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Oxygen for breathlessness in patients with chronic obstructive pulmonary disease who do not qualify for home oxygen therapy (Review)

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[Intervention Review]

Oxygen for breathlessness in patients with chronic obstructive pulmonary disease who do not qualify for home oxygen therapy

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ABSTRACT

Background

Breathlessness is a cardinal symptom of chronic obstructive pulmonary disease (COPD). Long-term oxygen therapy (LTOT) is given to improve survival time in people with COPD and severe chronic hypoxaemia at rest. The efficacy of oxygen therapy for breathlessness and health-related quality of life (HRQOL) in people with COPD and mild or no hypoxaemia who do not meet the criteria for LTOT has not been established.

Objectives

To determine the efficacy of oxygen versus air in mildly hypoxaemic or non-hypoxaemic patients with COPD in terms of (1) breathlessness; (2) HRQOL; (3) patient preference whether to continue therapy; and (4) oxygen-related adverse events.

Search methods

We searched the Cochrane Airways Group Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and Embase, to 12 July 2016, for randomised controlled trials (RCTs). We handsearched the reference lists of included articles.

Selection criteria

We included RCTs of the effects of non-invasive oxygen versus air on breathlessness, HRQOL or patient preference to continue therapy among people with COPD and mild or no hypoxaemia (partial pressure of oxygen (PaO_2) > 7.3 kPa) who were not already receiving LTOT. Two review authors independently assessed articles for inclusion in the review.

Data collection and analysis

Two review authors independently collected and analysed data. We assessed risk of bias by using the Cochrane 'Risk of bias tool'. We pooled effects recorded on different scales as standardised mean differences (SMDs) with 95% confidence intervals (CIs) using random-effects models. Lower SMDs indicated decreased breathlessness and reduced HRQOL. We performed subanalyses and sensitivity analyses and assessed the quality of evidence according to the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach.

Main results

Compared with the previous review, which was published in 2011, we included 14 additional studies (493 participants), excluded one study and included data for meta-analysis of HRQOL. In total, we included in this review 44 studies including 1195 participants, and we included 33 of these (901 participants)in the meta-analysis.

We found that breathlessness during exercise or daily activities was reduced by oxygen compared with air (32 studies; 865 participants; SMD -0.34, 95% CI -0.48 to -0.21; I^2 = 37%; low-quality evidence). This translates to a decrease in breathlessness of about 0.7 points on a 0 to 10 numerical rating scale. In contrast, we found no effect of short-burst oxygen given before exercise (four studies; 90 participants; SMD 0.01, 95% CI -0.26 to 0.28; I^2 = 0%; low-quality evidence). Oxygen reduced breathlessness measured during exercise tests (25 studies; 442 participants; SMD -0.34, 95% CI -0.46 to -0.22; I^2 = 29%; moderate-quality evidence), whereas evidence of an effect on breathlessness measured in daily life was limited (two studies; 274 participants; SMD -0.13, 95% CI, -0.37 to 0.11; I^2 = 0%; low-quality evidence).

Oxygen did not clearly affect HRQOL (five studies; 267 participants; SMD 0.10, 95% CI -0.06 to 0.26; I^2 = 0%; low-quality evidence). Patient preference and adverse events could not be analysed owing to insufficient data.

Authors' conclusions

We are moderately confident that oxygen can relieve breathlessness when given during exercise to mildly hypoxaemic and non-hypoxaemic people with chronic obstructive pulmonary disease who would not otherwise qualify for home oxygen therapy. Most evidence pertains to acute effects during exercise tests, and no evidence indicates that oxygen decreases breathlessness in the daily life setting. Findings show that oxygen does not affect health-related quality of life.

PLAIN LANGUAGE SUMMARY

Oxygen therapy for breathless people with chronic obstructive pulmonary disease with only mildly or moderately decreased oxygen in the blood

Review question

We reviewed the evidence regarding effects of oxygen compared with air on breathlessness in people with chronic obstructive pulmonary disease (COPD) with only mildly or moderately decreased blood oxygen levels.

Background

People with COPD are sometimes prescribed oxygen therapy to reduce the severity of breathlessness. However, the use of oxygen in people who do not have severely reduced levels of oxygen in their bloodstream remains controversial, as little is known about its effectiveness. Additionally, oxygen is relatively costly and is not given without risk, particularly to smokers because of the risk of fire.

Study characteristics

We examined the research published to 12 July 2016. We included studies of oxygen therapy versus air delivered through nasal prongs or mask during exertion, continuously, 'as needed' over a defined period or as short-burst oxygen before exertion. Study participants were 18 years of age or older, had received a diagnosis of COPD, had low oxygen levels in the blood and did not receive long-term oxygen therapy. We included a total of 44 studies (1195 participants) in this review. Compared with the previous review, which was published in 2011, we have added 14 studies (493 participants) to this review.

Key results

We found that oxygen can modestly reduce breathlessness. To be effective, oxygen has to be given during exercise. Most studies evaluated oxygen given during exercise testing in the laboratory. Oxygen therapy during daily life had uncertain effects on breathlessness and did not clearly change patient quality of life.

Quality of the evidence

We rated the quality of evidence using one of the following grades: very low, low, moderate or high. For very low-quality evidence, we were uncertain about the results. With high-quality evidence, we were very certain about the results. We found that evidence for oxygen given for breathlessness was moderate to low. We are moderately confident that oxygen can relieve breathlessness when given

during exercise to people with COPD with mildly or moderately decreased blood oxygen levels. However, most studies reported acute effects during an exercise test, and no evidence suggests that oxygen decreases breathlessness during daily life. Findings indicate that oxygen does not affect health-related quality of life.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Oxygen for breathlessness in patients with chronic obstructive pulmonary disease who do not qualify for home oxygen therapy

Patient or population: patients with chronic obstructive pulmonary disease who do not qualify for home oxygen therapy
Intervention: oxygen delivered through a non-invasive method
Comparison: air delivered through the same non-invasive method

Outcomes	Difference (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
Breathlessness - all trials Lower score indicates improvement in breathlessness	**SMD 0.31, SD lower** (0.43 lower to 0.2 lower)	865 (32)	⊕⊕◯◯ Low[a]	This corresponds to 0.65 points lower (0.90 lower to 0.42 lower) on a 0-10 NRS.*
Breathlessness - subgroup analysis - studies using short-burst oxygen Lower score indicates improvement in breathlessness	**SMD 0.03, SD lower** (0.28 lower to 0.22 higher)	90 (4)	⊕⊕◯◯ Low[b]	This corresponds to 0.06 points lower (0.59 lower to 0.46 higher) on a 0-10 NRS.*
Breathlessness - subgroup analysis - studies not using short-burst oxygen Lower score indicates improvement in breathlessness	**SMD 0.36, SD lower** (0.48 lower to 0.24 lower)	775 (28)	⊕⊕◯◯ Low[a]	This corresponds to 0.76 points lower (1.01 lower to 0.50 lower) on a 0-10 NRS.*
Breathlessness - subgroup analysis - studies measuring during exercise test Lower score indicates improvement in breathlessness	**SMD 0.34, SD lower** (0.46 lower to 0.22 lower)	591 (30)	⊕⊕⊕◯ Moderate[c]	This corresponds to 0.71 points lower (0.97 lower to 0.46 lower) on a 0-10 NRS.*
Breathlessness - subgroup analysis - studies not measuring during exercise test Lower score indicates improvement in breathlessness	**SMD 0.13, SD lower** (0.37 lower to 0.11 higher)	274 (2)	⊕⊕◯◯ Low[b]	This corresponds to 0.27 points lower (0.78 lower to 0.23 higher) on a 0-10 NRS.*

Health-related quality of life - all trials Higher scores indicate improved health-related quality of life	**SMD 0.12, SD higher** (0.04 lower to 0.28 higher)	267 (5)	⊕⊕◯◯ Low[b]	This corresponds to 0.25 points higher (0.09 lower to 0.59 higher) on a 0-10 NRS.*

*Difference on a 0-10 NRS calculated using the SD of 2.1 for the COPD group in Abernethy 2010 for individual participant data.
CI: confidence interval; OR: odds ratio; RR: risk ratio.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect but may be substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a] Although the effect was consistent in exercise tests in the laboratory setting, evidence of an effect was limited for domiciliary oxygen in daily life.
[b] Few studies.
[c] Graded as moderate, as most evidence pertained to breathlessness during exercise tests.

BACKGROUND

Description of the condition

Breathlessness, a cardinal symptom of chronic obstructive pulmonary disease (COPD), is distressing to both patients and caregivers. Breathlessness is defined as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity" (Parshall 2012). Breathlessness is multi-factorial (Laviolette 2014) and arises as a combination of underlying pathologies involving neural pathways and subjective central perception (Parshall 2012).

Description of the intervention

Treatment of patients with breathlessness includes management of the underlying cause(s). However, breathlessness often persists despite optimal management of underlying disease(s), that is, chronic breathlessness. Pharmacological treatment with the strongest evidence base for relieving breathlessness consists of low-dose opioids (Ekstrom 2015a). People with insufficiently relieved breathlessness are then left to try any of a number of interventions for which evidence is limited, such as supplemental oxygen therapy.

Supplemental oxygen therapy most often is administered through nasal prongs or a mask and may be prescribed continuously, during exercise or as a short burst before exercise (Hardinge 2015). Oxygen sources include oxygen concentrators (which concentrate oxygen from ambient air), cylinders of compressed oxygen and flasks of liquid oxygen. Equipment can be stationary in the home and/or portable (Hardinge 2015).

Long-term oxygen therapy (LTOT) refers to oxygen given for 15 or more hours per day to prolong survival time in people with COPD and chronic severe resting hypoxaemia (partial pressure of oxygen (PaO_2) < 7.4 kPa) or moderate hypoxaemia (PaO_2 7.4 to 7.8 kPa), together with signs of right-sided heart failure or secondary polycythemia (Cranston 2005; MRCWP 1981; NOTTG 1980). Studies in severe hypoxaemia have not evaluated whether LTOT relieves breathlessness or improves health-related quality of life (HRQOL) (Cranston 2008).

Palliative oxygen therapy refers to supplemental oxygen given to relieve symptoms in people with COPD who have no to moderate

hypoxaemia.

How the intervention might work

Oxygen given before or during physical activity might increase oxygen content of and oxygen delivery to exercising muscles. This might prolong aerobic metabolism during exertion and may decrease muscle fatigue and formation of lactic acid (O'Donnell 2001), which could lead to a decreased level of ventilatory drive and increased ventilatory capacity at a given work rate, thereby decreasing the mismatch between ventilatory drive and work and perceived severity of breathlessness (O'Donnell 2001; Parshall 2012).

Why it is important to do this review

A Cochrane review of the efficacy of palliative oxygen for breathlessness was published in 2011 (Uronis 2011; Uronis 2015). A meta-analysis of 18 trials (431 participants) reported that supplemental oxygen during exercise and activities reduced breathlessness to a greater extent than air. Short-burst oxygen before exercise did not decrease breathlessness. Review authors could not analyse HRQOL because data were insufficient. Most evidence pertained to exercise testing performed in the laboratory setting (Uronis 2011; Uronis 2015). A subsequent Cochrane review of four studies (331 participants) suggested that longer-term treatment with ambulatory oxygen relieves breathlessness more effectively than air after exercise in people with COPD (Ameer 2014). Current guidelines do not recommend palliative oxygen therapy in COPD, as evidence on treatment in the domiciliary and daily life setting remains insufficient (Ekstrom 2015b; Hardinge 2015). Despite this, palliative oxygen therapy might be commonly prescribed in clinical practice (Abernethy 2005; Stringer 2004).

The discrepancy between current clinical practice and available evidence has important implications. First, patients may be prescribed ineffective treatment. Second, oxygen therapy is not a benign intervention. Functional restriction caused by tubing, concentrators or cylinders and the "sick role" may limit quality of life. People also express concern about being reliant on a machine. Nasal cannulae can lead to nasal irritation and can increase the risk of nosebleeds. Oxygen therapy carries a fire risk, particularly for smokers (Robb 2003). Serious burn injuries seem infrequent in LTOT with strict adherence to eligibility criteria and contraindications, including smoking cessation (Tanash 2015). A small but increased risk of exacerbated hypercarbia is possible, and home oxygen therapy is relatively expensive. If patients do not meet the criteria for LTOT, they may have to pay for oxygen therapy themselves or may receive it on compassionate use grounds (Guyatt 2000). Improved evidence regarding optimal use of palliative oxygen therapy is needed.

Since the previous Cochrane reviews were published (Uronis 2011; Uronis 2015), several studies of palliative oxygen therapy have been reported, including some larger trials (Abernethy 2010 and Moore 2011).

This is an update of the Cochrane review published in 2011 (Uronis 2011; Uronis 2015).

OBJECTIVES

To determine the efficacy of oxygen versus air in mildly hypoxaemic or non-hypoxaemic patients with COPD in terms of (1) breathlessness; (2) HRQOL; (3) patient preference whether to continue therapy; and (4) oxygen-related adverse events.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs).

Types of participants

We included studies with participants 18 years of age or older who had COPD, had mild or no hypoxaemia (mean PaO_2 > 7.3 kPa) and did not receive LTOT. For studies that also included participants without COPD, we obtained from study authors individual participant data for those with COPD and included only these data in the analyses.

Types of interventions

We included studies of oxygen therapy versus air delivered by a non-invasive method at any inspired dose above that of ambient air (> 21%). Oxygen/air should have been delivered during exertion, continuously or 'as needed' over a defined period, or as short-burst oxygen before exertion. Short-burst oxygen was defined as therapy given during a short, defined period just before exertion. We did not include short-burst oxygen given only after exertion.

Types of outcome measures

Primary outcomes

1. Level of breathlessness measured on any validated scale

Secondary outcomes

1. HRQOL measured on any validated scale
2. Blinded participant preference to continue therapy
3. Adverse events

Search methods for identification of studies

Electronic searches

We searched the Cochrane Airways Group Specialised Register of trials, which is derived from systematic searches of multiple bibliographic databases and from handsearching of respiratory journals and meeting abstracts (see Appendix 1 for details). We conducted additional searches of the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 6), MEDLINE (to 12 July 2016) and Embase (to 12 July 2016). Search strategies are shown in Appendix 2; Appendix 3; Appendix 4; and Appendix 5. We also searched ClinicalTrials.gov (www.ClinicalTrials.gov) and the World Health Organization (WHO) trials portal (www.who.int/ictrp/en/) for ongoing trials by using appropriately adapted search terms. We searched all databases from their inception to 12 July 2016, with no restriction on language of publication.

Searching other resources

We handsearched relevant review articles and reference lists of identified articles.

Data collection and analysis

Selection of studies

Two review authors (ME and ZA) independently selected studies that fulfilled all inclusion criteria.

1. RCT.
2. Included participants 18 years of age or older.
3. At least one participant with COPD.
4. Mean PaO_2 > 7.3 kPa at baseline.
5. Only participants not already receiving LTOT.
6. Comparison of oxygen versus air at any dose delivered through a non-invasive method.
7. Endpoint of breathlessness or HRQOL.

Data extraction and management

Two review authors (ME and ZA) independently extracted data and resolved disagreements by consensus and discussion with a third review author (DC), if needed. We contacted the authors of primary studies to obtain additional information when necessary.

Assessment of risk of bias in included studies

Two review authors (ME and ZA) independently assessed each study for risk of bias in terms of allocation sequence generation, allocation concealment, blinding of participants and outcome assessors, handling of missing data, selective outcome reporting and other threats to the validity of studies, in line with recommendations provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We conducted a retrospective risk of bias assessment using the above method applied to all studies from the review published in 2011 (Uronis 2011).

Measures of treatment effect

We performed meta-analyses as appropriate and possible, given available data. We analysed outcomes on different scales as standardised mean differences (SMDs) using random-effects models. We compared within-patient effects from both periods of cross-over trials. Meta-analyses included post scores only. For studies for which post scores were not available, we reported changes from baseline scores separately. For breathlessness during exercise, we used scores measured at a similar time point in both groups (iso-scores) when available. For studies evaluating different oxygen doses, we included only the lowest dose in the analysis. We reversed St George's Respiratory Quotient (SGRQ) scores (as increasing scores indicate worse quality of life), so that higher scores on all HRQOL measures indicated better quality of life in all analyses.

Unit of analysis issues

We estimated standard errors for paired outcome data from cross-over trials, according to Follmann 1992. We estimated correlations between repeated outcomes from P values when available, and for studies for which little evidence was available to impute a correlation coefficient from another trial, we assumed a value of 0.5 (Follmann 1992). We performed sensitivity analyses using different imputed correlations.

Dealing with missing data

When statistics essential for analysis were missing (e.g. group means and standard deviations for both groups were not reported) and could not be calculated from other data, we attempted to contact study authors to obtain the missing data. We assumed that loss of participants that occurred before baseline measurements were taken had no effect on eventual outcome data provided by the study. We assessed any losses that occurred after baseline measurements had been taken and discussed them on an intention-to-treat basis.

Assessment of heterogeneity

We assessed statistical heterogeneity by using the I^2 statistic and by inspecting funnel plots.

Assessment of reporting biases

We assessed possible publication bias by using funnel plots.

Data synthesis

We performed meta-analyses by using Review Manager software version 5.3 (RevMan 2014).

Subgroup analysis and investigation of heterogeneity

We conducted the following a priori subgroup analyses on the presence/absence of:

1. short-burst oxygen therapy;
2. exertional desaturation (oxygen saturation (SaO_2) < 88% as entry criteria, or mean PaO_2 < 8 kPa on exertion);
3. baseline mean PaO_2 breathing air < 9.3 kPa;
4. measurement during exertion;
5. laboratory setting (compared with domiciliary setting);
6. measured acute oxygen effect (test on oxygen vs air) compared with long-term oxygen effect (test on the same inhaled gas after a period of oxygen or air); and
7. mean oxygen dose > 2 L/min. For studies that reported only administered fraction of inspired oxygen (FiO_2), an oxygen dose > 2 L/min was defined as FiO_2 > 0.27.

Sensitivity analysis

We conducted the following a priori sensitivity analyses by excluding studies with:

1. measurement at peak exertion (compared with iso-time);
2. high risk of bias for any bias category;
3. any participant without COPD; and
4. outlier findings (based on forest and funnel plots).

RESULTS

Description of studies

See Characteristics of included studies and Characteristics of excluded studies tables.

Participant characteristics

All 1195 participants included in the analysis had COPD (Table 1). Baseline PaO_2 was provided in 30 of 44 studies, ranging from 7.7 to 11.3 kPa. Twelve of the remaining studies provided baseline oxygen saturation ranging from 90% to 97% (Table 1).

Twenty studies reported mean baseline breathlessness at rest as follows: visual analogue score (VAS) score 5 to 40 mm (100 mm VAS); Borg score 0.1 to 1 point (Table 1).

Intervention characteristics

All studies compared oxygen versus air, delivered via the same non-invasive method in both groups. The most frequent mode of administration was the nasal cannula (22 studies) (Abernethy 2010; Davidson 1988; Dyer 2012; Eaton 2002; Eaton 2006; Haidl 2004; Jolly 2001a; Jolly 2001b; Knebel 2000; Kurihara 1989; Lewis 2003; McDonald 1995; McKeon 1988a; McKeon 1988b; Moore 2011; Nonoyama 2007; Ringbaek 2013; Rooyackers 1997a; Rooyackers 1997b; Spielmanns 2014; Wadell 2001; Woodcock 1981) followed by mouthpiece/valve (13 studies) (Bruni 2012a; Bruni 2012b; Dean 1992; Emtner 2003a; Emtner 2003b; Eves 2006; Laude 2006; Maltais 2001; Moore 2009; O'Donnell 1997; Scorsone 2010; Somfay 2001; Swinburn 1984) and mask (eight studies) (Killen 2000; Leach 1992; Miki 2012: Nandi 2003; O'Driscoll 2011; Oliveira 2012a; Oliveira 2012b; Voduc 2010) or unknown (one study) (Ishimine 1995).

Doses of oxygen provided ranged from 2 to 6 L/min via nasal cannula, and FiO_2 ranged from 24% to 75% via mask/mouthpiece (Table 1).

A total of 32 studies (Bruni 2012a; Bruni 2012b; Davidson 1988; Dean 1992; Eaton 2006; Emtner 2003a; Emtner 2003b; Eves 2006; Haidl 2004; Ishimine 1995; Jolly 2001a; Jolly 2001b; Killen 2000; Knebel 2000; Kurihara 1989; Laude 2006; Leach 1992; Maltais 2001; McKeon 1988b; Miki 2012; O'Donnell 1997; Oliveira 2012a; Oliveira 2012b; Rooyackers 1997a; Rooyackers 1997b; Scorsone 2010; Somfay 2001; Spielmanns 2014; Swinburn 1984; Voduc 2010; Wadell 2001; Woodcock 1981) provided continuous oxygen during exercise testing - six-minute walk test (6MWT), endurance shuttle walk test, incremental shuttle walk test, step test or cycle exercise test. .

Six studies (Abernethy 2010; Eaton 2002; McDonald 1995; Moore 2011; Nonoyama 2007; Ringbaek 2013) provided domiciliary oxygen during daily life and activities.

Four studies (Killen 2000; Lewis 2003; McKeon 1988a; Nandi 2003) gave participants short-burst oxygen therapy before exertion.

Outcome characteristics

Breathlessness

Twenty-nine studies (Bruni 2012a; Bruni 2012b; Dean 1992; Eaton 2002; Emtner 2003a; Emtner 2003b; Eves 2006; Haidl 2004; Jolly 2001a; Jolly 2001b; Kurihara 1989; Laude 2006; Lewis 2003; Maltais 2001; McDonald 1995; Miki 2012; Moore 2009; Nonoyama 2007; O'Donnell 1997; O'Driscoll 2011; Oliveira 2012a; Oliveira 2012b; Ringbaek 2013; Rooyackers 1997a; Rooyackers 1997b; Scorsone 2010; Somfay 2001; Voduc 2010; Wadell 2001) measured breathlessness using a modified Borg scale, nine studies (Davidson 1988; Killen 2000; Knebel 2000; Leach 1992; McKeon 1988a; McKeon 1988b; Nandi 2003;

Swinburn 1984; Woodcock 1981) used a VAS and five studies (Abernethy 2010; Dyer 2012; Eaton 2006; Ishimine 1995; Moore 2011) used other scales (Table 1).

