Breathing Control in Patients with Chronic Obstructive Pulmonary Disease

Effects on and fluctuations in quality of life outcomes

Doctoral thesis

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Summary

Background:

Chronic obstructive pulmonary disease (COPD) is a life-limiting disease with complex effects on the physical breathing system, such as chronic airway obstruction and insufficient breathing pattern. These may lead to breathlessness and subsequently impaired quality of life (QOL).

Non-pharmacological efforts to provide self-management support, such as breathing-control exercises, can help improve breathlessness and QOL outcomes in people with COPD.

There is limited evidence of positive effects of breathing-control exercises on breathlessness and QOL outcomes in people with COPD. The fluctuating pattern of QOL outcomes, which are often used in self-management programmes, has not been investigated thoroughly.

Aims:

The aims of this thesis were as follows: (1) to overview the systematic reviews on how breathing-control exercises and respiratory muscle training affect breathlessness, other symptoms and QOL in people with COPD (paper 1); (2) to explore the effects whether guided deep breathing using a device improves breathlessness, QOL and breathing pattern in people with a moderate or severe stage of COPD during a four-week intervention and after a four-month follow-up (paper 2); and (3) to explore the fluctuating pattern of changes in QOL outcomes over a four-month period (paper 3).

Methods:

Firstly, an overview article was written to describe the systematic reviews of the effects of breathing-control exercises and respiratory muscle training on breathlessness, other symptoms and QOL in people with COPD. In this paper methodological quality was assessed using the Measurement Tool to Assess Systematic Reviews (AMSTAR) criteria (paper 1).

Secondly, a double-blind, randomized controlled trial (RCT) of 150 patients with moderate or severe COPD was undertaken. The participants were assessed at the baseline, after a four-week intervention (n=143) and at the four-month follow-up (n=130). The randomization allocated 51 participants to a guided deep-breathing group, 50 participants to a music-listening group and 49 participants to a sham sitting-still group. A small device measuring

breathing pattern with a sensor belt while giving instructions by airphones was used to instruct the participants in the guided deep-breathing group. They were guided to breathe deeply on the background of a measured breathing pattern. The same device was used in the music-listening group, but only in association with music listening, and in the sitting-still group, which received no guidance on breathing deeply and did not listen to music. The main outcome in the RCT, breathlessness, was measured using the symptom score of the disease-specific QOL outcome; St. George's Respiratory Questionnaire (SGRQ) and a global rating change (GRC) scale of perceived change in breathlessness (paper 2). The secondary outcomes of the RCT were the subscores activity, impact and the total SGRQ score and variables related to breathing pattern (respiratory rate (RR), time on inspiration (TIN) and time on expiration (TEX)) (paper 2).

Thirdly, the longitudinal data (paper 3) from the RCT were analysed to measure the changes in QOL outcomes. Disease-specific QOL was measured with the SGRQ, general health-specific QOL was measured using the depression and anxiety subscales of the Hospital Anxiety and Depression Scale (HADS) and global-specific QOL was measured as well-being, using the World Health Organization (WHO)-5 Well-Being Index.

Analysis of covariance was used to evaluate the differences between groups, and a paired Student's *t* test was used to evaluate changes within groups in the RCT (paper 2). Change scores for the QOL outcomes were used in different combinations in multiple regression analyses of the longitudinal study (paper 3).

Results:

According to the AMSTAR criteria, one high-quality systematic review was found on breathing-control exercises (i.e., pursed-lip breathing, diaphragmatic breathing, yoga breathing) and two high-quality systematic reviews were found on respiratory muscle training in the overview article (paper 1). The pooled analysis showed an effect of pursed-lip breathing on improvement of breathlessness (p=0.0066). Single trials showed effects of diaphragmatic breathing and yoga breathing on disease-specific QOL. The pooled analysis in the two systematic reviews of respiratory muscle training showed effects on breathlessness (p<0.001–0.004), disease-specific QOL (p=0.007) and fatigue (p=0.024). The single RCT in the systematic reviews was rated by the authors as being of low to moderate quality (paper 1).

The RCT (paper 2) showed differences between groups in favour of guided deep breathing according to the GRC scale. These effects were significant for the change in perceived change

in breathlessness at four weeks (p=0.03) and between the guided deep-breathing group and the music-listening group (p=0.04), but not between the guided deep-breathing group and the sitting-still group at four months. The breathing pattern showed positive effect in favour of guided deep-breathing group (p<0.001) at four weeks. All groups showed significant changes in the within-group analysis (p<0.05–0.01) for the SGRQ symptom score at four weeks (paper 2).

The longitudinal data (paper 3) showed that changes in disease-specific QOL (p<0.01, partial (p) R^2=11–12%), depression (p<0.01, pR^2=9–12%) and anxiety (p<0.02–0.001, pR^2=4–15%) were significantly associated with the change in well-being over the four months. The change in disease-specific QOL was significantly associated with the change in anxiety at four months (p=0.02, pR^2=4%) but not with the change in depression.

Conclusions:

The overview article identified systematic reviews on the practice of breathing-control exercises and respiratory muscle training showing effect on breathlessness and disease-specific QOL. The sinlge studies included in the systematic reviews were of variable quality and few RCTs have been performed of breathing-control exercises. However, use of device-guided breathing had positive effects on the change in perceived breathlessness and breathing pattern and seemed to function as a self-management task for people with moderate or severe COPD in a home situation. Because all intervention groups showed positive changes in the symptom scores, music listening and relaxation may also be beneficial self-management tasks, although this requires confirmation. The changes in QOL outcomes fluctuated over time. These results showed that change in disease-specific QOL changed with change in well-being, but to a limited extent with change in anxiety and not with change in depression during the four-month period. By contrast, changes in depression and anxiety changed with change in well-being during the four-month period. These results suggest that well-being may be a useful measure of global-specific QOL in health research for people with moderate and severe COPD.

List of papers

1. Borge C.R., Hagen K.B., Mengshoel A.M., Omenaas E., Moum T., Wahl A.K. Effects of controlled breathing exercises and respiratory muscle training in people with chronic obstructive pulmonary disease: results from evaluating the quality of evidence in systematic reviews. *BMC Pulmonary Medicine* 2014, 14:184

2. Borge C.R., Mengshoel A.M., Omenaas E., Moum T., Ekman I., Lein M.P., Mack U., Wahl A.K. Effects of guided deep breathing on breathlessness and the breathing pattern in chronic obstructive pulmonary disease: A double-blind randomized control study. *Patient Education and Counseling* 2015, 98(2):182–90

3. Borge C.R., Moum T., Mengshoel A.M., Wahl A.K. Fluctuatating patterns in quality of life outcomes among patients with moderate- and severe- stage chronic obstructive pulmonary disease. Revised and resubmitted to *Quality of Life Research.*

Abbreviations

AMSTAR	A Measurement Tool to Assess Systematic Reviews
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ATS	American Thoracic Society
ATS/ERS	American Thoracic Society/European Respiratory Society
BDI/TDI	The Baseline Dyspnea Index/Transition Dyspnea Index
BS	Borg scale
C	Control
CAT	COPD Assessment Test
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic obstructive pulmonary disease
CRQ	Chronic Respiratory Questionnaire
DB	Diaphragmatic breathing
DLco	Diffusing capacity of carbon monoxide
DSS	Decision Support Systems
EXTRA	Norwegian Extra Foundation for Health and Rehabilitation
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
GDBG	Guided deep-breathing group
GOLD	Global Initiative for Chronic Obstructive Lung Diseases
GRC	Global Rating Change
HADS	The Hospital Anxiety and Depression Scale
HADS-a	Anxiety score of the HADS
HADS-d	Depression score of the HADS
I	Intervention
IMT	Inspiratory muscel training
kPa	kilopascal
LDS	Lovisenberg Diaconal Hospital

LHL	Norwegian Heart and Lung Association
LQ	Low quality
MD	Mean Difference
MLG	Music-listening group
mMRC	The Modified Medical Research Council dyspnoea scale
MQ	Moderate quality
Nr	Not reported
NRS	Numeric rating scale
NSF	Norwegian Nurses Association
$PaCO_2$	Pressure of carbon dioxide in arterial blood
PaO_2	Pressure of oxygen in arterial blood
PEP	Positive expiratory pressure
pH	Potentia hydrogenii
PLB	Pursed-lip breathing
QOL	Quality of life
RCT	Randomized controlled trial
RR	Respiratory rate
RV	Residual volume
SGRQ	The St. George's Respiratory Questionnaire
SPSS	Statistical package for the social sciences
SSG	Sitting-still group
T1	Baseline
T2	After four weeks
T3	After four months
TEX	Time on expiration
TIN	Time on inspiraton
TLC	Total lung capacity
USA	United States of America
WHO	World Health Organization
YB	Yoga breathing

1   Introduction

I have been working with people with chronic obstructive pulmonary disease (COPD) since the beginning of my nursing career in 1995. During this time, I have seen patients become breathless while performing almost every task in their daily lives. COPD impairs lung function and can cause an insufficient breathing pattern and breathlessness (Altose & Kawakami, 1999; Siela, 2013; The Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2015). As a consequence, life may become unbearable, and people with COPD can experience impaired quality of life (QOL) (Barnett, 2005; Ek, Sahlberg-Blom, Andershed, & Ternestedt, 2011; Disler et al., 2014).

Worldwide, 65 million people have COPD. This disease is considered to be the fifth-leading cause of death (World Helath Organisation (WHO), 2015) and presents social and economic burdens for patients (GOLD, 2015). In the past few decades, research and clinic studies have focused on helping to improve QOL in patients with COPD through the use of self-management programmes. However, more research is needed to identify the necessary self-management support skills and the best methods to measure QOL components and outcomes (Kaptein et al., 2009). This is in line with The Ministry of Health and Care Services' demand for high-quality research in the clinical treatment and management of people with chronic diseases (Helse og omsorgsdepartementet, 2014a). Further, the Coordination Reform in Norway states that the health care of Norway are obliged to provide proper treatment at the right place and at the right time (Helse og omsorgsdepartment, 2009) including for people with COPD in their environment (Helsedirektoratet, 2014). This implies that patients need to manage their illness and that new self-management strategies are needed.

Pharmacological treatment of COPD has limitations (American Thoracic Society/European Respiratory Society (ATS/ERS), 2004; Helsedirektoratet, 2012; GOLD, 2015), and non-pharmacological tasks or self-management support skills such as breathing-control exercises have been recommended as complementary treatment (Bourbeau, Nault, & ng-Tan, 2004; Leyshon, 2012; Parshall et al., 2012; Norweg & Collins, 2013; Spruit et al., 2013). These exercises can help COPD patients to modify their insufficient breathing pattern and may thereby improve their breathlessness and QOL (Raupach et al., 2008; Norweg & Collins, 2013). Breathing-control exercises may include activities such as pursed-lip breathing, diaphragmatic breathing, yoga breathing, deep breathing, relaxation exercises and changes in body position (Gosselink, 2004). Respiratory muscle training has been added to the list of breathing-control exercises (Gosselink, 2004) but is not considered a type of breathing-control

exercise in the recent literature (Holland, Hill, Jones, & McDonald, 2012). Breathing-control exercises have been shown to have variable effectiveness for improving breathlessness and QOL (Holland et al., 2012). Previous studies of breathing-control exercises provide limited information about the practice of breathing-control exercises in the home setting, and few blinded randomized controlled trials (RCTs) have been reported (Holland et al., 2012). Moreover, most studies have included customary care as the control group, and the intervention group has been taught the exercises by a health professional (Holland et al., 2012), which increases the risk of an attention effect (Miller, Colloca, & Kaptchuk, 2009).

The Ministry of Health and Care Services has requested the development of new technologies and management strategies to provide better and more effective treatment (Helse og omsorgsdepartementet, 2014a). For example may assistance in breathing-control exercises be given using a technological device that measures the breathing movement or breathing pattern with a sensor belt at the same time as auditory synchronization instructions about breathing are given through earphones (Gavish, 2010). Such a device can help the patient to modify an insufficient breathing pattern. Previous research on this device has reported reduced blood pressure (Mahtani, Nunan, & Heneghan, 2012) in hypertensive patients and improved symptoms (Ekman, Kjellstrom, Falk, Norman, & Swedberg, 2011), QOL (Parati G et al., 2008) and breathing patterns (Ekman et. al., 2011; Harada et al., 2014) in patients with heart failure. The use of such a device may allow researchers to perform blinded RCTs of breathing-control exercises in a home setting with less attention from a health professional.

QOL outcomes such as breathlessness, disease-specific QOL, depression, anxiety and well-being are closely related to each other (Barnett, 2005; Blinderman, Homel, Billings, Tennstedt, & Portenoy, 2009; Tsiligianni, Kocks, Tzanakis, Siafakas, & van der Molen, 2011). Well-being has been studied to only a limited extent in people with COPD (Lee, Lee, Mackenzie & Rosalie, 2002; Stridsman, Zingmark, Lindberg, & Skar, 2014). Research has shown that several QOL outcomes may vary in severity or may become worse over time (Spilker, 1996) in people with COPD (Walke et al., 2007; Espinosa de los Monteros MJ, Pena, Soto Hurtado, Jareno, & Miravitlles, 2012; Wilke et al., 2014). Only limited research has focused on whether and how disease-specific QOL, depression and anxiety fluctuate together over time (Oga et al., 2007; de Torres et al., 2014), and no study has included well-being as a QOL outcome in people with COPD.

Based on this background, the present thesis was undertaken to first review the literature on breathing-control exercises and respiratory muscle training and then to perform a double-blind RCT of the effects of breathing-control exercises using a guiding device in the home situation and to use the longitudinal data from the RCT to investigate the fluctuations in QOL outcomes in people with COPD over a period of four months.

2 Aims

The main goal of this thesis was to investigate the effects of breathing-control exercises and fluctuations in quality of life (QOL) outcomes over time in people with chronic obstructive pulmonary disease (COPD).

There were three specific aims, which were addressed in three papers.

Paper 1 aimed to summarize the results and the quality of systematic reviews that evaluated the effects of breathing-control exercises and respiratory muscle training on breathlessness, other symptoms and QOL in patients with COPD.

Paper 2 aimed to investigate, using a double-blind randomized controlled trial, whether people with moderate or severe COPD would report beneficial effects on breathlessness, QOL and breathing pattern after a four-week intervention programme using device-guided breathing control and after a four-month follow-up compared with a groups listening to music or sitting still.

Paper 3 aimed to investigate whether and how changes in disease-specific QOL fluctuate with changes in depression, anxiety and well-being, and whether and how changes in depression and anxiety fluctuate with change in well-being in non-hospitalized patients with moderate or severe COPD over a period of four months.

3   Background

3.1   Chronic obstructive pulmonary disease (COPD)

3.1.1 Definition, epidemiology and risk factors

COPD *"is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles and gases. Exacerbations and comorbidities contribute to the overall severity in individual patients"* (GOLD, 2015, page 2). This definition is similar to the 1962 definition of the American Thoracic Society (ATS) Committee. However, some of the earliest references to components that are now interpreted as COPD (e.g., voluminous lungs) date back to 1679 (Petty, 2006).

COPD often develops progressively and may increase in severity with time (GOLD, 2015). It is a serious disease as well as a public health problem, and the incidence is increasing both nationally and internationally (Helsedirektoratet, 2012; GOLD, 2015). About 250 000–300 000 people live with COPD in Norway (Helsedirektoratet, 2012), and the prevalence has increased from 7% to about 14% during a period of nine years (Waatevik et al., 2013) Worldwide, about 65 million people have moderate to severe COPD (WHO, 2015). The prevalence is almost the same in men and women, and increases with age (ATS/ERS, 2004). The disease is often found in people aged 60 years or older. COPD poses a social and economic burden and is estimated to become the third-leading cause of death by 2020. COPD is believed to be underdiagnosed and under-recognized in relation to the death rate (GOLD, 2015). The risk of disease is higher in people with lower socio-economic status (ATS/ERS, 2004).

Cigarette smoking is the main risk factor for developing COPD, but other noxious particles or gases such as smoke from biomass fuels, occupational dust or chemicals, and outdoor air pollution may increase the risk of COPD. A history of infections in childhood and genetic risk factors such as alpha-1 antitrypsin deficiency have also been found to contribute to the development of COPD. Alpha-1 antitrypsin deficiency leads to increased destruction of the alveolar wall and lung parenchymal tissue, which leads to emphysema. However, only small part of the world population have have alpha-1 antitrypsin deficiency and interactions with envirmonetal factors such as smoking may increase risk of COPD (GOLD, 2015).

3.1.2 Pathogenesis and comorbidities

Figure 1 shows the healthy respiratory system and the main characteristic changes that occur in COPD. The respiratory system consists of the organs and tissues involved in breathing. The lungs are essential for the intake of air and for the transport of oxygen from the lungs to the blood and carbon dioxide from the blood to the lungs. The lungs contain airways that branch into the smaller airways that form the bronchial tree. The walls of the airways have a thin layer of smooth muscle that helps to dilate or constrict the airway size. Small cilia and goblet cells help to trap and move organisms that do not belong in the lungs. Thousands of small alveoli (air spaces) form the end of the small airways (bronchioles) (McGowan, Jeffries & Turley, 2003; Bourke, 2007).

The main characteristic of the pathogenesis of COPD is a chronic inflammatory process in the central and peripheral airways. Inflammation causes impairment and destruction of ciliary movement, which lead to increased production of mucus and changes in the mucous membranes. Inflammation affects the contractile ability of smooth muscles in the airways, which leads to airway narrowing and minor airway disease. The alveoli located at the end of the tracheobronchial tree may be injured and may lose elasticity and/or may be damaged and lead to less aerial to use for gas exchange. This process may lead to two conditions of COPD: chronic bronchitis (i.e., a chronic inflammatory process with excess mucus; upper image in Figure 1) or emphysema (i.e., permanent destruction of alveoli; lower image in Figure 1). These conditions can overlap each other (ATS/ERS, 2004; Gulsvik & Bakke, 2004). These changes in the airways often lead to breathlessness, cough, sputum and wheeze (GOLD, 2015; ATS/ERS, 2004).

Although asthma differs in its aetiology and response to treatment, it is sometimes difficult to distinguish asthma from COPD, and some people with COPD are therefore diagnosed with asthma. Other differential diagnoses for COPD may include diseases such as heart failure, bronchiectasis, tuberculosis and bronchiolitis. These diseases may also be comorbidities of COPD as well as cardiovascular disease, osteoporosis, depression, anxiety, skeletal muscle dysfunction, diabetes mellitus and lung cancer. People in a more severe stage of COPD tend to be at high risk of exacerbations, and the presence of exacerbations is associated with a more rapid loss of lung function and increase in symptom severity, which lead to impaired health status (GOLD, 2015). Exacerbations have been reported to occur up to three times per year in people with COPD (Donaldson & Wedzicha, 2006).

Figure 1.

Chronic Obstructive Pulmonary Disease (COPD)

3.1.3 Pathophysiology: consequences for the breathing-control system

Control of breathing means the "central and peripheral regulation and control mechanisms of breathing" (Dean & Frownfelter, 2006, page 799). The term "breathing" has synonyms such as "ventilation" and "respiration", and involves the bodily process of inhalation and exhalation (Webster's Dictionary, 2015).

Figure 2 shows the physiological breathing-control system. This system involves a complex synergy between the respiratory centre in the brain, the control of signals through sensors and the effects on the system of breathing in humans (Caruana-Montaldo, Gleeson, & Zwillich, 2000). Humans have two types of systems to control breathing: the unconscious control system and the conscious control system (Dean & Frownfelter, 2006).

