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Symptomatic oxygen for non-hypoxaemic chronic obstructive pulmonary disease (Review)

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[Intervention Review]

Symptomatic oxygen for non-hypoxaemic chronic obstructive pulmonary disease

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ABSTRACT

Background

Dyspnoea is a common symptom in chronic obstructive pulmonary disease (COPD). People who are hypoxaemic may be given long-term oxygen relief therapy (LTOT) to improve their life expectancy and quality of life. However, the symptomatic benefit of home oxygen therapy in mildly or non-hypoxaemic people with COPD with dyspnoea who do not meet international funding criteria for LTOT (PaO_2< 55 mmHg or other special cases) is unknown.

Objectives

To determine the efficacy of oxygen versus medical air for relief of subjective dyspnoea in mildly or non-hypoxaemic people with COPD who would not otherwise qualify for home oxygen therapy. The main outcome was patient-reported dyspnoea and secondary outcome was exercise tolerance.

Search methods

We searched the Cochrane Airways Group Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE, to November 2009, to identify randomised controlled trials. We handsearched reference lists of included articles.

Selection criteria

We only included randomised controlled trials of oxygen versus medical air in mildly or non-hypoxaemic people with COPD. Two review authors independently assessed articles for inclusion.

Data collection and analysis

One review author completed data extraction and methodological quality assessment. A second review author then over-read evidence tables to assess for accuracy.

Main results

Twenty-eight trials on 702 patients met the criteria for inclusion; 18 trials (431 participants) were included in the meta-analysis. Oxygen reduced dyspnoea with a standardised mean difference (SMD) of -0.37 (95% confidence interval (CI) -0.50 to -0.24, P < 0.00001). We observed significant heterogeneity.

Authors' conclusions

Oxygen can relieve dyspnoea in mildly and non-hypoxaemic people with COPD who would not otherwise qualify for home oxygen therapy. Given the significant heterogeneity among the included studies, clinicians should continue to evaluate patients on an individual basis until supporting data from ongoing, large randomised controlled trials are available.

PLAIN LANGUAGE SUMMARY

Oxygen therapy for non-hypoxaemic chronic obstructive pulmonary disease

People with chronic obstructive pulmonary disease and breathlessness are sometimes prescribed oxygen therapy in an effort to reduce the sensation of breathlessness. However, the use of oxygen to relieve breathlessness in people who do not have reduced levels of oxygen in their blood stream (so called non-hypoxaemic people) remains controversial as not enough is known about its effectiveness. Additionally, oxygen is not without risk, particularly in those who continue to smoke because of the risk of fire, and it is costly over the long term. This review found that oxygen given to relieve symptoms can modestly reduce breathlessness with data collected from 28 trials (of which 18 had data which we could combine in meta-analyses). Given the magnitude of the effects and the variability in the results of the individual studies, further study is warranted before drawing firm conclusions. This type of oxygen therapy is sometimes called 'palliative oxygen', because it is used to make patients feel better rather than to aim to increase life expectancy.

BACKGROUND

Dyspnoea is a common symptom in chronic obstructive pulmonary disease (COPD) that both patients and physicians find frustrating. Dyspnoea is difficult to define because it is a combination of underlying pathology, a sensation involving neural pathways and a subjective perception on the part of the patient (ATS 1999). Descriptions of dyspnoea vary widely and depend, at least in part, on a patient's underlying disease, ethnic/racial background, previous experiences and emotional state. Additionally, patients often report dyspnoea that seems out of proportion to known underlying lung disease. Typically, the recommendation is to relieve dyspnoea by treating the underlying source but this is often not successful or simply not possible. Patients are then left to try any one of a number of interventions for which there is little evidence. One such intervention is home oxygen therapy.

Home oxygen is commonly prescribed for individuals who are hypoxaemic (PaO_2 < 55 mmHg) or who are mildly hypoxaemic (PaO_2 55 to 59 mmHg) but who suffer from pulmonary hypertension, cor pulmonale, secondary polycythaemia (haematocrit > 55%) or a combination. The evidence for home oxygen use is provided by two studies, one by the Medical Research Council Working Party (MRCWP 1981) and the other by the Nocturnal Oxygen Therapy Trial Group (NOTT) (NOTTG 1980). These studies evaluated the impact of long-term oxygen therapy (LTOT) on survival in patients with COPD. They do not report on other patient-valued outcome measures of oxygen therapy, i.e. symptomatic treatment of dyspnoea, improved function or quality of life outcomes. Current guidelines do not recommend symptomatic therapy in dyspneic individuals who do not meet criteria for home oxygen therapy. The goal of oxygen therapy for individuals who are either mildly hypoxaemic or not hypoxaemic is not increased life expectancy, but rather symptomatic or functional benefits (or both). Symptomatic oxygen is sometimes called 'palliative oxygen' for this reason. We will use the term palliative oxygen throughout the review.