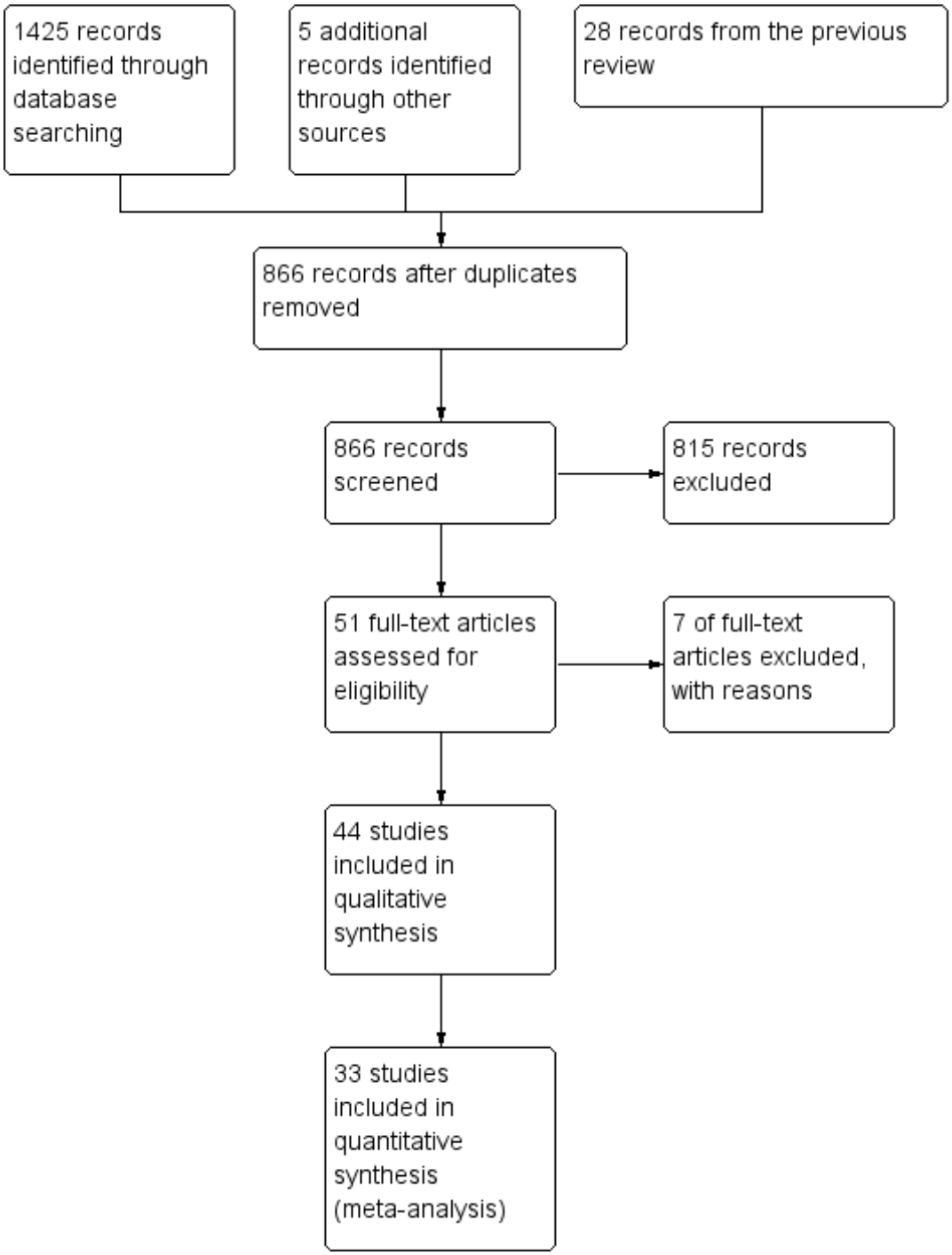
HRQOL

Seven studies (Eaton 2002; Eaton 2006; Emtner 2003a; Emtner 2003b; Moore 2011; Rooyackers 1997a; Rooyackers 1997b) measured HRQOL as Chronic Respiratory Questionnaire (CRQ) total score, 10 studies (Dyer 2012; Eaton 2002; Eaton 2006; Emtner 2003a; Emtner 2003b; McDonald 1995; Moore 2011; Nonoyama 2007; Rooyackers 1997a; Rooyackers 1997b) as CRQ subdomains, five studies (Eaton 2002; Eaton 2006; Emtner 2003a; Emtner 2003b; Spielmanns 2014) as Short Form-36 (SF-36) total score and two studies (Nonoyama 2007; Ringbaek 2013) as SGRQ total score. One study (Abernethy 2010) measured perceived overall well-being on a 0 to 10 VAS and HRQOL over weeks or months (Table 1), with higher scores indicating better HRQOL.

Results of the search

Of an identified 866 unique records, we included 44 studies (1195 participants) in this update review (Figure 1). Compared with the previous review, which was published in 2011 (Uronis 2011), we included 14 additional studies (Abernethy 2010; Bruni 2012a; Bruni 2012b; Dyer 2012; Miki 2012; Moore 2011; Nonoyama 2007; O'Driscoll 2011; Oliveira 2012a; Oliveira 2012b; Ringbaek 2013; Scorsone 2010; Spielmanns 2014; Voduc 2010), and we excluded one additional trial (Garrod 2000).

Figure 1. Study flow diagram.



Included studies

We have provided characteristics of the 44 included studies in the Characteristics of included studies table and in Table 1. Of 44 included studies, 31 were cross-over trials (Bruni 2012a; Bruni 2012b; Davidson 1988; Dean 1992; Eaton 2002; Eves 2006; Ishimine 1995; Jolly 2001a; Jolly 2001b; Killen 2000; Knebel 2000; Kurihara 1989; Laude 2006; Leach 1992; Lewis 2003; Maltais 2001; McDonald 1995; McKeon 1988a; McKeon 1988b; Miki 2012; Moore 2009; Nandi 2003; Nonoyama 2007; O'Donnell 1997; O'Driscoll 2011; Oliveira 2012a; Oliveira 2012b; Somfay 2001; Swinburn 1984; Voduc 2010; Woodcock 1981) and 13 were parallel-group trials (Abernethy 2010; Dyer 2012; Eaton 2006; Emtner 2003a; Emtner 2003b; Haidl 2004; Moore 2011; Ringbaek 2013; Rooyackers 1997a; Rooyackers 1997b; Scorsone 2010; Spielmanns 2014; Wadell 2001).

Ten studies (Bruni 2012a; Bruni 2012b; Emtner 2003a; Emtner 2003b; Jolly 2001a; Jolly 2001b; Oliveira 2012a; Oliveira 2012b; Rooyackers 1997a; Rooyackers 1997b) included two different comparisons of independent groups, which we included in the analysis.

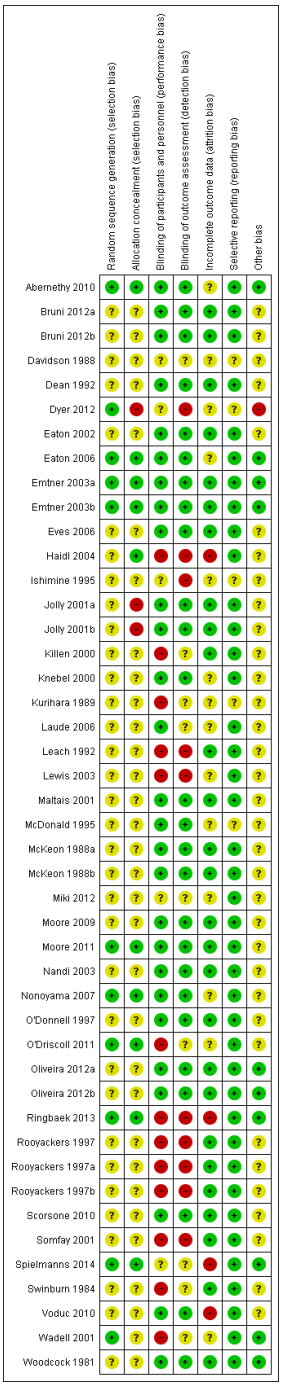
Excluded studies

We have presented excluded trials with reasons for exclusion in the Characteristics of excluded studies table. We identified two ongoing or recently completed trials but did not include them in this review, as data were unavailable: the Long-Term Oxygen Therapy Trial (LOTT; registered at ClinicalTrials.gov: NCT00692198) of supplemental oxygen in 738 participants with COPD and moderate hypoxaemia at rest and/or exertion, which included measures of breathlessness and HRQOL; and another recently completed cross-over study comparing effects of supplemental oxygen versus air on breathlessness during exercise testing in 11 participants with COPD, which was presented as an abstract (Vesteng 2015).

Risk of bias in included studies

We have provided risk of bias judgements for each study at the end of each Characteristics of included studies table and have summarised each risk of bias category in Figure 2. Methods were poorly reported in most of the included studies. We assessed risk of bias as mostly unclear regarding selection bias, but as low for more than half of studies regarding performance, detection, attrition and reporting bias, and as mostly unclear regarding other biases (Figure 2).

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation

Although all studies were described as randomised, we could verify that sequence generation was adequate in only 11 studies (Abernethy 2010; Dyer 2012; Eaton 2006; Emtner 2003a; Emtner 2003b; Moore 2011; Nonoyama 2007; O'Driscoll 2011; Ringbaek 2013; Spielmanns 2014; Wadell 2001). Concealment of allocation was adequate in 10 studies and inadequate in three studies (Figure 2). For remaining studies, we had insufficient information to determine risk of bias for allocation procedures.

Blinding

Masking of treatment was undertaken in several studies. For five studies, we were unable to determine how blinding of study participants or investigators had been achieved. For 12 studies (Haidl 2004; Killen 2000; Kurihara 1989; Leach 1992; Lewis 2003; O'Driscoll 2011; Ringbaek 2013; Rooyackers 1997a; Rooyackers 1997b; Somfay 2001; Swinburn 1984; Wadell 2001), we found that blinding was not undertaken, or investigators knew which containers contained oxygen. The remaining 27 studies attempted blinding of both study participants and study investigators (Figure 2).

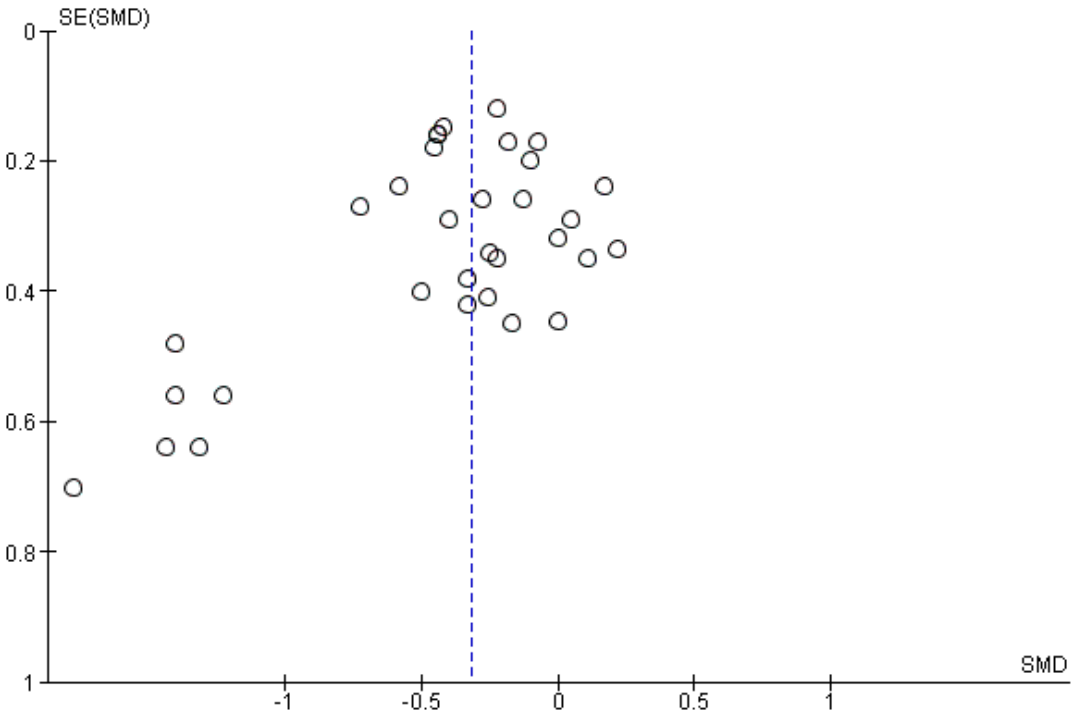
Incomplete outcome data

Twenty-six studies (Bruni 2012a; Bruni 2012b; Dean 1992; Eaton 2002; Emtner 2003a; Emtner 2003b; Eves 2006; Jolly 2001a; Jolly 2001b; Killen 2000; Leach 1992; Maltais 2001; McKeon 1988a; McKeon 1988b; Moore 2009; Moore 2011; Nandi 2003; O'Donnell 1997; Oliveira 2012a; Oliveira 2012b: Rooyackers 1997a; Rooyackers 1997b; Scorsone 2010; Somfay 2001; Swinburn 1984; Woodcock 1981) reported no withdrawals. Cross-over studies analyse within-participant differences; therefore, participants who did not complete both treatment periods were not included in the analyses. For the remaining studies, we could not reliably ascertain how missing data were handled (Figure 2).

Selective reporting

Possible publication bias on the effect of oxygen on breathlessness was indicated by the funnel plot shown in Figure 3. Studies showing a larger positive effect of oxygen on breathlessness were more likely to have lower precision. Asymmetry was apparent, with few studies with low precision reporting no or non-beneficial effects of oxygen on breathlessness (Figure 3).

Figure 3. Funnel plot of comparison: 1 Oxygen versus air, outcome: 1.1 Breathlessness - all trials.



Other potential sources of bias

We categorised the risk of other sources of bias as high for Dyer 2012 and as unclear for most studies.

Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings table

All comparisons consisted of oxygen versus air delivered by the same mechanism among participants with COPD and no or mild hypoxaemia.

Primary outcome: breathlessness

The meta-analysis of breathlessness included 32 studies with 865 participants (Abernethy 2010; Bruni 2012a; Bruni 2012b; Davidson 1988; Dean 1992; Eaton 2002; Emtner 2003a; Emtner 2003b; Eves 2006; Jolly 2001a; Jolly 2001b; Killen 2000; Knebel 2000; Kurihara 1989; Laude 2006; Lewis 2003; McDonald 1995; McKeon 1988a; Miki 2012; Moore 2011; Nandi 2003; Nonoyama 2007; O'Donnell 1997; Oliveira 2012a; Oliveira 2012b; Ringbaek 2013; Rooyackers 1997a; Rooyackers 1997b; Scorsone 2010; Somfay 2001; Voduc 2010; Woodcock 1981).

In pooled analysis of all trials, we found that oxygen reduced breathlessness (SMD -0.31, 95% CI -0.43 to -0.20; I^2 = 29%; Analysis 1.1; low-quality evidence).

A priori subgroup analyses of breathlessness

Short-burst oxygen therapy

Short-burst oxygen therapy before exertion did not reduce breathlessness (SMD -0.03, 95% CI -0.28 to 0.22; four studies; I^2 = 0%), whereas oxygen given during exercise or daily activities did reduce breathlessness (SMD -0.36, 95% CI -0.48 to -0.24; 28 studies; I^2 = 27%; Analysis 1.2; low-quality evidence). Differences between groups were statistically significant (P = 0.02).

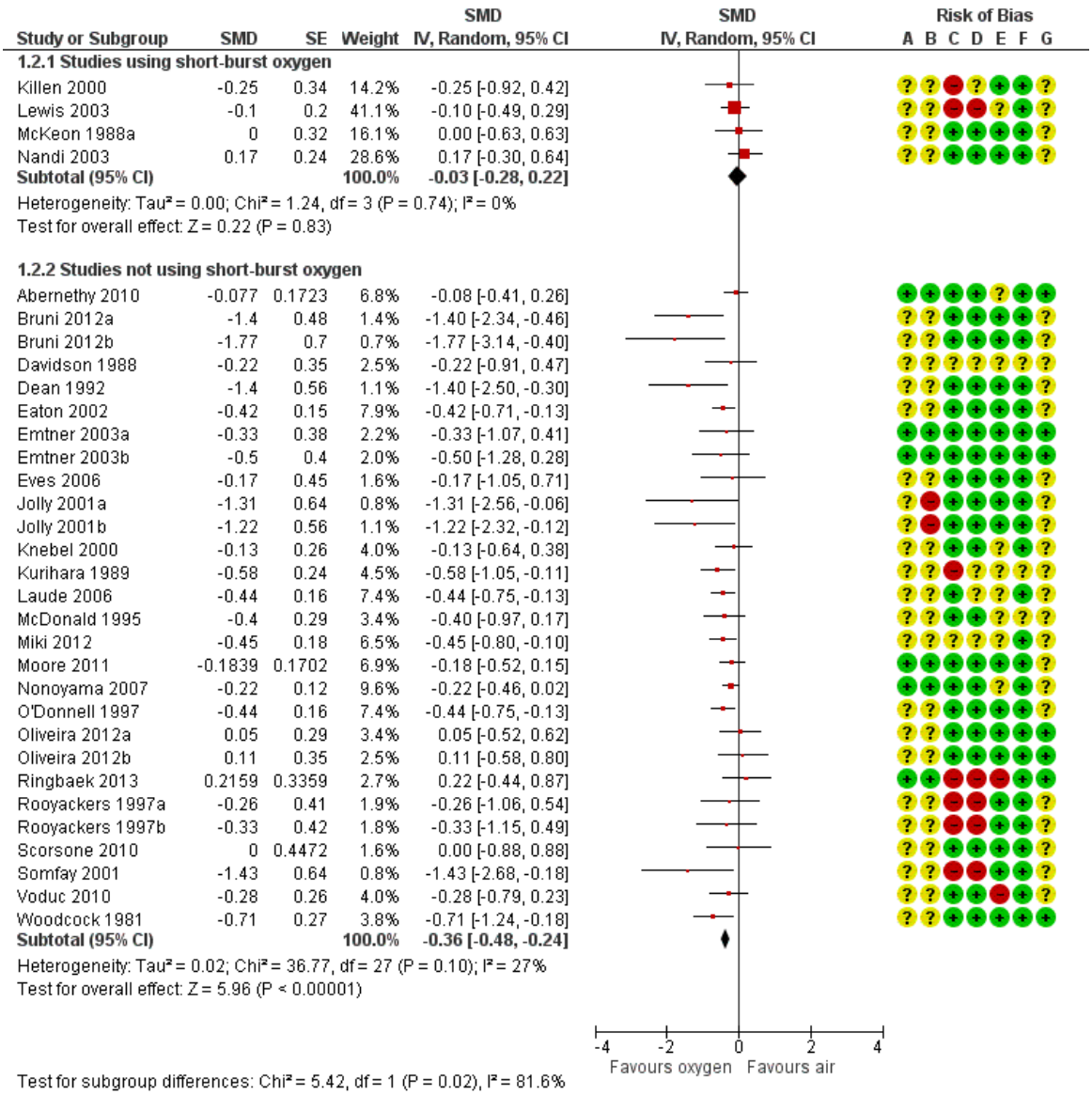
Exertional desaturation

In studies with desaturation during exercise, defined as SaO_2 < 88% among entry criteria or mean PaO_2 < 8 kPa on exertion, oxygen reduced breathlessness (SMD -0.28, 95% CI -0.39 to -0.16; 16 studies), but the effect tended to be greater in studies without exertional desaturation (SMD -0.47, 95% CI -0.69 to -0.24; 15 studies; Analysis 1.3). P = 0.14 for differences between groups.

Baseline mean PaO_2 (air) < 9.3 kPa

The effect of oxygen was similar among studies with baseline mean PaO_2 (air) < 9.3 kPa (SMD -0.28, 95% CI -0.48 to -0.07; seven studies) and studies with PaO_2 (air) $\geq$ 9.3 kPa (SMD -0.33, 95% CI -0.47 to -0.20; 25 studies; Analysis 1.4), as shown in Figure 4. P = 0.65 for differences between groups.

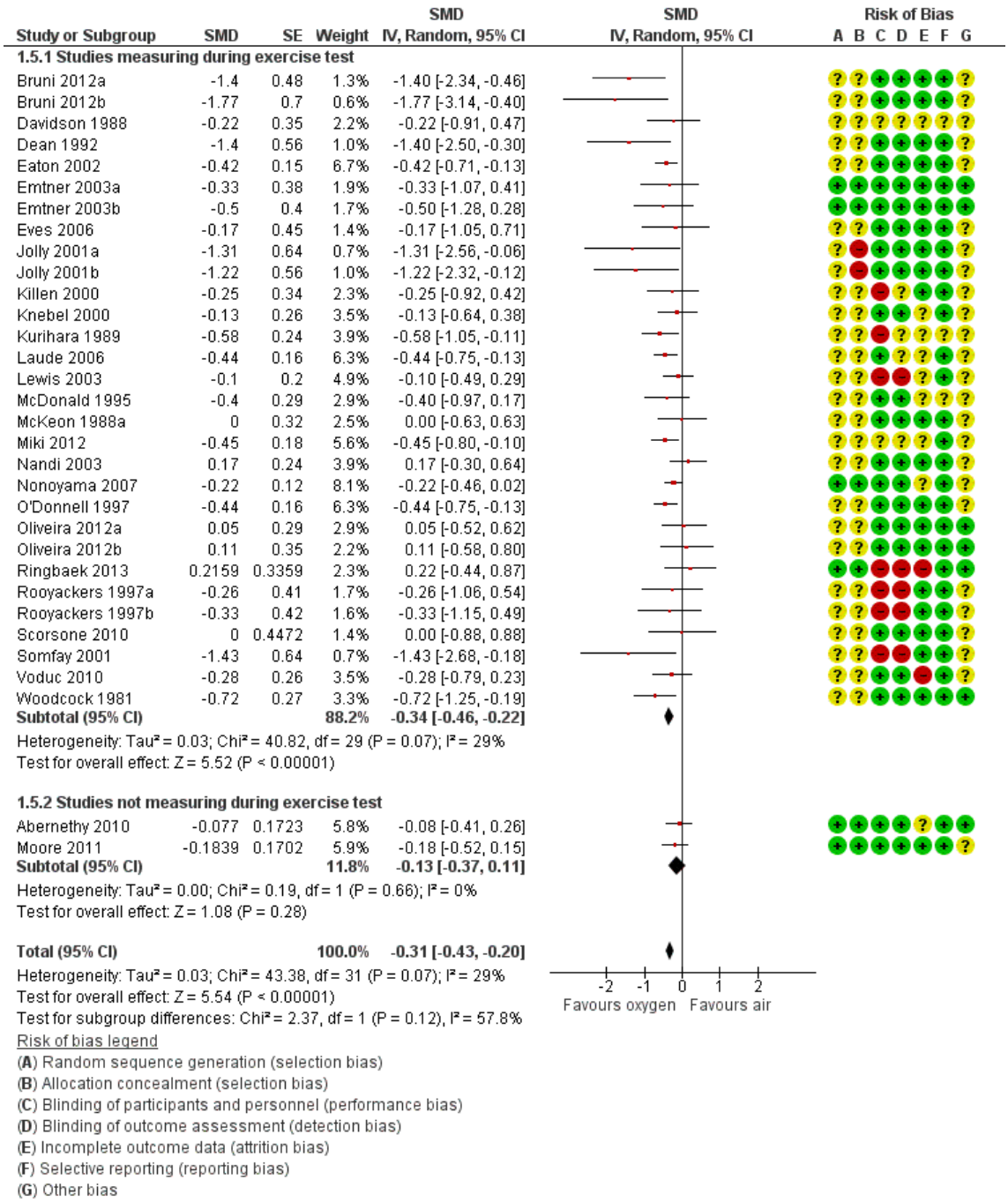
Figure 4. Forest plot of comparison: 1 Oxygen versus air, outcome: 1.2 Breathlessness - subgroup analysis - short-burst oxygen versus not.