Figure 2. The physiological breathing-control system
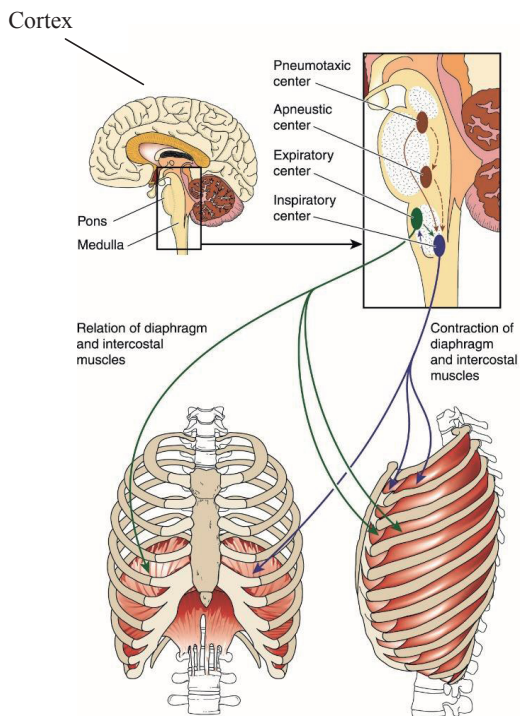
Cortex

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The conscious control system is located in the cortex and is stimulated by voluntary or emotional input. For example, the conscious control system may stimulate the respiratory muscles (McGowan et al., 2003; Dean & Frownfelter, 2006). The diaphragm and the intercostal muscles are the main muscles of respiration. In some diseases such as COPD, the muscles that assist respiration, such as the sternocleidomastoid (neck muscles) and scalenes, may also be used (Dean & Frownfelter, 2006). The conscious control system makes it possible to breathe voluntarily, for example by breathing quickly or holding the breath during speaking, coughing, blowing (Dean & Frownfelter, 2006) and singing (McGowan et al., 2003).

The unconscious control system is stimulated by changes in blood gas variables such as the partial pressures of carbon dioxide (P_aCO_2) and oxygen (P_aO_2) and pH. Adjustments are made through the actions of chemoreceptors (i.e. sensors that react to chemical stimuli) (McGowan et al., 2003) and by signals sent by nerves to the respiratory centre located in the pons and medulla of the midbrain. Other signals may be sent by nerves from the respiratory centre to the respiratory muscles such as the diaphragm and the intercostal muscles (Dean &

Frownfelter, 2006). Sensory receptors in the lungs, chest wall, nasal passage, trachea and larynx are also involved in the respiratory control system (McGowan et al., 2003; Dean & Frownfelter, 2006). The medulla stimulates the sequence of inspiration and expiration, and the pons regulates the rhythm of breathing (Dean & Frownfelter, 2006)

Obstruction and emphysema contribute to an overload of breathing as well as a decrease in oxygen saturation and an increase in carbon dioxide level in people with COPD. Further may the chest wall may be restricted. (O'Donnell et al., 2007; GOLD, 2015). Hence, the unconscious control system is activated. The body then reacts to the changes in blood gas by sending nerve signals to the brain, which stimulate an increase in ventilation with the help of respiratory muscles (Caruana-Montaldo et al., 2000). This may increase the load of the inspiratory muscles. The inspiratory muscles may weaken or fatigue, which may induce an inspiration before a full expiration can be completed, which leaves a larger residual volume (RV) of air in the lungs (i.e., air trapping). The increase in air flow limitation can lead to an increase in total lung capacity (TLC), called hyperinflation (ATS/ERS, 2004; O'Donnell et. al., 2007; GOLD, 2015). A shorter time is spent on inspiration and expiration, and the respiratory rate increases (Altose & Kawakami, 1999). All of this may induce an ineffective breathing pattern, meaning that the "*inspiration and/or the respiration does not provide adequate ventilation*" (Siela, 2013, page 175). The normal respiratory rate or respiratory frequency is 12–20 breaths per minute, but in general an abnormal respiratory rate is considered to be >12 breaths per minute (McGowan et al., 2003). It is believed that slow breathing suppresses sympathetic nerve activity, which may help to improve breathlessness (Raupach et al., 2008; Harada et al., 2014).

3.1.4 Diagnosis

The diagnosis of COPD is assessed by considering the patient's day-to-day experience of dyspnoea or breathlessness, cough, wheeze, chest tightness and sputum production and the effect of the disease on the patient's life in relation to their social and family life, work and psychological status such as feelings of depression or anxiety. The diagnosis will also consider a history of exposure to factors such as cigarette smoking, comorbidities, hospitalizations, exacerbations, medical history including history of COPD and family history of COPD (ATS/ERS, 2004; GOLD, 2015).

Traditionally, the disease is classified according to the lung function variables forced expiratory volume in one second (FEV_1) and forced vialcapacity (FVC). These values are

compared with those for the normal healthy population and are expressed as a percentage of the predicted value. An $FEV_1/FVC \leq 0.70$ confirms airflow limitation(ATS/ERS, 2004; GOLD, 2015).

The main aim of COPD assessment is to determine the severity of the disease (GOLD, 2015). In the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD), the stages of COPD are classified as follows (GOLD, 2015).

GOLD 1:   Mild stage $FEV_1 \geq 80\%$ predicted

GOLD 2:   Moderate stage $50\% \leq FEV_1 < 80\%$ predicted

GOLD 3:   Severe stage $30\% \leq FEV_1 < 50\%$ predicted

GOLD 4:   Very severe stage $FEV_1 < 30\%$ predicted

The American Thoracic Society/European Respiratory Society (ATS/ERS) (2004) has also included a risk stage for developing COPD, which is defined as $FEV_1/FVC > 0.70$ and $FEV_1\%$ $\geq 80\%$ of predicted.

Lately, have also disease related symptoms and the health status of people with COPD been assessed with the use of validated quesstionnaires, such as the Modified Medical Research Council (mMRC) dyspnoea scale, the COPD Assessment Test (CAT) and the St. George's Respiratory Questionnaire (SGRQ), for evaluation of the severity of the disease (GOLD, 2015). These instruments are useful for improving the management of COPD and for evaluating the risks of developing exacerbations (GOLD, 2015). However, the exact diagnosis of an exacerbation is controversial and may also be based on the presence of infection or the colour of sputum (Donaldson & Wedzicha, 2006; GOLD, 2015).

Additional investigations to diagnose COPD may include measurement of lung volumes such as RV and TLC using body plethysmography. These values can be used to determine the degree of hyperinflation (Criee et al., 2011). Other tests may include measurement of diffusing capacity of carbon monoixide (DL_{CO}), chest X-ray, oximetry or blood gas measurements (i.e., P_aCO_2, P_aO_2, pH), alpha-1 antitrypsin screening, exercise testing (e.g., 6-minute walk test, treadmill test), inspection of respiratory signs such as respiratory rate and respiratory muscle strength (ATS/ERS, 2004; GOLD, 2015).

3.1.5 Burden and course of COPD

Breathlessness is often the first symptom a person with COPD experiences (GOLD, 2015). The feeling of not getting enough air can be frightening, which may further increase the feeling of breathlessness (Bailey, 2004). Breathlessness may affect several aspects of life. It may occur often during physical effort such as stair climbing or walking uphill. With more progressive disease, breathlessness may increase and the person may be impaired or unable to perform certain tasks (Gulsvik & Bakke, 2004). Breathlessness can limit the person's ability to undertake self-care, housework and shopping. These effects may lead to loss of hope, and difficulty in finding and maintaining meaning in life is also often expressed (Disler et al., 2014). Symptoms of breathlessness may lead to anxiety, panic or fear, frustration and loss of social life (Barnett, 2005). COPD may therefore have an impact on several aspects of QOL (Ek & Ternestedt, 2008), such as impaired health-related QOL (Bentsen, Henriksen, Wentzel-Larsen, Hanestad, & Wahl, 2008), disease-specific QOL (Tsiligianni et al., 2011) and well-being (Stridsman et al., 2014). Several factors such as age, gender, smoking co-morbidities, education level, living status and infections may impact on different pattern of the experience of breathlessness and QOL in people with COPD (Haave &Hyland 2008; Borge, Wahl & Moum, 2010; GOLD, 2015)

The disease generally develops over several years and may become worse over time (GOLD, 2015). The course of the disease may lead to a negative downward spiral during which the patient becomes increasingly disabled (Bourbeau, 2002). A negative change in COPD-related problems such as breathlessness may predict a negative change in depression and anxiety over time (de Torres et al., 2014). Many with COPD experience exacerbations, which cause even more breathlessness and reduced QOL (GOLD, 2015). Patients can become more dependent on their family, but not all family members may understand COPD and be supportive (Bourbeau, 2002). Treatment and help from the health-care system is therefore important to prevent this negative spiral.

3.1.6 Treatment

The main treatment goal for stable COPD should be to lighten symptoms, improve physical function and health status, and reduce the risk of progression in terms of a decline in lung function, exacerbations and mortality (GOLD, 2015). If the patient is a smoker, smoking cessation courses are a key intervention. Both pharmacological and non-pharmacological follow-ups are relevant for people with COPD (ATS/ERS, 2004; GOLD, 2015).

Pharmacological treatment

The treatment is individualized by considering the severity of symptoms and airflow limitations before deciding on the medication (GOLD, 2015). The use of medication is supported by several studies, although until recently, no medication has shown long-term effects (GOLD, 2015). The effects are variable and depend on the severity and exacerbations (Montuschi, Malerba, Santini, & Miravitlles, 2014).

Bronchodilators and corticosteroids are the main treatment options. Bronchodilators act on the smooth muscles in the bronchioles to open the airways with the intention of improving breathlessness. Bronchodilators are classified as beta-agonists and anti-cholinergics, and are given as either a short-acting or a long-acting medication. To reduce inflammation in the airways, inhaled corticosteroid is often prescribed. However, the effect of this medication is not obvious in all patients with COPD (GOLD, 2015).

The combination of long-acting bronchodilators and corticosteroids is often more effective than either of these treatments prescribed separately. These medications are often administrated via inhalation as either an aerosol or a dry powder (GOLD, 2015). There is an increasing availability of different brands of inhalation devices. Multiple types of inhalation devices may cause confusion about how to use a particular device, and some people with COPD use their device incorrectly. Teaching the patient how to use their medication is therefore important. Using a spacer/chamber or a nebulizer may be an option if it is difficult for the patient to inhale the medication (Rau, 2006). Some brands may also be administered as pills or injections. Oral corticosteroids are an important medication during an exacerbation, and antibiotics are given during infection (GOLD, 2015).

Methyl xanthine medications also open the airways to improve breathlessness, but these are used mainly for exacerbations. Sometimes, a mucolytic is used to loosen and clear mucus. Long-term oxygen treatment is sometimes recommended if a patient has a $PaO_2 < 7.3$ kPa or arterial oxygen saturation $< 88\%$ with or without hypercapnia. Pharmacological treatment can also be used to help patients to stop smoking (e.g., nicotine replacement products, varenicline, bupropion, nortriptyline) and influenza vaccination and pneumococcal polysaccharide vaccination are also recommended as a preventive treatment (GOLD, 2015).

Non-pharmacological treatment

Specialist health-care services (Helsedirektoratet, 2011) and the community services (Helsedirektoratet, 1999a) are both responsible for following up patients with COPD in Norway. According to the law regarding patients' and users' rights, the patient is entitled to be informed and instructed (Helsedirektoratet, 1999b). COPD patients may be followed up using non-pharmacological actions involving self-management or pulmonary rehabilitation programmes, both of which are recommended in national and international guidelines (Helsedirektoratet, 2012; Spruit et al., 2013; GOLD, 2015). Much research has focused on whether and how these programmes work in people with COPD. Some pulmonary rehabilitation programmes involve self-management skills, and these concepts are sometimes used interchangeably (Gutenbrunner, 2010; Spruit et al., 2013). However, these two types of programmes have different agendas. The main difference is that pulmonary rehabilitation adds a medical approach for prevention, therapy, physically training and rehabilitation, whereas self-management programmes do not include a medical approach to treatment. The main similarity is the intention to help people with chronic health conditions to manage their disease (Gutenbrunner, 2010). Accordingly, both programmes aim to teach and help the individual patient with COPD to improve their symptoms, QOL, and physical functioning in daily life (ATS/ERS, 2004; Spruit et al., 2013; GOLD, 2015).

In recent years, self-management and pulmonary rehabilitation programmes have been offered by the specialist health-care services in Norway, for example in organized pulmonary rehabilitation hospitals such as Glittreklinikken Rehabilitation (Glittre, 2015), Granheim Pulmonary Hospital (Granheim, 2015) and at division hospitals or university hospitals in Norway. Because of the Coordination Reform in Norway, much of the responsibility has now been transferred to the community services (Helse og omsorgsdepartment, 2009). Despite these changes, the specialist health-care services are still a special responsibility for helping patients and their relatives. For example, both individual self-management support and group-based self-management assistance are offered in outpatient units and some hospitals also have an ambulant team that provides both treatment and self-management help for patients with COPD at home. However, the focus on helping people with COPD on self-mangment and rehabilitation in the community service are in developing and need more research (Helsedirektoratet, 2012).

In summary, both the community and the specialist health-care system are responsible for the non-pharmacological follow-up of patients with COPD. This assistance may be provided by programmes involving self-management help (Oxman, Bjørndal, Flottorp, Lewin, & Lindahl, 2008; Adams et al., 2007) and by more focus on the home situation (Helsedirektoratet 2012).

3.2 Self-management and self-management support

The term self-management has existed since the mid- 1960s and was first used in relation to asthma research on children. Since then, the term has changed in meaning, and there are now several definitions of self-management. In all definitions of self-management, the main issue is that a patient actively participates in her/his treatment (Lorig & Holman, 2003). One of the definitions of self-management is "*The individual's ability to manage the symptoms, treatment, physical and psychosocial consequences and life style changes inherent in living with a chronic condition. Efficacious self-management encompasses ability to monitor one's condition and to affect the cognitive, behavioral and emotional responses necessary to maintain a satisfactory quality of life. Thus a dynamic and continuous process of self-regulation is established*" (Barlow, Wright, Sheasby, Turner, & Hainsworth, 2002, page 178).

The definition focuses on the extent to which a person with a chronic illness is capable of managing different tasks and challenges in daily life. For patients with COPD, this may involve management of breathlessness at home.

The process of making changes as part of self-management may be considered under the concept self-management support. Self-management support is defined as "*the assistance caregivers give to patients with chronic disease in order to encourage daily decisions that improve health- related behaviors and clinical outcomes. Self-management support may be viewed in two ways: as a portfolio of techniques and tools that help patients choose healthy behaviors; and as a fundamental transformation of the patient–caregiver relationship into a collaborative partnership. The purpose of self-management support is to aid and inspire patients to become informed about their conditions and take an active role in their treatment*" (Bodenheimer, MacGregor, & Sharifi, 2005, page 4). According to this definition, information and assistance by a health professional in problem solving are important issues for each individual's self-management support (Department of Health: A Victorian Government Initiative, 2014). An interdisciplinary health team involving doctors, nurses, occupational therapists, physiotherapists and psychologists often provides this support. It may be given in a comprehensive programme or as separate tutoring on self-management skills

(Barlow et al., 2002; Desveaux, Janaudis-Ferreira, Goldstein, & Brooks, 2014). However, an interdisciplinary team is recommended in more comprehensive programmes (Kuzma et al., 2008).

A comprehensive programme contains a portfolio of self-management support skills, which may include a combination of one or more of the following topics: information about the disease; drug management; symptom management; management of psychological consequences: lifestyle advice, nutrition management and how to quit smoking; management of breathing and breathing pattern; social support; and communication and other components such as action planning, problem solving, constructive feedback, reinforcement and physical training (Barlow et al., 2002; Gallefoss, 2004; Bourbeau & Nault, 2007; Effing et al., 2007; Jonsdottir, 2013; GOLD, 2015). In Norway, comprehensive self-management programmes have been provided for people with COPD and shown to reduce the number of visits by general practitioners and improve disease-specific QOL (Gallefoss & Bakke, 2000), as well as providing increased patient satisfaction in terms of managing their disease and reducing the need of general practitioner and total costs per patient (Gallefoss, 2004).

It seems to be a tradition to provide self-management programmes as a complex intervention that covers several subjects or training procedures (Gallefoss & Bakke, 2000; Monninkhof et al., 2003; Bourbeau et al., 2004; Newman, Steed, & Mulligan, 2004). However, the barriers of depression, difficulty exercising, fatigue, limited communication with the physician, financial problems and poor family support can prevent people from participating in groups or attending appointments to learn self-management support skills. One suggestion has been that core self-management tasks could be taught and learned at home to reduce the effects of these barriers (Jerant, von Friederichs-Fitzwater, & Moore, 2005). This is in line with the Norwegian law about patients' and users' rights, which states that information should be adapted to the individual (Helsedirektoratet, 1999b). Adapting information to the individual can be difficult in more comprehensive self-management programmes (Stoilkova, Janssen, & Wouters, 2013). It has therefore been suggested that self-management programmes should focus on a specific exercise, strategy, skill or technique (Effing et al., 2007) and then be tailored to the individual patient (Effing et al., 2012). For instance, minimal education and interventions focused on a single task may be given via a short instruction session or written information, Web-based instruction, a telephone call, a text message or a combination of these methods (Osborne, Batterham, & Livingston, 2011).

In a recent review of educational programmes as part of COPD management, breathing-control exercises were found to be one of the main topics for educational support for people with COPD (Stoilkova et al., 2013). Breathing-control exercises have also been recommended in a number of published studies (Barlow et al., 2002; Gosselink, 2003; Dechman & Wilson, 2004; Gosselink, 2004; Bourbeau & Nault, 2007; von Leupoldt, Fritzsche, Trueba, Meuret, & Ritz, 2012; Spruit et al., 2013).

3.2.1 Breathing-control exercises as self-management support

The concept "breathing control" is defined as *"gentle breathing using the lower chest with relaxation of the upper chest and shoulders; it is performed at normal tidal volume, at a natural rate and expiration should not be forced"* (Prasad & Pryor, 2008, page 452).

There is an inaccuracy in the literature regarding the use of umbrella terms and what exercises or training procedures should be considered as breathing exercises. The often-cited author of breathing exercises (Nici et al., 2006; Spruit et al., 2013; Bott et al., 2009; Prasad & Pryor, 2008) Gosselink (2004) has used the term "breathing technique" as "*an all embracing term for a range of exercises,such as active expiration, slow and deep breathing, pursed-lip breathing, relaxation therapy, specific body positions, inspiratory muscle training and diaphragmatic breathing*" (page 26). In another paper by Gosselink (2003) the term "controlled breathing" is used for the same exercises. Yoga breathing is also mentioned in the literature as a type of breathing control for COPD patients (Holland et al., 2012). Another example of the varied use of this termis provided by von Leupoldt (2012) who use "Behavior Medicine Treatment" for the terms "breathing training" and "respiratory muscle training".

Although Gosselink included respiratory muscle training as a breathing technique or breathing-control exercise (Gosselink, 2003, 2004), the most recent guidelines in pulmonary rehabilitation have separated respiratory muscle training from breathing-control exercises (Spruit et al., 2013). Considering the diverse use of umbrella terms, in this thesis, I use the term breathing-control exercises to mean pursed-lip breathing, diaphragmatic breathing, deep breathing, yoga breathing and relaxation and device-guided breathing. I explain respiratory muscle training separately. Both of the concepts breathing-control exercises and respiratory muscle training are included as self-management support skills for people with COPD (Bourbeau et al., 2004; Bott et al., 2009). However, the procedure for and target of these exercises may vary (Gosselink, 2003). Some of the exercises, such as diaphragmatic breathing, pursed-lip breathing and relaxation, fit better within the definition of breathing

control (Prasad & Pryor, 2008), although the literature does not provide precise guidance on this point.