There are no systematic reviews on palliative oxygen in dyspneic COPD patients who do not meet criteria for home oxygen therapy. There are several Cochrane Reviews evaluating the use of long-term oxygen therapy in patients with COPD but these do not address the issue of palliative oxygen (Bradley 2005; Cranston 2005; Ram 2002). Bradley 2005 evaluated the efficacy of ambulatory oxygen using single assessment studies but the review differs

from ours in several important ways. First, it includes all patients with COPD and does not limit inclusion to non-hypoxaemic patients. Second, the primary aim of the review was to evaluate the impact of oxygen on exercise capacity. While breathlessness was a secondary outcome, the discussion was descriptive and no meta-analysis was performed. The authors concluded that ambulatory oxygen improved exercise capacity in patients with COPD but noted that the efficacy of oxygen in patients who do not meet criteria for long-term oxygen therapy and who do not have evidence of hypoxaemia remains unknown (Bradley 2005). Ram 2002 evaluated the efficacy of long-term domiciliary oxygen therapy. Included studies were randomised controlled trials of ambulatory oxygen at home; short-term assessment studies were excluded. All studies included patients who were hypoxaemic (PaO_2 < 7.3 kPa, 55 mmHg) at rest or on exertion. Ram 2002 concluded that further study was required to assess the effectiveness of ambulatory domiciliary oxygen therapy. A similar review evaluated the effect of long-term oxygen therapy on survival and quality of life in patients with COPD and hypoxaemia (Cranston 2005); the review also addressed breathlessness. Cranston 2005 concluded that long-term oxygen therapy improved survival in people with COPD and severe hypoxaemia but not in those with only mild to moderate hypoxaemia.

All three reviews (Bradley 2005; Cranston 2005; Ram 2002) evaluated populations with the need for long-term oxygen therapy and therefore do not answer the question of interest here, namely is palliative oxygen a useful treatment for symptom relief?

Despite the lack of convincing evidence for benefit, palliative oxygen for relief of breathlessness is commonly prescribed. A telephone survey of Canadian physicians found that breathlessness was a common reason for prescription of palliative oxygen (Stringer 2004). An email survey conducted by Abernethy et al reported similar results, noting that a majority of palliative medicine clinicians and respiratory physicians in Australia and New Zealand believe that palliative oxygen is beneficial; many cited refractory dyspnoea as the reason for prescription (Abernethy 2005).

The discrepancy between current clinical practice and available evidence has important implications. First, patients may be prescribed ineffective treatments. Second, oxygen therapy is not a benign intervention. Functional restriction from tubing, tanks or concentrators, and the "sick role" may limit quality of life. Nasal cannulae can irritate the nose and increase the risk of epistaxis. Oxygen therapy carries a fire risk, particularly for smokers, but also from other sources of ignition such as pilot lights (Robb 2003). Hypercarbia may be exacerbated, though this risk is small. Third, home oxygen therapy is expensive. If patients do not meet long-term oxygen therapy criteria, then they must either pay for oxygen therapy themselves or receive the intervention on compassionate use grounds. Funding for home oxygen therapy is a common reason for referral to hospice care in westernised countries. In Canada, about 40% of patients receiving long-term oxygen therapy do not meet current funding guidelines and receive oxygen therapy on a compassionate use basis (Guyatt 2000).

This systematic review aimed to answer the following question: 'In mildly hypoxaemic or non-hypoxaemic COPD patients with breathlessness, does oxygen therapy improve symptoms or function (or both)?'