Measurement during exercise test

Most studies measured breathlessness during exertion (SMD -0.34, 95% CI -0.46 to -0.22; 30 studies); only two studies measured breathlessness in daily life and found a smaller and less precise effect of oxygen (SMD -0.13, 95% CI -0.37 to 0.11; two studies; Analysis 1.5; moderate-quality evidence), as shown in Figure 5. P = 0.12 for differences between groups.

Figure 5. Forest plot of comparison: 1 Oxygen versus air, outcome: 1.5 Breathlessness - subgroup analysis - measured during exercise test versus not.



Laboratory setting

Most studies measured breathlessness during exercise testing in a laboratory setting (SMD -0.37, 95% CI -0.52 to -0.22; 25 studies). The effect of oxygen was less in non-laboratory domiciliary settings (SMD -0.23, 95% CI -0.36 to -0.09; seven studies; Analysis 1.6). P = 0.16 for differences between groups.

Short-term versus long-term (training) oxygen effects

Most studies evaluated acute effects of oxygen by comparing an exercise test on oxygen versus an exercise test on air (SMD -0.34, 95% CI -0.46 to -0.22; 29 studies). Investigators evaluated a potential longer-term (training) effect of oxygen by performing a test on the same gas after a (training) period with oxygen or air. Only three studies performed this evaluation and found no evidence of a long-term effect of oxygen (SMD -0.09, 95% CI -0.37 to 0.19; three studies; Analysis 1.7). P = 0.11 for differences between groups.

Mean oxygen dose > 2 L/min

Most studies evaluated oxygen at a dose > 2 L/min, which tended to reduce breathlessness more (SMD -0.35, 95% CI -0.49 to -0.21; 25 studies) than an oxygen dose $\leq$ 2 L/min (SMD -0.19, 95% CI -0.39 to 0.01; five studies; Analysis 1.8). P = 0.19 for differences between groups.

A priori sensitivity analyses of breathlessness

Analysis excluding trials measuring breathlessness at peak exertion

Oxygen reduced breathlessness measured at iso-time (SMD -0.37, 95% CI -0.50 to -0.24; 26 studies; I^2 = 32%) but had no effect on breathlessness measured at peak exertion (SMD -0.14, 95% CI -0.33 to 0.05; six studies; I^2 = 0%; Analysis 1.9).

Analysis excluding trials with high risk of bias

When we excluded trials with high risk of bias for any bias category (risk of bias shown in Figure 2), the effect of oxygen on breathlessness remained unchanged (SMD -0.30, 95% CI -0.41 to -0.20; 25 studies; I^2 = 14%; Analysis 1.10).

Analysis excluding trials with any participant without COPD

All participants included in the meta-analysis had COPD. For studies that included non-COPD participants, we used individual participant data for the COPD subgroup (Abernethy 2010).

Analysis excluding outlier findings

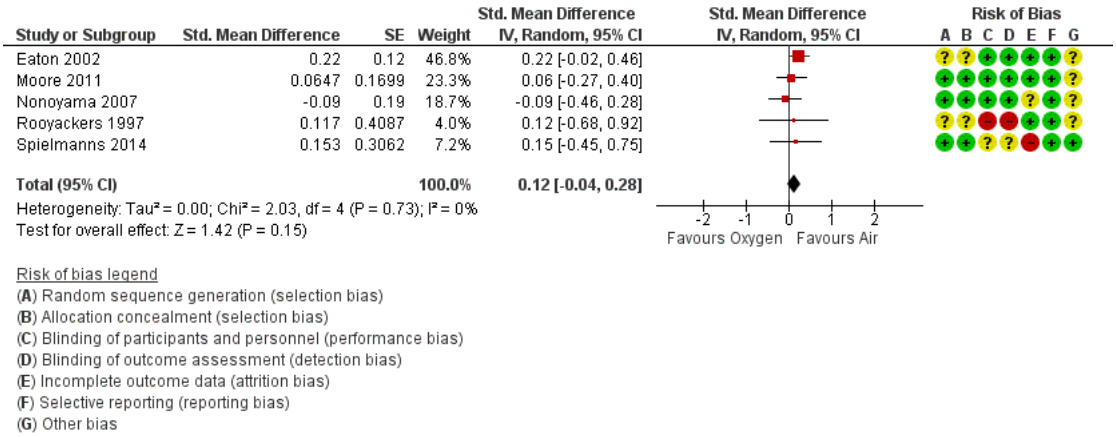
Upon inspecting forest and funnel plots (Figure 3; Figure 4), we identified five outlier findings (Bruni 2012a; Bruni 2012b; Dean 1992; Jolly 2001a; Jolly 2001b; Somfay 2001). Exclusion of the outliers revealed that oxygen reduced breathlessness, but the effect became slightly smaller (SMD -0.27, 95% CI -0.35 to -0.18; 26 studies; I^2 = 0%; Analysis 1.11). The effect of continuous oxygen during exertion or daily activities (no short-burst therapy) was similar after outliers were excluded (SMD -0.30, 95% CI -0.39 to -0.20; 22 studies; I^2 = 0%; Analysis 1.12).

Secondary outcome: HRQOL

Meta-analysis

Twelve studies (Abernethy 2010; Dyer 2012; Eaton 2002; Eaton 2006; Emtner 2003a; Emtner 2003b; McDonald 1995; Moore 2011; Nonoyama 2007; Ringbaek 2013; Rooyackers 1997; Spielmanns 2014) examined changes in HRQOL. Of these, we were able to include five studies (267 participants) (Eaton 2002; Moore 2011; Nonoyama 2007; Rooyackers 1997; Spielmanns 2014) in the meta-analysis. Oxygen had no clear effect on HRQOL (SMD 0.12, 95% CI -0.04 to 0.28; five studies; I^2 = 0%; Analysis 1.13; low-quality evidence), as shown in Figure 6. In the analysis, higher scores indicated better HRQOL.

Figure 6. Forest plot of comparison: 1 Oxygen versus air, outcome: 1.13 Health-related quality of life - all trials.



Descriptive analysis of studies not included in meta-analysis

We did not include seven studies in the meta-analysis, as they did not use a validated scale of HRQOL (Abernethy 2010), reported only HRQOL subdomain scores (Dyer 2012; McDonald 1995), reported change scores (Emtner 2003a; Emtner 2003b; Ringbaek 2013) or provided data that could not be combined in the analysis (Eaton 2006). For all scales used, higher scores indicated better quality of life.

Abernethy 2010 measured overall perceived quality of life over the past two days on a 0 to 10 numerical rating scale (NRS) based on a daily diary kept over seven days. In the subgroup with COPD (n = 158), improvement from baseline at day 7 was 0.8 points (standard deviation (SD) 2.0) in the oxygen group and 0.3 points (SD 1.9) in the air group.

Dyer 2012 measured change from baseline in CRQ subdomain scores after six to seven weeks of pulmonary rehabilitation using oxygen or air. The only statistically and clinically significant change was found in the CRQ mastery score. For oxygen compared with air, the mean difference was -0.1 (95% CI -0.9 to 0.7; P = 0.76) for the domain CRQ breathlessness, 0.5 (95% CI -0.2 to 1.2; P = 0.15) for CRQ emotion, 0.7 (95% CI -0.1 to 1.5; P = 0.10) for CRQ fatigue and 0.7 (95% CI 0.0 to 1.4; P = 0.006) for CRQ mastery scores.

Eaton 2006 was a randomised, controlled, parallel-group trial that included three arms as follows: oxygen, air and usual care. The only domain of the CRQ to show statistical significance (P = 0.045) was emotional function; the greatest improvement was noted in the usual care group, which received neither oxygen nor air.

For Emtner 2003a and Emtner 2003b, CRQ total score and subscores increased significantly in both groups. Only in mastery was a statistically significantly greater improvement detected in the oxygen-trained group (P < 0.05). For the Short Form-36, a significant difference (improvement) in general health was seen in the oxygen compared with the air group (P < 0.05).

McDonald 1995 measured subdomains of CRQ and noted statistically significant improvement in all CRQ subdomains for the comparison of baseline scores versus scores after six weeks of oxygen therapy (P < 0.02 for all domains). However, when scores after oxygen therapy were compared with scores after air, they reported no statistically or clinically significant differences.

Ringbaek 2013 measured total SGRQ score at 7 weeks compared with baseline. Mean changes from baseline were -1.8 (SD 8) for the oxygen group and -3.2 (SD 7.2) for no oxygen group; the difference between groups was not statistically significant (P = 0.80).

Secondary outcome: blinded patient preference

Five studies (Abernethy 2010; Eaton 2002; Killen 2000; McDonald 1995; Moore 2011) assessed patient preference to continue therapy (oxygen vs air delivered by the same mechanism) at a time when participants were still blinded. Owing to heterogeneity of the reported data, we could not perform a meta-analysis.

Abernethy 2010 assessed patient preference after seven days of blinded oxygen/air by asking the question, "Reviewing the benefits and burdens of your experience with the treatment over the past week, would you want to continue this treatment?" Among participants with COPD who answered (N = 139), preferences to continue treatment were as follows in the oxygen group: yes 50%, maybe 27% and no 23%. In the air group, preferences were yes 41%, maybe 23% and no 36%. The difference in preference between groups was not statistically significant (P = 0.25).

Eaton 2002 asked participants (N = 41) if they were interested

in clinical provision of oxygen at study completion. Among participants identified as having a short-term response to oxygen, 14 participants did not wish to be considered for continued therapy. Eleven of these 14 (76%) cited poor tolerability or acceptability as the reason.

Killen 2000 studied short-burst oxygen given immediately before and after walking up a flight of steps, asking participants which blinded gas they preferred. Of 18 participants, five preferred oxygen before ascending the stairs, three preferred air and three had no preference. The remaining seven participants preferred to receive oxygen at the top of the stairs. As a group, participants expressed no statistically significant preference for oxygen therapy (P = 0.12).

McDonald 1995 included both acute assessments and a domiciliary portion that lasted six weeks with each gas, asking participants (N = 26) at the end of the study which six-week period they preferred. Fifty percent preferred the period when they received oxygen; the remaining 50% preferred air or had no preference.

Moore 2011 asked participants whether they wanted to continue or discontinue the provision of domiciliary cylinders after the 12-week study period. Preferences were similar between groups; 35 of 65 (54%) wanted to continue in the oxygen group compared with 37 of 73 (51%) in the air group.

Secondary outcome: adverse events

Adverse events were insufficiently and inconsistently reported; therefore, meta-analysis was not possible.

Abernethy 2010 included a total of 65 participants in the oxygen group and 70 in the air group. Serious adverse events were rare, with no clinically meaningful differences between groups for moderate to extreme drowsiness (47% oxygen vs 51% air); moderate to extreme nasal irritation (29% oxygen vs 35% air); moderately to extremely troublesome nosebleeds (3% oxygen vs 3% air) and moderate to extreme anxiousness (26% oxygen vs 40% air).

Dyer 2012 included a total of 47 participants in the study. Investigators reported seven dropouts; three participants withdrew because of an exacerbation of their condition, one because of other medical problems and three for social reasons.

Eaton 2002 included a total of 41 participants in the study. Investigators reported nine dropouts; causes of dropout included morbidity for two participants and cancer for one participant in both study groups. Three in each group withdrew for personal reasons.

Eaton 2006 included a total of 25 participants in the oxygen group and 26 in the air group. Five participants in the oxygen group died, one was admitted to the hospital and three were prescribed LTOT. In the air group, two participants died, one was prescribed LTOT, one was admitted to a rest home and four were admitted to the hospital.

Emtner 2003a and Emtner 2003b included a total of 14 participants in the oxygen group and 15 in the air group. We excluded one participant from the oxygen-trained group because of illness post intervention.

Haidl 2004 included a total of 26 participants in the study. During three-year follow-up, four participants in the oxygen group died and one was given a diagnosis of cancer.

Knebel 2000 included a total of 31 participants in the study. Two participants were unable to complete all of the walks in the study because of unrelated problems (fever and migraine headache).

Laude 2006 included a total of 76 participants in the study. After randomisation, seven participants withdrew: five because of exacerbations and two for other reasons.

Lewis 2003 included a total of 18 participants in the study and reported four dropouts. Two participants failed to complete the first visit and attend the second visit (chest pain during 6MWT (n = 1), personal reasons (n = 1)). Furthermore, two participants failed to attend the second visit (clinically unstable (n = 1), other (n = 1)).

McDonald 1995 included a total of 26 participants in the study and reported seven dropouts; three participants withdrew during the first six weeks of domiciliary therapy (acute gout, muscular pain related to pulling the gas cylinder, unwillingness to continue in the study, respectively), each of whom had received cylinder air in the first six weeks. A total of four participants were withdrawn during the second six weeks: One participant died of a cerebrovascular accident and another of overwhelming pneumonia, a third was hospitalised with an acute exacerbation of COPD and the last incurred an incidental injury. All four participants had received cylinder oxygen during this second six-week trial period.

Moore 2011 included a total of 66 participants in the oxygen group and 73 in the air group. After randomisation, among those allocated to cylinder oxygen, one participant was deceased and one got unwell.

Nonoyama 2007 included a total of 27 participants in the study and reported 11 dropouts. Five were reluctant to continue, three developed resting hypoxaemia with a PaO_2 less than 55 mmHg, two died, and one was non-compliant, utilising the test mixtures for less than one hour per day.

Ringbaek 2013 included a total of 15 participants in the oxygen group and 22 in the air group. At study end (33 weeks), the mean number of adverse events did not differ significantly between treatment groups in terms of acute COPD exacerbations (P = 0.30) or number of participants with hospital admission or dropout (P = 0.59).

Spielmanns 2014 included a total of 19 participants in the oxygen group and 17 in the air group. After randomisation, in the oxygen group, five participants discontinued owing to comorbidities, and in the air group, seven discontinued because of comorbidities.

Voduc 2010 included a total of 15 participants in the study. After randomisation, three participants developed COPD exacerbations and one developed worsening of arthritis that limited exercise and thus was excluded.

Bruni 2012a; Bruni 2012b; Davidson 1988; Dean 1992; Eves 2006; Ishimine 1995; Jolly 2001a; Jolly 2001b; Killen

2000; Kurihara 1989; Leach 1992; Maltais 2001; McKeon 1988a; McKeon 1988b; Miki 2012; Moore 2009; Nandi 2003; O'Donnell 1997; O'Driscoll 2011; Oliveira 2012a; Oliveira 2012b; Rooyackers 1997a; Rooyackers 1997b; Scorsone 2010; Somfay 2001; Swinburn 1984; Wadell 2001; and Woodcock 1981 did not report adverse events.

DISCUSSION

Summary of main results

Since the previous version of this review was published in 2011 (Uronis 2011), we have included an additional 14 studies of the effects of oxygen versus air on breathlessness, we have excluded one study, and data for meta-analysis of health-related quality of life (HRQOL) are now available.

When compared with air, continuous oxygen (not short-burst oxygen) reduced breathlessness more during exercise or activity (standard mean difference (SMD) -0.36, 95% confidence interval (CI) -0.48 to -0.24), and most data pertaining to breathlessness were obtained during exercise testing in the laboratory setting. This effect translated to a mean decrease in breathlessness of 0.7 points on a 0 to 10 numerical rating scale (NRS) based on data from a recent large study (Abernethy 2010). The minimal clinically important difference in chronic breathlessness has been reported to be 1 point, with small, moderate and large effects seen at about 0.6, 1.1 and 1.8 points, respectively (Johnson 2013). It is unclear whether the effect of oxygen on breathlessness could be clinically meaningful for many participants in this setting.

Evidence for breathlessness pertains mostly to acute effects of exercise testing on breathlessness in the laboratory setting. Effects on breathlessness during daily life (not measured during an exercise test) in the domiciliary setting were smaller and were statistically non-significant (SMD -0.13, 95% CI -0.37 to 0.11).

Short-burst oxygen therapy before exertion did not affect breathlessness.

Oxygen did not clearly affect HRQOL (SMD 0.10, 95% CI -0.06 to 0.26). Blinded patient preference to continue therapy did not differ between groups given oxygen and groups given air. Investigators insufficiently reported adverse events, and we could not meta-analyse adverse event data.

Overall completeness and applicability of evidence

After an extensive database and literature search, we included 44 studies (1195 participants) in this update review. Although two relatively large studies of ambulatory oxygen have been published in recent years (Abernethy 2010; Moore 2011), additional high-quality data on effects of ambulatory oxygen in daily life, including effects on HRQOL, are needed. Good methodological rigour would include publication of a prespecified protocol outlining trial design, adequate sequence generation, randomisation, blinding (for participants and for outcome assessors) and transparent reporting of appropriate outcomes at baseline in a format suitable for meta-analysis (e.g. mean with standard deviation and sample size).

Mechanism of effect on breathlessness

The likely mechanism underpinning an effect on breathlessness is that supplemental oxygen prevents or decreases hypoxaemia during exercise, thereby reducing a hypoxaemia-related increase in ventilatory demand, dynamic hyperinflation and increased exertional breathlessness in some patients (O'Donnell 2001). This mechanism is supported by the present finding that a higher oxygen dose (> 2 L/min) was associated with a larger decrease in breathlessness. The finding that the oxygen effect was not stronger in studies of patients with exertional desaturation might reflect that the analysis was based on the study mean, and that heterogeneity in the level of exertional hypoxaemia among individual participants might have attenuated the association. Some people developed hypoxaemia during exercise despite supplemental oxygen therapy that could have increased their breathlessness scores. The issue is further complicated in that some patients might have adapted to exertional hypoxaemia, with a reduced ventilatory response to hypoxaemia and therefore less benefit of oxygen during exercise. Another hypothesis is that airflow to the face and upper airways could relieve breathlessness, possibly through increased afferent feedback mimicking increased ventilatory work (Johnson 2016; Schwartzstein 1987). This could reduce the imbalance between ventilatory demand and perceived ventilatory work and thus the level of breathlessness, and may explain why participants did not prefer to go on, or why no significant change in HRQOL was evident when oxygen was compared with air delivered through the same method.

Evidence for use in clinical care

Most evidence of the benefit of oxygen for breathlessness pertains to symptoms noted during standardised exercise testing in the laboratory setting. The oxygen effect during domiciliary treatment in daily life was smaller and more uncertain (SMD -0.12, 95% CI -0.39 to 0.15). More recent double-blinded randomised controlled trials (RCTs) of oxygen compared with medical air have found no statistically or clinically relevant effects of domiciliary/ambulatory oxygen on breathlessness in daily life (Abernethy 2010; Moore 2011). Less efficacy of domiciliary oxygen might reflect insufficient adherence to therapy or low physical activity due to deconditioning, or the fact that breathlessness in daily life is not assessed at a comparable time point or after a standardised workload. A

patient who benefits from oxygen (decreased breathlessness at a given workload and improved exercise capacity) might increase his/her activity up to maximal tolerable levels of breathlessness. We found that the level of breathlessness at peak exercise did not seem to be affected by oxygen. When breathlessness is recalled in daily life, reported symptom level might therefore be similar between people receiving oxygen and those given air, even if oxygen would in fact be beneficial in some patients. Whether palliative oxygen in the domiciliary setting is beneficial remains unclear. We found no evidence to show that oxygen improved HRQOL, but the data were limited.

Quality of the evidence

We rated the quality of evidence for the effect of oxygen compared with air on breathlessness as low overall upon completing a GRADE assessment (Summary of findings for the main comparison). Most evidence pertained to breathlessness measured during a standardised exercise test (moderate-quality evidence), whereas evidence was limited for breathlessness during daily life (low-quality evidence). We rated the quality of evidence showing an effect of oxygen on HRQOL as low (Summary of findings for the main comparison).

Potential biases in the review process

Limitations of this systematic review and meta-analysis mainly reflect the heterogeneity and methodological limitations of the currently available body of literature. Although we excluded studies of participants already qualifying for home oxygen therapy according to current guidelines, the review population still included a wide range of baseline oxygen saturation/partial pressure of oxygen (PaO_2). This variability could affect our results if a relationship is found between oxygen saturation and effects of oxygen on breathlessness. We addressed this issue by performing a subgroup analysis based on baseline PaO_2 ($\geq$ 9.3 kPa) and obtained consistent findings. Additionally, baseline breathlessness and physical capacity were often insufficiently reported. The review population likely included participants with varied perceptions of breathlessness and physical capacity.

We explored potential bias due to methodological limitations by excluding studies with high risk for any bias category; this yielded consistent findings. A possible limitation of this review is that many studies did not report data on participants dropping out or withdrawing from the study. Reporting of data only for participants who completed the trial might have introduced selection bias.

Palliative oxygen is prescribed most commonly for seriously ill patients nearing the end of life; however, these patients are not likely to participate in randomised trials, especially studies involving an exercise test. The applicability of review findings to all individuals with chronic obstructive pulmonary disease (COPD) who require palliative oxygen is unclear.

Effects of oxygen on breathlessness were driven in part by five outlier findings among studies with small sample sizes/low levels of precision. This asymmetry in the funnel plot might indicate the presence of publication bias. When we excluded the outliers, the oxygen effect became somewhat smaller (SMD -0.24, 95% CI -0.34 to -0.15).

Although the funnel plot indicated potential publication bias, we did not downgrade the quality of the evidence, as a sensitivity analysis excluding outlying studies yielded similar findings.

Agreements and disagreements with other studies or reviews

Compared with the 2011 version of this review (Uronis 2011; Uronis 2015), we have included an additional 14 studies (493 participants) in this update. The finding of the main analysis of breathlessness is consistent with the previous estimate but is more precise because we included more studies. Subgroup analyses by short burst and by oxygen dose were also in agreement with those of the previous review. Novel subgroup analyses in the present review show that evidence of effects of oxygen pertains mostly to breathlessness during exercise tests performed in the laboratory standardised rehabilitation training setting. Evidence is less consistent and of low quality for effects of supplemental oxygen during daily life. The novel analysis of HRQOL showed no clear effect of supplemental oxygen compared with air on quality of life.