Music listening is sometimes used in combination with breathing-control exercises such as relaxation, but may also be a single self-management support task as a distraction stimuli to the experience of symptoms in people with pulmonary diseases (McBride, Graydon, Sidani, & Hall, 1999; Graydon, Sidani, & Hall, 1999; Raskin & Azoulay, 2009; Norweg &Collins, 2013). Technology also provides the option of using continuous guided instruction for breathing-control exercises (Gavish, 2010). This may be given using a biofeedback system through which an individual learns to change his/her physiological activity to improve health (Biofeedback Certification International Alliance, 2015). In this thesis, biofeedback guidance of breathing is called device-guided breathing. Table 1 presents the different techniques, performance, teaching and goals of treatment (Table 1).

Breathing-control exercises and respiratory muscle training require guidance by a trained respiratory health practitioner (Bott et al., 2009). After the patient learns the actual activity, the breathing-control exercise may be practised in a distressing situation to control breathlessness. As for respiratory muscle training, a training programme is required to improve the capacity of the respiratory muscles before symptoms of breathlessness may be reduced (Bott et al., 2009).

Guidelines in COPD provide little or minimal information on the actual benefits or performance of breating controle exercises or respiratory mucle training as self-management support skills (ATS/ERS, 2004; GOLD, 2015). More research on these technqueis may increase understanding about how to help patients with COPD both in the clinic and at home. The aim should be to guide behavioural change so that the patient with COPD can gain control over the condition and improve their breathlessness and general well-being (Effing et al., 2012).

Table 1. Breathing-control exercises and respiratory muscle training

Performance	Instruction	Aims of self-management support task
BREATHING-CONTROL EXERCISES (Dechman & Wilson, 2004; Gosselink, 2004; Dean & Frownfelter, 2006; Prasad & Pryor, 2008; Raskin & Azoulay, 2009; Gavish, 2010; Norweg & Collins, 2013)		
Pursed-lip breathing: Performed by breathing out with half-open lips. The pressure of expiration is about 5 cm H_2O.	- Several patients with COPD use this technique spontaneously when experiencing breathlessness. - Taught by a trained health professional. - Recommended to practise the technique and use it in situations causing breathlessness.	- Decrease the work of breathing - Improve ventilation - Assist relaxation - Mobilize and maintain mobility of thorax - Improve airway clearance - Increase strength, coordination and efficiency of respiratory muscles - Feel self-control - Aim to improve symptoms
Diaphragmatic breathing: The patients are given instructions to breathe with the diaphragm muscle.	- Taught by a trained health professional. - Recommended to practise the technique and use it in situations causing breathlessness.	
Yoga breathing: Slow breathing; also called pranayama. The breathing is often performed in combination with body positions and/or meditation.	- A trained yoga instructor. - Often performed in classes.	
Body position: Sometimes described as relaxation exercises. Examples include high side lying, relaxed sitting, forward lean standing and knee leaning position. The patient is instructed to relax the upper chest, shoulders and arms to give a favourable position for movement of the lower chest and abdomen. Often used in combination with other breathing-control exercises.	- Taught by a trained health professional. - Recommended to practise the technique and use it in situations causing breathlessness.	
Relaxation: The patient is instructed to sit in a comfortable chair or lie down in a comfortable position, close their eyes and focus on breathing. It may be used in combination with music listening.	- May be used in classes. - An instruction CD may also be used.	
Distraction: Music listening acts as a distractive auditory stimulus, sometimes during other breathing-control exercises.	No instruction needed.	Focus on music instead of symptoms
Device-guided breathing: A device that involves monitoring a biological or physical function while the patient's bodily functions are measured or the patient reads or performs changes based on the monitored data. This may be used to guide the user to breathe slowly and deeply and in combination with music.	- A device that guides the user on breathing control based on the feedback provided from the measured breathing pattern. - Instruction booklet and/or a person proficient with the instrument should teach the patient how to use the instrument.	Improved breathing pattern with the aim to improve symptoms

RESPIRATORY MUSCLE TRAINING (Dean & Frownfelter, 2006)		
Inspiratory muscle training: The patient trains the respiratory muscles voluntarily at a high level for an extended time either by inhaling through a mouthpiece with an adapter with an adjustable diameter or breathing through a flow of independent resistance. **Expiratory muscle training:** This training can be performed during low-intensity endurance training or high-intensity strength training. It is not used much.	- A training programme with a protocol and instruction from a trained health professional. - Practised every day.	Improve strength and endurance of inspiratory muscles with the aim to improve symptoms and QOL

3.3 Quality of life

The reports on breathing control (Holland et al., 2012), respiratory muscle training (Gosselink et al., 2011) and self-management programmes give several examples of different QOL outcomes that are used to examine the benefits in COPD and/or chronic diseases (Newman et al., 2004; Effing et al., 2007; Nolte & Osborne, 2013; Jordan et. al. 2015).

There are several definitions of QOL (Hanestad &Wahl, 2011). QOL may involve both health-related and non-health-related aspects of an individual's life experiences such as physical, psychological, social, spiritual, economic and political well-being. It is a multidimensional concept and difficult to define (Spilker, 1996). QOL may be seen on different levels, as shown in Figure 3 (Spilker, 1996; Hanestad & Wahl, 2011). The levels of QOL may be conceptualized as disease/symptom-specific QOL, health-specific QOL and global-specific QOL (Hanestad & Wahl, 2011). Different domains within the same level may be associated with each other, and the different levels may also be connected. The relationships may be hierarchical, whereby disease-specific QOL influences health-specific QOL, which in turn influences global-specific QOL. Fluctuating patterns in each QOL domain may also occur over time (Spilker, 1996).

Figure 3. Levels of QOL (adapted from Spilker (1996))
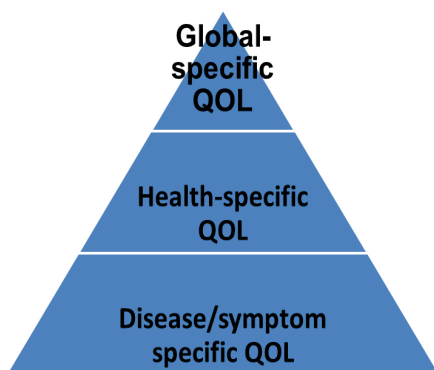
There are few studies that focus on the distinction between the different perspectives of QOL concepts. One review found that articles do not separate overall QOL from health-related QOL (Gill & Feinstein, 1994).

The QOL concepts investigated in this thesis are disease/symptom-specific QOL relating to breathlessness and the impact of breathlessness on life, health-specific QOL relating to generic depression and anxiety, and global-specific QOL relating to well-being (Spilker, 1996; Hanestad & Wahl, 2011).

Disease/symptom-specific QOL

Disease/symptom-specific QOL focuses on the individual's experience and functional status of a disease (Spilker, 1996; Handestad & Wahl, 2011). Disease-specific QOL refers to the experience of impairment in a person's "*ability to perform physical, mental and social activities in daily life*" (Spilker, 1996, page 364). In COPD, disease-specific QOL is often investigated in relation to how breathlessness affects activities, housework, social life and mental health (Bausewein, Farquhar, Booth, Gysels, & Higginson, 2007; Jones, Miravitlles, van der Molen, & Kulich, 2012).

The symptom of breathlessness or dyspnoea are described in different words by patients. Descriptions such as "my breath is heavy", "my chest feels tight", "I feel air hunger", "I feel that I am breathing more easily", "I can't get enough air", "work/effort" and "tightness" are given by patients with cardio-respiratory disease to explain breathlessness (Mahler et al., 1996; O'Donnell et al., 2007). The concepts of breathlessness and dyspnoea are often used interchangeably in the literature (Harver, Mahler, Schwartzstein, & Baird, 2000), but the two

concepts have also been shown to have distinct meanings. Dyspnoea has been defined as "*difficult or laboured breathing observable to another person*" and breathlessness as a "*subjective feeling of laboured breathing with or without dyspnoea and/or abnormal pulmonary function*" (West & Popkess-Vawter, 1994, page 622). In this way, dyspnoea is defined as an objective sign and breathlessness as a subjective experience reported by the patient. The subjective experience was investigated in this thesis, and the term breathlessness has therefore been mostely used. However, in some situations when referring to others who have used the concept dyspnoea, this term is utilized.

Health-specific QOL

Health-specific QOL includes the experience of "*physical, psychological, social, spiritual and role functioning as well as general well-being*" (Spilker, 1996, page 25). In this thesis, health-specific QOL emphasizes generic depression and anxiety (Fayers & Machin, 2007).

The Merriam-Webster Dictionary defines anxiety as "*an abnormal and overwhelming sense of apprehension and fear ...*" (Merriam-Webster Dictionary, 2015a) and it may involve nervousness, tension, worry, apprehension and/or fearfulness (panic) (Bech, 2012). The main component of anxiety symptoms is considered to be autonomic arousal (Norton, Cosco, Doyle, Done, & Sacker, 2013), which is part of the general state of physiological arousal (Bruns D. & Disorbio J.M., 2003). Depression is defined as "*a state of feeling sad*" and may involve sadness, inactivity, difficulty concentrating, decreased or increased appetite, sleeping problems, feeling hopelessness and having suicidal thoughts (Merriam-Webster Dictionary, 2015b). An example is a negative view of the future, past or present (Bech, 2012). The main component of depressive symptoms is anhedonia, which is characterized by a loss of interest and pleasure in life (Norton et al., 2013).

The overlap between depression and anxiety can appear as distress symptoms (Norton et al., 2013). Studies have reported significant correlations between anxiety and depression in people with COPD (Putman-Casdorph & McCrone, 2009; Borge et. al., 2010). Anxiety and depression are also often listed as comorbidities of COPD and may reflect the personality of the patient (Hynninen, Breitve, Wiborg, Pallesen, & Nordhus, 2005). However, this thesis focuses not on the disorders of anxiety and depression but on COPD as a disease and on generic health-specific QOL, which includes measures of the symptoms of anxiety and depression.

Global-specific QOL

Global-specific QOL emphasizes perspectives such as "well-being". Well-being is a challenge to define, and several researchers have used it interchangeably with QOL (Dodge, Daly, Huyton, & Sanders, 2012). As defined above under health-focused QOL, well-being can involve more general aspects of health (Lu et al., 2012). The concept of "psychological well-being" (i.e., meaningful life) and "subjective well-being" (i.e., satisfaction in life) has often been distinguished in the litteratur (Bech, Gudex &Johansen, 1996; Sisask, Värnik, Kõlves, Konstabel, & Wasserman, 2008; Chen, Jing, Hayes, & Lee, 2013), but these two concepts may also overlap each other (Chen et. al., 2013). Other similar concepts such as "zest for life" have also been explained in relation to satisfaction of life and well-being (Fagerström, 2010; Glasberg, Pellfolk & Fagerström, 2014). The World Health Organization supports the diverse use of the term (World Health Organization, 2013b; World Health Organization, 2013a) and a proposed definition has been given by an expert group as "*Well-being exist in two dimensions, subjective and objective. It comprises an individual experience of their life as well as a comparison of life circumstances with social norms and values*" (World Health Organization, 2013b, page 1). Subjective well-being is explained as how satisfied one is in life as a whole, whereas objective well-being is a set of indicators such as education, living standard, personal finance, etc. (World Health Organization, 2013a). The concept of subjective well-being is therefore similar to the definition of well-being of Diener et al. (Snyder & Lopez, 2009) as "*a person's cognitive and affective evaluations of his or her life as a whole*" (page 187). The evaluation may be positive (i.e., satisfaction) or negative (i.e., sadness) (Diener & Ryan, 2009). In this thesis, well-being is understood to be a positive evaluation (de Wit et. al., 2007; Jester &Palmer, 2015).

3.4 Previous research

This chapter explores previous research on the effects of breathing-control and respiratory muscle training techniques on QOL outcomes and breathing pattern.

3.4.1   Effects of breathing-control exercises and respiratory muscle training

Several reviews have been written on breathing-control exercises and respiratory muscle training (Breslin, 1995; Cahalin, Braga, Matsuo, & Hernandez, 2002; Raub, 2002; Gosselink, 2003; Dechman & Wilson, 2004; Gosselink, 2004). Considering the amount of reviews found, it has been difficult to gain an overview of the effect found on breathing-control exercises and respiratory muscle training in people with chronic obstructive pulmonary disease (COPD). Thus, this thesis included an overview of the systematic reviews written on breathing-control exercises and respiratory muscle training from 2002 until 2013. Some of the studies described in this section are also presented in that overview article (paper 1). However, this section also provides a broader perspective of the outcomes, such as breathing pattern and lung function, in addition to QOL outcomes. This section also reviews some breathing-control exercises that was not found covered in the overview (i.e., device-guided breathing, exercises, music listening and distraction exercises) based on an additional search of databases of published journals. Appendix 1 presents this search strategy and the results of the review of the RCTs found on breathing-control exercises and respiratory muscle training.

Breathing control exercises

Several of the reviews on breathing-control exercises in people with COPD evaluate diaphragmatic breathing (Cahalin et al., 2002; Gosselink, 2003; Gosselink, 2004; Breslin, 1995; Dechman & Wilson, 2004a), pursed-lip breathing (Breslin, 1995; Dechman & Wilson, 2004; Gosselink, 2003; Gosselink, 2004), yoga (Raub, 2002) and relaxation (Gosselink, 2003; Gosselink, 2004). The reviews give examples of improved breathlessness, QOL, breathing pattern and lung function, but the results differ according to the techniques used. Most of the results are based on pre–post designs, and there are few RCTs, which are considered the "gold standard" when trying to establish a causal relationship (Moher et al., 2010).

The evidence from the systematic review covered in the overview of this thesis showed that pursed-lip breathing has an effect on breathlessness and that both diaphragmatic breathing and

yoga breathing have effects on disease-specific QOL. Reduced respiratory rate was found in a study of pursed-lip breathing. Ventilation feedback training was defined as a breathing-control exercise in this systematic review that showed a reduced respiratory rate and increased expiratory time but no effect on breathlessness in a ventilation feedback group (Holland et al., 2012). However, the results from the two systematic reviews included in the overview of this thesis were based on few RCTs (i.e. up to 16 whereof only a few studies evaluated breathlessness and QOL) (Holland et. la., 2012). Further, the RCTs that were included reported low- to moderate-quality evidence, meaning that more research is required before a conclusion can be drawn (Roberts, Stern, Schreuder, & Watson, 2009; Holland et al., 2012).

The additional search (Appendix 1) found an RCT of pursed-lip breathing that used instruction via Skype. The findings of this RCT suggested that in a person experiencing breathlessness, the exercise seems to have a greater effect on QOL (Mark, Ikehara, Matsuura, Hara, & Li, 2013). An RCT on deep breathing for seven days at home found an effect on pulmonary function (Mathew & D'Silva, 2011). Three RCTs were conducted on relaxation (Gift , Moore, & Soeken, 1992, Louie, 2004; Singh, Rao, Prem, Sahoo, & Keshav Pai, 2009) in combination with music or instruction. Two of these studies reported a reduction in anxiety and breathlessness (Gift et al., 1992; Singh et al., 2009), while one reported a postivie effect on respiratory rate (Singh et al., 2009).

RCTs have also combined different kinds of breathing-control exercises in their experimental interventions. For instance, Valenza et al. (2013) combined pursed-lip breathing, relaxation and diaphragmatic breathing, and found a positive effect on breathlessness, anxiety and mobility in favour of the training group. Another RCT combined pursed-lip breathing, diaphragmatic breathing and unsupported upper extremity exercises, and found a positive effect on lung function and disease-specific QOL in favour of the training group (Lin et al., 2012). Further in another study, combination of pursed-lip breathing, diaphragmatic breathing and coughing had a positive effect on fatigue in favour of the training group (Zakerimoghadam, Tavasoli, Nejad, & Khoshkesht, 2011).

Two RCTs were found on intervnetions that could be interpreded as device guided breathing control (Louie, 2004; van Gestel et al., 2012). In one of the studies, relaxation was guided by a device reporting on skin temperature and thoracic movement. A positive effect was found on oxygen saturation in favour of the training group (Louie, 2004). In the other RCT, slow breathing was guided by a device that displayed the patient's breathing pattern, with no other

guidance provided. No effect was found on breathlessness, QOL or physical variables (van Gestel et al., 2012).

The search found no information about RCTs that used device-guided breathing control combined with verbal instructions to follow music tones on expiration and inspiration in people with COPD (Gavish, 2010). However, a separate search in ClinicalTrials.gov found one trial of this kind on device-guided breathing control using a pre–post design, but no results have been published (Benzo, 2013). A review of previous research that was not part of the search strategy (Appendix 1) shows that device-guided breathing control has been studied in people with heart failure (Ekman et al., 2011) and hypertension (Mahtani et al., 2012), and that effects or changes have been found on blood pressure (Mahtani et al., 2012), breathlessness (Ekman et al., 2011) , QOL (Parati et. al., 2008) and breathing pattern (Harada et.al., 2014) in favour of the study group.

Respiratory muscle training

Several systematic reviews have been written on the effect of respiratory muscle training. These systematic reviews included also several RCTs (i.e., up to 32, whereof more studies than breathing control studies evaluated breathlessness, other symptoms and QOL). A beneficial effect was found in relation to breathlessness (Geddes, O'Brien, Reid, Brooks, & Crowe, 2008; O'Brien, Geddes, Reid, Brooks, & Crowe, 2008; Shoemaker, Donker, & Lapoe, 2009; Gosselink et al., 2011; Thomas, Simpson, Riley, & Grant, 2010), fatigue (Gosselink et al., 2011) and disease-specific QOL (Geddes et al., 2008; Shoemaker et al., 2009; Gosselink et al., 2011). In addition, positive effects were found for the lung function variables maximum pressure of inspiration (Geddes et al., 2008; O'Brien et al., 2008; Shoemaker et al., 2009; Gosselink et al., 2011) and inspiratory muscle endurance time (Geddes et al., 2008; Shoemaker et al., 2009; Gosselink et al., 2011). The additional search (Appendix 1) captured two RCTs of respiratory muscle training (Battaglia, Fulgenzi, & Ferrero, 2009; Petrovic, Reiter, Zipko, Pohl, & Wanke, 2012) that were not captured in the systematic reviews noted above. A positive effect of inspiratory muscle training on breathlessness was found. One of these RCTs also provided data indicating an improved breathing pattern (Petrovic et al., 2012). Except for this RCT, few studies of respiratory muscle training have reported the breathing pattern as an outcome.

Summary

The literature search makes it clear that self-management skills that include breathing-control exercises and respiratory muscle training can be performed using several techniques, which may be performed either alone or in combination, and that these have positive effects on breathlessness, disease-specific QOL and generic health-specific QOL. However, especially in terms of breathing-control exercises, additional research is needed to draw conclusions about the effects of these exercises in people with COPD. Device-guided deep-breathing exercises such as those used in people with heart failure or hypertension (Ekman et al., 2011; Mahtani et al., 2012) may make it possible to perform a blinded RCT in people with COPD whose participation has been limited in other breathing-control studies (Holland et al., 2012). This method may also help provide continuous guidance for deep-breathing exercises in the home situation for people with COPD. It may also be possible to measure and store information about the breathing pattern during sessions, which may provide data about how people with COPD breathe under guidance and their compliance with performing the exercises.