OBJECTIVES

To determine the efficacy of oxygen for relief of dyspnoea in non-hypoxaemic and mildly hypoxaemic individuals with chronic obstructive pulmonary disease. The major endpoints were: (1) impact on dyspnoea; (2) impact on function or exercise tolerance (or both); and (3) impact on quality of life.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomised controlled trials comparing oxygen delivered via cylinder, concentrator or Douglas bag to medical air or room air. Studies must have included the outcome of dyspnoea. Studies did not have to be blinded. We only included studies evaluating long-term oxygen therapy or ambulatory domiciliary oxygen therapy if assessments of the effects of oxygen on dyspnoea, function or both following short-term administration were performed and data were available.

Types of participants

We only included trials with adult patients with chronic obstructive pulmonary disease who were not hypoxaemic (room air PaO_2 $\geq$ 60 mmHg) or who were mildly hypoxaemic (room air PaO_2 55 to 59 mmHg). Included patients must not have been on home oxygen therapy at the time of enrolment.

Types of interventions

We included trials with oxygen versus medical air. Oxygen/air had to be delivered by a non-invasive ventilatory method (nasal cannula, Ventimask or mouthpiece). Allowable sources of oxygen included cylinder, concentrator or Douglas bag. Inspired oxygen concentrations between 25% and 100% were permitted. Oxygen/air should have been delivered in single-dose fashion during exertion, in a short-burst fashion pre-or post-exertion, or on an as-needed (PRN pro re nata meaning "take as needed") basis over a defined period of time.

Types of outcome measures

Primary outcomes

Dyspnoea as measured by visual analogue scale (VAS), modified Borg or dyspnoea numerical rating scale (NRS), or any other validated scale for measuring dyspnoea. For those studies measuring dyspnoea during exercise, isotime scores were used when available. Isotime is defined as the end of exercise while receiving medical air.

Secondary outcomes

1. Quality of life
2. Patient preference
3. Functional status as recorded on a recognised scale

Search methods for identification of studies

Electronic searches

We identified trials using the Cochrane Airways Group Specialised Register of trials, which is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO, and handsearching of respiratory journals and meeting abstracts (please see the Airways Group search methods for further details). We searched all records in the Specialised Register coded as 'COPD' using the following terms: (dyspnea OR dyspnoea OR breathless* or non-hypoxaemic or non-hypoxemic) AND (oxygen* OR "inhalation therapy" OR 02 or LTOT or palliative)

The most recent search of the Cochrane Airways Group Specialised Register was conducted in November 2009. We ran additional searches of MEDLINE and EMBASE (1966 to 2009) using the above search terms, adapted for each database as appropriate.

Searching other resources

We identified additional manuscripts by checking the reference lists of those articles identified by searching the electronic databases as well as by checking other reviews published on this topic.

Data collection and analysis

Selection of studies

Two review authors (HEU, APA) independently reviewed all relevant articles identified by the search strategy. We selected trials satisfying the following inclusion criteria:

1. randomised controlled trial;
2. adult patients with chronic obstructive pulmonary disease and a normal oxygen saturation on room air;
3. oxygen as primary intervention;
4. oxygen supplied by non-invasive method (nasal canula, Ventimask or mouthpiece);
5. available data on dyspnoea scores.

Data extraction and management

We assessed agreement regarding inclusion/exclusion of studies using simple kappa statistics and resolved disagreements by consensus and/or third investigator (DCC). For each included article, one review author (HEU) extracted basic study parameters into evidence tables summarising study design, patients, interventions, outcomes and quality. A second review author (APA) then overread evidence tables to ensure accuracy. When necessary, we contacted the authors of the primary studies to obtain additional information.

Assessment of risk of bias in included studies

We assessed included articles for internal and external validity. We applied internal validity criteria to assess protection from bias in the following domains: randomisation (sequence generation and allocation concealment), blinding (of participants and assessors), withdrawals/dropouts and full publication of outcomes. We assessed external validity by evaluating patient description, intervention description and reported dyspnoea outcomes.

Unit of analysis issues

Cross-over trials should be included in meta-analyses using results from paired analyses. However, these data are often not available. In these cases, we estimated standard errors using methods described by Follman 1992. We estimated correlations between repeat outcomes from P values when available. When correlations could not be calculated, we used the lowest estimate from other studies. In parallel-group studies that included blinded, randomised, cross-over comparisons of oxygen to medical air during exercise, we used outcomes from these evaluations to obtain within-patient differences, and analysed these with data from other cross-over studies.

