the Angel Ball, Stephen and Lillian Vineberg and the Lila Sigal Hockey Marathon
Declaration of interest	The authors declare that they have no conflicts of interest
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was done using a computer-generated number sequence assigning consecutive participant ID numbers either 1 or 2, to denote QG or SET. A block randomization algorithm was used to ensure equal distribution of variables including cancer type, sex and CRP level "
Allocation concealment (selection bias)	Unclear risk	No details reported.
Blinding of participants and personnel (performance bias)	Unclear risk	No details reported.
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear, if participants were blinded.
Incomplete outcome data (attrition bias)	High risk	Complete-case analysis
Selective reporting (reporting bias)	Low risk	Results of all outcomes described in the methods section were presented.
Sample Size	High risk	36 participants randomised.
Other bias	Low risk	No indication for additional bias.

Wilson 2015

Methods	**Publication type:** Full report **Design:** RCT (NCT00925171)
Participants	**Inclusion criteria:** COPD; > 35 years **Exclusion criteria:** Significant cardiac or pulmonary disease; Myocardial infarction within the previous 6 months or unstable angina; Respiratory infection defined as cough, antibiotic use or purulent sputum within 4 weeks prior to randomisation Severe or uncontrolled co-morbid disease; Abnormalities in cognitive functioning; Unable to give written informed consent. **Patient characteristics:** *presented in mean (SD) or n (%)* Age: 68.3 (12.4) Gender: 57 (41.3%) female; 91 (65.9%) male FEV_1 % pred: 41 (16) **Number of participants:** *Randomised*: 148; *Analysed*: 73/75 (intervention/control) **Setting:** Hospital/community PR; United Kingdom
Interventions	**Duration:** 52 weeks **Intervention:** *(category counselling and support)* Education sessions; delivery: face-to-face, group **Comparison:** *(category inactive control)* Usual care
Outcomes	**assessment:** Baseline and 52 weeks **breathlessness measure:** CRQ-D; CRQ-M **other measures:** HADS (total score): 11.7 (6.9); EQ-5D
Funding	This paper presents independent research funded by the National Institute for Health Research (NIHR) under its Research for Patient Benefit (RfPB) Programme (Grant Reference Number PB-PG-0408-16225). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health
Declaration of interest	None
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Eligible patients were randomised after baseline post-PR measure on a 1:1 basis using a computer generated randomised sequence"
Allocation concealment (selection bias)	Low risk	"Randomisation was undertaken by an independent researcher (CB), using the code generated by the statistician, who had no role other than this in the study and had no knowledge of the patients' details or characteristics. This researcher mailed letters to the patients informing them of their allocation group and inviting those in the intervention group to attend the maintenance PR sessions."
Blinding of participants and personnel (performance bias)	High risk	Open-label study.
Blinding of outcome assessment (detection bias)	High risk	Self-reported outcome measures of participants not blinded to the intervention.
Incomplete outcome data (attrition bias)	Low risk	"Analysis was on the intention-to-treat principle with any drop-outs being replaced using imputation."
Selective reporting (reporting bias)	Low risk	Results of all outcomes described in the methods section were presented.
Sample Size	Unclear risk	148 participants randomised.
Other bias	Low risk	No indication of additional bias.

Xiao 2015

Methods	**Publication type:** Full report; **Design:** RCT
Participants	**Inclusion criteria:** COPD, medically stable not smoked for at least 6 months, no other disabling diseases (e.g., stroke, Parkinsonism) **Exclusion criteria:** Not applicable **Patient characteristics:** *presented in mean (SD) or n (%)* Age: 71.1 (2.7) Gender: 5 (4.0%) female; 117 (92.9%) male FEV_1 % pred: 41.1 (4.3) **Number of participants:** *Randomised*: 126; *Analysed*: 59/60 (intervention/control) **Setting:** Outpatient/Home; China
Interventions	**Duration:** 24 weeks **Intervention:** *(category meditative movements)* Liuzijue qigong; frequency: 4 times a week; duration: 45 minutes; providers: trained therapist **Comparison:** *(category active control)* Walking and other training sessions
Outcomes	**Assessment:** Baseline, 6 and 24 weeks **Breathlessness measures:** CRQ-D; CRQ-M **Other measures:** SF-36
Funding	No funding was received for this study
Declaration of interest	The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details reported.
Allocation concealment (selection bias)	Unclear risk	No details reported.
Blinding of participants and personnel (performance bias)	High risk	Open-label study.
Blinding of outcome assessment (detection bias)	High risk	Self-reported outcome measures of participants not blinded to the intervention.
Incomplete outcome data (attrition bias)	Low risk	Intent-to-treat analysis
Selective reporting (reporting bias)	Low risk	Results of all outcomes described in the methods section were presented.
Sample Size	Unclear risk	126 participants randomised.
Other bias	Low risk	No indication for additional bias.

Appendix J. Eidesstattliche Versicherung

Ich erkläre hiermit an Eides statt, dass ich die vorliegende Dissertation mit dem Titel

“The Relationship of Breathlessness with Psychological Distress and Quality of Life in Adults with Advanced Disease”

selbständig verfasst, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

Ich erkläre des Weiteren, dass die hier vorgelegte Dissertation nicht in gleicher oder in ähnlicher Form bei einer anderen Stelle zur Erlangung eines akademischen Grades eingereicht wurde.

Hannover, 04.02.2021	Anna Bolzani
Ort, Datum	Unterschrift Doktorandin