Ameer 2014 performed a Cochrane meta-analysis (four studies; 331 participants) of the effects of ambulatory oxygen therapy given for two weeks or longer on breathlessness and HRQOL in the home setting. When compared with air or no therapy, ambulatory oxygen therapy was associated with a small reduction in breathlessness as measured on the Borg scale (mean difference 0.28, 95% CI, 0.10 to 0.45). This finding is consistent with our finding in the non-laboratory setting. The analysis of breathlessness performed by Ameer 2014 included only three studies (McDonald 1995; Eaton 2002; Nonoyama 2007), which we also included in the present review. Effects on HRQOL as noted in Ameer 2014 were inconsistent, with mean improvements in breathlessness and fatigue domains but were not related to emotional function or mastery. Small or inconsistent effects of supplemental oxygen on HRQOL and lack of clear effect on exercise capacity in Ameer 2014 support the present conclusion that the evidence base for supplemental oxygen therapy during daily life is limited.

Findings of this review are consistent with recent British Thoracic Society (BTS) guidelines stating that although ambulatory oxygen therapy should be offered to patients for use during exercise in a pulmonary rehabilitation programme, it "should not be routinely offered to patients who are not eligible for LTOT" (Hardinge 2015).

AUTHORS' CONCLUSIONS

Implications for practice

Oxygen given continuously during exercise or activity can relieve breathlessness in patients with COPD who have no or mild hypoxaemia and would not qualify for long-term oxygen therapy. Evidence was of moderate quality for breathlessness during exercise testing in the laboratory setting and of low quality for effects on breathlessness during daily life. It is not clear whether the reduction in breathlessness shown in the laboratory setting translates into a clinically important benefit, and no evidence supports a clinically important benefit from oxygen for breathlessness in daily life. Short-burst oxygen therapy given before exercise had no effect and should not be used.

Clinical recommendations

Based on the present findings, supplemental oxygen therapy is not a first-line treatment for patients with breathlessness. Management of underlying disease(s) should be optimised. Evidence-based symptomatic treatment should include individualised rehabilitation training (McCarthy 2015), the fan and low-dose opioids (Ekstrom 2015a; Ekstrom 2015b; Hardinge 2015). In patients with intractable breathlessness despite these interventions, a trial of supplemental oxygen could be considered. Guidelines recommend that palliative oxygen should be evaluated only in patients with hypoxaemia (saturation < 92%) at rest (Hardinge 2015). We found that the oxygen effect was similar in studies with mean $PaO_2 \geq 9.3$ kPa compared with $PaO_2 < 9.3$ kPa, and that a trial of supplemental oxygen might be reasonable in patients without resting hypoxaemia, especially in the presence of hypoxaemia during limited exertion. Evaluation of the potential benefit of ambulatory oxygen should involve the patient's levels of physical capacity and activity, along with the benefits of oxygen for breathlessness and physical capacity in a standardised test such as the six-minute walking test (6MWT) when compared with air (Hardinge 2015). Patients who perceive decreased breathlessness when receiving oxygen most often experience this effect within two to three days of the start of treatment (Abernethy 2010). Therefore, palliative oxygen therapy should be evaluated after a few days and withdrawn if patients do not perceive benefit.

Patient quality of life (QOL) factors such as convenience and adverse consequences should be considered in the decision whether to prescribe oxygen as treatment for patients with breathlessness who may already be burdened by their illness and other life changes prominent in the advanced illness setting.

Finally, in considering these results, one must be sure to remember the downsides of administering oxygen. Oxygen is costly, and, with current stresses on healthcare systems in many countries, this needs to be taken into account. Evidence of the effect of supplemental oxygen on HRQOL is lacking.

In conclusion, we are moderately confident that oxygen can relieve breathlessness when given during exercise to mildly hypoxaemic and non-hypoxaemic people with COPD who would not otherwise qualify for home oxygen therapy. Most evidence pertains to acute effects during exercise testing; evidence of long-term effects of oxygen during daily life is less consistent. Findings show that oxygen did not affect HRQOL.

Implications for research

Current findings on the effect of oxygen therapy versus air have several important implications for research. First, oxygen affected breathlessness measured only at iso-time, not at peak exercise. This confirms the importance of measuring breathlessness at iso-time with comparable workloads in mechanistic studies and interventional trials.

Although this review confirms that oxygen can decrease exertional breathlessness in the laboratory setting, studies should focus on effects of domiciliary and ambulatory oxygen in clinical and daily life settings. Studies on effects of oxygen on HRQOL and on different aspects (dimensions) of breathlessness (Laviolette 2014) are needed, and investigators should identify optimal doses and routes of oxygen administration, while determining which patients are most likely to receive beneficial symptomatic effects of oxygen. Studies of symptomatic benefit should also account for changes in physical capacity and activity to explore whether oxygen given during daily living could allow increased exercise activity, although it might not affect reported breathlessness scores. Tools for measuring physical activity in COPD were recently validated (Gimeno-Santos 2015).

We found that adverse events were insufficiently assessed and/or reported. The first population-based longitudinal study of the risk of burn injury during LTOT was published only recently (Tanash 2015). Studies quantifying adverse events, patient burden and potential risks associated with supplemental oxygen therapy are needed to determine the net clinical benefit of palliative oxygen.

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Professor Phillippa Poole was the Editor for this review and commented critically on the review.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abernethy 2010

Methods	Randomised, controlled, triple-blinded (participants, practitioners, investigators), parallel-group trial
Participants	**Inclusion criteria**: patients with COPD older than 18 years; PaO_2 > 7.3 kPa; refractory breathlessness related to life-limiting illness (as determined by referring physicians); maximum treatment for underlying disease; breathlessness at rest or with negligible exertion ≥ 3 on the MRC categorical breathlessness scale; on stable medications during the previous week; expected survival ≥ 1 month (as judged by the responsible physician)) **Exclusion criteria**: met criteria for long-term oxygen therapy; history of hypercarbic respiratory failure related to oxygen; anaemia (haemoglobin < 100 g/L); hypercapnia ($PaCO_2$ > 6.7 kPa); cognitive impairment (Folstein mini-mental status score < 24/30); smoking; respiratory or cardiac event in the previous week Setting: outpatient pulmonary, palliative care, oncology and primary care clinics at 5 sites in Australia, 2 in the USA and 2 in the UK Method of recruitment of participants: patients referred to the clinics 239 participants randomised (211 completed) 152 participants with COPD Male 103 (68%) Mean age: 73.2 (SD 9.9) Lung function: no data available Mean baseline SaO_2 (%): no data available Mean baseline PaO_2 (kPa): 10.0 (SD 1.5) Mean $PaCO_2$ (kPa): 5.2 (SD 0.6) Mean breathlessness morning and evening NRS scores at baseline: 4.7 (SD 2.0) overall; 4.6 (SD 2.0) in the oxygen group; 4.8 (SD 2.0) in the air group
Interventions	Domiciliary oxygen (2 L/min) versus room air (2 L/min) delivered continuously from concentrator by nasal cannula; prescribed for at least 15 hours per day. Duration 7 days
Outcomes	Breathlessness measured by NRS (0-10, 0 "none" to 10 "maximal"), defined as breathlessness "right now" during morning and evening. Mean of morning and evening scores used in the meta-analysis Overall well-being on NRS (0-10) scores in the evening day 7 Treatment preference - categorical at day 7 Adverse effects - day 3 telephone contact, reported drowsiness, nasal irritation, nasal bleeds, anxiousness
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Abernethy 2010 (*Continued*)

Random sequence generation (selection bias)	Low risk	"Randomised to treatment by a central computer-generated system available (via web or telephone) through the pharmacy service at Repatriation General Hospital (Adelaide, Australia) with balanced blocks of four patients per stratum, on the basis of Fisher and Yates' statistical tables."
Allocation concealment (selection bias)	Low risk	"Patients, individuals delivering the interventions, investigators, and nurses were masked to treatment assignments. Oxygen and room air concentrators were identical in appearance. By use of a standard protocol, the medical gas company serving each site modified half the concentrators to dispense room air without setting off the internal alarm that sounds when oxygen concentrations are low."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As above
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	7% attrition for oxygen (overall) and 17% for air (overall)
Selective reporting (reporting bias)	Low risk	According to the aims, adequately reported variables
Other bias	Low risk	We judged that this trial appeared to be free of other sources of bias

Bruni 2012a

Methods	Randomised, controlled, double-blinded (participants and investigators), cross-over trial
Participants	**Inclusion criteria**: no formal criteria reported. Male patients with severe airway obstruction and hyperinflation participated in the study. COPD was diagnosed on the basis of history, physical examination, chest radiograph and results of pulmonary function studies. All patients had a long history of smoking and were clinically stable and taking appropriate medication **Exclusion criteria**: not stated Setting: laboratory (Italy) Method of recruitment of participants: not described 10 participants with COPD classified as "hyperinflators" who exhibited a 0.47 (SD 0.

Bruni 2012a (*Continued*)

	35 L) increase in chest wall volume All male Mean age: 68.1 (SD 6.6) Mean FEV_1 (L): 0.91 (SD 0.3) Mean FEV_1 (% predicted): 32.7 (SD 8.7) FEV_1/FVC: 0.29 (SD 0.1) Mean baseline SaO_2 (%): no data available Mean baseline PaO_2 (kPa): 9.5 (SD 1.2) Mean $PaCO_2$ (kPa): 5.6 (SD 0.6) Mean breathlessness at baseline: no data available
Interventions	Oxygen (FiO_2 0.5) vs room air during 1 symptom-limited cycle test at 75% of peak work rate Participants wore a nose-clip and breathed through a low-dead-space mouthpiece; Douglas bag
Outcomes	Breathlessness measured by modified Borg at iso-time (mBorg 0-10, 0 "none" to 10 "maximal") HRQOL - no data available Treatment preference - no data available Adverse effects - no data available
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"In randomised order"; other information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Subjects were blinded to the oxygen concentration being breathed as was the investigator evaluating subjective responses and performing data analysis."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No data on whether saturation was measured; but self-rated
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study.
Selective reporting (reporting bias)	Low risk	Important outcomes were reported.
Other bias	Unclear risk	Unclear how participants were selected and whether participants withdrew; data re-

Bruni 2012a (*Continued*)

		ported only for participants completing the study

Bruni 2012b

Methods	Randomised, controlled, double-blinded (participants, investigators), cross-over trial
Participants	**Inclusion criteria**: no formal criteria reported. Male patients with severe airway obstruction and hyperinflation participated in the study. COPD was diagnosed on the basis of history, physical examination, chest radiograph and results of pulmonary function studies. All patients had a long history of smoking and were clinically stable and taking appropriate medication **Exclusion criteria**: not stated Setting: laboratory (Italy) Method of recruitment of participants: not described 6 participants with COPD classified as "non-hyperinflators" because of constant chest wall volume Mean age: 68.1 (SD 6.6) Mean FEV_1 (L): 0.91 (SD 0.3) Mean FEV_1 (% predicted): 32.7 (SD 8.7) FEV_1/FVC: 0.29 (SD 0.1) Mean baseline SaO_2 (%): no data available Mean baseline PaO_2 (kPa): 10.3 (SD 0.9) Mean $PaCO_2$ (kPa): 5.2 (SD 0.1) Mean breathlessness at baseline: no data available
Interventions	Oxygen (FiO_2 0.5) vs room air during 1 symptom-limited cycle test at 75% of peak work rate Participants wore a nose-clip and breathed through a low-dead-space mouthpiece; Douglas bag
Outcomes	Breathlessness measured by modified Borg at iso-time (mBorg 0-10, 0 "none" to 10 "maximal") HRQOL - no data available Treatment preference - no data available Adverse effects - no data available
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"In randomised order"; other information not available
Allocation concealment (selection bias)	Unclear risk	Information not available

Bruni 2012b (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Subjects were blinded to the oxygen concentration being breathed as was the investigator evaluating subjective responses and performing data analysis."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No data on whether saturation was measured; but self-rated
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study.
Selective reporting (reporting bias)	Low risk	Important outcomes were reported.
Other bias	Unclear risk	It is unclear whether or not there was risk of other bias due to the lack of detail in the methods

Davidson 1988

Methods	Randomised, double-blinded (participants and investigators), cross-over trial
Participants	**Inclusion criteria**: exercise tolerance limited by breathlessness secondary to severe chronic airflow obstruction **Exclusion criteria**: angina; impaired cardiac function or locomotor disability that might contribute to exercise limitation Setting: laboratory 17 participants (14 completed) Gender not specified Mean age: 64.4 (SEM 2.1) Mean FEV_1 (L): 0.79 (SEM 0.0) Mean FVC (L): 2.1 (SEM 0.11) Mean baseline SaO_2 (%): no data available Mean baseline PaO_2 (kPa): 8.6 (SEM 0.3) Mean $PaCO_2$ (kPa): 6.0 (SEM 0.4) Mean breathlessness at baseline: no data available
Interventions	Compressed air (4 L/min) vs oxygen (2, 4 or 6 L/min) during 6MWT, cycle ergometer test or endurance shuttle walk test
Outcomes	Breathlessness measured by VAS at the end of exercise (10 cm VAS, "not at all breathless" to "extremely breathless") HRQOL - no data available Treatment preference - no data available Adverse effects - no data available
Notes	

Davidson 1988 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised: "The order of testing in both the oxygen dosing study and the walking tests was allocated randomly"; other information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as double-blind (walking test) and single-blind (cycle test); other information not available "For walking exercise the tests were performed double blind. For cycling endurance it was necessary for the investigator to determine the bias flow composition and this part of the study was therefore single (patient) blind. To ensure that this did not affect performance, care was taken to provide a similar degree of encouragement as detailed above."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	As above
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data reported only for participants completing the study. "Not all patients completed six minutes of exercise when breathing air or the low concentration of oxygen. " Reported VAS scores only for 4 L/min for 14 participants after 6 minutes of exercise
Selective reporting (reporting bias)	Unclear risk	As above
Other bias	Unclear risk	It is unclear whether or not there was risk of other bias due to the lack of detail in the methods

Dean 1992

Methods	Randomised, double-blinded (participants and investigators), cross-over trial
Participants	**Inclusion criteria**: age > 50; DLCO < 80% predicted; extensive smoking history; resting PaO_2 > 55 mmHg **Exclusion criteria**: active coronary artery disease; congestive heart failure; vascular, orthopaedic or neurological problems that would interfere with cycling Setting: laboratory 12 participants All male Age > 50, but specifics not reported Mean FEV_1 (L): 0.89 (SEM 0.1) Mean FVC (L): 2.4 (SEM 0.2) Mean DLCO (mL/min/mmHg): 9.8 (SEM 1.5) Mean baseline SaO_2 (%): no data available Mean baseline PaO_2 (kPa): 9.5 (SE 0.3) Mean baseline $PaCO_2$ (kPa): no data available Mean breathlessness at baseline: no data available
Interventions	Compressed air vs 40% oxygen during incremental and endurance exercise shuttle walk tests
Outcomes	Breathlessness measured by modified Borg at iso-time (mBorg) HRQOL - no data available Treatment preference - no data available Adverse effects - no data available
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; other information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blind (participants, study personnel)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Oximetry values were not available to the patient or supervising physician during endurance testing to preserve blinding."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study.
Selective reporting (reporting bias)	Low risk	Important outcomes were reported.

Dean 1992 (*Continued*)

Other bias	Unclear risk	It is unclear whether or not there was risk of other bias due to the lack of detail in the methods

Dyer 2012

Methods	Randomised, controlled, single-blinded (investigators), parallel-group trial
Participants	**Inclusion criteria**: COPD; desaturated by > 4% to < 90% on exertion at baseline; improved ≥ 10 % in ESWT with ambulatory O_2 (mean 280 m) **Exclusion criteria**: any existing home oxygen Setting: laboratory (Surrey, UK) Method of recruitment of participants: consecutive patients with COPD referred to 3 PR services in Surrey, UK 55 participants with COPD (47 completed) Male 30 (64% of 47 completing) Mean age: air 70 (SD 7); oxygen 68 (SD 8) Mean FEV_1 (L): 1.12 (SD 0.5); oxygen 0.96 (SD 0.4) Mean FEV_1 (% predicted): room air 44 (SD 11); oxygen 39 (SD 16) Mean baseline SaO_2 (%): 94 (SD 2) Mean baseline PaO_2 (kPa): no data available Mean baseline $PaCO_2$ (kPa): no data available Mean breathlessness at baseline: CRQ dyspnoea score 3 (SD 1); MRC 3 (SD 1)
Interventions	Ambulatory oxygen (2-6 L/min) vs room air during PR and during exertion at home; delivered via nasal prongs; most participants had cylinders and a few were supplied with liquid oxygen. Duration of treatment: 6-7 weeks of training, as well as at home during all activities that induced breathlessness but not at rest
Outcomes	Breathlessness measured by CRQ dyspnoea subdomain on a 7-point Likert scale (higher = good) HRQOL - CRQ subdomains Treatment preference - no data available Adverse effects - number of dropouts
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	By random number tables and sealed envelopes
Allocation concealment (selection bias)	High risk	Measured SaO_2 during PR; participants were unblinded; limited blinding for staff. "It was not possible to blind participants to group allocation as sham O_2 was not avail-

Dyer 2012 (*Continued*)

		able [...] due to limited study resources."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Single-blinded (staff) "Exercise tolerance at the end of PR for all participants was reassessed by [author], with blinding maintained by all participants wearing nasal cannulae with an oxygen cylinder attached, carried in a backpack by an assistant, which was switched off for the RA group. At the end of PR, exercise tolerance was reassessed by [author] (blind to group allocation)."
Blinding of outcome assessment (detection bias) All outcomes	High risk	As above
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data reported only for participants completing the study. The number of dropouts was equal in both groups
Selective reporting (reporting bias)	Unclear risk	No protocol. Did not report breathlessness during exercise test after PR
Other bias	High risk	Per-protocol analysis only

Eaton 2002

Methods	Randomised, controlled, double-blind (participants, investigators), cross-over trial
Participants	**Inclusion criteria**: COPD as defined by ATS criteria, exertional breathlessness impacting daily activities, not fulfilling criteria for LTOT, exertional desaturation (O_2 saturation $\leq$ 88%), ex-smoker, clinically stable for 2 months with standard optimal medical care, completion of a formal 6-week pulmonary rehabilitation programme **Exclusion criteria**: "important co-morbidities (e.g. limiting angina or significant musculoskeletal disability)" Setting: non-laboratory 50 participants (41 completed) 70% male Mean age: 57.1 (SD 9.3) Mean FEV_1 (% predicted): 25.9 (SD 8) Mean baseline SaO_2 (%): 94 (SD 1.9) Mean baseline PaO_2 (kPa): 9.2 (SD 1.0) Mean baseline $PaCO_2$ (kPa): 5.8 (SD 0.7) Mean breathlessness at baseline: 0.7 (SD 1.0)
Interventions	Compressed air (4 L/min) vs oxygen (4 L/min) during both 6MWT and 6-week period at home during which participants were instructed "to use flow rate of 4 L/min intranasally

Eaton 2002 (*Continued*)

	for any activity during which they would normally experience breathlessness"
Outcomes	Breathlessness measured by modified Borg (mBorg 0-10, 0 "none" to 10 "maximal") HRQOL - CRQ total score, CRQ subdomains, SF-36 Treatment preference - no data available Adverse effects - number of dropouts
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; other information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Patients were randomly assigned in a double blinded manner to cylinder air or O_2. All cylinders were painted pink, prefilled with either air or O_2 and identifiable only by a unique cylinder number, ensuring blinding of both participants and observers."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above
Incomplete outcome data (attrition bias) All outcomes	Low risk	"A mixed model approach to crossover trials was employed, which used information from all patients, including those who did not complete both time periods."
Selective reporting (reporting bias)	Low risk	Important outcomes were reported
Other bias	Unclear risk	It is unclear whether or not there was risk of other bias due to the lack of detail in the methods

Eaton 2006

Methods	Randomised, controlled, double-blind (participants, investigators), parallel-group trial
Participants	**Inclusion criteria**: 78 hospital inpatients with an acute exacerbation of COPD; moderate or severe COPD as defined by British Thoracic Society criteria; exertional dyspnoea interfering with daily activity; resting PaO_2 > 60 mmHg at discharge; ability to complete

	HRQOL questionnaires **Exclusion criteria**: current smoker; severe comorbidity likely to cause death within the 6-month study period; resident of a long-term facility in which SBOT is available; hypercapnia ($PaCO_2$ > 45 mmHg) Setting: non-laboratory 51 participants (34 completed); 25 in oxygen group; 26 in air group 56% male in oxygen group; 50% male in air group Mean age: oxygen 77.4 (SD 7.2); air 77.6 (SD 5.7) Mean FEV_1 (L): oxygen 0.9 (SD 0.5); air 0.9 (SD 0.4) Mean FEV_1 (% predicted): oxygen 44 (SD 22); air 39 (SD 17) Mean baseline SaO_2 (%): oxygen 95 (SD 1.9); air 95 (SD 1.6) Mean baseline PaO_2 (kPa): oxygen 9.6 (SD 1.3); air 10.1 (SD 1.7) Mean baseline $PaCO_2$ (kPa): oxygen 5.3 (SD 0.6); air 5.4 (SD 0.4) Mean breathlessness at baseline, CRD dyspnoea: oxygen 17.8 (SD 5.0); air 17.5 (SD 4.2)
Interventions	Cylinder oxygen (2 L/min) vs cylinder air (2 L/min) vs usual care during 6-month domiciliary period. Participants were given standardised instructions "to use they cylinder gas at 2 L/min via nasal prongs, as necessary for distressing or limiting breathlessness." No short-term assessments were performed
Outcomes	Breathlessness measured by CRQ dyspnoea score HRQOL - CRQ total score, CRQ subdomains, SF-36 Treatment preference - no data available Adverse effects - number of dropouts
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Patients were randomised using computer-generated randomisation numbers."
Allocation concealment (selection bias)	Low risk	"Allocation of cylinders was by a separate member of the research team not involved in patient assessment."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"To ensure double-blinding, cylinders, prefilled with air or oxygen, were identifiable only by a unique cylinder number. Cylinders were painted pink to ensure they would not be used in routine clinical care."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above

Eaton 2006 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data reported only for participants completing the study. 17 dropouts in total; number of dropouts was equal in both groups
Selective reporting (reporting bias)	Low risk	Important outcomes were reported.
Other bias	Low risk	We judged that this trial appeared to be free of other sources of bias