Data synthesis

We combined all trial data using Review Manager software (RevMan 2011). We performed meta-analysis for the primary and secondary outcomes as appropriate and possible given available data. Results from within-patient effects from both periods of cross-over trials were to be used. In the case of studies evaluating multiple different doses of oxygen, we considered only the

lowest dose in the analysis. We analysed breathlessness and exercise tolerance as continuous outcomes. We calculated standardised mean differences for breathlessness and exercise tolerance when outcomes were measured on different scales. We performed all analyses using a random-effects model. In the event that significant statistical heterogeneity was observed, we applied a random-effects model.

We inspected funnel plots to test for the presence of publication bias.

Subgroup analysis and investigation of heterogeneity

We conducted the following a priori subgroup analyses:

1. studies by primary focus (sensation versus function versus both);
2. studies including patients with exertional desaturation versus studies including patients that did not desaturate on exertion;
3. studies involving patients with baseline PaO_2 less than 70 mmHg versus studies involving patients with baseline PaO_2 greater than or equal to 70 mmHg; and
4. studies involving short-burst oxygen therapy versus those not involving short-burst oxygen therapy.

Sensitivity analysis

We conducted the following sensitivity analyses:

1. analysis excluding trials that measure breathlessness only at the end of maximal exercise testing (because of a difficulty in comparing this assessment to studies measuring breathlessness at the end of a six-minute walk test and/or at isotime of maximal exercise testing);
2. analysis excluding trials where bias protection is poor;
3. analysis excluding trials where imputed quantities were used; and
4. analysis excluding trials noted to be outliers (we undertook this analysis to ensure that results were not influenced by the presence or absence of these results).

RESULTS

Description of studies

The electronic searches yielded a total of 333 references, which were screened on the basis of title/abstract or examination of the full text. Of 28 studies included in this systematic review, three assessed additional treatment arms which we included as unique studies. Therefore this review summarises evidence from 31 study comparisons. Twenty-two were blinded, randomised, cross-over trials (Davidson 1988; Dean 1992; Eaton 2002; Eves 2006; Garrod 1999; Ishimine 1995; Killen 2000; Knebel 2000; Kurihara 1989; Laude 2006; Leach 1992; Lewis 2003; Maltais 2001; McDonald 1995; McKeon 1988a; McKeon 1988a; Moore 2009; Nandi 2003; O'Donnell 1997; Somfay 2001; Swinburn 1984; Woodcock 1981), five were randomised, controlled, parallel trials (Eaton 2006, Emtner 2003 (group 1)/Emtner 2003 (group 2); Haidl 2004, Rooyackers 1997 (group 1)/Rooyackers 1997 (group 2); Wadell 2001) and one was part of a non-randomised parallel trial (Jolly 2001 (group 1)/Jolly 2001 (group 2)). Three trials included two different comparisons (Emtner 2003 (group 1); Emtner 2003 (group 2); Jolly 2001 (group 1); Jolly 2001 (group 2); Rooyackers 1997 (group 1); Rooyackers 1997 (group 2). Four of the six parallel trials were designed to assess the impact of oxygen versus air during pulmonary rehabilitation and included blinded, randomised, cross-over evaluations of oxygen versus medical air as part of the follow-up evaluation after completion of rehabilitation (Emtner 2003 (group 1)/Emtner 2003 (group 2); Jolly 2001 (group 1)/Jolly 2001 (group 2); Rooyackers 1997 (group 1)/Rooyackers 1997 (group 2); Wadell 2001).

In cross-over trials, participants receive two or more consecutive treatments in random order (Sibbald 1998). Treatment A can be compared to treatment B while each patient acts as his/her control, therefore decreasing concern over issues involving unknown or unmeasured factors and requiring fewer subjects to answer the same question, since between-participant variation is usually greater than within-patient variation