3.4.2   Change in QOL outcomes over time in people with COPD

Previous research illustrates several studies investigating QOL outcomes in people with COPD. For instance, disease-specific QOL, generic depression, anxiety and well-being have been found associated in people with COPD (Blinderman et al., 2009). Althoguh, few studies have included well-being in COPD (Lee et. al, 2002; Stridsman et.al. 2014), a study of elderly people have shown that impaired life satisfaction is strongly associated with depression (Glasberg et.la., 2014). Lopez-Campos, Calero & Quintana-Galllego (2013) investigated how experience of symptoms varies over time in people with COPD. They found that breathlessness, cough, sputum, tightness, fatigue and sleep quality are not stable, but vary from morning to evening and over years, and that symptoms worsen during the winter (Lopez-Campos et al., 2013). Another study (Espinosa de los Monteros et al., 2012) also found that respiratory symptoms vary over the course of a day and weeks. Walke et al. (2007) investigated a range of symptoms (breathlessness, physical discomfort, fatigue appetite, anxiety, pain and depression) among community-dwelling older persons with COPD or heart failure over a period of 24 months. They found a significant increase in symptom burden over time. A study by Wilke et al. (2014) reported that 41.2% of COPD patients reported improved

disease-specific QOL, 43.5% reported deterioration and 15.3% reported stable disease-specific QOL over a period of 12 months. No study was found on how well-being varies over time in people with COPD. However, reports have shown that life satisfaction changes during adulthood (Mroczek & Spiro 2005).

Several studies of predictors of COPD have focused on whether and how exacerbations (Ferrari, Tanni, Caram, Naves, & Godoy, 2011) and low lung function predict QOL (Hesselink et al., 2006). QOL has been found to predict readmission to hospital (Osman, Godden, Friend, Legge, & Douglas, 1997) and increased breathlessness (Hesselink et al., 2006). Researchers have also investigated whether and how depression and anxiety predict other aspects of QOL. For instance, during a five-year period, depression and anxiety were found to be predictors of disease-specific QOL (Oga, Tsukino, Hajiro, Ikeda, & Nishimura, 2012).A review reported that anxiety and depression predict both disease-specific and generic health-specific QOL (Blakemore et al., 2014). Another study by Andenæs, Moum, Kalfoss & Wahl (2006) found that disease-specific QOL was a predictor of psychological distress and impaired health status after hospitalization because of an exacerbation.

The aim of a recent study by de-Torres et al. (2014) was to examine the change in disease-specific QOL in relation to the change in depression and anxiety in people with COPD. They found that the change in disease-specific QOL was significantly associated with changes in breathlessness, anxiety and depression after one year. The multivariate analysis identified breathlessness as the variable with the strongest association. Oga et al. (2007) also found a significant association between changes in disease-specific QOL and changes in breathlessness, depression and anxiety in a five-year follow-up study in patients with COPD. However, the authors considered these associations to be weak. Similar findings and changes in well-being have been reported during a two-year period for people with other diseases such as inflammatory bowel syndrome (Lix et al., 2008).
No study explored whether COPD-specific symptoms, disease-specific QOL, depression and anxiety change with well-being over time in people with COPD.

Summary

Much of the previous literature on the relationships between QOL outcomes has involved cross-sectional designs (Tsiligianni et al., 2011), although some studies have reported variations in QOL outcomes from day to day and over a longer time period (Mroczek & Spiro, 2005; Walke et al., 2007; Espinosa de los Monteros et al., 2012; Wilke et al., 2014). Although there are longitudinal studies of the changes in disease-specific QOL in relation to generic health-specific QOL, such as changes in depression and anxiety in people with COPD (Oga et al., 2007; de-Torres et al., 2014), no study has included measures of well-being as a dimension of global-specific QOL. In general, few studies have investigated well-being as an outcome, even though well-being is considered to be an important outcome to investigate in people with COPD (Lee, et. al. 2002; Stridsman et al., 2014) and elderly people (Glasberg et al., 2014). According to the theory of QOL; the well-being concept may be seen as a component of general health-specific QOL measured as part of mental or psychological health, or it may be seen as a global-specific QOL (Spilker, 1996). However, in research, well-being is often used without adequate understanding of the concept (Dodge R. et al., 2012).

Therefore, exploring the patterns of fluctuations in disease-specific QOL, depression, anxiety and well-being may help us to understand the complexity of the components of QOL outcomes that often are used in self-management interventions.

4   Methods

One overview of systematic reviews was performed to examine the effects of breathing-control exercises and respiratory muscle training on breathlessness, other symptoms and quality of life (QOL) in people with chronic obstructive pulmonary disease (COPD) (paper 1). A three-armed double-blind randomized controlled trial (RCT) was then performed to examine the immediate post-intervention effect of a four-week intervention involving device-guided breathing control and the longer-term effects after four months. The variables included in the RCT analysis were breathlessness, disease-specific QOL and breathing pattern, and the subjects were people with moderate or severe COPD (paper 2). The longitudinal data from the RCT were analysed to explore whether and how changes in disease-specific QOL fluctuate with changes in depression and anxiety and whether and how these changes fluctuated with well-being over a period of four months in people with moderate or severe COPD (paper 3).

4.1   The overview article (paper 1)

4.1.1 Design (paper 1)

In paper 1, the effects of breathing-control exercises and respiratory muscle training on breathlessness, other symptoms and QOL in people with COPD were assessed by overviewing the existing systematic reviews. The intent was to "*compile evidence from multiple systematic reviews of interventions into one accessible and usable document*" (Higgins, Green & Cochrane, 2008, page 607).

4.1.2 Literature search, inclusion criteria and exclusion criteria (paper 1)

The principle of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins et.al., 2008) was used as the guide for the sampling procedure. In the sample collection for the overview article, one reviewer performed the main search, which was controlled by a librarian at the medical faculty library of the University of Oslo. Two independent reviewers then assessed the lists of titles, abstracts, full text articles and evaluations of the quality of the systematic reviews. Initially, the lists of titles were evaluated before feasible abstracts for inclusion were read for further detailed information to determine whether the article would be included or excluded. The full texts of the eligible articles were then read and included in the overview if the selection criteria were met.

When reviewing the literature on breathing-control exercises and respiratory muscle training (Dean & Frownfelter, 2006; Gosselink, 2004; Gosselink, 2003), we searched for the main breathing-control exercises; diaphragm breathing, pursed-lip breathing, relaxation techniques, body positions to achieve deeper breathing, yoga breathing and respiratory muscle training. The search was performed between January 2002 and December 2013 using the following databases: PubMed, OVID, CINAHL, PsycINFO, AMED, Cochrane and PEDro. The following search terms and combinations were used: 1) "Lung disease", 2) "Lung disease, obstructive", 3) "Pulmonary disease, chronic obstructive", 4) "Pulmonary emphysema", 5) "Bronchitis, chronic", 6) "Pharmacology", 7) "Oxygen therapy", 8) "Respiration", 9) "Breathing exercises", 10) "Yoga", 11) "Pranayama", 12) "Mind–body therapies", 13) "Muscle-stretching exercises", 14) "Relaxation", 15) "Breathing-control exercises", 16) "Diaphragmatic breathing" and 17) "Pursed-lip breathing". Additional categories were: 18) combinations of search terms 1–5 using "OR", 19) combinations of search terms 6 and 7 using "NOT" (searched in PubMed only) and 30) combinations of search terms 20–29 using "OR" (paper 1, Appendix 1). Table 2 shows the inclusion and exclusion criteria.

Table 2. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
- Systematic reviews defined by authors of respiratory muscle training, deep breathing, diaphragmatic breathing, pursed-lip breathing, relaxation techniques and body position exercises in humans that focused on breathlessness or dyspnoea, other symptoms and quality of life in adults (<18 years) - All stages of COPD - Systematic reviews including a search of at least one data base - Systematic reviews in all languages - The last written in an update - Met at least one of the AMSTAR criteria	- Guidelines and lists of general management advice - Diseases other than COPD - Narrative reports, reviews titled as literature reviews or integrative reviews - Evaluation of ventilator support (such as non-invasive ventilation) - Evaluation of pulmonary rehabilitation/self-management courses in which breathing-control exercise was one of several treatments - Evaluation of general muscle training and cardiovascular exercise programmes, medication interventions and mini-PEP or active sputum mobilization - Explanation of how the respiratory system works - Not evaluating the outcomes breathlessness, other symptoms and quality of life - Systematic review that did not meet any of the AMSTAR criteria

AMSTAR: A Measurement Tool to Assess Systematic Reviews, PEP: Positive Expiratory Pressure

4.1.3 Evaluating the quality of systematic reviews (paper 1)

A Measurement Tool to Assess Systematic Reviews (AMSTAR) was used to evaluate the methodological quality of the different systematic reviews (Shea et al., 2007b; Shea et al., 2009). This measurement tool is based on two other measurement tools (Sacks, Berrier, Reitman, Ancona-Berk, & Chalmers, 1987; Shea B, Dube C, & Moher D, 2001). The tool comprises 11 components as a checklist, which is used to assess the methodological quality of systematic reviews. These 11 components evaluate the design (criterion 1), selection and extraction of studies (criterion 2), literature search (criterion 3), types of publications (criterion 4), whether a list of studies was provided (criterion 5), whether characteristics of the individual studies were listed (criterion 6), whether the scientific quality of the included studies was evaluated (criterion 7), whether the scientific quality was considered in the article (criterion 8), whether pooled statistics were evaluated (criterion 9), whether publication bias analyses were performed (criterion 10) and whether conflicts of interest were noted in the article (criterion 11) (AMSTAR, 2015). Appendix 2 shows the components of AMSTAR.

The criteria were rated as either "yes", "no", "can't answer" or "not applicable". Each item was scored as 1 for "yes" and 0 for "no", "can't answer" or "not applicable". The highest possible score is 11 (Shea et al., 2007b; Shea et al., 2009). Several authors have evaluated the quality of systematic reviews by classifying them according to the AMSTAR score using a scale whereby 0–4 indicates low quality, 5–8 indicates moderate quality and 9–11 indicates high quality (Mikton & Butchart, 2009; Jaspers, Smeulers, Vermeulen, & Peute, 2011; Seo & Kim, 2012; Macedo, Riera, & Torloni, 2013). The tool has been shown to be a reliable and valid measurement instrument for assessing the methodological quality of systematic reviews (Shea et al., 2009). This instrument was chosen because of its simplicity and because it is a recommended instrument for evaluating the quality of systematic reviews (Shea et al., 2009)**.**

4.1.4 Analysis of the overview article (paper 1)

The quality was evaluated according to the AMSTAR criteria (Shea et al., 2007b). The AMSTAR items were scored for each of the included systematic reviews and then grouped into low quality, moderate quality and high quality (Mikton & Butchart, 2009; Jaspers et al., 2011; Seo & Kim, 2012; Macedo et al., 2013). This classification is shown in Table 1 in paper 1. The synthesis of the effects on breathlessness, other symptoms and QOL was captured by thoroughly reading the tables and text of each systematic review. The pooled statistics included in each systematic review are listed in Table 3 in paper 1.

4.2 The RCT (papers 2 and 3)

4.2.1 Design (papers 2 and 3)

In paper 2, a double-blind RCT with three arms was performed to evaluate the effects of device-guided breathing control on breathlessness, disease-specific QOL and breathing pattern in people with moderate or severe COPD after four weeks and four months follow up (paper 2). Figure 4 shows the study design.

In the study, a guided deep-breathing group was compared with a music-listening group and a sham sitting-still group.The main outcome was breathlessness, and the secondary outcomes were disease-specific QOL and breathing pattern. The participants were measured at baseline (T1), at four weeks (T2) and four months (T3) (Figure 4).

In paper 3, the longitudinal (Figure 4) data (i.e., total) from the three groups included in the RCT (paper 2) were analysed to evaluate to what extent changes in disease-specific QOL fluctuated with changes in depression, anxiety and well-being over a period of four months in non-hospitalized patients with moderate or severe COPD (paper 3).

Figure 4. Study design
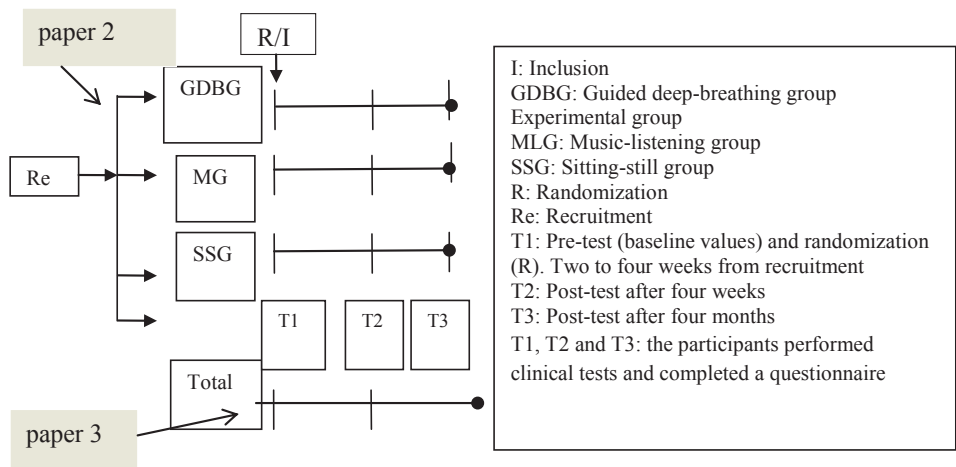
4.2.2 Approvals (papers 2 and 3)

The studies included in this thesis had received approval from the Medical Ethics Committee (reference number: 2010/1521), the Data Inspectorate of Lovisenberg Diaconal Hospital (reference number: 11-2010 LDS), Ullevål University Hospital (reference number: 2010/22192) and Diakonhjemmet Hospital (reference number: 14-2010 LD) that all recruited the participants as well as reported to ClinicalTrials.gov (identifier NCT015120043). A request for a change was approved by the Medical Ethics Committee after two pilots (March 2011) and extension of the project period to December 2018 (June 2014).

4.2.3 Sample size calculation (paper 2)

The sample size was calculated on the background of the main outcome variable of the symptom score on the SGRQ. Using an SD=16 (Griffiths et al., 2000), expected difference >8 (Jones, 2002), confidence level of 5% and power of 80%, the estimated sample size was 150, with 50 in each group. Because of anticipated drop-out, an oversampling of 20 per group was added, giving a total of 70 for each group. The calculator in the Decision Support System (DSS) (2015) research web page was used to calculate the sample size. We planned to sample over a period of 18 months. However, because of difficulties recruiting patients, the sample period was extended to 26 months, and recruitment ceased after 150 participants had been recruited.

4.2.4 Blinding (paper 2)

The blinding of the participants was performed by not informing patients about which group they were allocated to. The patients were informed orally and in the invitation letter that the study would be examining whether breathing control, relaxation or being calm could change their experience of breathlessness. The researcher was blinded by receiving no information about the group randomization during the entire project period. To secure blinding of the researcher, a study nurse undertook most of the contact with the participants during the study procedure (4.2.9 Procedure). Another uninvolved person was hired for the project to enter the data into a statistical program.

4.2.5 Randomization (paper 2)

The groups were randomized in advance using sealed envelopes containing the numbers 1–210, which had been prepared by a person who was not involved in the project. This person prepared coded names for each group (n=70 in each group). Because of seasonal variation in COPD (Rabe et al., 2013), the randomization was performed in 14 blocks of 14–16 patients per block. The unequal number in each block was chosen to reduce the possibility of patients being able to guess which group they had been randomized to (Laake, Lydersen, & Veierd, 2012). Each block contained 4–6 coded names for each group. Because of the unequal numbers in each block, unequal numbers of patients were recruited to the group from each block at the end of the study when 150 particpants had been recruited (4.2.8 Recruitment).

4.2.6 Intervention (paper 2)

The planning of the RCT was a complex and time-consuming process. The same device (RespeRate, InterCure Inc., New York, USA) (RespeRate, 2009; Gavish, 2010) as used in previous studies on breathing control in people with other diseases (Ekman et al., 2011; Mahtani et al., 2012) was used during the intervention. However, the guiding information had to be translated into Norwegian, the device software had to be changed in each group (guided deep-breathing group, music-listening group, sitting-still group), two feasibility studies had to be performed and several QOL outcome instruments had to be tested.

The voice in the device and the written manual for the study device were originally in English (RespeRate, 2009), therefore we spent time translating the voice and recording in Norwegian (the recording was performed by the company that sold us the device). The translation and the voice were then checked to ensure that the translation was correct and made sense. The translation was performed using the forward and backward translation procedure (Fayers & Machin, 2007). Different software programs were also applied to the device to deliver the right intervention to each group in the study.

In the intervention, all participants used this device with earphones and a sensor belt around the waist to measure the breathing pattern (Figure 5). All participants also received messages through the earphones to move the sensor to the chest or upper abdominal sensor position if the device did not capture the breathing pattern from the waist position (Figure 5). However, they received different information depending on the group they were randomized to.

Figure 5. The device used in the study

- *The guided deep-breathing group (experimental group)* used the device in a way that guided the participant to breathe slowly according to the breathing pattern measured by the sensor belt around the waist. This guidance was given through earphones by a voice in Norwegian, which was accompanied by a two-tone melody. The participant was then asked to perform inspiration on the high note for as long as it lasted and expiration on the low note for as long as that lasted. Meanwhile, non-rhythmic music was being played in the background. The instruction stopped when the session ended.

- *The music-listening group (control group)* used the same device, but without the guidance about deep breathing. The sensor belt was worn around the waist to measure the breathing pattern, and earphones were worn. This group received no instruction to breathe slowly, but listened to the same background music as the guided deep-breathing group. The music stopped when the session ended.

- *The sham sitting-still group (control group)* used the same device, but without either guidance about deep breathing or background music. They wore the sensor belt around the waist to measure the breathing pattern, and earphones. However, apart from the instruction to sit down and the music being played the first minute of each session, they did not receive any listening to music for the rest of the session. A voice delivered a message when the session ended.

Pilot studies

Two feasibility studies were performed before the start of the main double-blind RCT. The aim of feasibility study 1 was to test the translated device and any discomfort with the use of the device. Eleven patients with moderate or severe COPD tested the guided deep-breathing instructions for 20 minutes at the hospital and for 20 minutes per session twice a day for one week at home. Patients with very severe of COPD were difficult to recruit, and the session time was experienced as being too tiresome for these patients. Conversely, patients with mild COPD were considered to be too well to participate in this study. Hence, patients with mild or very severe COPD were excluded, and the duration of each session was changed to 15 minutes for the main project. There was no discomfort with the use of the device.

The aim of feasibility study 2 was to test the logistics of the study design for a four-week intervention for 15 patients—five patients from each of the three groups. After this study, the software in the device was changed to ensure blinding of the participants and the researcher. The breathing pattern measured by the device was also compared with that recorded using a capnograph in this study, and similar values were found.

Several standardized questionnaires that are used to investigate breathlessness and disease-specific QOL were tested in the feasibility studies to identify the most suitable instrument. Section 4.3 and Table 3 give the details of the outcomes of the use of these instruments to assess breathlessness and the other health outcomes assessed in this thesis (4.3 Instruments, Table 3).

4.2.7 Exclusion and inclusion criteria (papers 2 and 3)

Based on the feasibility studies, the exclusion and inclusion criteria used in the studies reported in papers 2 and 3 were as follows. To be included in the study, participants had to (1) have been classified as having a moderate or severe stage of COPD according to the GOLD classification (3.1.4 Diagnosis) (GOLD, 2015), (2) have a Modified Medical Research Council (mMRC) dyspnoea scale score of ≥1 (4.3.1 Standardized questionnaires), (3) be in a stable phase and (4) be able to read and write Norwegian.
Participants were excluded if they (1) had changed their pulmonary medication in the past four weeks, (2) had experienced previous lung cancer or an ongoing cancer, (3) had dementia or neuromuscular disease, (4) had participated in a pulmonary rehabilitation or a similar course during the past six months, (5) had an ongoing exacerbation, (6) were using oxygen treatment or (7) abused alcohol or narcotics at that time.