Emtner 2003a

Methods	Randomised, controlled, double-blind (participants, investigators), parallel-group trial
Participants	**Inclusion criteria**: COPD that is clinically stable with no recent exacerbations; FEV_1 < 50% predicted; FEV_1/VC < 0.65; resting PaO_2 > 55 mmHg; SpO_2 > 88% during constant work rate test while breathing room air **Exclusion criteria**: symptomatic cardiovascular comorbidity or other disease that might contribute to exercise limitation; regular participation in a formal exercise programme or participation in a formal rehabilitation programme within the past 2 years Setting: laboratory 30 participants overall (29 completed) 15 participants categorised as "air trained group" 10 male and 5 female Mean age: 67 (SD 10) Mean FEV_1 (L): 1.01 (SD 0.27) Mean FVC (L): 2.58 (SD 0.7) Mean TLC (L): 7.3 (SD 1.2) Mean RV (L): 4.6 (SD 1.3) Mean DLCO (mL/min/mmHg): 11.4 (SD 4.4) Mean baseline SaO_2 (%): no data available Mean baseline PaO_2 (kPa): 9.8 (SD 1.0) Mean baseline $PaCO_2$ (kPa): 5.5 (SD 0.5) Mean breathlessness at baseline: no data available
Interventions	Supplemental oxygen (FiO_2 0.30) vs compressed air during constant work rate exercise During training sessions, gas was delivered at 3 L/min via nasal cannula, connected to the appropriate tank (compressed air or oxygen) by an unblinded investigator Incremental and constant work rate tests were performed by inhaling compressed air or 30% oxygen (4 tests). Participants were blinded to the inhaled mixture and breathed through mouthpiece and low-resistance valve with a nose-clip in place
Outcomes	Breathlessness measured by modified Borg (mBorg 0-10, 0 "none" to 10 "maximal") HRQOL - CRQ total score, CRQ subdomains, SF-36 Treatment preference - no data available Adverse effects - number of dropouts
Notes	

Emtner 2003a (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"The randomization sequence was generated using numbered sealed envelopes."
Allocation concealment (selection bias)	Low risk	Sealed envelopes were used to conceal generated randomisation sequence from study investigators
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The nasal cannula tubing was connected to the appropriate tank (compressed air or oxygen) by an unblinded investigator. Patient and staff did not know which gas mixture the patient received (...). Exercise intensity was subsequently adjusted, considering the subject's breathlessness and fatigue sensations, by blinded therapists."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"An unblinded investigator measured oxygen saturation periodically; the findings were never reported to the patients or therapists."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants withdrew from this arm of treatment.
Selective reporting (reporting bias)	Low risk	According to the aims, adequately reported variables
Other bias	Low risk	We judged that this trial appeared to be free of other sources of bias

Emtner 2003b

Methods	Randomised, controlled, double-blind (participants, investigators), parallel-group trial
Participants	**Inclusion criteria**: COPD that is clinically stable with no recent exacerbations; FEV_1 < 50% predicted; FEV_1/VC < 0.65; resting PaO_2 > 55 mmHg; $SpO_2 \geq$ 88% during constant work rate test while breathing room air **Exclusion criteria**: symptomatic cardiovascular comorbidity or other disease that might contribute to exercise limitation; regular participation in a formal exercise programme or participation in a formal rehabilitation programme within the past 2 years Setting: laboratory 30 participants overall (29 completed) 14 participants categorised as "oxygen-trained group" 8 male and 6 female

Emtner 2003b (*Continued*)

	Mean age: 66 (SD 7) Mean FEV_1 (L): 1.01 (SD 0.33) Mean FVC (L): 2.7 (SD 0.8) Mean TLC (L): 7.2 (SD 1.6) Mean RV (L): 4.1 (SD 0.9) Mean DLCO (mL/min/mmHg): 10.9 (SD 3.5) Mean baseline SaO_2 (%): no data available Mean baseline PaO_2 (kPa): 9.5 (SD 1.1) Mean baseline $PaCO_2$ (kPa): 5.4 (SD 0.7) Mean breathlessness at baseline: no data available
Interventions	Supplemental oxygen (FiO_2 0.30) vs compressed air during constant work rate exercise During training sessions, gas was delivered at 3 L/min via nasal cannula, connected to the appropriate tank (compressed air or oxygen) by an unblinded investigator Incremental and constant work rate tests were performed by inhaling compressed air or 30% oxygen (4 tests). Participants were blinded to the inhaled mixture and breathed through mouthpiece and low-resistance valve with a nose-clip in place
Outcomes	Breathlessness measured by modified Borg (mBorg 0-10, 0 "none" to 10 "maximal") HRQOL - CRQ total score, CRQ subdomains, SF-36 Treatment preference - no data available Adverse effects - number of dropouts
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomization sequence was generated using numbered sealed envelopes."
Allocation concealment (selection bias)	Low risk	Sealed envelopes were used to conceal generated randomisation sequence from study investigators
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The nasal cannula tubing was connected to the appropriate tank (compressed air or oxygen) by an unblinded investigator. Patient and staff did not know which gas mixture the patient received (...). Exercise intensity was subsequently adjusted, considering the subject's breathlessness and fatigue sensations, by blinded therapists."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"An unblinded investigator measured oxygen saturation periodically; the findings were never reported to the patients or therapists."

Emtner 2003b (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	"One patient from the oxygen-trained group was excluded because of illness during the postintervention testing period."
Selective reporting (reporting bias)	Low risk	According to the aims, adequately reported variables
Other bias	Low risk	We judged that this trial appeared to be free of other sources of bias

Eves 2006

Methods	Randomised, controlled, double-blinded (participants, investigators), cross-over trial
Participants	**Inclusion criteria**: clinically stable moderate to severe COPD **Exclusion criteria**: dependence on supplemental oxygen, cardiovascular disease and/or musculoskeletal abnormality Setting: laboratory 10 participants All men Mean age: 65 (SD 11) Mean FEV_1 (L): 1.66 (0.59) Mean FVC (L): 3.81 (0.99) Mean baseline SaO_2 (%): no data available Mean baseline PaO_2 (kPa): 9.1 (SD 0.9) Mean baseline $PaCO_2$ (kPa): 4.9 (SD 0.4) Mean breathlessness at baseline: no data available
Interventions	Medical air vs 40% oxygen vs heliox vs heliox/oxygen during constant-load cycling. Throughout exercise, humidified gases were passed into a reservoir bag and supplied through a low-resistance 2-way breathing valve
Outcomes	Breathlessness measured by modified Borg (mBorg 0-10, 0 "none" to 10 "maximal") HRQOL - no data available Treatment preference - no data available Adverse effects - no data available
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"During the other two visits, four constant-load symptom-limited exercise trials were performed in a random order"; other information not available

Eves 2006 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Information on concealment of allocation not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Throughout exercise, humidified gases were passed into a reservoir bag and supplied through a low-resistance two-way breathing valve. The patients were blinded to the gas mixture used and were asked not to talk during, or for a short period after, exercise due to the change in vocal tone with helium."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Two research assistants, blinded to the gas mixture used, consistently encouraged patients to exercise for as long as possible."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study.
Selective reporting (reporting bias)	Low risk	According to the aims, adequately reported variables
Other bias	Unclear risk	It is unclear whether or not there was risk of other bias due to the lack of detail in the methods

Haidl 2004

Methods	Randomised, controlled, unblinded, parallel-group trial
Participants	**Inclusion criteria**: COPD diagnosis (per "current clinical guidelines"); $FEV_1/FVC < 0.70$; $PCO_2 > 45$ mmHg at rest on 2 different days or increase in PCO_2 after cycle testing > 45 mmHg; PO_2 at rest > 55 mmHg; mean nocturnal oxygen saturation > 90% **Exclusion criteria**: malignant disease; left heart failure or other significant comorbidities (e.g. severe renal failure, severe diabetes) Setting: non-laboratory 28 participants (15 dropouts during 3-year follow-up) 26 (93%) male Mean age: oxygen group 65.7 (SD 6.7); controls 64.5 (SD 6.4) Mean FEV_1 (% predicted): oxygen group 38.8 (8.4); controls 42.7 (11.8) Mean baseline SaO_2 (%): no data Mean baseline PaO_2 (kPa): oxygen group 9.0 (SD 0.9); controls 8.7 (SD 0.8) Mean baseline $PaCO_2$ (kPa): oxygen group 5.3 (SD 0.4); controls 5.6 (SD 0.5) Mean breathlessness at baseline: oxygen group 5.0 (SD 2.1); controls 5.0 (SD 1.5)
Interventions	LTOT (2 L/min $\geq$ 15 hours/d) vs control (no treatment) delivered through nasal cannula connected to gas concentrators

Haidl 2004 (*Continued*)

Outcomes	Breathlessness measured by modified Borg (mBorg 0-10, 0 "none" to 10 "maximal") HRQOL - no data available Treatment preference - no data available Adverse effects - number of dropouts
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not available
Allocation concealment (selection bias)	Low risk	Participants' randomisation status was unknown to staff performing their tests
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded. Control group received usual care (no sham oxygen)
Blinding of outcome assessment (detection bias) All outcomes	High risk	See above.
Incomplete outcome data (attrition bias) All outcomes	High risk	Data reported only for participants completing the study. Both treatment groups were complete at 1 year, when assessment was undertaken. Study planned to measure differences at 3 years, but attrition rates prevented this (15 dropouts during 3-year follow-up)
Selective reporting (reporting bias)	Low risk	Important outcomes were reported.
Other bias	Unclear risk	It is unclear whether or not there was risk of other bias due to the lack of detail in the methods

Ishimine 1995

Methods	Randomised, controlled, double-blinded (participants, investigators), cross-over study
Participants	**Inclusion criteria**: male with "stable" COPD or chronic bronchitis; moderate to severe obstruction; PaO_2 > 60 torr at rest **Exclusion criteria**: not available (not specified in Cochrane translation) Setting: laboratory 22 participants

Ishimine 1995 (*Continued*)

	All men Mean age: 69 (SD 7) Mean FEV_1 (L): 1.02 (0.51) Mean FVC (L): 2.26 (0.57) Mean baseline SaO_2 (%): no data Mean baseline PaO_2 (kPa): 10.1 (SD 1.1) Mean baseline $PaCO_2$ (kPa): no data Mean breathlessness at baseline: no data
Interventions	Room air vs compressed air (3 L/min) vs oxygen (3 L/min) during 6MWT
Outcomes	Breathlessness measured by a questionnaire involving 8 questions; each question was answered on a 100-mm horizontal line with anchors from the modified Borg HRQOL - no data available Treatment preference - no data available Adverse effects - no data available
Notes	Translated from Japanese and assessed with the translation sheet

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; other information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Placebo controlled; blinding of assessors could not be ascertained
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of assessors could not be ascertained.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data reported only for participants completing the study
Selective reporting (reporting bias)	Unclear risk	Information not available
Other bias	Unclear risk	Unclear how participants were selected and whether they withdrew; blinding unclear

Jolly 2001a

Methods	Randomised, double-blinded (participants, investigators), placebo-controlled, cross-over trial
Participants	**Inclusion criteria**: participants with COPD (ATS grade II/III) with ≥ 30 days of clinical stability; participating in respiratory rehab programme; FEV_1 < 55% and/or FEV_1 ratio < 50%; resting PaO_2 > 60 mmHg **Exclusion criteria**: peripheral vascular disease; cardiac failure; active CAD Setting: laboratory 9 participants, classified as "non-de-saturators" All male Mean age: 70 (SEM 3) Mean FEV_1 (L): 0.9 (SEM 0.8) Mean FVC (% predicted): 63 (SEM 6) Mean TLC (L): 7.4 (SEM 0.4) Mean RV (L): 4.4 (SEM 0.39) Mean baseline SaO_2 (%): 96 (SEM 0.5)) Mean baseline PaO_2 (kPa): 10.5 (SE 0.4) Mean baseline $PaCO_2$ (kPa): 5.3 (SE 0.2) Mean breathlessness at baseline: 0.56 (SE 0.3)
Interventions	Room air vs compressed air (3, 6, 9, 12 L/min) vs oxygen (3, 6, 9, 12 L/min) during 6MWT - amount of oxygen increased on the basis of desaturation during exercise. Two indistinguishable cylinders located at the middle of the corridor - 1 with compressed air (CA) and 1 with oxygen - were connected by a Y-piece to a 15-m tube, ending in a nasal cannula
Outcomes	Breathlessness measured by modified Borg (mBorg 0-10, 0 "none" to 10 "maximal") HRQOL - no data available Treatment preference - no data available Adverse effects - no data available
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; other information not available
Allocation concealment (selection bias)	High risk	"One person, who knew the randomly assigned sequence, opened the valve and regulated the gas flow as requested by another technician, who walked behind the patient recording the SaO_2 measured by pulse oximetry (SpO_2) values. Both this technician and the patient were blind about which gas was added."

Jolly 2001a (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	As above, and "Two indistinguishable cylinders located at the middle of the corridor, one with compressed air (CA) and one with oxygen, were connected by a Y-piece to a 15-m tube ending in a nasal cannula."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study.
Selective reporting (reporting bias)	Low risk	According to the aims, adequately reported variables
Other bias	Unclear risk	It is unclear whether or not there was risk of other bias due to the lack of detail in the methods

Jolly 2001b

Methods	Randomised, double-blinded (participants, investigators), cross-over trial
Participants	**Inclusion criteria**: patients with COPD (ATS grade II/III) with ≥ 30 days of clinical stability; participating in respiratory rehab programme; FEV_1 < 55% and/or FEV_1 ratio < 50%, resting PaO_2 > 60 mmHg **Exclusion criteria**: peripheral vascular disease; cardiac failure; active CAD Setting: laboratory 11 participants classified as "desaturators," defined by a fall in SpO_2 ≥ 5% to < 90% during the 6MWT on air 10 male and 1 female Mean age: 67 (SEM 2) Mean FEV_1 (L): 0.9 (SEM 0.8) Mean FVC (% predicted): 68 (SEM 8) Mean TLC (L): 7.1 (SEM 0.6) Mean RV (L): 4.2 (SEM 0.45) Mean baseline SaO_2 (%): 95 (SE 0.3) Mean baseline PaO_2 (kPa): 9.9 (SE 0.3) Mean baseline $PaCO_2$ (kPa): 5.5 (SE 0.2) Mean breathlessness at baseline: 0.7 (SD 1.0)
Interventions	Room air vs compressed air (3, 6, 9, 12 L/min) vs oxygen (3, 6, 9, 12 L/min) during 6MWT - amount of oxygen increased on the basis of desaturation during exercise. Two indistinguishable cylinders located at the middle of the corridor - 1 with compressed air (CA) and 1 with oxygen - were connected by a Y-piece to a 15-m tube, ending in a nasal cannula

Jolly 2001b (*Continued*)

Outcomes	Breathlessness measured by modified Borg (mBorg 0-10, 0 "none" to 10 "maximal") HRQOL - no data available Treatment preference - no data available Adverse effects - no data available
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; other information not available
Allocation concealment (selection bias)	High risk	"One person, who knew the randomly assigned sequence, opened the valve and regulated the gas flow as requested by another technician, who walked behind the patient recording the SaO_2 measured by pulse oximetry (SpO_2) values. Both this technician and the patient were blind about which gas was added."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As above, and "Two indistinguishable cylinders located at the middle of the corridor, one with compressed air (CA) and one with oxygen, were connected by a Y-piece to a 15-m tube ending in a nasal cannula."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study.
Selective reporting (reporting bias)	Low risk	According to the aims, adequately reported variables
Other bias	Unclear risk	It is unclear whether or not there was risk of other bias due to the lack of detail in the methods

Killen 2000

Methods	Randomised, single-blind (participants), cross-over trial
Participants	**Inclusion criteria**: COPD predominantly related to smoking; considered for symptomatic oxygen therapy; had stairs at home and found that ascending these produced breathlessness; desaturation to below 90% on ascent of 22 steps **Exclusion criteria**: history of ischaemic heart disease, left ventricular failure or other cause of reduced mobility such as severe arthritis; already on long-term oxygen or fulfilling the criteria for long-term oxygen therapy Setting: non-laboratory 18 participants 8 male and 10 female Mean age: 67.5 (IQR 60.5 to 74.3) Median FEV_1 (L): 0.53 (IQR 0.45 to 0.76) Median DLCO (% predicted): 44 (IQR 28 to 64) Mean baseline SaO_2 (%): median 94 (IQR 91 to 95) Mean baseline PaO_2 (kPa): no data available Mean baseline $PaCO_2$ (kPa): no data available Mean breathlessness at baseline: no data available
Interventions	Oxygen (2 L/min) vs compressed air 5 minutes before and/or 5 minutes after ascending 22 steps. During the 5 minutes before and after these ascents. they breathed from a cylinder of compressed air or oxygen, delivered at 2 L/min via face mask
Outcomes	Breathlessness measured by 100-mm VAS ("not at all breathless" to "extremely breathless") HRQOL - no data available Treatment preference - no data available Adverse effects - no data available
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The order of the ascents was determined by randomisation within a Latin square."
Allocation concealment (selection bias)	Unclear risk	Information on concealment of allocation not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	"During the five minutes before and after these ascents they breathed from a cylinder of either compressed air or oxygen, delivered at 2 l/min via a face mask, in a single blind manner."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	As above

Killen 2000 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed
Selective reporting (reporting bias)	Low risk	According to the aims, adequately reported variables
Other bias	Unclear risk	It is unclear whether or not there was risk of other bias due to the lack of detail in the methods

Knebel 2000

Methods	Randomised, double-blinded (participants, investigators), cross-over trial
Participants	**Inclusion criteria**: adults with obstructive lung disease due to AAT deficiency; FEV_1 < 70% of predicted; FEV_1/FVC < 0.70 **Exclusion criteria**: FEV_1 < 1 L; hospitalisation in preceding 3 weeks; conditions prohibiting or limiting exercise; current use of oxygen; inability to understand English Setting: laboratory 33 participants (31 completed) 22 male and 13 female Mean age: 47 (SD 7) Mean FEV_1 (% predicted): 48 (SD 13) Mean TLC (% predicted): 105 (SD 14) Mean baseline SaO_2 (%): 97.1% (SD 1.7) Mean baseline PaO_2 (kPa): no data available Mean baseline $PaCO_2$ (kPa): no data available Mean breathlessness at baseline: 0.5 (SD 0.9)
Interventions	Oxygen (4 L/min) vs compressed air (4 L/min) during 6MWT. Both gases were delivered by nasal cannula, using the minimum dose shown to improve exercise performance, 4 L/min
Outcomes	Breathlessness measured by 10-cm horizontal VAS (0 = "No shortness of breath" and 10 = "Shortness of breath as bad as it can be") HRQOL - no data available Treatment preference - no data available Adverse effects - number of dropouts
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"A table of random numbers identified the order of administration."

Knebel 2000 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The tanks were covered so neither the patient nor the researcher knew which gas was being used."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"Two patients were unable to complete all of the walks because of unrelated problems. " Data on remaining participants were analysed in the study
Selective reporting (reporting bias)	Low risk	According to the aims, adequately reported variables
Other bias	Unclear risk	It is unclear whether or not there was risk of other bias due to the lack of detail in the methods

Kurihara 1989

Methods	Randomised, single-blind, cross-over trial
Participants	**Inclusion criteria**: "COPD" **Exclusion criteria**: none mentioned (Cochrane translation) Setting: laboratory 14 participants 11 male and 3 female Mean age: 62 (SD 10.2) Mean FEV_1 (L): 0.67 (SD 0.23) Mean FVC (% predicted): 58.3 (SD 6.2) Mean baseline SaO_2 (%): no data available Mean baseline PaO_2 (kPa): 9.2 (SD 1.2) Mean baseline $PaCO_2$ (kPa): no data available Mean breathlessness at baseline: no data available
Interventions	Breathlessness by modified Borg scale and distance walked on treadmill
Outcomes	Breathlessness measured by modified Borg (mBorg, 1 "none" to 10 "extremely severe") HRQOL - no data available Treatment preference - no data available Adverse effects - no data available
Notes	Worked from translation sheet from Japanese as opposed to from the entire article

Kurihara 1989 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; no other information available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single-blind study; no other information available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See above.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information not available
Selective reporting (reporting bias)	Unclear risk	Information not available
Other bias	Unclear risk	It is unclear whether or not there was risk of other bias due to the lack of detail in the methods

Laude 2006

Methods	Randomised, controlled, double-blinded (participants, investigators), cross-over trial
Participants	**Inclusion criteria**: COPD confirmed by FEV_1 < 80% predicted, FEV_1/FVC < 70%, a change in FEV_1 < 200 mL or < 15% of baseline, 15 minutes after inhaled salbutamol, dyspnoea on exertion defined by a Borg score after exercise ≥ 3 and freedom from exacerbations in the 6 weeks preceding the study **Exclusion criteria**: required domiciliary oxygen therapy; had resting hypercapnia, anaemia or a significant cardiac diagnosis Setting: laboratory Method of recruitment of participants: outpatients recruited from respiratory clinics at the 3 hospitals 82 participants (76 participants analysed in air group, 78 participants in oxygen group) Gender not specified Mean age: 69.7 (range 46 to 84) Mean FEV_1 (L): 1.1 (SD 0.4) Mean FVC (L): 2.6 (SD, 0.8) Mean baseline SaO_2 (%): 94 (SD 2.3) Mean baseline PaO_2 (kPa): no data available Mean baseline $PaCO_2$ (kPa): no data available Mean breathlessness at baseline: 1.8 (SD 1.1)

Laude 2006 (*Continued*)

Interventions	Oxygen (0.28) vs medical air during treadmill exercise, delivered through a non-rebreathing mask and demand valve system connected to a portable cylinder
Outcomes	Breathlessness measured by modified Borg (mBorg 0-10, 0 "none" to 10 "maximal") and 100-mm VAS HRQOL - no data available Treatment preference - no data available Adverse effects - number of dropouts
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Independent randomisation of the gas mixtures was done using a Latin square design."
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"In all tests, the investigator carried the gas cylinder walking beside the patient and gave no encouragement. Patients were instructed not to speak while breathing the gas mixtures and for 2 min afterwards to avoid unblinding...would have un-blinded both patient and investigator." "Cylinders were coded as to content to maintain blinding."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	As above
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Intention-to-treat population reported; specific details of how missing data were handled in the analysis not available
Selective reporting (reporting bias)	Low risk	Important outcomes reported
Other bias	Unclear risk	Unclear how participants were selected, data reported only for participants completing the study (7 withdrawals in total)

Leach 1992

Methods	Randomised, double-blinded (participants, investigators), cross-over trial
Participants	**Inclusion criteria**: severely reduced exercise tolerance secondary to chronic respiratory disease; no previous experience of exercise testing **Exclusion criteria**: angina pectoris; impaired left ventricle heart function; locomotor disability Setting: laboratory 20 participants Gender not specified Mean age: 63.4 Mean FEV_1 (L): 0.74 (0.3) Mean FVC (L): 1.94 (0.5) Mean baseline SaO_2 (%): no data available Mean baseline PaO_2 (kPa): 8.7 (SD 2.3) Mean baseline $PaCO_2$ (kPa): 5.6 (SD 1.2) Mean breathlessness at baseline: no data available
Interventions	Oxygen (2, 4 or 6 L/min) vs compressed air (4 L/min) delivered through face mask during 6MWT and endurance shuttle walk test (walk as far as possible and stop when unable to go farther)
Outcomes	Breathlessness measured by 10-cm VAS ("not at all breathless" to "extremely breathless") HRQOL - no data available Treatment preference - no data available Adverse effects - no data available
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The order of the four tests in which the gas was carried by the patient was randomised on each day."
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	"The subject and the investigator were blinded to the flow rate and type of gas supplied, although in practice the investigator was frequently able to determine those patients having oxygen from the oxygen saturation shown by ear oximetry."
Blinding of outcome assessment (detection bias) All outcomes	High risk	See above.