Of the 31 included study comparisons, four had a main focus on the sensation of breathlessness (Eaton 2002; Killen 2000; Moore 2009; Swinburn 1984), 17 were focused on function (Davidson 1988; Dean 1992; Emtner 2003 (group 1); Emtner 2003 (group 2); Eves 2006; Garrod 1999; Haidl 2004; Kurihara 1989; Laude 2006; Leach 1992; McDonald 1995; McKeon 1988b; Maltais 2001; O'Donnell 1997; Rooyackers 1997 (group 1); Rooyackers 1997 (group 2); Somfay 2001), and 10 were equally focused on both sensation and function without reference to which was the most important (Eaton 2006; Jolly 2001 (group 1); Jolly 2001 (group 2); Ishimine 1995; Knebel 2000; Lewis 2003; McKeon 1988a; Nandi 2003; Wadell 2001; Woodcock 1981). Twenty-four of the included studies were single-assessment trials in controlled laboratory conditions while four had a domiciliary component. It should be noted that even in those trials with a domiciliary component, the benefits of oxygen were evaluated using assessment of function as the key outcome such as performance on a six-minute walk test (6MWT). Dyspnoea was measured as follows: modified Borg - 16 studies (Dean 1992; Eaton 2002; Emtner 2003 (group 1); Eves 2006; Garrod 1999; Haidl 2004; Jolly 2001 (group 1); Laude 2006; Lewis 2003; Maltais 2001; McDonald 1995; Moore 2009; O'Donnell 1997; Rooyackers 1997 (group 1); Somfay 2001; Wadell 2001), VAS - nine studies (Davidson 1988; Evans 1986; Killen 2000; Leach 1992; McKeon 1988a; McKeon 1988b; Nandi 2003; Swinburn 1984; Woodcock 1981), and other - three studies (Eaton 2006; Ishimine 1995; Kurihara

1989). Three studies evaluated quality of life (Eaton 2002; Eaton 2006; McDonald 1995); this assessment did take place over a longer period of time (i.e. weeks). Sample sizes of included studies were small with a median of 20 participants per study and a mean of 25 (standard deviation (SD) 18).

Patient characteristics

The 31 included study comparisons represented 702 participants, all of them adults. Fifteen of the 28 studies had inclusion criteria requiring moderate to severe COPD for study entry. Baseline PaO_2 was provided in 20 of 28 studies; mean PaO_2 was 70.8 mmHg (SD 5.9) (19 studies) and median PaO_2 was 70.6 mmHg (one study). Baseline oxygen saturation by pulse oximetry was provided by the remaining eight studies as follows: mean 94.6% (SD 3.2) (Moore 2009), mean 94.4% (SD 1.6) (Lewis 2003), mean 95.7% (SD 0.8) (Somfay 2001), mean 91.9% (SD 5.2) (Nandi 2003), mean 93.9% (SD 2.3) (Laude 2006), mean 97.1% (SD 1.7) (Knebel 2000), median 94% (Killen 2000) and mean 93.2% (SD 0.8) (Swinburn 1984). Mean baseline dyspnoea at rest was provided by nine studies as follows: 1.8 (SD 1.1) by modified Borg and 24.2 (SD 19) by 100 mm VAS (Laude 2006), 0.4 (SD 0.5) by modified Borg (Lewis 2003), 0.7 (1.0) by modified Borg (Eaton 2002), 0.56 (standard error (SE) 0.34) by modified Borg (Jolly 2001 (group 1) - non-desaturators) and 1.27 (SE 0.43) (Jolly 2001 (group 2) - desaturators), 5.1 (SE 0.3) by dyspnoea index (O'Donnell 1997), 6.11 (SD 7.72) by 100 mm VAS (Evans 1986), 0.5 (SD 0.9) by 10 cm VAS (Knebel 2000), 4 (SD 0.94) by Medical Research Council (MRC) dyspnoea grade (Woodcock 1981), and 17.1 (SD 0.91) by chronic respiratory questionnaire (CRQ) (Eaton 2006).