4.2.8 Recruitment (papers 2 and 3)

The participants were recruited from July 2011 to September 2013. Responsible nurses and respiratory physicians at each hospital asked eligible patients to participate. If approved to participate, the participants were contacted by the main researcher by telephone (papers 2 and 3). Figure 6 shows the flow diagram for papers 2 and 3 (Figure 6). A total of 341 patients with COPD were assessed for eligibility from three hospitals in Oslo: Lovisenberg Diaconal Hospital (main project hospital); Ullevål University Hospital; and Diakonhjemmet Hospital. Hospital A assessed 243 patients, hospital B assessed 32 patients, and hospital C assessed 66 patients. An amount of 150 patients were included. In paper 2, the participants were randomized into the guided deep-breathing group (n=51), the music-listening group (n=50) or a sham sitting-still group (n=49) (Figure 6). In paper 3, the pooled data from the three groups were used. One hundred and fifty patients participated at the baseline, 143 after four weeks and 130 after four months. See figure 6 for further information (Figure 6).

Figure 6. Flow diagram
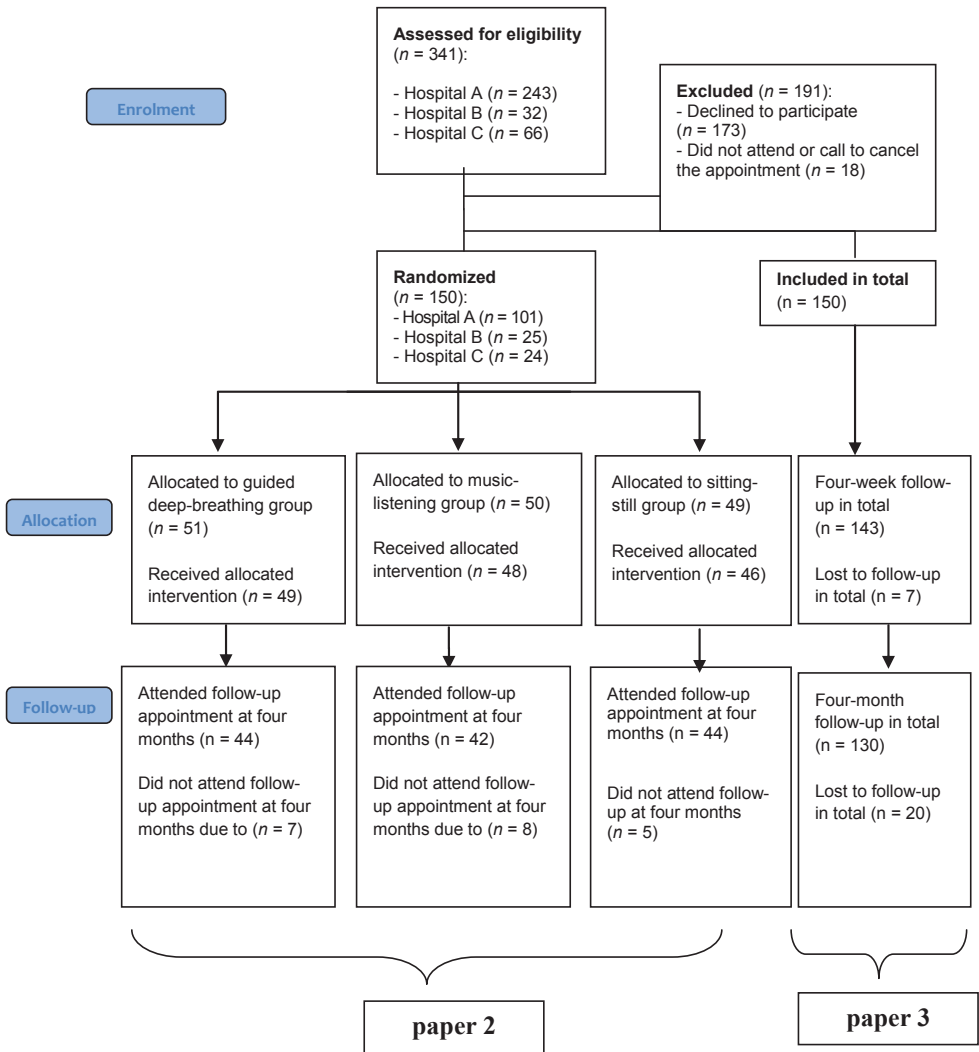
4.2.9 Procedure (papers 2 and 3)

In papers 2 and 3, the eligible participants who agreed to participate in the study were given an appointment at the main hospital for recruitment. A questionnaire booklet was sent to the participants one week before all appointments (T1, T2 and T3), and they were asked to complete it 1–2 days before they came to the hospital. The lung function test and the blood gas analyses were conducted by the researcher at T1, T2 and T3 (only the baseline variables were used in this thesis). The questionnaire booklet was checked for incomplete answers by the researcher before randomization at T1, and at T2 and T3 it was checked by a study nurse

(papers 2 and 3). If questions were not answered, the participants were asked to complete them without help from the study nurse. However, a small proportion of the participants asked the study nurse to read the questions to them and then complete the questionnaire based on their verbal answers.

After the questionnaire booklet was checked for incomplete answers and the participants performed the physical tests at baseline, they were taught by the study nurse how to use the device in the manner that was relevant for the group they had been randomized into (Figure 4). All participants used the device for 15 minutes for the first time at the hospital. They were instructed by the study nurse how to use the device for 15 minutes twice a day for four weeks. All participants in the study received the same attention. The study nurse telephoned the participants after two days and once a week during the four weeks to collect breathing statistics from the display and to ask the participants how they felt about using the device. The study nurse instructed the participants how to read out the breathing statistics from the display and gave them advice if they had difficulty using the device. The devices were returned at the four-week follow-up and the stored breathing patterns were downloaded from the device by the study nurse (paper 2). Four months after T1, they returned to a follow-up visit at the hospital, but without having used the device and measured the breathing pattern (T3) (papers 2 and 3).

4.3 Instruments (papers 2 and 3)

Table 3 presents an overview of the instruments used in papers 2 and 3. Standardized questionnaires were used to capture information about breathlessness, disease-specific QOL, depression, anxiety and well-being in the questionnaire booklet. Information about socio-demographic characteristics (gender, age, marital status, education, employment, smoking status, living status, diseases and medications) was collected from the study questionnaire booklet. The physical tests; lung function and blood gas values were captured at the visits at the hosptial and the data of the breathing pattern were captured from the device used in the intervention.

4.3.1 Standardized questionnaires

St. George's Respiratory Questionnaire (SGRQ) (papers 2 and 3)

The SGRQ (Jones, Quirk, Baveystock, & Littlejohns, 1992) four-week version was used to record COPD-related symptoms (paper 2) and disease-specific QOL (papers 2 and 3). The questionnaire was developed to investigate the response to changes in disease activity and how diseases with chronic airflow limitation affect health (Jones et al., 1992). It is often used in research to quantify aspects of breathlessness, cough, sputum and wheeze (i.e., symptom score). It is also used to assess the impact of breathlessness on social and psychological functioning (i.e., impact score) and activities of daily living and physical activity (i.e., activity score). All of the 50 items measure disease-specific QOL, as reflected in the total score (American Thoracic Society (ATS), 2014). The range for each score is 0–100, with a higher score indicating greater disability (Jones et al., 1992; ATS, 2014). The SGRQ was chosen because it is a frequently used instrument that has been shown to have satisfactory reliability, validity and responsiveness to changes in patients with COPD (Jones et al., 1992; Engstrom, Ferrer et al., 1996; Rutten-van, Roos, & Van Noord, 1999; Jones, 2002; Puhan et al., 2007; Bentsen, Langeland & Holm, 2012). It has been translated into Norwegian (ATS, 2014). A threshold change of 4 units is recommended as an indicator of a change (Jones, 2002). A permission/license was obtained for the use of the questionnaire in this study (ATS, 2014). In this study, the Cronbach's alpha values were 0.79 for the symptom score, 0.82 for the activity score, 0.89 for the impact score and 0.90 for the total score. The questionnaire was completed at T1, T2 and T3 (Table 3).

Global Rating Change (GRC) scale (paper 2)

The GRC scale was used to measure perceived changes in breathlessness (paper 2). This is a commonly used scale designed to quantify improvement and/or deterioration over time (Kamper, Maher, & Mackay, 2009). The participants were asked whether they had experienced a positive change in breathlessness after having used the device. All patients in all groups were asked the same question. The responses were rated on a scale from 0 to 10, where 0=no improvement and 10=great improvement. A numeric rating scale has been shown to be easier to answer than a visual analogue scale, and is therefore recommended (Bausewein et al., 2007). We chose this scale because of its simplicity and ease of scoring, and because it has been shown to be reliable, valid and sensitive to change. It has been used in previous

RCTs. The minimal important difference has been measured at 1.3–2.0 in diseases other than COPD (Kamper et al., 2009). We have found no study that reported the minimal important difference in COPD. This question was included in the questionnaire booklet at T2 and T3 (Table 3).

The mMRC dyspnoea scale (inclusion criteria in papers 2 and 3)

The Modified Medical Research Council dyspnoea scale was used as an inclusion criterion to identify participants having breathlessness in papers 2 and 3 (i.e., mMRC≥1) (4.2.7 Exclusion and inclusion). The scale was developed by Fletcher (1960) and has been used in several studies (Bestall et. al., 1999; Mahler & Wells, 1988; Wedzicha et al., 1998; Stenton, 2008; GOLD, 2015). The scale has five items and is scored as follows: 0="I only get breathless with strenuous exercise", 1="I get short of breath when hurrying on the level or walking up a slight hill", 2="I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level", 3="I stop for breath after walking about 100 yards or after a few minutes on the level" and 4="I am too breathless to leave the house" or "I am breathless when dressing" (GOLD, 2015). It has previously been used to evaluate breathlessness (Mahler & Wells, 1988; Bestall et. al., 1999) and determine inclusion of COPD participants in interventions (Mahler & Wells, 1988; Wedzicha et al., 1998).

The Hospital Anxiety and Depression Scale (HADS) (paper 3)

The HADS was used to measure anxiety (HADS-a) and depression (HADS-d). The HADS was developed in hospital practice by Zigmond and Snaith (1983) and comprises 14 items, seven to capture depression and seven to capture anxiety; all items are answered on a four-point Likert scale. The index is expressed as a score of 0–21, with a higher score representing more severe symptoms. The questionnaire has been used in COPD patients (Dowson et al., 2001) and has been translated into Norwegian (Patient-Rported Outcomes and Quality of life Instruments Database (proqolid), 2015). We chose this instrument because it is easy to use and has been shown to be a reliable and valid instrument, and to be responsive to change (Bjelland, Dahl, Haug, & Neckelmann, 2002; Baldacchino, Bowman, & Buhagiar, 2002). Permission/license was obtained for the use of the questionnaire in this study (proqolid,

2015), and we found acceptable Cronbach's alpha values of 0.76 for depression and 0.87 for anxiety.

The World Health Organization Well-being-5 Index (WHO-5) (paper 3)

The WHO-5 was used to capture well-being. The WHO-5 comprises five questions to measure positive well-being (i.e., being happy, interested in things, lots of energy, calm and peaceful, fresh and rested) (Mental Health Service, 2015; Bech, Olsen, Kjoller, & Rasmussen, 2003). The scale has been developed from the Psychological General Well-being Index, where 5 itmes that measures positive well-being was used in the WHO-5 (Jeste & Palmer).The answers are given using a six-point scale of "at no time", "some of the time", "less than half of the time", "more than half of the time", "most of the time" and "all of the time". The total score is 0–25 and is recalculated to a score of 0–100 by multiplying the initial score by 4. A higher score indicates positive well-being. The instrument has been translated into Norwegian. We chose this instrument because it is short and uncomplicated (Mental Health Service, 2015). It has been validated in diabetes patients (de Wit et. al., 2007) and the elderly population (Heun, Burkart, Maier, & Bech, 1999). The questionnaire can be obtained at no cost on the Internet (Mental Health Service, 2015). In this study, the Cronbach's alpha was 0.86 for the WHO-5. The questionnaire was assessed at T1, T2 and T3 (Table 3).

4.3.2 Physical tests

Measure of breathing pattern and session information (paper 2)

In paper 2, the same device as that used in the different groups described above (4.2.6 Intervention) was used to measure the breathing pattern (RespeRate, InterCure Inc., New York, USA) (RespeRate, 2009; Gavish, 2010). This unit comprises a sensor belt placed on the patient's waist that measures the respiratory rate (RR), time on inspiration (TIN) and time on expiration (TEX). The device stores breathing statistics for each session for 30 days. These data can be viewed on the device's display or by transferring the statistics from the device to an Excel document.

The device displays session information for the following variables: number of sessions, therapeutic minutes of breathing, initial breathing rate and final breathing rate,

synchronization of breathing with the guidance provided and the ability of the sensor to detect the breathing pattern. These statistics can be found for the last session, the average of the last 7 days and the average of the last 30 days (RespeRate, 2009).

The data can be transferred to an Excel document along with additional information about how many seconds the device had been used for, TIN and TEX. These statistics are given minute by minute during each session for 30 days (RespeRate, 2009; Gavish, 2010). Variables measured at T1 and T2 were used in this thesis.

Lung function (papers 2 and 3)

The lung function parameters forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) and the FEV_1/FVC ratio were measured using spirometry or body plethysmography. The patients were told to use their usual medication before the lung function test. All tests were performed in accordance with the guidelines from The American Thoracic Society and The European Respiratory Society (ATS/ERS) (Pellegrino et al., 2005; Wanger et al., 2005). The variables measured at T1 were used in this thesis.

Blood gas analysis (papers 2 and 3)

The arterial blood gas measures include the arterial pressure of oxygen (PaO_2) and arterial pressure of carbon dioxide tension ($PaCO_2$). The participant breathed room air for at least 20 min, and blood was drawn from the radial artery at the wrist for blood gas analysis (Roche OMNI C, Mannheim, Germany). The variables measured at T1 were used in this thesis.

Table 3. Description of instruments (papers 2 and 3)

Instrument N=150	Scales/Variables	Score	Cronbach's alpha	Time	Paper
Standardized questionnaires					
SGRQ	Symptoms	$0-100^a$	0.79	At T1, T2 and T3	Papers 2 and 3
	Activity		0.82		
	Impact		0.89		
	Total score		0.90		
GRC scale- NRS	Change of breathlessness	$0-10^b$		At T2 and T3	Paper 2
mMRC dyspnoea scale	Breathlessness	$0-4^b$		Inclusion criteria	Papers 2 and 3
HADS	Anxiety	$0-21^b$	0.87	T1,T2 and T3	Paper 3
	Depression		0.76		
WHO-5	Well-being	$0-100^c$	0.86	T1, T2 and T3	Paper 3
Physical tests					
Breathing pattern (RespeRate)	TIN	$0-max^e$		During the intervention from T1 to T2	Paper 2
	TEX	$0-max^e$			
	RR	$0-max^f$			
Lung function (Body plethysmography)	FVC	$0-max^g$		T1	Papers 2 and 3
	FEV1				
	FEV%				
Blood gas variables	PaO$_2$	$0-max^h$		T1	Paper 2
	PaCO$_2$	$0-max^i$			
Socio-demographic and other clinical variables					
Questionnaire booklet	Age	30–max		T1	Papers 2 and 3
	Gender	Female/male		T1	Papers 2 and 3
	Living status	Living alone Living with someone		T1	Papers 2 and 3
	Education	Primary school Vocational school Secondary school University ≤4 years University >4 years		T1	Papers 2 and 3
	Smoking	Yes No		T1	Papers 2 and 3
	Infection the last four weeks	No infection Infection at four weeks		T1	Papers 2 and 3
	Number of diseases	1–max		T1	Papers 2 and 3
	Use of breathing exercises	Yes No		T1	Paper 2
	Years of COPD	0–max		T1	Paper 2

T1=baseline, T2=after four weeks, T3=after four months, FEV$_1$=forced expiratory volume in one second, (FEV%)=ratio between FEV$_1$ and FVC, FVC=forced vital capacity,GRC= Global Rating change, HADS= The Hospital Anxiety and depression Scale, mMRC= The Modified Medical Research Council, PaCO$_2$=pressure of carbon dioxide in arterial blood, PaO$_2$=pressure of oxygen in arterial blood, TEX= time expiration, TIN=time inspiration, RR=respiratory rate, SGRQ=St.George's Respiratory Questionnaire, WHO-5 Index= The World Health organization Well-being-5 index.
[a] Higher score=higher degree of disability, [b] Higher score=more symptoms, [c] Higher score=greater well-being, [e] Higher score=longer time on inspiration or expiration, [f] Higher score=higher respiratory rate, [g] Higher score=better lung function, [h] Higher score=more oxygen in blood, [i] Higher score=more carbon dioxide in blood.

4.3.3 Analysis (papers 2 and 3)

The Statistical package for the social sciences (SPSS) version 22 (SPSS Inc., Chicago, IL, USA) was used to analyse the data in papers 2 and 3. Descriptive analyses, statistical analyses of differences and statistical analyses of relationships were performed according to the different aims. To establish the reliability of the different standardized questionnaires, Cronbach's alpha was determined for the total score and each of the subscales. The level of significance was set at 0.05 in all analyses.

Descriptive analyses (papers 2 and 3)

Descriptive analyses were used for the socio-demographic and clinical data and the scores for the questionnaire variables (papers 2 and 3). The data are described as frequency, proportion, mean and standard deviation (papers 2 and 3) and min–max values (paper 3).

Statistical analyses of difference (paper 2)

In paper 2, within-group analyses (symptom score on the SGRQ) and between-group analyses (symptom score on the SGRQ and GRC scale) were performed for the main outcome variables (symptom score on the SGRQ and GRC scale) and for the secondary outcome variables (activity, impact and total scores on the SGRQ, TIN, TEX, RR). To examine the differences in changes between groups, the general linear model procedure of SPSS, which uses analysis of covariance (ANCOVA) was used to analyse the changes between T1 and T2 and between T1 and T3. T2 and T3 variables were entered as dependent variables, and T1 variables and group variables as independents (factors). ANOVA and t-test were used to analyse difference between group at T2 and T3 for the GRC scale (i.e., between the guided deep-breathing group and music-listening group, and between the guided deep-breathing group and sitting-still group).

Analyses of variance (ANOVA) and Pearson chi-square were used to evaluate the differences between groups at T1, T2 and T3 on demographic anc clinical variables. Paired Student's *t* tests were used within each group to compare between T1 and T2 and between T1 and T3. Non-parametric tests were performed when the data were not normally distributed. See paper 2 for further details.

Statistical analysis of relationships (paper 3)

In paper 3, bivariate correlational analyses and multiple regression analyses were performed on the main outcome variables (i.e., total score on the SGRQ, HADS-a, HADS-d and WHO-5). Change variables were calculated by subtracting the values at T2 from those at T1 and the values at T3 from those at T1 for all of the main outcome variables. Bivariate correlational analyses were used to assess the relationships between the main outcome variables at T1. Multiple regression analyses were performed by entering the change score of the HADS-a, HADS-d and the WHO-5 score as dependent variables and after controlling for the baseline values of the dependent variable, group dummies, age, gender, baseline scores of the independent variables and the change scores for the SGRQ, HADS-a, HAD-d and WHO-5 score. These analyses were performed in a sequence of 10 multiple regression analyses. See paper 3 for further details.

Statistical analyses of interactions (papers 2 and 3)

ANCOVA was used to identify possible interactions between independent variables in the main equations by searching for effects among specific groups of patients as defined by age, gender, infection, smoking status, COPD stage, comorbidities, living status (papers 2 and 3) and education level (paper 3).