Leach 1992 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed
Selective reporting (reporting bias)	Low risk	Adequately reported variables
Other bias	Unclear risk	It is unclear whether or not there was risk of other bias due to the lack of detail in the methods

Lewis 2003

Methods	Randomised, single-blinded (participants), placebo-controlled, cross-over trial
Participants	**Inclusion criteria**: moderate to severe COPD according to BTS criteria; significant self-reported breathlessness; on optimal treatment; no exacerbation of disease for > 4 weeks before study, with exacerbation defined as "a deterioration in respiratory symptoms requiring treatment with corticosteroids or antibiotics or both" **Exclusion criteria**: significant limiting or unstable comorbidities Setting: laboratory Method of recruitment of participants: Participants were identified through respiratory outpatient services at Green Lane Hospital, Auckland, New Zealand 22 participants (18 completed) 16 male and 2 female Mean age: 68.7 (SD 10.1) Mean FEV_1 (L): 0.91 (SD 0.4) Mean baseline SaO_2 (%): 94 (SD 1.6) Mean baseline PaO_2 (kPa): no data available Mean baseline $PaCO_2$ (kPa): no data available Mean breathlessness at baseline: 0.4 (SD 0.5)
Interventions	Oxygen (2 L/min) vs air (2 L/min) before 6MWT, delivered via nasal cannulae
Outcomes	Breathlessness measured by modified Borg at end of exercise (mBorg 0-10, 0 "none" to 10 "maximal") HRQOL - no data available Treatment preference - no data available Adverse effects - number of dropouts
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; other information not available
Allocation concealment (selection bias)	Unclear risk	Information not available

Lewis 2003 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	"...identical cylinders in a single-blind fashion. Due to the need for monitoring of oxygen saturation by the physiotherapist, double-blinding was not possible."
Blinding of outcome assessment (detection bias) All outcomes	High risk	As above
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data reported only for participants completing the study (4 withdrawals)
Selective reporting (reporting bias)	Low risk	Important outcomes were reported.
Other bias	Unclear risk	It is unclear whether or not there was risk of other bias due to the lack of detail in the methods

Maltais 2001

Methods	Randomised, double-blinded (participants, investigators), cross-over trial
Participants	**Inclusion criteria**: "moderate to severe" COPD with diagnosis based on previous or current smoking history and PFTs (including spirometry, lung volume and CO diffusing capacity); "stable disease" **Exclusion criteria**: clinical cardiovascular, neurological or any condition that could alter the capacity to perform an exercise test according to medical history, physical exam, resting and exercise electrocardiogram and chest x-ray Setting: laboratory 14 participants Gender not specified Mean age: 63 (SEM 3) Mean FEV_1 (L): 1.04 (SEM 0.1) Mean FVC (L): 2.64 (SEM 0.2) Mean baseline SaO_2 (%): no data available Mean baseline PaO_2 (kPa): 11.3 (SEM 0.5) Mean baseline $PaCO_2$ (kPa): 4.9 (SEM 0.3) Mean breathlessness at baseline: no data available
Interventions	Room air vs oxygen (FiO_2 0.75) delivered through a mouthpiece during exercise testing
Outcomes	Breathlessness measured by modified Borg (mBorg 0-10, 0 "none" to 10 "maximal") HRQOL - no data available Treatment preference - no data available Adverse effects - no data available
Notes	

Maltais 2001 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Patients performed two exercise tests in a random order"; other information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Patients and the physician supervising the exercise tests were blinded as to which inspiratory gas was used."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study.
Selective reporting (reporting bias)	Low risk	Adequately reported variables
Other bias	Unclear risk	It is unclear whether or not there was risk of other bias due to the lack of detail in the methods

McDonald 1995

Methods	Randomised, double-blinded (participants, investigators), cross-over trial
Participants	**Inclusion criteria**: stable severe COPD; resting PaO_2 > 60 mmHg; exertional breathlessness sufficient to interfere with daily activities; non-smoker; no exacerbations in preceding 3 months; maximal bronchodilator and/or corticosteroid therapy **Exclusion criteria**: symptomatic cardiac dysfunction; angina pectoris; locomotor disability Setting: non-laboratory 33 participants (26 completed) 24 male and 2 female Mean age: 73 (SD 6) Mean FEV_1 (L): 0.9 (SD 0.4) Mean DLCO (mL/min/mmHg): 10.6 (SD 2.4) Mean baseline SaO_2 (%): 94 (SD 2.1) Mean baseline PaO_2 (kPa): 9.2 (SD 1.1) Mean baseline $PaCO_2$ (kPa): 5.5 (SD 0.4) Mean breathlessness at baseline: no data available

Interventions	Oxygen vs compressed air delivered via nasal cannula at 4 L/min over long-term (successive 6-week periods during which participants were instructed to use portable gas cylinder during "any activity that would normally induce dyspnoea). Participants used portable gas cylinders fitted with a demand gas delivery system at a flow rate of 4 L/min intranasally
Outcomes	Breathlessness measured by modified Borg at end of exercise (mBorg 0-10, 0 "none" to 10 "maximal") HRQOL - CRQ subdomains Treatment preference - no data available Adverse effects - number of dropouts
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; other information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All gases were delivered from camouflaged cylinders, and both the patients and the investigator performing the tests were blinded to their contents."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data reported only for participants completing the study (7 withdrawals)
Selective reporting (reporting bias)	Unclear risk	According to the aims, adequately reported variables
Other bias	Unclear risk	It is unclear whether or not there was risk of other bias due to the lack of detail in the methods

McKeon 1988a

Methods	Randomised, double-blind (participant and investigator), cross-over trial
Participants	**Inclusion criteria**: COPD with "significant disability with exertional breathlessness despite treatment with inhaled and oral bronchodilators"; $FEV_1/FVC < 0.60$ and TLC > 80% predicted with no significant change after bronchodilator; "stable condition" **Exclusion criteria**: not studied during exercise with history of angina, recent myocardial infarction, exercise-induced syncope or left ventricular failure Setting: laboratory Method of recruitment of participants: consecutive patients with COPD referred for assessment of need for oxygen therapy (Newcastle, Australia) 20 participants 13 male and 7 female Mean age: 63.2 (SD 10) Mean FEV_1 (L): 0.79 (SD 0.3) Mean FVC (L): 2.30 (SD 0.7) Mean TLC (% predicted): 122 (SD 24) Mean RV (% predicted): 206 (SD 60) Mean DLCO (% predicted): 55 (SD 32) Mean baseline SaO_2 (%): 90 (SD 3) Mean baseline PaO_2 (kPa): 7.7 (SD 1.2) Mean baseline $PaCO_2$ (kPa): 5.9 (SD 1.2) Mean breathlessness at baseline: no data available
Interventions	Compressed air vs oxygen via nasal cannula at 2.5 L/min during treadmill test
Outcomes	Breathlessness measured by 300-mm VAS HRQOL - no data available Treatment preference - no data available Adverse effects - no data available
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Neither the patient nor the operator knew whether compressed air or supplemental oxygen had been given. Patients were told that both cylinders contained oxygen, but in different concentrations."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above.

McKeon 1988a (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study.
Selective reporting (reporting bias)	Low risk	According to the aims, adequately reported variables
Other bias	Unclear risk	It is unclear whether or not there was risk of other bias due to the lack of detail in the methods

McKeon 1988b

Methods	Randomised, controlled, double-blind (participant and investigator), cross-over trial
Participants	**Inclusion criteria**: COPD with "significant disability with exertional breathlessness despite treatment with inhaled and oral bronchodilators"; "stable condition" at the time of the study **Exclusion criteria**: not stated Setting: laboratory 21 participants 11 women and 10 men Mean age: 62 (SD 9) Mean FEV_1 (L): 0.77 (SD 0.4) Mean FEV_1 (% predicted): 29 (SD 13) Mean FVC (L): 2.00 (SD 0.9) Mean FVC (% predicted): 58 (SD 20) Mean RV (L): 3.53 (SD 0.9) Mean TLC (L): 5.97 (SD 1.3) Mean baseline PaO_2 (kPa): 8.9 (SD 1.5) Mean breathlessness at baseline: no data available
Interventions	Oxygen vs air delivered via nasal cannula at 4 L/min during treadmill test
Outcomes	Breathlessness measured by 300-mm VAS HRQOL - no data available Treatment preference - no data available Adverse effects - no data available
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; no other information available

McKeon 1988b (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Cylinders prepared by technician not involved in the study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical cylinders used in the study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study.
Selective reporting (reporting bias)	Low risk	According to the aims, adequately reported variables
Other bias	Unclear risk	It is unclear whether or not there was risk of other bias due to the lack of detail in the methods

Miki 2012

Methods	Randomised, controlled, single-blinded (participants), cross-over trial
Participants	**Inclusion criteria**: COPD not stated as criterion, but study included patients with FEV_1 / FVC < 0.7; clinical stability defined as no respiratory infection for ≥ 4 weeks before the exercise test; ability to tolerate exercise test for ≥ 4 minutes; and exercise limitation due primarily to exertional breathlessness during CPET (breathing discomfort alone or in conjunction with leg discomfort was the primary reason for stopping exercise) **Exclusion criteria**: significant pathology including neuromuscular, cardiac and/or peripheral vascular disease, malignancy or anaemia; qualified for LTOT before the exercise test Setting: laboratory (Japan) Method of recruitment of participants: no data 35 participants All male Mean age: 70.4 (SD 5.7) Mean FEV_1 (L): 1.13 (SD 0.5) Mean FEV_1 (% predicted): 43.1 (SD 17.4) FEV_1/FVC: 0.46 (SD 13.5) Mean baseline SaO_2 (%): no data available Mean baseline PaO_2 (kPa): oxygen: 12.5 (SD 1.7); air: 10.2 (SD 1.3) Mean baseline $PaCO_2$ (kPa): oxygen: 5.3 (SD 0.7); air: 5.1 (SD 0.7) Mean breathlessness at baseline: oxygen: 0.1 (SD 0.2); air: 0.1 (SD 0.4)
Interventions	Oxygen (FiO_2 0.24) vs compressed air during 2 symptom-limited incremental exercise tests. Breathed through a mask attached to a low-resistance, 2-way, non-rebreathing valve

Miki 2012 (*Continued*)

	from gas cylinders through 200-L Douglas bag
Outcomes	Breathlessness measured by modified Borg at iso-time (mBorg 0-10, 0 "none" to 10 "maximal") HRQOL - no data available Treatment preference - no data available Adverse effects - no data available
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; no other information available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Single-blinded (participants): "Patients were blinded as to which oxygen concentration they were breathing."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All participants completed the study.
Selective reporting (reporting bias)	Low risk	Important outcomes were reported.
Other bias	Unclear risk	Unclear how participants were selected; blinding not optimal

Moore 2009

Methods	Randomised, controlled, double-blinded (participants and study personnel), cross-over trial
Participants	**Inclusion criteria**: patients with a clinical diagnosis of COPD attending the respiratory laboratory for routine breathing tests **Exclusion criteria**: use of short-term bronchodilators within 4 hours; receipt of supplemental oxygen within 20 minutes Setting: tertiary hospital, not stated if single-centre, Melbourne, Australia Method of recruitment of participants: Patients with a clinical diagnosis of COPD attending the respiratory laboratory for routine breathing tests were invited to participate in the study 55 participants (51 completed)

	Male 40 Mean age: 72.6 (SD 9.7) Mean FEV_1 (L): 1.40 (SD 0.78) Mean FEV_1 (% predicted): 54.7 (SD 24.9) Mean baseline SaO_2 (%): 95 (SD 3.2) Mean baseline PaO_2 (kPa): no data available Mean baseline $PaCO_2$ (kPa): no data available Mean breathlessness at baseline: no data available
Interventions	Oxygen (44%) vs medical air via mouthpiece. Breathing circuit included a 100-L Douglas bag, a Hans Rudolf wide bore, non-rebreathing valve
Outcomes	Breathlessness - modified Borg HRQOL - no data available Treatment preference - no data available Adverse effects - no data available
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; other information not available
Allocation concealment (selection bias)	Unclear risk	As above
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded. "The study gases were delivered to the Douglas bag from cylinders of identical appearance."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data reported only for participants completing the study (1 withdrawal)
Selective reporting (reporting bias)	Low risk	Important outcomes were reported.
Other bias	Unclear risk	It is unclear whether or not there was risk of other bias due to the lack of detail in the methods

Moore 2011

Methods	Randomised, controlled, double-blinded (participants and study personnel), parallel-group trial
Participants	**Inclusion criteria**: clinically stable ex-smokers with COPD on optimal medical treatment; PaO_2 > 7.3 kPa at rest breathing room air; and moderate to severe exertional breathlessness (mMRC Dyspnoea Scale grade > 2) **Exclusion criteria**: patients with $PaCO_2$ > 6.0 kPa undergoing repeat arterial blood gas analysis after breathing oxygen at 6 L/min, at rest, for 30 minutes; excluded if $PaCO_2$ increased by more than 0.7 kPa Setting: tertiary hospital, not stated if single centre, Melbourne, Australia Method of recruitment of participants: not described. 143 participants (139 completed) Male 99 (69%), female 44 Mean age: 71.8 (SD 9.8) Mean FEV_1 (L): 1.16 (SD 0.51) Mean baseline SaO_2 (%): no data available Mean baseline PaO_2 (kPa): oxygen: 9.7 (SD 8.2); air: 9.3 (SD 1.1) Mean baseline $PaCO_2$ (kPa): oxygen: 5.4 (SD 0.7); air: 5.4 (SD 0.6) Mean breathlessness at baseline: oxygen: 17.6 (SD 5.2); air: 17.5 (SD 4.9)
Interventions	Domicilary oxygen vs air at 6 L/min with 2-week run-in; 12 weeks ambulatory treatment. Delivered through nasal prongs by gas cylinders
Outcomes	Breathlessness measured by CRQ dyspnoea domain HRQOL - CRQ total score, CRQ subdomains Treatment preference - no data available Adverse effects - number of dropouts
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Assigned them randomly to cylinder air or cylinder oxygen using a computer-generated sequence and concealed allocation"
Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Study personnel and participants were blinded to group allocation. Cylinders were of identical appearance."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above

Moore 2011 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Data reported only for participants completing the study. The number of dropouts was equal in both groups (4 dropouts in total)
Selective reporting (reporting bias)	Low risk	According to the aims, adequately reported variables.
Other bias	Unclear risk	It is unclear whether or not there was risk of other bias due to the lack of detail in the methods

Nandi 2003

Methods	Randomised, controlled, double-blinded (participants, investigators), cross-over trial
Participants	**Inclusion criteria**: FEV_1 < 60% predicted with < 15% reversibility to inhaled salbutamol; smoking history > 20 pack-years; exertional desaturation ≥ 4% on pulse oximetry during submaximal exertion (corridor walking) **Exclusion criteria**: any other complicating medical condition Setting: laboratory 34 participants 18 male and 16 female Mean age: 68 (SD 6.0) Mean FEV_1 (L): 0.88 (SD 0.3) Mean baseline SaO_2 (%): 92 (SD 5.2) Mean baseline PaO_2 (kPa): 7.7 (SD 1.5) Mean baseline $PaCO_2$ (kPa): no data available Mean breathlessness at baseline: no data available
Interventions	Oxygen (28% at 4 L/min) vs compressed air (4 L/min) before exercise. Gas was supplied via constant performance masks, which supply 28% oxygen at the mouth over a wide range of flow rates and breathing patterns
Outcomes	Breathlessness measured by 100-mm VAS ("not breathless at all" to "the most breathless I have ever been") HRQOL - no data available Treatment preference - no data available Adverse effects - no data available
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; information not available

Nandi 2003 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"...neither the patient nor the test supervisor was aware of the gas mixture being used, or of oxygen saturation levels which were recorded by another observer."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study.
Selective reporting (reporting bias)	Low risk	According to the aims, adequately reported variables
Other bias	Unclear risk	It is unclear whether or not there was risk of other bias due to the lack of detail in the methods

Nonoyama 2007

Methods	Randomised, controlled, double-blind (participants and study personnel), N-of-1 crossover trial
Participants	**Inclusion criteria**: patients with a diagnosis of COPD (5) with dyspnoea limiting daily activities, and with desaturation $\leq$ 88% for 2 continuous minutes during a room-air 6-minute-walk test **Exclusion criteria**: 18 years or younger; those who met criteria for mortality reduction with long-term oxygen; those who received oxygen for palliative care or isolated nocturnal hypoxaemia; those unable to complete the questionnaires or provide informed consent Setting: home setting, Canada, outpatient Method of recruitment of participants: Participants were recruited from local respiratory rehabilitation programmes, respirology offices and home oxygen companies. The study co-ordinator (MLN) was responsible for recruitment and enrolment 38 participants (27 completed) Male 17 (63%) Mean age: 69 (SD 10) Lung function: no data available Mean baseline SaO_2 (%): no data available Mean baseline PaO_2 (kPa): no data available Mean baseline PaO_2 (kPa): no data available Mean breathlessness at baseline: CRQ dyspnoea score 3.7 (SD 1.1)
Interventions	Ambulatory oxygen (1-3 L/min) vs medical air (2 L/min) at exertion delivered through nasal prongs by gas cylinders. Participants undertook 3 pairs of 2-week treatment periods. Range of each period 9 to 21 days. Threshold for an adequate number of activities was

Nonoyama 2007 (*Continued*)

	set at 2 activities (chosen by participant), for a minimum duration of 1 hour a day
Outcomes	Breathlessness measured by modified Borg (mBorg 0-10, 0 "none" to 10 "maximal") and CRQ dyspnoea domain 1-7 p HRQOL - CRQ subdomains, SGRQ total score Treatment preference - no data available Adverse effects - number of dropouts
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Random allocation was centralized; method of randomization was computer generated."
Allocation concealment (selection bias)	Low risk	"Allocation was concealed and the order was randomly assigned to one of the eight possible orders of the pairs of placebo and active periods."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Oxygen and placebo gas in identical E-sized and D-sized cylinders, marked only with a code number indicating their contents." "Patients and the outcome assessors were blind to the gas mixture provided. This was achieved by an independent person ordering, receiving and preparing the appropriate cylinders and concentrator (oxygen or placebo)."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data reported only for participants completing the study. High proportion of dropouts (11 dropouts in total)
Selective reporting (reporting bias)	Low risk	According to the aims, adequately reported variables
Other bias	Unclear risk	It is unclear whether or not there was risk of other bias due to the lack of detail in the methods

O'Donnell 1997

Methods	Randomised, placebo-controlled, double-blinded (participant, investigators), cross-over trial
Participants	**Inclusion criteria**: advanced chronic airway limitation (FEV_1 < 60% predicted); mild hypoxaemia; did not meet criteria for LTOT; referred to an exercise programme because sedentary; poor exercise tolerance; severe activity-related breathlessness **Exclusion criteria**: clinical evidence of significant cardiovascular disease, other pulmonary disease (including cor pulmonale) or other disorders that could contribute to breathlessness or exercise limitation Method for recruiting participants: Patients were referred to an exercise programme because they were sedentary/had poor exercise tolerance/experienced severe activity-related breathlessness Setting: laboratory (Ontario, Canada) 11 participants 7 male and 4 female Mean age: 68 (SEM 2) Mean FEV_1 (% predicted): 0.97 (SEM 0.13) Mean FVC (% predicted): 2.3 (SEM 0.3) Mean TLC (% predicted): 7.0 (SEM 0.5) Mean RV (% predicted): 4.4 (SEM 0.3) Mean DLCO (mL/min/mmHg): 8.8 (SEM 1.1) Mean baseline SaO_2 (%): no data available Mean baseline PaO_2 (kPa): 9.9 (SEM 0.4) Mean baseline $PaCO_2$ (kPa): 5.5 (SEM 0.3) Mean breathlessness at baseline: 5.1 (SD 0.3)
Interventions	Oxygen (FiO_2 0.60) vs room air (FiO_2 0.21) on endurance cycle exercise test. Participants breathed through a mouthpiece and a low-resistance 2-way nonrebreathing valve with the nose clipped
Outcomes	Breathlessness measured by modified Borg (mBorg 0-10, 0 "none" to 10 "maximal") HRQOL - no data available Treatment preference - no data available Adverse effects - no data available
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; no other information available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Subjects were blinded with respect to the oxygen concentration being breathed, as was the investigator evaluating subjective responses and performing the data analysis;

O'Donnell 1997 (*Continued*)

		Identical breathing apparatus used in the study."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study.
Selective reporting (reporting bias)	Low risk	According to the aims, adequately reported variables
Other bias	Unclear risk	It is unclear whether or not there was risk of other bias due to the lack of detail in the methods

O'Driscoll 2011

Methods	Randomised, controlled, single-blind (participants), cross-over trial
Participants	**Inclusion criteria**: patients over 50 years of age; smoking history > 20 pack-years; severe COPD with FEV_1 < 40% of predicted; oxygen saturation at rest ≥ 93% breathing room air at time of recruitment to study and on arrival on study day; breathless during modest exercise such as climbing 1 or 2 flights of stairs; stable for 4 weeks (not requiring oral steroids or antibiotics or both); able to give informed consent; able to undertake a simple step test on an 18-cm exercise step **Exclusion criteria**: unable or unwilling to give informed consent; unable or unwilling to undertake step test for any reason; complicating comorbid conditions (e.g. arthritis of knees) that might interfere with exercise test or with the conduct of the trial; and already using oxygen at home Setting: laboratory Method of recruitment of participants: Participants were recruited from the chest clinic or pulmonary rehabilitation service at Salford Royal University Hospital (UK) 39 participants (34 completed) Male 24 (71%) Mean age 69 (SD 10) Mean FEV_1 (L) 0.80 (SD 0.2) Mean FEV_1 (% predicted) 31.4 (SD 5.5) Mean baseline PaO_2 (kPa): no data available Mean baseline $PaCO_2$ (kPa): no data available Mean breathlessness at baseline: 1.5 (SD 1.1)
Interventions	Oxygen (4 L/min) vs air (4 L/min) via face mask after exercise (step test)
Outcomes	Breathlessness measured by modified Borg after step exercise test (mBorg 0-10, 0 "none" to 10 "maximal") HRQOL - no data available Treatment preference - categorical, at study end

O'Driscoll 2011 (*Continued*)

	Adverse effects - no data available
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients received one of the following interventions in random order based on the patient drawing four pieces of folded paper sequentially from an opaque container prior to the commencement of the exercise task."
Allocation concealment (selection bias)	Low risk	See above.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single-blind. "The oxygen and air treatments were single blind. To achieve blinding for these two interventions, the investigator connected a concealed air or oxygen cylinder delivering a gas flow of 4 litres per minute to the same face mask for each patient."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Breathlessness on a Borg scale reported by participants; unclear whether they were aware of saturation during, at the end of exercise and during the recovery period. The SpO_2 and pulse rate were recorded in the patient´ s trial record sheet each minute during the exercise test, at the end of exercise and every minute during recovery until 5 minutes after finishing the exercise task."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data reported only for participants completing the study. 5 dropouts in total
Selective reporting (reporting bias)	Low risk	According to the aims, adequately reported variables
Other bias	Unclear risk	It is unclear whether or not there was risk of other bias due to the lack of detail in the methods

Oliveira 2012a

Methods	Randomised, controlled, double-blind (participants and study personnel), cross-over trial
Participants	**Inclusion criteria**: stable, non-hypercapnic ($PaCO_2$ < 45 mmHg at rest) COPD; > 20 pack-years of smoking; resting saturation > 90% and PaO_2 > 8 kPa; no evidence of polycythemia or cor pulmonale. No participant had qualified previously for ambulatory O_2 therapy. **Exclusion criteria**: recent exacerbation (within 1 month); treatment with oral corticosteroids; previous or current heart disease Method of recruitment of participants: no data Setting: laboratory (UK) 8 participants with COPD classified as "desaturators" with a drop in SaO_2 and end-exercise values < 88% All male Mean age: 66.7 (SD 7.9) Mean FEV_1 (L): 1.31 (SD 0.48) Mean FEV_1 (% predicted): 45.1 (SD 12.9) Mean baseline SaO_2 (%): no data available Mean baseline PaO_2 (kPa): 8.5 (SD 1.1) Mean baseline $PaCO_2$ (kPa): 5.2 (SD 0.6) Mean breathlessness at baseline: no data available
Interventions	Hyperoxia (FiO_2 0.40) vs normoxia (FiO_2 0.21) during incremental cycle tests; 2 tests ≥ 2 days apart. Gas delivered through a facial mask connected to a low-resistance Douglas bag
Outcomes	Breathlessness measured by modified Borg at peak exercise (mBorg 0-10, 0 "none" to 10 "maximal") HRQOL - no data available Treatment preference - no data available Adverse effects - no data available
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Test sequence was randomised"; other Information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Both patients and accompanying physician were blinded to the mixture being breathed."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above.