Intervention characteristics

All included studies compared oxygen to medical air; two studies also included evaluation for the effects of a novel agent containing both helium and oxygen (Eves 2006; Laude 2006). Both oxygen and medical air were delivered via the same mechanism; the most frequent mode of administration was nasal cannula (16 studies) (Davidson 1988; Eaton 2002; Eaton 2006; Emtner 2003 (group 1); Garrod 1999; Haidl 2004; Jolly 2001 (group 1); Knebel 2000; Kurihara 1989; Lewis 2003; McDonald 1995; McKeon 1988a; McKeon 1988b; Rooyackers 1997 (group 1); Wadell 2001; Woodcock 1981) followed by mouthpiece/valve (eight studies) (Dean 1992; Eves 2006; Laude 2006; Maltais 2001; Moore 2009; O'Donnell 1997; Somfay 2001; Swinburn 1984) and then mask (three studies) (Killen 2000; Leach 1992; Nandi 2003). Twenty-three of the included studies provided continuous oxygen during activity, either 6MWT, endurance walk, shuttle walk, step test or cycle exercise (Davidson 1988; Dean 1992; Eaton 2002; Eaton 2006; Emtner 2003 (group 1); Eves 2006; Garrod 1999; Haidl 2004; Ishimine 1995; Jolly 2001 (group 1); Jolly 2001 (group 2); Knebel 2000; Kurihara 1989; Laude 2006; Leach 1992; Maltais 2001; McDonald 1995; McKeon 1988b; O'Donnell 1997; Rooyackers 1997 (group 1); Rooyackers 1997 (group 2); Somfay 2001; Swinburn 1984; Wadell 2001; Woodcock 1981). The remaining four studies provided oxygen for a short, pre-determined period immediately before exercise (Killen 2000; Lewis 2003; McKeon 1988a; Nandi 2003), so-called 'short-burst oxygen'. While several of the studies examining short-burst oxygen also looked at oxygen delivered after exercise, these evaluations were not included in this review as the outcome measure was not one that could be combined with other studies for analysis. One study provided oxygen at rest (Moore 2009). Doses of oxygen ranged from 2 litres/min (L/min) to 5 L/min (median 3 L/min) in 20 studies (Davidson 1988; Eaton 2002; Eaton 2006; Emtner 2003 (group 1); Emtner 2003 (group 2); Garrod 1999; Haidl 2004; Ishimine 1995; Jolly 2001 (group 1); Jolly 2001 (group 2); Killen 2000; Knebel 2000; Kurihara 1989; Leach 1992; Lewis 2003; McDonald 1995; McKeon 1988a; McKeon 1988b; Nandi 2003; Rooyackers 1997 (group 1); Rooyackers 1997 (group 2); Wadell 2001; Woodcock 1981) and from 28% to 75% oxygen (median 42%) in the remaining eight studies (Dean 1992; Eves 2006; Laude 2006; Maltais 2001; Moore 2009; O'Donnell 1997; Somfay 2001; Swinburn 1984).

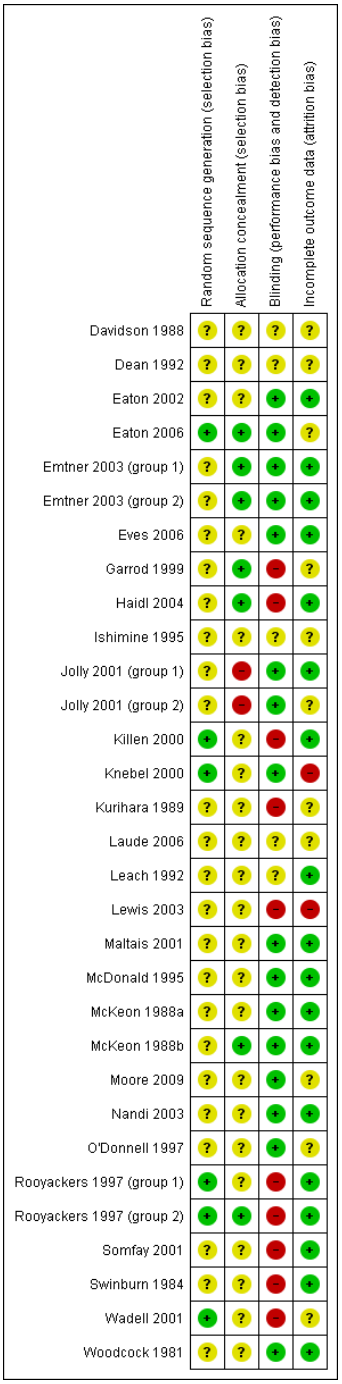
Risk of bias in included studies

Two independent review authors (HEU and APA) judged the quality of reporting (Jadad 1996), reported for each study in Table 1. Disagreements were resolved by consensus. Methods were poorly reported in most of the included studies.

Allocation

While all studies were described as randomised, we could verify that sequence generation was adequate in only six studies. The concealment of allocation was adequate in seven studies and inadequate in two (Figure 1). For the remaining trials we did not have sufficient information to determine the risk of bias for their allocation procedures.