To evaluate the interaction effects involving group differences in paper 2; the interaction terms used were intervention groups (i.e., guided deep-breathing group, music-listening group, sitting-still group) × other independent variables entered as one set of pairs at a time (paper 2).

To evaluate the interactions in paper 3, the interaction terms were entered as independent variables for change (i.e., changes in SGRQ, HADS-d, HADS-a, WHO-5 score from T1 to T2 and from T1 to T3) × specific group (paper 3). Multiple regression analyses were performed when significant interactions were found to calculate the standardized betas for the appropriate independent variables within each of the groups (paper 3).

Missing data (paper 2)

A standard protocol was used in the analyses (paper 2). An alternative intention-to-treat analysis for the last observation carried forward was used for missing data. We found minor differences (paper 2), and therefore the results of the standard protocol are reported when evaluating the effects.

Effect sizes (papers 2 and 3)

The effect sizes for differences between groups and within groups were calculated using the method of Cohen (Cohen, 1988) (paper 2). The within-group difference was found by dividing the mean changes by the average SD at T1 and T2, and at T1 and T3. The between-group difference was found by calculating the difference between the mean changes in the guided deep breathing group and the music-listening group and between the guided deep breathing group and the sitting-still group, and then dividing by the average SD of these groups at T2 and T3. Effect sizes were assessed as follows: small effect size=0.2, medium effect size=0.5 and large effect size=0.8 (Cohen, 1988; Ellis, 2010).

The adjusted R^2 values (paper 3) provide information about how much the variance of the dependent variables was explained by the models in the different equations. The partial R^2 was used to evaluate how much of the total variance in the dependent variable was explained by one of the independent variables in the equations (i.e., in this case, the change variables) (paper 3). These were calculated by squaring the partial correlation coefficient found in SPSS (Pallant, 2010). Effect sizes were assessed as follows: small effect size=0.02, medium effect size=0.15 and large effect size=0.26 (Cohen, 1988; Ellis, 2010).

4.4 Ethical issues (paper 1, 2, and 3)

The Declaration of Helsinki Ethical Principles for Medical Research on Human Subjects (World Medical Association, 2013), the health register law (Helse og omsorgsdepartementet, 2014b) and the Norwegian data protection law (Justis-og beredskapsdepartementet, 2013) were followed in the studies. The main aim of the declaration and the laws is to ensure that ethical aspects are covered in a way that avoids harm to the participants. The research protocol was approved by an ethics committee before the start of the study and was registered

in an accessible database (Justis-og beredskapsdepartementet, 2013; World Medical Association, 2013; Helse og omsorgsdepartementet, 2014b).

In the ethical conduct of research, it is important that all participants receive understandable and correct information about the study and that their participation is voluntary and anonymity is ensured (Justis-og beredskapsdepartementet, 2013; World Medical Association, 2013; Helse og omsorgsdepartementet, 2014b). In the studies included in papers 2 and 3, the ethical considerations about information, anonymity and voluntary participation were conveyed through oral and written information provided both at the time of recruiting and on inclusion. First, eligible patients were informed and asked to participate at the different hospitals. The main researcher phoned the participants after they had given their approval to be contacted by a contact person at the different hospitals. More information about the content of the study was given if needed, and an appointment was set up at the main hospital if the participant had agreed to participate. Written approval forms were completed by the participants before attending the appointment. The data from the participants were coded and handled anonymously and the information containing sensitive data was stored in a locked cabinet to which only the researcher and the project nurse had the key. The identification code list was stored in another locked cabinet. All data were entered into a statistical program stored at a locked network location in the main hospital. Only a few people (the researcher, the study nurse and the person who entered the data into the statistical program) had access to this network location. The participants could withdraw from the study without any consequences for their treatment at the outpatient unit.

The laws and the Helsinki Declaration imply that no harm in life—physical, psychological or social—should occur and that the researcher should have no obligation because of any possible conflict of interest (Justis- og beredskapsdepartementet, 2013; World Medical Association, 2013; Helse og omsorgsdepartementet, 2014b). The research included in this thesis used a breathing-control device in the three-armed double-blind RCT (paper 2). Before starting the study, no information was found about how people with COPD experience the use of the device or whether they might experience side effects. However, because of this lack of information about the use of this device in COPD patients, the pilot studies were performed to ensure that the device would not harm the patients. All devices used in this study were purchased in a manner that ensured that there were no competing interests or relationships with the firm that sells the devices.

To minimize any distress that might occur when participating in the study, the participants were reimbursed for taxi expenses to and from the hospital. The questionnaire booklet contained several standardized questionnaires that may have presented a challenge or created tension for some of the participants. To avoid causing stress, the questionnaire was posted to the participants so that they could complete it at their convenience in the two days prior to attending the hospital. At the hospital, the participants were allowed to ask questions and to comment on the questionnaire. Among the various tasks, the participants had to perform a pulmonary function test and provide a blood sample for the test of blood gases. The pulmonary function test and providing a blood sample are routine tests, although the pulmonary function test may be tiresome and the blood test may be uncomfortable for people with COPD. In consideration of this possible discomfort, the participants were able to decline the tests while still completing the other aspects of the study appointment. The blood test samples were analysed and only the results were stored as data in the study. Thus, there was no need for biobanking in the investigation. It is important that all results should be presented accurately so that the study will not provide any misleading information. This has been taken into consideration in all the papers in this thesis by involving several authors who provided reliable reports and discussions (papers 1–3).

5   Results

5.1 Paper 1: Effects of controlled breathing exercises and respiratory muscle training in people with chronic obstructive pulmonary disease: results from evaluating the quality of evidence in systematic reviews

The aim of this paper was to evaluate and summarize the results of systematic reviews that had assessed the effects of breathing-control exercises and respiratory muscle training on breathlessness, other symptoms and quality of life (QOL) in patients with COPD, taking into account the quality of the systematic reviews.

A total of 642 reviews were identified in the literature search. Fourteen of these focused on breathing-control exercises and respiratory muscle training. One systematic review was excluded because it was a previous version (Geddes, Reid, Crowe, O'Brien, & Brooks, 2005) that was later updated (Geddes et al., 2008). Five called their reviews a literature review, an integrative review or simply a review (Cahalin et al., 2002; Raub, 2002; Dechman & Wilson, 2004; Padula & Yeaw, 2006; Rossi, Pastre, Ramos, & Vanderlei, 2012) and were therefore excluded. Finally, one systematic review was excluded due to combining several exercises not interpreted as breathing control exercises in the pooled statistics (Coventry et. al. 2013). A total of seven systematic reviews are included in the overview paper (paper 1, Table 2 and Figure 1) (Geddes et.al. 2008; O'Brian et. al. 2008; Roberts et. al. 2009; Shoemaker et.al. 2009; Thomas et.al. 2010; Gosselink et.al., 2011; Holland et.al. 2012)

Table 4 provides a summary of the studies included, their AMSTAR scores and the significant effects.

Table 4. Summary of included studies, AMSTAR scores and effects found in the systematic reviews

	Focus of the systematic review	Number of control trials	AMSTAR score out of 11	Significant results: Measure (scale), p-value (in favour of)
Breathing-control exercises	DB, PLB and YB compared with control groups (Holland et al., 2012)	- 8 pooled analyses (2 single trials included in the pooled statistics) - n=16 studies in total*	11 (HQ)	*One pooled analysis:* PLB: Dyspnoea (Hiratsuka Scale), p=0.0066 (I) *Single analyses:* PLB: Dyspnoea (mMRC), p=nr (I) DB: QOL (SGRQ), p=nr (I) YB: QOL (SGRQ), p=nr (I)
	PLB (Roberts et al., 2009)	- 5 different trial designs	4 (LQ)	Different measures on dyspnoea reported 40% relief (range 0%–63%), p=nr
Respiratory muscle training	IMT compared with control group (Gosselink et al., 2011)	- 7 pooled analyses (4–14 single trials in the pooled statistics) - n=32 studies in total*	10 (HQ)	Dyspnoea (BS), p<0.001 (I) Dyspnoea (TDI), p<0.001 (I) Dyspnoea (CRQ), p=0.068 (I) QOL (CRQ), p=0.007 (I) Fatigue (CRQ), p=0.024 (I)
	IMT at home with control group (Thomas et al., 2010a)	- 1 pooled analysis (3 single trials in the pooled statistics) - n=7 studies in total*	9 (HQ)	Dyspnoea (TDI), p=0.004 (I)
	IMT compared with sham (Geddes et al., 2008)	- 6 pooled analyses (2–5 single trials in the pooled statistics) - n=16 studies in total*	7 (MQ)	Dyspnoea (BS, p<0.00001 (I) Dyspnoea (TDI focal score), p=0.002 (I) Dyspnoea (TDI functional impairment), p=0.02 (I) Dyspnoea (TDI magnitude of task), p<0.00001 (I) Dyspnoea (TDI magnitude of effort), p<0.0001 (I) QOL (CRQ), p<0.00001 (I)
	IMT compared with exercise (O'Brien et al., 2008)	- 2 pooled analyses (2 single trials in the pooled statistics) - n=16 studies in total*	6 (MQ)	Dyspnoea (CRQ), p<0.001 (I)
	IMT compared with control (Shoemaker et al., 2009)	- No pooled analyses 9 single trials - n=15 studies in total*	5 (MQ)	Results based on single trial quality No p-value was reported

AMSTAR= A measurement tool to assess systematic reviews, BS=Borg scale, C=in favour of control group, CI=95% confidence interval, CRQ= Chronic Respiraotry Questionnaire, DB=diaphragmatic breathing, HQ=high quality, I=in favour of intervention group, IMT=inspiratory muscle training, LQ=low quality, MD=mean difference, mMRC= Modified Medical Research Council score, MQ=moderate quality, nr=not reported, PLB=pursed-lip breathing, QOL=quality of life, , TDI=Transition Dyspnoea Index, YB= yoga breathing.
* Not all studies measured the main outcomes assessed in paper 1 of breathlessness/dyspnoea, other symptoms and QOL.

Of the seven systematic reviews, five evaluated respiratory muscle training (i.e. inspiratory muscle training) (Geddes et al., 2008; O'Brien et al., 2008; Shoemaker et al., 2009; Thomas et al., 2010; Gosselink et al., 2011) and two evaluated breathing-control exercises (Roberts et al., 2009; Holland et al., 2012;). Two systematic reviews conducted on respiratory training were rated using the AMSTAR criteria and given a score of 9 or 10 (high quality) (Thomas et al., 2010; Gosselink et al., 2011). The results showed that out of the eight pooled analyses, four pooled statistics showed effects on breathlessness (Gosselink et al., 2011; Thomas et al., 2010), one showed effects on fatigue (Gosselink et al., 2011) and one showed effects on QOL (Gosselink et al., 2011). One systematic review of several breathing-control exercises (pursed-lip breathing, diaphragmatic breathing, yoga breathing) was rated on the AMSTAR criteria with a score of 11 (high quality) (Holland et al., 2012). Of the eight pooled analyses, only one showed effects on breathlessness in favour of pursed-lip breathing. Single trials showed effects on disease-specific QOL in favour of diaphragmatic breathing and yoga breathing.

The quality of the single trials included in the high-quality systematic reviews (Thomas et al., 2010; Gosselink et al., 2011; Holland et al., 2012) was rated by the authors as low to moderate in those studies that evaluated breathing-control exercises (Holland et al., 2012); 30–83% (median 59%) (Gosselink et al., 2011) and 5–7 (out of 10) (Thomas et al., 2010) for those evaluating respiratory muscle training.

In conclusion, of the seven systematic reviews, two high-quality systematic reviews were on respiratory muscle training and one was on breathing-control exercises. These systematic reviews show that there is stronger evidence about the effects on breathlessness, other symptoms and QOL for respiratory muscle training than for breathing-control exercises. The single trials including breathing-control exercises using pursed-lip breathing, diaphragmatic breathing and yoga breathing were of variable quality. Thus, more RCTs are needed to study all types of breathing-control exercises (pursed-lip breathing, diaphragmatic breathing, yoga breathing, relaxation, body position) and respiratory muscle training before firm conclusions can be drawn.

5.2 Paper 2: Effects of guided deep breathing on breathlessness and the breathing pattern in chronic obstructive pulmonary disease: A double-blind randomized control study

The aim of paper 2 was to investigate, in an RCT, whether people with moderate or severe COPD would report beneficial effects on breathlessness, disease-specific QOL and breathing pattern after a four-week intervention programme using device-guided breathing-control exercises and at the four-month follow-up compared with a music-listening group and a sham sitting-still control group.

No difference was found between groups for the symptom score measured with the SGRQ at T2 and T3. However, a significantly improved symptom score was found within all groups (p<0.05–0.01) at T2. The improved symptom score remained significant within groups for the music-listening group and the sitting-still group at T3. For the GRC score of perceived change of breathlessness, a significant between-group effect was found in favour of the guided deep-breathing group at T2 (p=0.03, effect size=0.45–0.53). At T3, the main analyses showed no effect between groups on the GRC score of perceived change in breathlessness (paper 2). However, in a separate analysis, a difference was found between the guided deep-breathing group and the music-listening group (p=0.04, effect size=0.48), but not between the guided deep-breathing group and the sitting-still group at T3.

For the secondary outcome variables, a significant effect was found on the breathing pattern variables respiratory rate (start of session and end of session), TIN (end of session) and TEX (start of session and end of session) in favour of the guided deep-breathing group (p≤0.001, effect size=0.43–0.74). As for the activity score, the impact score and the total score measured with the SGRQ, no significant effect was found between groups at T2 and T3.

In conclusion, the analyses indicate that device-guided breathing seems to be effective for changing the perception of breathlessness and breathing pattern in people with moderate or severe COPD. However, all groups showed improvement in the disease-specific symptom score. This result suggests that aslo music listening and relaxation may be useful to some extent.

5.3 Paper 3: Fluctuating patterns in quality of life outcomes among patients with moderate- and severe- stage chronic obstructive pulmonary disease

The aim of paper 3 was to investigate over a period of four months to what extent changes in disease-specific QOL fluctuate with changes in depression, anxiety and well-being in non-hospitalized patients with moderate or severe COPD.

Our main results show that the changes in disease-specific QOL (i.e., SGRQ), depression (HADS-d) and anxiety (HADS-a) fluctuated significantly with the change in well-being (WHO-5) between T1 and T2 and between T1 and T3 ($p<0.001$ to $p=0.02$, partial $R^2=4$–15%). The change in disease-specific QOL (i.e., SGRQ) fluctuated together with the changes in anxiety (i.e. HADS-a) between T1 and T3 ($p=0.02$, partial $R^2=4$%), but not with change in depression (i.e.HADS-d) during the four months.

In conclusion, the changes in disease-specific QOL, depression and anxiety contributed a moderate amount to the change in change in well-being over a period of four months. However, the change in disease-specific QOL contributed only a small amount to the change in anxiety at four months and not at all to the change in depression. These results may increase our knowledge about how people with moderate and severe COPD experience parallel changes or no changes in QOL over time. Measuring well-being as global-secific QOL may be useful in health research for people with moderate and severe COPD.

6 Discussion

6.1 Discussion of main findings

At the start of this study, it was difficult to gain an overview of studies on breathing-control exercises and respiratory muscle training in people with chronic obstructive pulmonary disease (COPD). Several reviews were found on breathing-control exercises and respiratory muscle training (Breslin, 1995; Cahalin et. al., 2002; Raub, 2002; Gosselink, 2003; Dechman & Wilson, 2004; Gosselink, 2004), and the decision was made to write an overview article to systematize the results of the effects of these training techniques based on the quality of the systematic reviews. The overview article of this thesis found that breathing-control exercises and respiratory muscle training are both examples of self-management support tasks that can affect breathlessness and disease-specific quality of life (QOL) (paper 1). Using A Measurement Tool to Assess Systematic Reviews (AMSTAR) criteria, one systematic review of breathing-control exercises (Holland et al., 2012) was scored as high quality (Table 4). Based on two single randomized controlled trials (RCTs) in the pooled analyses, a positive effect was found on breathlessness in favour of pursed-lip breathing. One single RCT of diaphragmatic breathing and one of yoga breathing showed effects on disease-specific QOL in people with COPD (Holland et al., 2012). Similar findings have been found in people with asthma (Holloway & Ram, 2004; Cramer, Posadzki, Dobos, & Langhorst, 2014) and heart failure (Gomes-Neto, Rodrigues-Jr, Silva-Jr, & Carvalho, 2014). The overview article of this thesis (paper 1) indicates that breathing-control exercises may be useful for improving breathlessness in people with COPD.

Of the five systematic reviews of respiratory muscle training (Geddes et al., 2008; O'Brien et al., 2008; Shoemaker et al., 2009; Thomas et al., 2010; Gosselink et al., 2011), two (Thomas et al., 2010; Gosselink et al., 2011) were considered high quality according to the AMSTAR criteria (Table 4). The pooled analyses showed a positive effect on breathlessness (Thomas et al., 2010; Gosselink et al., 2011), fatigue and QOL (Gosselink et al., 2011) in favour of respiratory muscle training. Respiratory muscle training has been defined as a breathing-control exercise (Gosselink, 2003; Gosselink, 2004), but it may not be interpreted as such according to the definition of breathing control (Prasad & Pryor, 2008). This definition states that breathing control should be performed using gentle breathing at a natural rate without forced expiration (Prasad & Pryor, 2008). Respiratory muscle training requires the use of a training device with a resistance nipple to train the respiratory muscles (Dean & Frownfelter,

2006). Therefore, the breathing may not be gentle, or at a natural rate, or without forced expiration. Hence, it is difficult to compare the results from the respiratory muscle training intervention with the results from the breathing-control exercises.

Although the overview article (paper 1) demonstrates that breathing-control studies have found effects on breathlessness and disease-specific QOL, there have been few RCTs and it is difficult to draw conclusions about these effects because of the limitations of the individual studies. Several other points require further investigation. For instance, several of the studies lacked blinding of the participants, the researcher and the outcomes (Holland et al., 2012). This is discussed further below under Methodological considerations. In addition, few of the breathing-control studies investigated the breathing pattern as an outcome (Holland et al., 2012). Investigating the breathing pattern is important for evaluating whether the effects were caused by the intervention. Moreover, in these studies, the exercises were mainly taught and evaluated in an institution (Holland et al., 2012), and little information is available about whether and how the exercises were practised at home. People with COPD may experience the disease as an everyday struggle and find themselves in increasing need of help (Ek et al., 2011), and it is therefore important to know whether and how these exercises can be used in the home situation. This is supported in a quality study where people with COPD have expressed that learning breathing control exercises has helped them to handle breathlessness when it is needed in their lives (Mousing & Lomborg, 2012).

Finally, several of the interventions using breathing-control exercises combined two or more exercises (Holland et al., 2012). It may therefore be questioned which of the breathing-control exercises were most effective, or whether all of the exercises had an effect. For example, in the systematic review by Holland et al. (2012), which was included in the overview article, the combination of pursed-lip breathing and diaphragmatic breathing (Wu, Hou & Bai, 2006) as well as the combination of pursed-lip breathing and pulmonary rehabilitation (Zhang et al., 2008) were used in the pooled analyses of pursed-lip breathing. As for other studies not included in the systematic reviews, Valenza et al. (2013) combined pursed-lip breathing, relaxation and diaphragmatic breathing. An effect on breathlessness and anxiety was found in favour of the training group. Another study by Lin et al. (2012) combined pursed-lip breathing, diaphragmatic breathing and unsupported upper extremity exercises, and found an effect on disease-specific QOL in favour of the training group.