Oliveira 2012a (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants
Selective reporting (reporting bias)	Low risk	According to the aims, adequately reported variables
Other bias	Low risk	We judged that this trial appeared to be free of other sources of bias

Oliveira 2012b

Methods	Randomised, controlled, double-blind (participants and study personnel), cross-over trial
Participants	**Inclusion criteria**: stable, non-hypercapnic ($PaCO_2$ < 45 mmHg at rest) COPD; > 20 pack-years of smoking; resting saturation > 90% and PaO_2 > 8 kPa; no evidence of polycythemia or cor pulmonale. No participant had qualified previously for ambulatory O_2 therapy. **Exclusion criteria**: recent exacerbation (within 1 month), treatment with oral corticosteroids; previous or current heart disease Method of recruitment of participants: no data Setting: laboratory (UK) 12 participants classified as "non-desaturators" All male Mean age: 60.3 (SD 5.9) Mean FEV_1 (L): 1.56 (SD 0.41) Mean FEV_1 (% predicted): 48.6 (SD 10.8) Mean baseline SaO_2 (%): no data available Mean baseline PaO_2 (kPa): 10.0 (SD 1.3) Mean baseline $PaCO_2$ (kPa): 4.7 (SD 0.6) Mean breathlessness at baseline: no data available
Interventions	Hyperoxia (FiO_2 0.40) vs normoxia (FiO_2 0.21) during incremental cycle tests; 2 tests ≥ 2 days apart. Gas delivered through facial mask connected to a low-resistance Douglas bag
Outcomes	Breathlessness measured by modified Borg at peak exercise (mBorg 0-10, 0 "none" to 10 "maximal") HRQOL - no data available Treatment preference - no data available Adverse effects - no data available
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Oliveira 2012b (*Continued*)

Random sequence generation (selection bias)	Unclear risk	"Test sequence was randomised"; other Information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Both patients and accompanying physician were blinded to the mixture being breathed."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study.
Selective reporting (reporting bias)	Low risk	According to the aims, adequately reported variables
Other bias	Low risk	We judged that this trial appeared to be free of other sources of bias

Ringbaek 2013

Methods	Randomised, controlled, single-blinded (participants), parallel-group trial
Participants	**Inclusion criteria**: stable COPD (FEV_1 < 80% of predicted and FEV_1/FVC < 0.70); breathlessness with MRC score 3-5; motivated for PR; oxygen saturation at rest > 90%; desaturation > 4% and < 90% during ISWT or ESWT **Exclusion criteria**: LTOT; significant musculoskeletal, cardiac or cognitive problems Method of recruitment of participants: Of 391 participants starting PR at the centre between March 2007 and March 2011, 163 eligible patients were encouraged to participate in this trial Setting: ambulatory rehabilitation training (Denmark) 45 participants Male 53.3% Mean age: 69.0 (SD 8.7) Mean FEV_1 (% predicted): 31.8 (SD 13.8) Mean baseline SaO_2 (%): 94 (SD 2.0) Mean baseline PaO_2 (kPa): no data available Mean baseline $PaCO_2$ (kPa): no data available Mean breathlessness at baseline, MRC (min-max): oxygen 4.7 (3-5); controls 4.3 (3-5)
Interventions	Ambulatory oxygen (2 L/min) vs control (no ambulatory oxygen); oxygen delivered through a 2.3-kg portable oxygen concentrator. Participants were asked to use oxygen during supervised and unsupervised exercise (≥ 30 min/d) for up to 33 weeks

Ringbaek 2013 (*Continued*)

Outcomes	Breathlessness measured by modified Borg after 7 weeks of training (mBorg 0-10, 0 "none" to 10 "maximal") HRQL - SGRQ total score Treatment preference - no data available Adverse effects - COPD exacerbations, all hospital admissions, deaths at study end
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Were randomised to either ambulatory oxygen (AO) (n=22) or to a control group (n=23) in blocks of 6, using sealed envelopes." Other information not available
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	"without use of a sham concentrator"
Blinding of outcome assessment (detection bias) All outcomes	High risk	See above.
Incomplete outcome data (attrition bias) All outcomes	High risk	Data reported only for participants completing the study. High and unequal proportion of dropouts (7 missing for intervention; only 1 for comparison). "Baseline and week 7 only in the analysis"
Selective reporting (reporting bias)	Low risk	Have protocol and IPD data
Other bias	Low risk	We judged that this trial appeared to be free of other sources of bias

Rooyackers 1997

Methods	Randomised, controlled, unblinded, parallel-group trial
Participants	**Inclusion criteria**: hypoxaemia (SaO_2 < 90%) at maximal exercise; increase in alveolar-arterial difference in oxygen tension ≥ 2 kPa from rest to maximal incremental exercise test; former smoker **Exclusion criteria**: resting PaO_2 < 64 mmHg; mean nocturnal SaO_2 < 90%; mean pulmonary artery pressure > 25 mmHg measured at rest by Doppler echocardiography; neuromuscular or cardiovascular disease; any medication change during the study

Rooyackers 1997 (*Continued*)

	Setting: laboratory Method for recruitment of participants: Patients were referred to the hospital for PR (Dekkerswald, Netherlands) 24 participants in total 12 participants allocated to 10 weeks of general exercise training breathing room air; "air group" 12 participants allocated to supplemental oxygen (4 L/min) during general exercise training for 10 weeks; "oxygen group" 10 male and 2 female in each group See Rooyackers 1997a; Rooyackers 1997b for baseline characteristics and resting pulmonary function data
Interventions	See Rooyackers 1997a; Rooyackers 1997b.
Outcomes	HRQOL - CRQ total score (higher = better QoL), CRQ subdomains
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information available
Allocation concealment (selection bias)	Unclear risk	"The patients were randomly allocated either to general exercise training while breathing room air or while breathing at a flow rate of 4 L·min-1 through a dual-prong nasal cannula." No other information available
Blinding of participants and personnel (performance bias) All outcomes	High risk	While performing the tests: "During oxygen breathing, it was not possible to measure V'O2, and blood gas analysis was not performed."
Blinding of outcome assessment (detection bias) All outcomes	High risk	As above
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study.
Selective reporting (reporting bias)	Low risk	According to the aims, adequately reported variables
Other bias	Unclear risk	It is unclear whether or not there was risk of other bias due to the lack of detail in the

Rooyackers 1997 (*Continued*)

		methods

Rooyackers 1997a

Methods	Randomised, controlled, unblinded, parallel-group trial
Participants	**Inclusion criteria**: hypoxaemia (SaO_2 < 90%) at maximal exercise; increase in alveolar-arterial difference in oxygen tension ≥ 2 kPa from rest to maximal incremental exercise test; former smoker **Exclusion criteria**: resting PaO_2 < 64 mmHg; mean nocturnal SaO_2 < 90%, mean pulmonary artery pressure > 25 mmHg measured at rest by Doppler echocardiography; neuromuscular or cardiovascular disease; any medication change during the study Setting: laboratory Method for recruitment of participants: Patients were referred to the hospital for PR (Dekkerswald, Netherlands) 12 participants allocated to 10 weeks of general exercise training breathing room air; "air group" 10 male and 2 female Mean age: 59 (SD 13) Mean FEV_1 (L): 1.2 (SD 0.5) Mean TLC (% predicted): 114 (SD 20) Mean baseline SaO_2 (%): no data available Mean baseline PaO_2 (kPa): 10.5 (SD 1.1) Mean baseline $PaCO_2$ (kPa): 5.0 (SD 0.8) Mean breathlessness at baseline: no data available
Interventions	Room air (RA) vs oxygen (4 L/min) during maximal incremental cycle exercise test, single-stage exercise test and 6MWT
Outcomes	Breathlessness measured by modified Borg (mBorg 0-10, 0 "none" to 10 "maximal") HRQOL - CRQ total score (higher = better QoL), CRQ subdomains Treatment preference - no data available Adverse effects - no data available
Notes	In both groups, the work rate was not allowed to exceed the level at which SaO_2 fell below 90%.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information available
Allocation concealment (selection bias)	Unclear risk	"The patients were randomly allocated either to general exercise training while breathing room air or while breathing supplemental oxygen at a flow rate of 4 L·min-1 through a dual-prong nasal cannula." No

Rooyackers 1997a (*Continued*)

		other information available
Blinding of participants and personnel (performance bias) All outcomes	High risk	While performing the tests: "During oxygen breathing, it was not possible to measure V'O2, and blood gas analysis was not performed."
Blinding of outcome assessment (detection bias) All outcomes	High risk	As above
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study.
Selective reporting (reporting bias)	Low risk	According to the aims, adequately reported variables
Other bias	Unclear risk	It is unclear whether or not there was risk of other bias due to the lack of detail in the methods

Rooyackers 1997b

Methods	Randomised, controlled, unblinded, parallel-group trial
Participants	**Inclusion criteria**: hypoxaemia (SaO_2 < 90%) at maximal exercise and increase in alveolar-arterial difference in oxygen tension ≥ 2 kPa from rest to maximal exercise during maximal incremental exercise; former smoker; no medication changes during the study **Exclusion criteria**: resting PaO_2 < 64 mmHg, mean nocturnal SaO_2 < 90%, mean pulmonary artery pressure > 25 mmHg measured at rest by Doppler echocardiography; neuromuscular or cardiovascular disorder Setting: laboratory Method for recruitment of participants: Patients were referred to the hospital for PR (Dekkerswald, Netherlands) 12 participants allocated to supplemental oxygen (4 L/min) during general exercise training for 10 weeks; "oxygen group" 10 male and 2 female Mean age: 63 (SD 5) Mean FEV_1 (L): 0.9 (SD 0.3) Mean TLC (% predicted): 109 (SD 17) Mean baseline SaO_2 (%): no data available Mean baseline PaO_2 (kPa): 10.2 (SD 1.6) Mean baseline $PaCO_2$ (kPa): 5.1 (SD 1.1) Mean breathlessness at baseline: no data available
Interventions	Oxygen (4 L/min) vs room air (RA) during maximal incremental cycle exercise test, single-stage exercise test and 6MWT

Rooyackers 1997b (*Continued*)

Outcomes	Breathlessness measured by modified Borg (mBorg 0-10, 0 "none" to 10 "maximal") HRQOL - CRQ total score (higher = better QoL), CRQ subdomains Treatment preference - no data available Adverse effects - no data available
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information available
Allocation concealment (selection bias)	Unclear risk	"The patients were randomly allocated either to general exercise training while breathing room air or while breathing supplemental oxygen at a flow rate of 4 L·min-1 through a dual-prong nasal cannula." No other information available
Blinding of participants and personnel (performance bias) All outcomes	High risk	While performing the tests: "During oxygen breathing, it was not possible to measure V'O2, and blood gas analysis was not performed."
Blinding of outcome assessment (detection bias) All outcomes	High risk	As above
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study.
Selective reporting (reporting bias)	Low risk	According to the aims, adequately reported variables
Other bias	Unclear risk	It is unclear whether or not there was risk of other bias due to the lack of detail in the methods

Scorsone 2010

Methods	Randomised, controlled, double-blind (participants and study personnel), parallel-group trial
Participants	**Inclusion criteria**: clinical diagnosis of COPD and airflow obstruction confirmed by spirometry; although not stated as criteria, all participants had a history of smoking and were under regular bronchodilator treatment **Exclusion criteria**: not stated

	Method of recruitment of participants: not stated Setting: pulmonary rehab programme (Italy) 20 participants Male 14 (70%) Mean age: air 68 (SD 7); oxygen 67 (SD 9) Mean FEV_1/FVC: air 47 (SD 12); oxygen 51 (SD 8) Mean FEV_1 (% predicted): air 50 (SD 12); oxygen 47 (SD 10) Mean baseline SaO_2 (%): no data available Mean baseline PaO_2 (kPa): oxygen 9.9 (SD 1.0); air 10.2 (SD 1.2) Mean baseline $PaCO_2$ (kPa): oxygen 5.3 (SD 0.4); air 5.1 (SD 0.4) Mean breathlessness at baseline: oxygen 7 (SD 3); air 7 (SD 3)
Interventions	Supplemental oxygen (FiO_2 0.4) vs air delivered by mouthpiece from a Douglas bag; an 8-week, 3 times a week training programme conducted on a calibrated cycle ergometer
Outcomes	Breathlessness measured by modified Borg at isotime of exertion (mBorg 0-10, 0 "none" to 10 "maximal") HRQOL - no data available Treatment preference - no data available Adverse effects - no data available
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; other information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"PaO_2 saturation was continuously monitored by a technician blind to the design of the study." ".. according to a randomised, double-blind design in which subjects breathed humidified air, supplemental O_2 40%, or heliox 60:40 at random through a mouthpiece from a Douglas bag"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study.

Scorsone 2010 (*Continued*)

Selective reporting (reporting bias)	Low risk	According to the aims, adequately reported variables
Other bias	Unclear risk	It is unclear whether or not there was risk of other bias due to the lack of detail in the methods

Somfay 2001

Methods	Randomised, controlled, single-blind (participants), cross-over trial
Participants	**Inclusion criteria**: severe COPD (FEV_1 < 40% predicted); no more than mildly hypoxaemic (O_2 sat at rest > 92% and during exercise > 88%); none had previously qualified for home oxygen **Exclusion criteria**: clinically manifest cor pulmonale; severe cardiovascular comorbidity or other disease that might contribute to breathlessness or exercise limitation 10 participants Setting: laboratory 6 male and 4 female Mean age: 67 (SD 7) Mean FEV_1 (L): 0.92 (SD 0.43) Mean FVC (% predicted): 76 (SD 15) Mean TLC (L): 7.3 (SD 1.5) Mean RV (L): 4.3 (SD 1.3) Mean baseline SaO_2 (%): 96 (SD 0.8) Mean baseline PaO_2 (kPa): no data available Mean baseline $PaCO_2$ (kPa): no data available Mean breathlessness at baseline: no data available
Interventions	Oxygen (30%, 50%, 75% or 100%) vs compressed air during constant work rate test at 75% of peak work rate. Compressed air and oxygen were blended from gas cylinders into a 200-L meteorological balloon to be inspired during exercise. Participants breathed through a mouthpiece attached to a low-resistance, 2-way, nonrebreathing valve
Outcomes	Breathlessness measured by modified Borg (mBorg 0-10, 0 “none” to 10 “maximal”) HRQOL - no data available Treatment preference - no data available Adverse effects - no data available
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; no other information available

Somfay 2001 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single-blind study; "Subjects were blinded with respect to the oxygen concentration they breathed."
Blinding of outcome assessment (detection bias) All outcomes	High risk	As above
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study.
Selective reporting (reporting bias)	Low risk	Adequately reported variables
Other bias	Unclear risk	It is unclear whether or not there was risk of other bias due to the lack of detail in the methods

Spielmanns 2014

Methods	Randomised, controlled, parallel-group trial
Participants	**Inclusion criteria**: diagnosis of COPD and $FEV_1/FVC < 0.7$ after bronchodilation; $FEV_1 < 80\%$ of predicted; stable clinical condition for ≥ 4 weeks; normoxaemia ($SaO_2 > 90\%$) at rest and during exercise without oxygen supply **Exclusion criteria**: comorbidity that could interfere with training, such as ischaemic cardiac disease, musculoskeletal problems and psychological disorders Method of recruitment of participants: invited to take part when referred by general practitioners to the St Remigius Hospital, in Leverkusen, Germany, from September 2009 to March 2011 Setting: 1 outpatient pulmonary rehabilitation programme (St Remigius Hospital, Leverkusen, Germany) 85 participants with COPD (39 withdrawals; 18 oxygen group; 21 medical air) No data on sex Mean age: oxygen 65 (SD 8.7); air 64 (SD 8.4) Mean FEV_1 (L): oxygen 1.2 (SD 0.5); air 1.5 (SD 0.4) Mean FEV_1 (% predicted): oxygen 44 (SD 10); air 43 (SD 12) Mean baseline SaO_2 (%): > 90% according to inclusion criteria Mean baseline PaO_2 (kPa): no data available Mean baseline $PaCO_2$ (kPa): no data available Mean breathlessness at baseline: no data available
Interventions	Oxygen (4 L/min) vs compressed air (4 L/min) during training cycle tests delivered via nasal cannula. Duration of treatment: training sessions throughout 24 weeks; 3 sessions/wk

Spielmanns 2014 (*Continued*)

Outcomes	Breathlessness - no data available HRQL - SF-36; subscores with range from 0 to 100; measured at baseline and after 12 weeks Treatment preference - no data available Adverse effects - number of dropouts
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomization scheme was generated using the website Randomization.com using a computer-generated list of random numbers to assign subjects to either the oxygen or compressed air group."
Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not sufficient information. "Tests were conducted by an unblinded coach; the subjects and investigator were not aware of the group to which they belonged until the end of all experiments."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	As above
Incomplete outcome data (attrition bias) All outcomes	High risk	Data reported only for participants completing the study. High proportion of drop-outs (39 in total; 18 from oxygen group; 21 from medical air)
Selective reporting (reporting bias)	Low risk	Adequately reported variables
Other bias	Low risk	We judged that this trial appeared to be free of other sources of bias

Swinburn 1984

Methods	Randomised, single-blinded (participants), cross-over trial
Participants	**Inclusion criteria**: advanced obstructive airways disease but in "stable clinical state" **Exclusion criteria**: not stated Setting: laboratory 5 participants

Swinburn 1984 (*Continued*)

	Mean age: 65 (range 53-72) Mean FEV_1 (L): 0.8 (SD 0.2) Mean FVC (L): 1.8 (SD 0.4) Mean baseline SaO_2 (%): 93.2 (SD 0.8) Mean baseline PaO_2 (kPa): no data available Mean baseline $PaCO_2$ (kPa): no data available Mean breathlessness at baseline: no data available
Interventions	Room air (RA) vs oxygen (60%) delivered through a mouthpiece during incremental cycle exercise test
Outcomes	Breathlessness measured by 10-cm VAS scale ("minimum" to "maximum") HRQOL - no data available Treatment preference - no data available Adverse effects - no data available
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; other information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single-blind. "The patients were informed that the purpose of the study was to investigate the effects of different gas mixtures on exercise performance."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study.
Selective reporting (reporting bias)	Low risk	Adequately reported outcomes
Other bias	Unclear risk	It is unclear whether or not there was risk of other bias due to the lack of detail in the methods

Voduc 2010

Methods	Randomised, controlled, double-blind (participants and study personnel), cross-over trial
Participants	**Inclusion criteria**: clinically stable COPD; accepted into the pulmonary rehabilitation programme; clinical diagnosis of COPD; $FEV_1/FVC < 0.7$; $FEV_1 < 70\%$ of predicted **Exclusion criteria**: hypoxia ($SaO_2 < 89\%$) at rest or during ambulation; non-pulmonary conditions that could affect exercise performance (e.g. angina, congestive heart failure, severe musculoskeletal problems) or lung diseases other than COPD (e.g. asthma, bronchiectasis); and recent COPD exacerbations or changes in regular medications within the past 2 months Method of recruitment of participants: All patients were initially referred for pulmonary rehabilitation for improvement of exertional dyspnoea that was not satisfactorily managed by pharmacological therapy alone Setting: 1 rehabilitation programme (Ottawa, Ontario, Canada) 24 participants (16 completed) Male 14 (70%) Mean age: 65.9 (SD 6.6) Mean FEV_1/FVC: 41.5 (SD 13.8) Mean baseline SaO_2 (%): 97 (SD 1.9) Mean baseline PaO_2 (kPa): no data available Mean baseline $PaCO_2$ (kPa): no data available Mean breathlessness at baseline: no data available
Interventions	Oxygen (FiO_2 0.5) vs room air delivered through a mask connected to a Douglas bag during 2 symptom-limited constant-load exercise tests
Outcomes	Breathlessness measured by modified Borg at isotime (mBorg 0-10, 0 "none" to 10 "maximal") HRQOL - no data available Treatment preference - no data available Adverse effects - number of dropouts
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The order of testing was randomised."
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Both the patient and the supervising physician were blinded to the nature of the inhaled gas."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above.