Several studies also used usual care as the control (Holland et al., 2012; Valenza et al., 2013), and it is possible that the effect found in the training groups may have been affected by the attention given to the participants (Miller et al., 2009). The study performed as part of this thesis is the first double-blind RCT to use a device to guide on breathing in order to examine the effects of breathing-control exercises on breathlessness and breathing pattern in people with moderate or severe COPD in a home setting (paper 2). The research design of this thesis attempted to avoid the limitations of previous studies (paper 2).

There is limited supporting evidence from other studies using a device on guided breathing. By examples, Van Gestel et al. (2012) tested a device for guided breathing in COPD patients and found no effect on QOL outcomes. However, the device used in that study only displayed visual guidance, which was different from the RCT in this thesis (4.2.6 Intervention). Interventions involving guided deep breathing using the same device as used in this thesis have been performed in people with other diseases. For instance, device-guided breathing has been shown to affect breathlessness (Ekman et al., 2011), QOL (Parati G et al., 2008) and breathing pattern (Harada et al., 2014) in people with heart failure. Excluding these studies, most of the studies on device-guided breathing have involved people with hypertension and have shown no effect on QOL (Mahtani et al., 2012) and mixed results in terms of effects on blood pressure variables (Mahtani et al., 2012; Landman et al., 2013; van Hateren, Landman, Logtenberg, Bilo, & Kleefstra, 2014). Although the positive effects on the perceived changes in breathlessness and breathing patterns of device-guided breathing in this thesis (paper 2) are supported by other breathing control studies showing positive effects on breathlessness in the overview article (paper 1), more research is needed before conclusions can be drawn.

A physical explanation of the importance of learning to breathe slowly and improving breathlessness is unclear (van Gestel et al., 2012). One explanation is that slow breathing reduces sympathoexcitation (Raupach et al., 2008; Harada et al., 2014), which may explain the improved breathlessness in COPD (Raupach et al., 2008). Thus, it may be important to measure the breathing pattern in people with COPD. Often, the breathing pattern is assessed by a person counting the movements of the thorax. However, the breathing pattern is variable and therefore difficult to measure (Gail, 2007). This could explain why the breathing pattern has not been assessed in other studies of breathing-control exercises (Holland et al., 2012) (3.4 Previous research). On the other hand, changing the breathing pattern is one of the main purposes of interventions in breathing-control studies (Dean & Frownfelter, 2006), and it should therefore be an important outcome in such studies. The device used in the RCT in this thesis (paper 2) (4.2.6 Intervention) provided the opportunity to measure and store breathing

pattern data during all sessions performed at home. A positive effect in favour of the guided deep-breathing group was found for almost all breathing pattern variables. These data provide information about how the participants breathed during the sessions and show also their compliance with the exercises in a home situation. The changes in the breathing pattern at the start of the sessions from the baseline to four weeks (respiratory rate and time used in expiration (TEX) at the start of sessions) may indicate that the participants learned to breathe more slowly.

By contrast, the main univariate analyses at the four-month follow-up showed no effect on the perceived change in breathlessness (paper 2). This may indicate that there was no learned effect on deep breathing and that the participants need continuous guidance to obtain the desired effect. Self-management knowledge is considered to be perishable (Kaptein, Fischer, & Scharloo, 2014). In the RCT in this thesis (paper 2), the participants did not have the opportunity to use the device after four weeks. Self-management by the individual comprises the cognition and emotions needed to change QOL outcomes (3.2 Self-management and self-management support), and the participants may not have learned how to use deep breathing without guidance from the device. Nevertheless, surprisingly, a separate analysis comparing two groups at a time (paper 2) showed an effect on the perceived change in breathlessness in the guided deep-breathing group compared with the music-listening group but not compared with the sitting-still group. This may indicate that the participants in the guided deep-breathing group learned the skill and were able to use it without the device. The positive change in breathlessness in the sitting-still group suggests that relaxation has a positive effect on patients with COPD. However, this result may also be biased because the participants in the sitting-still group were content not to use the device and thus showed a positive improved breathlessness from four weeks to four months. Thus, the long-term effects of guided deep breathing on the perceived change in breathlessness remain uncertain.

The guided deep breathing used in the RCT in this thesis (paper 2) may be considered as a combination of exercises, as shown in other training groups (Holland et al., 2012). The guided deep-breathing group received guidance about breathing listening to   music being played in the background. Conversely, the study included two types of controls: one with music only (music-listening group) and one without music or guidance (sitting-still group). This design strengthens the results showing an effect on the perceived change in breathlessness and breathing pattern found in the guided deep-breathing group. Choosing a suitable control group is an issue in the discussion on RCTs, which is the gold standard in research (Grossman & Mackenzie, 2005).

Despite the efforts that were made to provide the same level of attention to all participants, the amount of attention may still have affected the results in the RCT used in this study. For instance, it is possible that an attention effect may explain the positive change in the symptom score for all groups in the RCT in this thesis (paper 2). Emphatic support has previously been discussed to affect symptoms in other studies of people with COPD (Graydon & Ross, 1995; Ketelaars et al., 1998). The RCT in this thesis (paper 2) could have included a control group that received the usual care, but this would have made this complex study even more difficult to undertake, especially given the difficulties involved in recruiting a sufficient number of participants. On the other hand, an attention effect is difficult to identify, and we cannot be certain whether such an effect was evident in other studies (McCambridge, Witton, & Elbourne, 2014).

The significant change in the symptom score may show that, in addition to guided deep-breathing exercises, other distracting stimuli such as listening to music, sitting quietly or relaxing may influence symptoms of COPD. The symptom score measures how often a person experiences breathlessness, cough, sputum and wheeze (Jones et al., 1992). Listening to music may have provided a distraction from these symptoms, and sitting still may have provided time for relaxation in people experiencing these symptoms. Previous research has found that music listening and relaxation have positive effects or change on breathlessness in people with COPD (Norweg & Collins, 2013; Raskin & Azoulay, 2009). All interventions included elements of relaxation that may have affected the participants' breathing (Table 1). Thus, different types of self-management support strategies may help to improve symptoms in people with COPD.

Guided deep breathing using a device (paper 2) may be seen as a new way of performing continuous guided deep breathing (paper 1) to improve breathlessness symptoms and as a self-management support task at home. According to the Ministry of Health and Care Services in Norway (Helse og omsorgsdepartementet, 2014a), the results from the RCT may meet the requirements of the ministry in response to an inquiry that recommended the development of new technology to provide better and more effective treatment in a home situation (Helse og omsorgsdepartementet, 2014a). The device may require a short learning period and perhaps several follow-up visits to ensure that it is being used correctly, but it will be on hand to assist as a guide for continuous breathing whenever needed. However, since no similar study can support the result of the RCT in this thesis, more research on the effect of device-guided breathing control in COPD is necessary. Research should focus on including

suitable control groups and providing follow-up visits before any conclusions are drawn regarding the long-term effect of device-guided breathing control.

Although the overview article and the RCT in this thesis showed effects of breathing-control exercises on breathlessness (papers 1 and 2) and disease-specific QOL (paper 2), several other studies have not shown such effects (paper 1, Table 3). This shows that changing QOL outcomes can be complex. Changes in QOL outcomes often depend on whether the outcome is seen to measure the dimension in the intervention (Walters, 2009). The symptom score and the total score of the disease-specific QOL outcome used in the RCT in this thesis (paper 2) measured breathlessness from the broader perspective, such as how breathlessness affected life in general and activity (4.3.1 Standardized questionnaires). However, it may not have fully captured the improved breathlessness after the guided deep-breathing intervention. Alternatively, the Global Rating Change (GRC) Scale question, which asked about the participants' perceived change in breathlessness by the use of the device after the intervention, may have been a better question for determining whether guided deep breathing can improve breathlessness. This may be why we found an effect in favour of guided deep breathing (paper 2). More research is needed to determine which questions and QOL outcomes can best capture this dimension in studies of breathing control. However, this has also been noted as a general need for studies of self-management interventions (Nolte, Elsworth, Newman, & Osborne, 2013).

The longitudinal data on disease-specific QOL, depression, anxiety and well-being from the RCT in this thesis (paper 3) investigated fluctuating patterns over the four months from baseline to four months. Disease-specific QOL, depression and anxiety are often used as outcomes in studies of self-management of people with COPD (Jonsdottir, 2013), but well-being has not been investigated thoroughly in self-mangment programs (Lee et.al., 2002) or in general of people with COPD (Stridsman et. al., 2013). The findings from paper 3 not only illustrate the complexity of how these QOL outcomes change, either together or individually, over time, but also improve our conceptual understanding. Several investigations have found close bivariate associations between breathlessness, depression, anxiety (Borge et al., 2010) and disease-specific QOL (Tsiligianni et al., 2011), but few have investigated the association with well-being (Blinderman et al., 2009). Analyses of the changes in QOL outcomes in longitudinal studies may extend our understanding of how the burden of COPD changes over time. The findings in paper 3 showed that the changes in disease-specific QOL, depression and anxiety fluctuated with the change in well-being during a period of four-month (paper 3).

However, the change in disease-specific QOL did not fluctuate with the change in depression and only slightly with the change in anxiety at four months.

The theory of QOL states that QOL is variable over time and shows fluctuating patterns (Spilker, 1996). The short follow-up of four months may be one reason why there was no association between the change in disease-specific QOL and changes in depression and limited to change in anxiety (paper 3). Studies over longer periods have found different results. For example, the change in disease-specific QOL was associated with changes in depression (Oga et al., 2007; de-Torres et al., 2014) and anxiety (Jones et al., 1992; de-Torres et al., 2014) in follow-ups of 1–5 years.

The results of changes in disease-specific QOL, anxiety and depression being associated together with changes in well-being over time, may be supported by longitudinal studies of other diseases such as multiple sclerosis (Tepavcevic et al., 2014) and schizophrenia (Priebe et. al., 2011). The result in this thesis suggests that well-being is also an important outcome to consider when studying people with COPD (paper 3). However, well-being is difficult to define and understand in research (Dodge R. et al., 2012). According to Spilker (Spilker, 1996), well-being may be both an overlapping concept with general health-specific QOL and an outcome of global-specific QOL. The results from paper 3 tend to support this. For instance, depression and anxiety changed significantly with the change in well-being over time, which suggests that these outcomes may provide a measure of generic health-specific QOL. It is also interesting that the HADS, which was used to capture generic depression and anxiety, and the WHO-5, which was used to capture well-being in paper 3, have both been used to capture depression or state of mental health in primary care and the clinic (Zigmond & Snaith, 1983; Primack, 2003). However, the analyses also showed that disease-specific QOL changed with well-being but to only a limited extent with changes in depression and anxiety over time (paper 3). These differences may indicate that well-being measures more than generic health-specific QOL. Thus, according to Spilker's (Spilker, 1996) QOL theory, well-being as measured in this thesis may provide a measure of both global-specific QOL and health-specific QOL.

More research is needed to determine whether and how these QOL outcomes fluctuate over longer periods of time and to assess the use of outcomes other than those studied in this thesis. This will generate new knowledge about how the changes in one outcome affect other outcomes in research, clinics and self-management interventions. The results from paper 3 in this thesis suggest that research should focus more on how people with COPD perceive their well-being.

6.2 Methodological considerations

6.2.1 Internal validity

Evaluation of quality and bias

The validity of a review depends on whether the results from included studies can be trusted. Internal validity therefore addresses whether the answer to the research question is correct (Higgins, et. al.,2008). AMSTAR criteria were used to evaluate the quality of the systematic reviews (Shea et al., 2007b; Shea et al., 2009). Although several authors (Mikton & Butchart, 2009; Jaspers et al., 2011; Seo & Kim, 2012; Macedo et al., 2013) have used the same cut-off points to identify low-, moderate- and high-quality systematic reviews, the AMSTAR criteria have not been validated for this purpose. The result of one low-quality (Roberts et al., 2009), three moderate-quality (Geddes et al., 2008; O'Brien et al., 2008; Shoemaker et al., 2009) and three high-quality systematic reviews (Thomas et al., 2010; Gosselink et al., 2011; Holland et al., 2012) may therefore have been different if other cut-off points in relation to the AMSTAR criteria had been used. The problems when evaluating findings according to cut-off points or scores are that this type of analysis does not identify strengths and weaknesses, and that all criteria seem to be of equal importance because they are all given a score of 1. However, some elements may be more important than others when evaluating quality, and this will not be captured by scores based on cut-off points. It is therefore recommended that each criterion should be assessed individually, because each one may measure a different element (Shea et al., 2009). The overview article discusses the effects of breathing-control exercises and respiratory muscle training on breathlessness, other symptoms and QOL as identified in systematic reviews that were scored as being of high quality. Important information that may have confirmed the internal validity by reflecting the separate AMSTAR criteria may therefore have been lost. By contrast, because the systematic reviews that were rated as being of high quality had few items with a score of 0, it is more likely that those results are based on

the best evidence. Further research is needed to be able to discriminate between high and low methodological quality using AMSTAR (Shea et al., 2007a).

Systematic reviews of high-quality trials have been stated to give high internal validity (Mickenautsch, 2010). An evaluation of high-quality systematic reviews may therefore indicate high validity of an overview article. In order to achieve high internal validity of the effects found in systematic reviews, the included trials should be free from bias in relation to selection (i.e., differences between baseline variables); blinding of participants, personnel, and outcome assessors; incomplete outcome data; and differences in the determination and reporting of outcomes (Higgins et al., 2008). All the systematic reviews included in the overview article of this thesis used a checklist to evaluate bias in the included studies (paper 1, Table 3). However, the included studies in the different systematic reviews seemed to be of variable quality (paper 1). For instance, in the high-quality systematic review that evaluated studies of breathing-control exercises (Holland et al., 2012), most of the separate controlled trials were rated as being of low to moderate quality.

One of the main biases identified was that participants and assessor(s) were not blinded (Holland et al., 2012). Blinding is important to prevent the participants having expectations about their treatment (i.e., better treatment in the intervention group or no improvement in a control group) or to prevent the researcher(s) or outcome assessor(s) affecting the outcomes (Higgins et al., 2008). Not blinding the participants also seemed to be a bias in the systematic review of respiratory muscle training by Thomas et al. (2010), in which the quality of the studies included in the meta-analysis was rated as 5–7 out of 10. As in the systematic review by Gosselink et al. (2011) which used another evalution measure of quatliy than Thomas et. al. (2010), it is difficult to determine which biases may have been encountered in the included studies. The mean quality in Gosselink et. al. (2011) was rated as 59%, which can be interpreted to mean that the studies included in this review had several biases. Detailed information may be lost in systematic reviews (Mickenautsch, 2010), and this may be more critical in an overview. This may have influenced the effects reported in the overview article (paper 1).

The same biases mentioned above in relation to evaluating the quality of systematic reviews may also have affected the results of the RCT in this thesis (paper 2). The Consolidated Standards of Reporting Trials (CONSORT) guidelines give advice about how RCTs should be designed and performed with minimal systematic errors (Moher et al., 2010). Most of the

points on the CONSORT checklist were fulfilled in the RCT in this thesis. However, some of the points, such as randomization and blinding, require further discussion (paper 2).

Randomization is the best way to obtain comparable groups of for instance sex and social factors and to avoid preselecting patients (Polit & Beck, 2004). In this thesis, block randomization was used to assign an alsmot equal number of participants to each group and to adjust for the seasonal variation inherent in COPD (Silkoff et al., 2005). However, lung function was higher in the sitting-still group than in the other groups at T1. Lung function is used to assess the severity of COPD (GOLD, 2015). However, no strong interaction effect was found between severity and group or between the other interaction terms (i.e., group × age, infection, smoking status, comorbidities, or living status). Consequently, this result may be interpreted as reflecting only a limited difference between groups in regard to any of the interaction variables tested (paper 2, Table 1).

The blinding of the participants with regard to which group they were randomized into may not have been sufficient in the RCT (paper 2). Although the participants received no indication of which group was the test group, they may   have guessed or got suspicious about which group they were assigned to (i.e. the experimental group or a control group). The sitting-still group may have felt it odd to be asked only to sit still, and may therefore have assumed that they were in the control group and have answered the questionnaire according to their assumption.

The results described in both papers 2 and 3 could have been affected by the blinding of outcomes. The study nurse was the only one who knew which group the participants were randomized into (paper 2) and was also the person who checked the questionnaires for incomplete answers at four weeks and four months (papers 2 and 3). This knowledge may have affected the QOL outcomes captured in the questionnaire. On the other hand, the participants completed the questionnaires at home, and only a few participants needed help with questions they had been unable to answer, which may have reduced the risk of this potential bias. All participants performed the physical tests given by the researcher before randomization at baseline and after having talked to the study nurse in the follow-ups. They were told not to talk with the researcher about the device. It is therefore believed that the researcher was sufficiently blinded.

Outcomes

The two feasibility studies tested several patient-reported outcomes for the measurement of breathlessness and disease-specific QOL. The SGRQ was interpreted as being similar to other disease-specific QOL outcomes (Bausewein et al., 2007). The SGRQ is often used, and is responsive to changes after self-mangment programs and pulmonary interventions (Bentsen et. al., 2012; GOLD, 2015), which is why it was chosen. However, other instruments may have produced different results. For instance, the Baseline Dyspnea Index/Transition Dyspnea Index (BDI/TDI) indicates the effects of respiratory muscle training (Geddes et al., 2008; O'Brien et al., 2008; Thomas et al., 2010; Gosselink et al., 2011). The COPD assessment test (CAT) was used to identify significant changes in disease-specific QOL related to changes in anxiety and depression over time in another study (Oga et al., 2012). Both of these instruments could have shown a different outcome in the result of this thesis as well.

The reason for minor changes in the HADS in paper 3 may be that the participants may not have had much depression or anxiety. For example, the mean scores were 4.8 for the HADS-d and 5.7 for the HADS-a, which are low compared with the cut-off points for depression and anxiety disorders of 7 or 8 (Herrmann, 1997; Bjelland et al., 2002).

The GRC scale (Kamper et al., 2009) was used to capture specific changes in perceived breathlessness. This scale usually includes both a negative and positive scale ranging from –5 to +5 (Kamper et al., 2009), but the scale used in the RCT in this thesis (paper 2) was 0–10 (0=no improvement and 10=great improvement). As a consequence, this study did not provide information on negative changes, which is one limitation. However, the participants had the opportunity to answer 0 if no change was experienced. On this background, it is believed that not capturing negative perceived changes in breathlessness has introduced only limited bias into the results in paper 2 of this thesis.

Statistical considerations

The statistical considerations that were applied in papers 1–3 are important in the evaluation of internal validity (Laake et al., 2012). In paper 1, several of the systematic reviews had performed pooled statistics analyses (Geddes et al., 2008; O'Brien et al., 2008; Gosselink et al., 2011; Thomas et al., 2010; Holland et al., 2012). Using pooled statistics in meta-analyses of studies with small sample sizes is considered an advantage that strengthens the findings (Mickenautsch, 2010). However, it is important that the studies included in a meta-analysis

are considered to be equal (i.e., homogeneous). When unequal studies are combined (i.e., heterogeneity), a random-effects model should be used to analyse the pooled statistics to take into account the fact that there may be unpublished studies that are overlooked in the systematic review (Ried, 2006). The I² statistic is often calculated as a measure of the heterogeneity or homogeneity of the included studies (Ried, 2006). This measure is also evaluated with the AMSTAR criteria (Shea et al., 2009). All systematic reviews that used pooled analyses (Geddes et al., 2008; O'Brien et al., 2008; Thomas et al., 2010; Gosselink et al., 2011; Holland et al., 2012) considered the I^2 test, except for the study by O'Brien et al. (2008), but they used a random-effects model for pooled statistics. All pooled analyses reported in the overview article therefore seemed to have been assessed satisfactorily.

The AMSTAR criteria recommend the inclusion of a funnel plot (Shea et al., 2007a; Shea et al., 2007b). This is a graphical plot of each individual study included in a systematic review that illustrates the biases of low-quality studies. Bias can arise from publication bias, language bias, poor methodological design or small sample size. If there is bias, the graph will not appear as a funnel. The funnel plot is recommended only when at least 10 studies are included in a meta-analysis (Higgins et al., 2008). Thus, only one systematic review had the opportunity to include a funnel plot (Gosselink et al., 2011). Although a funnel plot was shown in this systematic review, it did not include breathlessness, other symptoms or QOL, which were the outcomes evaluated in the overview article (paper 1). Based on this background, evidence about publication bias is difficult to obtain for the systematic reviews included in the overview article.

The sample size for the study included in paper 2 was calculated based on the data provided for the use of the SGRQ given in pulmonary rehabilitation (Griffiths et al., 2000). No other RCT of breathing control had used the SGRQ at the time of the planning of this study in this thesis. Thus, there was no comparative information. However, because no difference in the SGRQ symptom scores was found between groups (paper 2), an additional sample size calculation has been performed. Using the SD of 22 from the main findings of paper 2 and the recommended minimal detectable significant change of four points (Jones, 2002), it would be necessary to include about 370 patients in each group (β=80%, α=5%) (DSS, 2015). With this number of participants and only a four-point score change on a 0–100 scale, it is reasonable to question whether the study would show clinical relevance. For paper 3, using the sample size that was calculated in paper 2 could be interpreted as a limitation. On the other hand, an evaluation was performed on the number of participants studied which was necessary to allow for the number of variables entered into the multiple regression analysis. It is recommended

that at least 10 people per independent variable are included for multiple regression analysis (Altman, 1991). In our regression analyses, only six variables were entered for each equation (4.3.3 Analysis), thus 130–150 participants should have been sufficient.

The loss to follow-up of seven participants at four weeks and 20 participants at four months may have influenced the results. In paper 2, the analyses were performed as for the standard protocol; however, in RCTs, an intention-to-treat analysis is recommended (Moher et al., 2010). Thus a separate intention-to-treat analysis (i.e., the last carried forward) was performed in paper 2, and this analysis showed only marginal differences in the mean outcome and no effect on the main conclusion (paper 2). In a longitudinal design, it is recommended that the loss to follow-up is reported, as was done in paper 3. In this study, the drop-out rate was <15%, which is considered good (Herbert R, Jamtvedt G, Hagen KB, & Mead J, 2014). Based on this background, the results of both paper 2 and paper 3 should only have been affected to a minor degree by drop-out bias.

The baseline variables showed no significant differences between groups for the main and secondary outcome variablesin paper 2. However, to adjust for possible imbalance in baseline variables between groups, ANCOVA (general linear model) was used, as recommended (Moher et al., 2010), in paper 2. In the main analyses of paper 3, multiple regression analyses were used to explore the associations between the change scores for the different outcomes. Although ANCOVA uses a regression method (ordinary least squares), the procedure used in SPSS does not provide information about the standardized betas. However, standardized betas are included in the standard multiple regression analysis and may give a better sense of the strength of a given association.

Interaction analyses were performed to explore whether subgroups responded differently in the RCT (paper 2) and to explore the relationships between the change scores and the dependent variables in paper 3. Because the study was not planned or designed to analyse subgroups as a main aim, the significant interaction terms in paper 3 may have been biased by the small group sizes, and there is a potential for type II error (Jamieson, 2004) Therefore, these results should be interpreted with caution.

The p-values and effect sizes of the results are presented in papers 2 and 3. The p-values only provide an indication of the precision of an estimate, whereas the effect size is more informative and therefore of greater practical and clinical significance. An effect size provides more information about the magnitude or strength of an association (Ellis, 2010). An important example of an effect size providing more information than a p-value is the analysis

of the association between the change in disease-specific QOL with the change in anxiety at four months (p=0.02) (paper 3). The explained variance of R^2 or pR^2 of 4% indicates that the changes occurred in only a few of the participants in our sample (Ellis, 2010).

6.2.2 External validity

Findings from a study can be safely generalized only to the population that is studied (Polit & Beck, 2004). Therefore, the generalization of the findings in the three papers of the thesis should be discussed. The overview article (paper 1) demonstrated that most of the included studies in the systematic reviews (Geddes et al., 2008; O'Brien et al., 2008; Roberts et al., 2009; Shoemaker et al., 2009; Thomas et al., 2010) were published in English journals, which may bias the generalization of the results. However, two systematic reviews (Gosselink et al., 2011; Holland et al., 2012) had no language restrictions, which could be interpreted as indicating that the results are more generalizable. For instance, Holland et al. (2012) found that ten of the studies were published in English, five in Chinese and one in French. However, of the four studies showing effects after the intervention period, two were performed in China (Wu et al., 2006; Zhang et al., 2008), one in Brazil (Yamaguti et al., 2012) and one in the USA (Donesky-Cuenco, Nguyen, Paul, & Carrieri-Kohlman, 2009). The fact that these studies were performed in different countries and all showed trends towards a positive effect in the same direction suggests that the results may be generalizable.

In this thesis, the participants were recruited at three different hospitals in Oslo to reduce any bias arising from socio-economic factors that can influence health. For instance, socio-economic and health factors differ between different parts of Oslo (Claussen, 2007). Although, a larger proportion of participants were from one hospital, the results can be considered to be more generalizable to COPD patients from different socio-economic backgrounds than if participants had been recruited from only one hospital.

Only patients with moderate or severe COPD were included in papers 2 and 3 of this thesis. As for the overview article (paper 1), only patients with stable COPD were included, but their lung function tests indicated that they had moderate or severe COPD (paper 1, Table 2). Thus, the results from all papers in this thesis may be generalizable to moderate and severe stages of COPD.

A response rate of 44% may also raise questions about representativeness (papers 2 and 3). It was not possible to obtain information about those who did not participate, and therefore it is difficult to know whether the results found in the studies would have applied to all patients. Barriers to participation in self-management support programmes are lack of awareness, physical symptoms, transportation problems and lack of insurance (Jerant et al., 2005). An offer of transport was made during recruitment of the participants. However, the other barriers may have contributed to the low participation rate in these studies.

6.3 Conclusions

Self-management support tasks in the form of breathing-control exercises such as pursed-lip breathing, diaphragmatic breathing and yoga breathing have been shown to have a positive effect on breathlessness and disease-specific QOL in people with COPD. However, few RCTs have been performed, and these studies have several limitations; thus, more research is needed (paper 1). A study design including three different groups—one receiving guided deep-breathing, another one listening to music and one simply sitting still—all using a device to give information or listening to music and measuring breathing pattern, made it possible to perform a double-blind RCT in people with moderate and severe COPD in a home setting. A positive effect was found in favour of guided deep-breathing on perceived change in breathlessness and breathing pattern. A significant positive change was also found in all groups in terms of symptom scores for disease-specific QOL (paper 2).

The results of paper 3 showed that the changes in disease-specific QOL, depression and anxiety fluctuated together with the change in well-being over a period of four months. However, the change in disease-specific QOL did not fluctuate with depression and changed only slightly with the change in anxiety over the same period. Therefore, including measures of well-being when studying COPD patients may help clinicians and future researchers to better understand the implications of living with COPD.

6.4 Suggestions for further research

The results from the overview article (paper 1) imply that more research is needed on breathing-control exercises and device-guided breathing. One individual exercise should be compared with another one or with comprehensive self-management programs. Studies should also control for the amount of attention received by participants and should be extended to other settings. Examples of extension to other settings include the use of device-

guided breathing in an in-patient unit, in people with COPD who also have an infection or exacerbation, combined with other self-management tasks such as those used in pulmonary rehabilitation and as a method to help patients normalize their breathing after non-invasive ventilation therapy .

Papers 2 and 3 both demonstrate the difficulties in choosing and investigating QOL outcomes. Further research is needed to identify the best health outcomes and instruments when studying self-management support interventions including breathing-control exercises. The recent guidelines focus on using breathlessness outcomes (e.g., mMRC dyspnoea scale) and disease-specific QOL outcomes (e.g., SGRQ, CAT) to guide the treatment and follow-up of COPD patients (GOLD, 2015). The results of paper 3 suggest that well-being should be an important QOL outcome in future research and that its assessment should be tested in the clinic to evaluate patients global-specific QOL.

6.4.1 Relevance

The results from this thesis indicate that breathing-control exercises and respiratory muscle training can be used as self-management support techniques in people with COPD. Device-guided deep-breathing exercises may be a new way of self-management to provide continuous guidance to help people with COPD to improve their perceived breathlessness and breathing pattern in the home setting whenever needed. Device-guided breathing as used in this thesis is less expensive and requires less resources than having a health professional provide continuous guidance on deep breathing. Traditionally, a physiotherapist teaches breathing-control exercises, but also nurses teach these exercises to people with COPD (Langer et al., 2009; Barnett, 2008). Several different members of the multi-disciplinary team may be able to provide instruction on the use of the guided-breathing device used in this study to COPD patients.

The findings of this thesis also show that guided deep breathing, listening to music or simple relaxation in a chair may also help improve symptoms of COPD. These are all simple self-management tasks that can easily be performed by patients with COPD.

The findings of paper 3 may be relevant to both clinical work and research. Changes in disease-specific QOL, depression and anxiety may lead to changes in well-being. However, a change in disease-specific QOL may not necessarily cause changes in depression and anxiety. Investigating well-being as a global-specific QOL outcome may provide more information for health research.

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ERRATA

Page 8**:** "… moderate- and severe- chronic obstructive disease" is changed to "…moderate- and severe- stage chronic obstructive pulmonary disease"

Page 10: "TIN Time on expiration" is changed to "TIN Time on inspiration"

Page 32: "…has often been been distinguished in the literature…" is changed to "….   has often been distinguished in the literature…"

Page 47: "… 145 after four weeks and…" is changed to "…143 after four weeks and …."

Page 56: "…interaction effects involving group difference in paper 3;…" is changed to "…interaction effects involving group difference in paper 2;…"

In paper 2 page 182, page 186 and table 3 page, 187, the abbreviation SRGQ is supposed to be SGRQ.

In paper 2, page 185 in figure 1, the excluded number under enrollment is supposed to be n=191. In total n= 173 declined to participate and n=18 did not attend or called to cancel the appointment.

Appendix 1 – Previous randomized control trials on breathing-control exercises and respiratory muscle training that are not covered in the overview article in this thesis (paper 1).

Study (year)	Aim	Study design (n)	Intervention	Outcome measures	Authors' conclusion
Combination of breathing-control exercises					
Valenza et al. (2013)	To assess the effects of controlled breathing techniques among patient hospitalized with COPD exacerbation on dyspnea, sleep disturbance, anxiety, depression and quality of life	Pilot RCT TG (n=23) CG (n=23)	- Controlled breathing programme that included relaxation exercises, pursed-lip breathing and active expiration (i.e., diaphragmatic breathing) at the hospital for 30 min × 2 per day with training by a physiotherapist during the hospital period. - Control group received standard care.	HADS, SGRQ (symptom, activity, impact, total score), mMRC, EUroQOL 5D, Handgrip strength, Respiratory muscle strength	Significant effects were found in favour of intervention group on dyspnoea, anxiety and mobility.
Lin. et al. (2012)	To assess the effects of respiratory training on lung function, activity and quality of life in patients with COPD	RCT TG (n=20) CG (n=20)	- Health education and respiratory training containing pursed-lip breathing (10 min), diaphragmatic breathing (10 min) and unsupported upper extremity exercises (30 times) × 2 per day for 12 weeks. - Control group received routine health education for 12 weeks.	SGRQ (symptom, activity, impact, total score), mMRC, CO_2, SpO_2, spirometry, 6-min walk test	Significant effects were found in favour of intervention group in lung function variables (i.e., FEV_1, FVC), 6-min walk test and quality of life (i.e., symptom, activity, impact and total score).
Zakerimogha dam et al. (2011)	To assess the effect of breathing exercises on fatigue level of patients with COPD	RCT TG (n=30) CG (n=30)	- Respiratory group practised pursed-lip breathing, diaphragmatic breathing and effective coughing 4 times per day for 10 days. - Control group received routine treatment.	Fatigue severity scale and the respiratory exercises usages checklist	Fatigue improved in favour of respiratory exercise group.
Deep breathing					
Mathew and D'Silva (2011)	To evaluate the effect of deep-breathing exercise on pulmonary function in patients with COPD	RCT TG (n=20) CG (n=20)	- Deep breathing performed 2 times per day for 7 days. - No information on control group.	Breathing pattern, lung function variables FVC and FEV1	Authors concluded that the practice of deep breathing improves pulmonary function.

Pursed-lip breathing via Skype

Mark et al. (2013)	To measure the effect of pursed-lip breathing delivered over Skype on dyspnoea, physical activity, health-related quality of life and self-efficacy in patients with COPD	RCT TG (n=12) CG (n=12)	- A one-hour face-to-face session was given by a respiratory physiotherapist. Information was given on anatomy and physiology of the lung and pursed-lip breathing introduction was given before instruction via Skype on pursed-lip breathing for 15 minutes over four weeks. - There was a waiting list control group.	SOBQ, VAS, HAP, SF-36, Stanford Chronic Disease Self-efficacy Scale	Conclusions from the authors are mixed. They suggested that when dyspnoea worsens, pursed-lip breathing seems to be more effective in relation to activity and quality of life.

Biofeedback breathing

van Gestel et al. (2012)	To assess the effect of pulmonary rehabilitation plus controlled breathing intervention compared with only pulmonary rehabilitation in patients with COPD	RCT TG (n=20) CG (n=20)	- Four weeks pulmonary rehabilitation programme plus controlled breathing training 30 min × 10 using a biofeedback device for daily home practice and trained diaphragmatic breathing. The patients were instructed to breathe more slowly with the background breathing pattern showing up on a display on the device. No instruction was given during the sessions. - Control group received pulmonary rehabilitation.	Pulmonary function, 6-min walk test, CRQ and cardiac autonomic function	No effect was found on lung function, 6-min walk test, cardiac autonomic function and quality of life.

Relaxation, music listening and/or distraction stimuli

Singh et al. (2009)	To evaluate the effects of music and progressive muscle relaxation in hospitalized patients with COPD exacerbations	RCT Music group (n=32) Muscle relaxation group (n=32)	- Music group listened to self-selected music on tape (i.e., between six non-lyrical Indian classical instrumental music pieces). - Relaxation group sat comfortably and listened to a tape with instruction on muscle relaxation techniques. - Two sessions were performed by both groups.	Dyspnea on VAS, Spielberger Anxiety Inventory (i.e., state anxiety, trait anxiety), blood pressure, pulse rate and respiratory rate	Music and relaxation were effective in reducing anxiety, dyspnoea, systolic blood pressure, pulse rate and respiratory rate in two sessions in people with COPD. The changes in the music-listening group were greater than in the relaxation group.
Louie (2004)	To determine whether guided imagery relaxation affects anxiety-related physical symptoms in people with COPD	RCT TG (n=13) CG (n=13)	- Sessions on guided imagery, listening to a relaxation tape with instruction on how to construct a pleasant mental picture and how to perform abdominal breathing with soft music playing in the background for 30 minutes × 6. - Control group was instructed to sit quietly without listening to the relaxation tape.	SpO₂, heart rate, upper thoracic EMG, skin conductance, peripheral skin temperature and Borg Scale for breathlessness	There was a significant increase in oxygen saturation, but no significant effect on the other parameters.

Author	Aim	Design	Measures	Results
Gift et al. (1992)	To evaluate whether individuals with COPD can be taught progressive muscle relaxation using a tape with instruction to improve anxiety, dyspnoea and airway obstruction compared with a control group	RCT TG (n=13) CG (n=13)	- Treatment group was placed in a comfortable position while listening to a tape with instruction on relaxation techniques that aimed at releasing tension in 16 muscle groups in six sessions. - Control group sat quietly for 20 minutes in four sessions.	Skin temperature, heart rate, respiratory rate, Spielberger Anxiety Inventory (i.e., state anxiety, trait anxiety), VAS breathlessness and Peak flow meter	Dyspnoea, anxiety and airway obstruction were reduced in the relaxation group but became worse or remained the same in the control group.

Respiratory muscle training

Author	Aim	Design	Measures	Results
Petrovic et al. (2012)	To analyse the effect of inspiratory muscle training on exercise capacity, dyspnoea and inspiratory fraction during exercise in patients with COPD	RCT TG (n=10) CG (n=10)	- Treatment group trained to improve inspiratory muscle strength and endurance every day for eight weeks. - Control group. - All patients were in stage II or III of COPD.	Pulmonary function test, ergometer cycle test with Borg dyspnoea rating	Inspiratory muscle strength and endurance training increased exercise capacity and respiratory muscle endurance performance and reduced dynamic hyperinflation, breathing pattern and breathlessness during exercise.
Bataglia et al. (2009)	To examine the use of a new expiratory device in association with a previously used inspiratory device to improve MIP, MEP and dyspnoea in patients with mild to very severe COPD	RCT TG (n=16) CG (n=16)	- Treatment group trained for 15 minutes with an expiratory device and inspiratory device seven days a week for 12 months. - Control group received sham.	MIP, MEP and Borg dyspnoea rating	Home exercise with expiratory and inspiratory devices lead to significant improvement of MIP, MEP and dyspnoea perception.

CG=control group, CO₂=carbon dioxide, CRQ=chronic respiratory questionnaire, EUroQOL 5D=European Quality of Life Questionnaire, FEV₁=forced expiratory volume in one second, FVC=forced volume capacity, MEP=maximal expiratory pressure, MIP=maximal inspiratory pressure, mMRC=Modified Medical Research Council, HADS=Hospital Anxiety and Depression Scale, HAP=Human Activity Profile, RCT=randomized controlled trial, SF-36=Short-form 36, SGRQ=St. George's Respiratory Questionnaire, SOBQ=Shortness of Breath Questionnaire, SpO₂=saturation pressure of oxygen, TG=training group, VAS=visual analogue scale

Data bases: PubMed, OVID, CINAHL, PsycINFO and AMED.

Search terms: The MeSH terms/keyword/search words were: 1. "pulmonary disease, chronic obstructive", 2. "pulmonary emphysema", 3. "bronchitis chronic", 4. "respiration", 5. "breathing control" (this MeSH term contains respiratory muscle training), 6. "yoga", 7. "pranayama", 8. "mind–body therapies", 9. "muscle-stretching exercises", 10. "relaxation", 11. "breathing-control exercises", 12. "diaphragmatic breathing", 13. "pursed-lip breathing", 14. "device-guided breathing", 15. "biofeedback", 16. "music therapy" and 17. "distraction". Studies were included if they were a randomized control trial on breathing-control exercises and respiratory muscle training. The search was performed up to 26 September 2014.
Combinations: 18. 1–3 or 19–30. 18 and 4–17, 19–30, or limit RCT and control trial.
Search result: n=458 with accounting for duplicates

Appendix 2 – AMSTAR

1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable

7. Was the scientific quality of the included studies assessed and documented?
'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.

☐ Yes
☐ No
☐ Can't answer
☐ Not applicable

8. Was the scientific quality of the included studies used appropriately in formulating conclusions?
 The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.

☐ Yes
☐ No
☐ Can't answer
☐ Not applicable

9. Were the methods used to combine the findings of studies appropriate?
For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I²). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).

☐ Yes
☐ No
☐ Can't answer
☐ Not
 applicable

10. Was the likelihood of publication bias assessed?
An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).

☐ Yes
☐ No
☐ Can't answer
☐ Not applicable

11. Was the conflict of interest stated?

Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.

☐ Yes
☐ No
☐ Can't answer
☐ Not applicable

With permission from AMSTAR (2015)