Voduc 2010 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	Included only participants who completed the whole 12-week training period. In total, 8 dropouts. They could have had a different acute response to oxygen
Selective reporting (reporting bias)	Low risk	Adequately reported variables
Other bias	Unclear risk	It is unclear whether or not there was risk of other bias due to the lack of detail in the methods

Wadell 2001

Methods	Randomised, controlled, single-blind (participants), parallel-group trial
Participants	**Inclusion criteria**: age < 75 years; stopped smoking ≥ 6 months before entering the study; PaO_2 > 60 mmHg at rest; hypoxaemia (SaO_2 ≤ 92%) during exercise (6MWT test); FEV_1 < 70% of predicted; no infection in the 3 weeks preceding study enrolment; no change in medical treatment in the month preceding enrolment **Exclusion criteria**: past or present major illness, such as cardiac, orthopaedic or neurological disease that might have interfered with exercise performance Setting: laboratory Method of recruiting participants: recruited from previously diagnosed outpatients who had been treated at the Department of Respiratory Medicine and Allergy at the University Hospital in Umea, Sweden 22 participants (20 completed) 10 in air group and 10 in oxygen group Median age: air 69 (60 to 72); oxygen 65 (52 to 73) Median FEV_1 (% predicted): air 51.6 (24 to 66); oxygen 39.3 (23 to 59) Median baseline SaO_2 (%): air 95 (91 to 97); oxygen 95 (93-97) Median baseline PaO_2 (kPa): air 9.3 (7.9 to 11.4); oxygen 9.5 (8.6 to 11.6) Median baseline $PaCO_2$ (kPa): 9.3 (7.9 to 11.4); oxygen 5.4 (4.5 to 5.8) Median breathlessness at baseline: 1.5 (0 to 3)
Interventions	Oxygen (5 L/min) vs air (5 L/min) delivered through a dual-prong nasal cannula during 6MWT on treadmill - baseline effect of 2 interventions, as complete study involved training over an 8-week period
Outcomes	Breathlessness measured by modified Borg (mBorg 0-10, 0 “none” to 10 “maximal”) HRQOL - no data available Treatment preference - no data available Adverse effects - no data available
Notes	The treadmill was stopped if participants rated 7/17 (respectively) or more on Borg scales and/or if participants’ SaO_2 fell below 90%.
Risk of bias	

Wadell 2001 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The included patients were randomly allocated (randomization by blocks, men and women were randomised separately) to train either with air (AG) or with oxygen (OG)."
Allocation concealment (selection bias)	Unclear risk	Not enough information available to determine how order of treatment group assignment was concealed from investigators
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Single-blind study"; "SaO_2 and heart rate were continuously monitored with a pulse oximeter using a finger probe or a forehead probe."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Outcomes self-reported by participant
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data reported only for participants completing the study (2 withdrawals)
Selective reporting (reporting bias)	Low risk	Adequately reported variables
Other bias	Low risk	We judged that this trial appeared to be free of other sources of bias

Woodcock 1981

Methods	Randomised, double-blind (participants and study personnel), cross-over trial
Participants	**Inclusion criteria**: fixed airways obstruction; "moderate or severe breathlessness on exertion" (method of defining not stated); normal or low PaO_2 **Exclusion criteria**: none stated Setting: laboratory 10 participants 9 male and 1 female Mean age: 62 (range 43-70) Mean FEV_1 (L): 0.71 (SD 0.29) Mean FVC (L): 2.65 (SD 1.04) Mean baseline SaO_2 (%): no data available Mean baseline PaO_2 (kPa): 9.6 (SD 1.5) Mean baseline $PaCO_2$ (kPa): 4.6 (SD 0.6) Mean breathlessness at baseline: 4 (SD 0.94)

Woodcock 1981 (*Continued*)

Interventions	Oxygen (described as 100% delivered at 4 L/min) vs compressed air (4 L/min) during treadmill test and 6MWT	
Outcomes	Breathlessness measured by 10-cm VAS HRQOL - no data available Treatment preference - no data available Adverse effects - no data available	
Notes		

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; other information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Compressed air versus oxygen delivered via coded unmarked cylinders"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study.
Selective reporting (reporting bias)	Low risk	Adequately reported outcomes
Other bias	Low risk	We judged that this trial appeared to be free of other sources of bias

6MWT: six-minute walk test; AAT: alpha-1 antitrypsin; ABG: arterial blood gas; ATS: American Thoracic Society; BTS: British Thoracic Society; CA: compressed air; CAD: coronary artery disease; CO: carbon monoxide; COPD: chronic obstructive pulmonary disease; CPET: cardiopulmonary exercise testing; CRQ: Chronic Respiratory Questionnaire; DLCO: diffusing capacity of the lung for carbon monoxide; ESWT: endurance shuttle walk test; FEV_1: forced expiratory volume in one second; FiO_2: fraction of inspired oxygen; FVC: forced vital capacity; HR: heart rate; HRQOL: health-related quality of life; IPD: individual patient data; IQR: interquartile range; ISWT: incremental shuttle walk test; LTOT: long-term oxygen relief therapy; $PaCO_2$: partial pressure of carbon dioxide in arterial blood; PaO_2: partial pressure of oxygen in arterial blood; PCO_2: partial pressure of carbon dioxide; PFT: pulmonary function test; PO_2: partial pressure of oxygen; PR: pulmonary rehabilitation; RA: room air; RV: right ventricle; SaO_2: oxygen saturation; SBOT: short-burst oxygen therapy; SD: standard deviation; SEM: standard error of the mean; SF-36: Short Form 36; SGRQ: St George's Respiratory Quotient; SMD: standard mean difference; SpO_2: oxygen saturation; TLC: total lung capacity; TR: tricuspid regurgitation; VAS: visual analogue scale; VC: vital capacity.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Alexandre 2010	Other - abstract, no suitable outcome
Arnold 2008	Other - abstract
Balkissoon 2006	Other - review of another manuscript
Bjørgen 2009	No suitable outcome
Bradley 1978	No suitable outcome
Bye 1985	No suitable outcome
Campbell 2013	Patients already receiving home oxygen
Caspersen 2012	Other - abstract
Criner 1987	No suitable outcome
Cuvelier 2002	Patients already receiving home oxygen
Edvardsen 2007	Patients already receiving home oxygen
Evans 1986	No suitable outcome
Fraser 2013	Patients already receiving home oxygen
Fujimoto 2002	No suitable outcome
Garrod 2000	Patients already receiving home oxygen
Gosselin 2004	No suitable outcome
Heinzelmann 2011	Other - abstract
Helgerud 2010	No suitable outcome
King 1973	Mean PaO_2 < 55 mmHg
King 2012	Other - abstract
Lane 1987	Not a randomised controlled trial
Leggett 1977	Mean PaO_2 < 55 mmHg No suitable outcome

(*Continued*)

Lellouche 2011	Other - abstract
Light 1989	No suitable outcome
Liss 1988	Patients already receiving home oxygen
Lock 1992	Mean PaO_2 < 55 mmHg No placebo or control arm
Maldonado 2014	Mean PaO_2 < 55 mmHg; study performed at Bogota altitude
Mannix 1992	No suitable outcome
Marques-Magallanes 1998	Mean PaO_2 < 55 mmHg No suitable outcome
Matsuzawa	Japanese with no capacity for translation
Nasilowski 2008	Patients already receiving home oxygen
Nguyen 2008	Intervention not oxygen vs medical air
Noseda 1997	Intervention not oxygen vs medical air
O'Donnell 2001	Patients already receiving home oxygen
O'Driscoll 2003	Other - editorial
O'Driscoll 2007	No suitable outcome
O'Neill 2006	No suitable outcome
Ouyang 2006	Intervention not oxygen vs medical air
Palwai 2010	Patients already receiving home oxygen
Peters 2006	Intervention not oxygen vs medical air
Raimondi 1970	No suitable outcome
Roberts 1996	Mean PaO_2 < 55 mmHg Patients already receiving home oxygen
Sandland 2008a	Patients hypoxic at rest
Sandland 2008b	Patients already receiving home oxygen or PRN oxygen No dyspnoea outcome

(*Continued*)

Sforza 2010	Other - abstract
Stein 1982	No suitable outcome
Stevenson 2004	No suitable outcome
Swinburn 1991	Mean PaO_2 < 55 mmHg
Vyas 1971	No suitable outcome
Waterhouse 1983	No suitable outcome
Wedzicha 2006	Other - editorial
Womble 2010	Other - abstract
Womble 2012	No suitable outcome

PaO_2: partial pressure of oxygen in arterial blood; PRN: pro re nata, or 'as needed'.

DATA AND ANALYSES

Comparison 1. Oxygen versus air

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Breathlessness - all trials	32		Std. Mean Difference (Random, 95% CI)	-0.31 [-0.43, -0.20]
2 Breathlessness - subgroup analysis - short-burst oxygen vs not	32		SMD (Random, 95% CI)	Subtotals only
2.1 Studies using short-burst oxygen	4		SMD (Random, 95% CI)	-0.03 [-0.28, 0.22]
2.2 Studies not using short-burst oxygen	28		SMD (Random, 95% CI)	-0.36 [-0.48, -0.24]
3 Breathlessness - subgroup analysis - exertional desaturation vs not	31		SMD (Random, 95% CI)	Subtotals only
3.1 Studies with exertional desaturation	16		SMD (Random, 95% CI)	-0.28 [-0.39, -0.16]
3.2 Studies with no exertional desaturation	15		SMD (Random, 95% CI)	-0.47 [-0.69, -0.24]
4 Breathlessness - subgroup analysis - mean PaO_2 < 9.3 kPa vs higher	32		SMD (Random, 95% CI)	Subtotals only
4.1 Studies with mean PaO_2 < 9.3 kPa	7		SMD (Random, 95% CI)	-0.28 [-0.48, -0.07]
4.2 Studies with mean PaO_2 ≥ 9.3 kPa	25		SMD (Random, 95% CI)	-0.33 [-0.47, -0.20]
5 Breathlessness - subgroup analysis - measured during exercise test vs not	32		SMD (Random, 95% CI)	-0.31 [-0.43, -0.20]
5.1 Studies measuring during exercise test	30		SMD (Random, 95% CI)	-0.34 [-0.46, -0.22]
5.2 Studies not measuring during exercise test	2		SMD (Random, 95% CI)	-0.13 [-0.37, 0.11]
6 Breathlessness - subgroup analysis - laboratory vs other	32		SMD (Random, 95% CI)	-0.31 [-0.43, -0.20]
6.1 Studies in laboratory setting	25		SMD (Random, 95% CI)	-0.37 [-0.52, -0.22]
6.2 Studies in non-laboratory setting	7		SMD (Random, 95% CI)	-0.23 [-0.36, -0.09]
7 Breathlessness - subgroup analysis - short-term vs long-term (training) effect of oxygen	32		Std. Mean Difference (Random, 95% CI)	-0.31 [-0.43, -0.20]
7.1 Studies of short-term effect of oxygen	29		Std. Mean Difference (Random, 95% CI)	-0.34 [-0.46, -0.22]
7.2 Studies of long-term effect of oxygen	3		Std. Mean Difference (Random, 95% CI)	-0.09 [-0.37, 0.19]

8 Breathlessness - subgroup analysis - mean oxygen dose > 2 L/min vs lower	30	Std. Mean Difference (Random, 95% CI)	-0.31 [-0.43, -0.18]
8.1 Studies with a mean oxygen dose > 2 L/min	26	Std. Mean Difference (Random, 95% CI)	-0.35 [-0.49, -0.21]
8.2 Studies with a mean oxygen dose ≤ 2 L/min	5	Std. Mean Difference (Random, 95% CI)	-0.19 [-0.39, 0.01]
9 Breathlessness - sensitivity analysis - excluding measurements at peak exertion	26	Std. Mean Difference (Random, 95% CI)	-0.37 [-0.50, -0.24]
10 Breathlessness - sensitivity analysis - excluding studies with high risk of bias	25	SMD (Random, 95% CI)	-0.30 [-0.41, -0.20]
11 Breathlessness - sensitivity analysis - excluding outliers	26	Std. Mean Difference (Random, 95% CI)	-0.27 [-0.35, -0.18]
12 Breathlessness - sensitivity analysis - post hoc - excluding short-burst and outliers	22	SMD (Random, 95% CI)	-0.30 [-0.39, -0.20]
13 Health-related quality of life - all trials	5	Std. Mean Difference (Random, 95% CI)	0.12 [-0.04, 0.28]

ADDITIONAL TABLES

Table 1. Characteristics of included trials

Study	Design	Setting	Blinding	O_2 delivery	O_2 dose	Baseline PaO_2 (kPa)	Baseline SaO_2 (%)	Baseline dyspnoea	Breathlessness outcome measure	HRQOL outcome measure
Abernethy 2010	Parallel	Non-laboratory	Double-blind	NC	2 L/min	10.0 (SD 1.5)	NA	4.8 (SD 2.1)	NRS	10-cm VAS
Bruni 2012a	Crossover	Laboratory	Double-blind	Mouthpiece	50%	9.5 (SD 1.2)	NA	NA	Modified Borg	-
Bruni 2012b	Crossover	Laboratory	Double-blind	Mouthpiece	50%	10.3 (SD 0.9)	NA	NA	Modified Borg	-
Davidson 1988	Crossover	Laboratory	Double-blind	NC or valve	4 L/min	8.6 (SE 0.3)	NA	NA	10-cm VAS	-
Dean 1992	Crossover	Laboratory	Double-blind	Mouthpiece	40%	9.5 (SE 0.3)	NA	NA	Modified Borg	-
Dyer 2012	Parallel	Laboratory	Single-blind	NC	2-6 L/min	NA	94 (SD 2)	3 (SD 1)	CRQ dyspnoea	CRQ subdomains

Table 1. Characteristics of included trials (*Continued*)

Eaton 2002	Cross-over	Non-laboratory	Double-blind	NC	4 L/min	9.2 (SD 1.0)	94 (SD 1.9)	0.7 (SD 1.0)	Modified Borg	CRQ total CRQ subdomains SF-36
Eaton 2006	Parallel	Non-laboratory	Double-blind	NC	2 L/min	Oxygen: 9.6 (SD 1.3) Air: 10.1 (SD 1.7)	Oxygen: 95 (SD 1.9) Air: 95 (SD 1.6)	Oxygen: 17.8 (SD 5.0) Air: 17.5 (SD 4.2)	CRQ dyspnoea	CRQ total CRQ subdomains SF-36
Emtner 2003a	Parallel	Laboratory	Double-blind	Mouthpiece	30%	9.8 (SD 0.8)	NA	5.8 (SD 1.8)	Modified Borg	CRQ total CRQ subdomains SF-36
Emtner 2003b	Parallel	Laboratory	Double-blind	Mouthpiece	30%	10.0 (SD 1.2)	NA	6.3 (2.5)	Modified Borg	CRQ total CRQ subdomains SF-36
Eves 2006	Crossover	Laboratory	Double-blind	Mouthpiece	40%	9.1 (SD 0.9)	NA	NA	Modified Borg	-
Haidl 2004	Parallel	Non-laboratory	Unblinded	NC	2 L/min	Oxygen: 9.0 (SD 0.9) Controls: 8.7 (SD 0.8)	NA	Oxygen: 5.0 (SD 2.1) Controls: 5.0 (SD 1.5)	Modified Borg	-
Ishimine 1995	Crossover	Laboratory	Double-blind	Unknown	3 L/min	10.1 (SD 1.1)	NA	NA	Dyspnoea questionnaire	-
Jolly 2001a	Crossover	Laboratory	Double-blind	NC	3 L/min	10.5 (SE 0.4)	95.8 (SE 0.46)	0.56 (SE 0.34)	Modified Borg	-
Jolly 2001b	Crossover	Laboratory	Double-blind	NC	3 L/min	9.9 (SE 0.3)	94.7 (SE 0.27)	1.27 (SE 0.43)	Modified Borg	-

Table 1. Characteristics of included trials (*Continued*)

Killen 2000	Crossover	Non-laboratory	Single-blind	Mask	2 L/min	NA	Median 94 (IQR 91, 95)	NA	100-mm VAS	-
Knebel 2000	Crossover	Laboratory	Double-blind	NC	4 L/min	NA	97.1 (SD 1.7) (range 92-100)	0.5 (SD 0.9)	10-cm VAS	-
Kurihara 1989	Crossover	Laboratory	Single-blind	NC	3 L/min	9.2 (SD 1.2)	NA	NA	Modified Borg	-
Laude 2006	Crossover	Laboratory	Unclear	Mask/valve	28%	NA	93.9 (SD 2.3)	VAS 24.2 (19.0) Borg 1.8 (1.1)	100-mm VAS modified Borg	-
Leach 1992	Crossover	Laboratory	Single-blind	Mask	2 L/min	8.7 (SD 2.3)	NA	NA	10-cm VAS	-
Lewis 2003	Crossover	Laboratory	Single-blind	NC	2 L/min	NA	94.4 (1.6)	0.4 (0.5)	Modified Borg	-
Maltais 2001	Crossover	Laboratory	Double-blind	Mouthpiece	75%	11.3 (SEM 0.5)	NA	NA	Modified Borg	-
McDonald 1995	Crossover	Non-laboratory	Double-blind	NC	4 L/min	9.2 (SD 1.1) (range 7.7-10.9)	94 (SD 2.1)	NA	Modified Borg	CRQ subdomains
McKeon 1988a	Crossover	Laboratory	Double-blind	NC	2.5 L/min	7.7 (SD 1.2) (range 5.7-10.9)	90 (SD 3) (range 84-96)	NA	300-mm VAS	-
McKeon 1988b	Crossover	Laboratory	Double-blind	NC	4 L/min	8.9 (SD 1.5)	NA	NA	300-mm VAS	-
Miki 2012	Crossover	Laboratory	Single-blind	Mask/valve	24%	10.1 (SD 1.3)	NA	Oxygen: 0.1 (SD 0.2) Air: 0.1 (SD 0.4)	Modified Borg	-
Moore 2009	Crossover	Laboratory	Double-blind	Mouthpiece	44%	NA	95 (SD 3.2)	NA	Modified Borg	-

Table 1. Characteristics of included trials (*Continued*)

Moore 2011	Parallel	Non-laboratory	Double-blind	NC	6 L/min	9.5 (SD 1.1)	NA	Oxygen: 17.6 (SD 5.2) Air: 17.5 (SD 4.9)	CRQ dyspnoea	CRQ total CRQ subdomains
Nandi 2003	Crossover	Laboratory	Double-blind	Mask	4 L/min	7.7 (SD 1.5)	91.9 (SD 5.2) (range 76 to 97)	NA	100-mm VAS	-
Nonoyama 2007	Crossover	Non-laboratory	Double-blind	NC	1-3 L/min	NA	NA	3.7 (SD 1.1)	Modified Borg	CRQ subdomains SQRQ total
O'Donnell 1997	Crossover	Laboratory	Double-blind	Mouthpiece	60%	9.9 (SEM 0.4)	NA	5.1 (SD 0.3)[a]	Modified Borg	-
O'Driscoll 2011	Crossover	Laboratory	Single-blind	Mask	4 L/min	NA	95.0 (SD, 1.3)	1.5 (SD 1.1)	Modified Borg	-
Oliveira 2012a	Crossover	Laboratory	Double-blind	Mask	40%	8.5 (SD 1.1)	NA	NA	Modified Borg	-
Oliveira 2012b	Crossover	Laboratory	Double-blind	Mask	40%	10.0 (SD 1.3)	NA	NA	Modified Borg	-
Ringbaek 2013	Parallel	Non-laboratory	Single-blind	NC	2 L/min	NA	93.6 (SD 2.0)	5.3 (SD 1.8)	Modified Borg	SQRQ total
Rooyackers 1997a	Parallel	Laboratory	Unclear	NC	4 L/min	10.2 (SD 1.2)	NA	NA	Modified Borg	CRQ total CRQ subdomains
Rooyackers 1997b	Parallel	Laboratory	Unclear	NC	4 L/min	9.5 (SD 2.0)	NA	NA	Modified Borg	CRQ total CRQ subdomains
Scorsone 2010	Parallel	Laboratory	Double-blind	Mouthpiece	40%	Oxygen: 9.9 (SD 1.0) Air: 10.2	NA	7 (SD 3)	Modified Borg	

Table 1. Characteristics of included trials (*Continued*)

						(SD 1.2)				
Somfay 2001	Cross-over	Laboratory	Single-blind	Mouthpiece	30%	NA	95.7 (0.8)	NA	Modified Borg	-
Spielmanns 2014	Parallel	Laboratory	Unclear	NC	4 L/min	NA	> 90%	NA	-	SF-36 total
Swinburn 1984	Cross-over	Laboratory	Single-blind	Mouthpiece	60%	NA	93.2 (SD 0.8)	NA	10-cm VAS	-
Voduc 2010	Cross-over	Laboratory	Double-blind	Mask	50%	NA	97.1 (SD 1.9)	NA	Modified Borg	-
Wadell 2001	Parallel	Laboratory	Single-blind	NC	5 L/min	Median 9.3 (range 7.9-11.4)	Median 94.6 (range 90.7-97.2)	Median 1.5 (range 0-3)	Modified Borg	-
Woodcock 1981	Cross-over	Laboratory	Double-blind	NC	4 L/min	9.6 (SD 1.5)	NA	4 (SD 0.94)[b]	10-cm VAS	-

CRQ: Chronic Respiratory Questionnaire; NA: not available; NC: nasal cannula; SD: standard deviation; SE: standard error; SF-36: Short Form-36 questionnaire; VAS: visual analogue scale.

Data presented as mean (standard deviation (SD)) unless otherwise specified.

[a] As measured by dyspnoea index.

[b] As measured by MRC dyspnoea grade.

WHAT'S NEW

Last assessed as up-to-date: 12 July 2016.

Date	Event	Description
12 July 2016	New search has been performed	The systematic search, review and meta-analysis have been updated to 12 July 2016
12 July 2016	New citation required and conclusions have changed	This review update added14 studies including 493 participants to the review. With the addition of these studies, the precision of the main analyses has been improved. Several new subanalyses have been performed, including level of desaturation during exercise, setting (laboratory or daily life)

(*Continued*)

		, short-term versus long-term effects, type of measurement (iso-time or maximal exertion) and oxygen dose. We graded the quality of evidence and were able to meta-analyse data for health-related quality of life

CONTRIBUTIONS OF AUTHORS

ME designed the first draft of the review update, participated in data collection and management and wrote the first draft of the review update, together with ZA.

ZA collected the review data and wrote the first draft of the review update, together with ME.

ABH contributed to the analysis plan and performed the statistical analyses.

DC contributed to the conception, design and analysis plan for this review.

AA conceived of, designed and co-ordinated the original review published in 2011 and contributed to the design of this review update.

All review authors contributed to generation of the review manuscript.

DECLARATIONS OF INTEREST

ME, ZA, ABH and DC declare no conflicts of interest relevant to this work.

AA is the Chief Medical Officer and Chief Scientific Officer at Flatiron Health, a cancer-focused health technology company in New York, New York, USA. Collaborators and end-users of the dataset and Flatiron's research & analytics services include academic researchers, pharmaceutical manufacturers and government users, including the US FDA. Investors in Flatiron include three pharmaceutical manufacturers (Roche, Amgen, Celgene), but these venture investments do not relate to any drug products. These companies have no specific data rights and no say in the day-to-day research activities at Flatiron.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

After statistical review, we included only post scores and not change scores in the meta-analyses, so as not to compare SMDs on the same scale. We also added a post hoc sensitivity analysis of breathlessness that excluded outliers and short-burst oxygen therapy.

INDEX TERMS

Medical Subject Headings (MeSH)

Dyspnea [etiology; *therapy]; Exercise; Health Status; Home Care Services; Oxygen Inhalation Therapy [*methods]; Pulmonary Disease, Chronic Obstructive [complications; *therapy]; Quality of Life; Randomized Controlled Trials as Topic

MeSH check words

Humans