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Blinding

Masking of treatment was undertaken in a number of studies. In five studies we were unable to determine how blinding study participants or investigators had been achieved. In 10 studies blinding was not undertaken, or investigators knew which containers contained oxygen (Garrod 1999; Haidl 2004; Killen 2000; Kurihara 1989; Lewis 2003; Rooyackers 1997 (group 1); Rooyackers 1997 (group 2); Somfay 2001; Swinburn 1984; Wadell 2001). For the remaining 16 studies blinding of both study participants and study investigators was attempted (Figure 1).

Incomplete outcome data

In 19 studies there were no withdrawals (Emtner 2003 (group 1); Emtner 2003 (group 2); Eves 2006; Haidl 2004; Jolly 2001 (group 1); Jolly 2001 (group 2); Killen 2000; Leach 1992; Maltais 2001; McDonald 1995; McKeon 1988a; McKeon 1988b; Nandi 2003; O'Donnell 1997; Rooyackers 1997 (group 1); Rooyackers 1997 (group 2); Somfay 2001; Swinburn 1984; Woodcock 1981). Since cross-over studies only analyse within-participant differences, participants withdrawing from the first arm of treatment will not have contributed to the analysis (Knebel 2000; Lewis 2003; Moore 2009). In the remaining studies we could not reliably ascertain how missing data were handled (Figure 1).

Effects of interventions

Results from the meta-analysis are reported by outcome. All comparisons concern oxygen versus medical air.

Data from seven cross-over studies (Garrod 1999; Ishimine 1995; Leach 1992; Maltais 2001; McKeon 1988b; Swinburn 1984; Wadell 2001) could not be included in meta-analyses due to presentation of the outcomes data in a manner that could not be summarised in meta-analyses and source data which could not be obtained. Data from one cross-over study (Moore 2009) could not be included in meta-analysis due to the fact that a statistically significant order effect was noted in primary analysis of the data. Additionally, it was noted that this study was an outlier. Data from the two parallel-group studies (Eaton 2006; Haidl 2004) that did not include any cross-over comparison of oxygen versus air were also excluded from meta-analyses due to the methodologic issues of combining data from cross-over and parallel studies in the same analysis. Review of results from these studies that were not included in the meta-analysis reveals that five (Haidl 2004; Ishimine 1995; Leach 1992; Maltais 2001; McKeon 1988b) demonstrated improvement in dyspnoea with oxygen versus compressed air while four (Eaton 2006; Garrod 1999; Swinburn 1984; Wadell 2001) found no significant difference.

Primary outcome: dyspnoea

Data from 18 studies, representing 431 patients, were included in this analysis (Davidson 1988; Dean 1992; Eaton 2002; Emtner 2003 (group 1); Emtner 2003 (group 2); Eves 2006; Jolly 2001 (group 1); Jolly 2001 (group 2); Killen 2000; Knebel 2000; Kurihara 1989; Laude 2006; Lewis 2003; McDonald 1995; McKeon 1988a; Nandi 2003; O'Donnell 1997; Rooyackers 1997 (group 1); Rooyackers 1997 (group 2); Somfay 2001; Woodcock 1981). Oxygen improved dyspnoea in mildly or non-hypoxaemic patients with chronic obstructive pulmonary disease (COPD) (standardised mean difference (SMD) -0.37, 95% confidence interval (CI) -0.50 to -0.24, P < 0.00001, Analysis 1.1). We observed no significant heterogeneity (I^2 = 14%).

A priori subgroup analyses

Studies by primary focus

We divided studies by whether they focused on the sensation of breathlessness, the patient's physical function or both. Two review authors (HEU and APA) made the group assignments independently. Data were available for two studies focused on the sensation of breathlessness (Eaton 2002; Killen 2000); oxygen improved dyspnoea (SMD -0.39, 95% CI -0.66 to -0.12; P = 0.004, Analysis 1.2). We observed no heterogeneity (I^2 = 0%).

Data were available for 10 studies primarily focused on physical function (Davidson 1988; Dean 1992; Emtner 2003 (group 1); Emtner 2003 (group 2); Eves 2006; Kurihara 1989; Laude 2006; McDonald 1995; O'Donnell 1997; Rooyackers 1997 (group 1); Rooyackers 1997 (group 2); Somfay 2001); oxygen improved dyspnoea when compared to medical air (SMD -0.45, 95% CI -0.61 to -0.30; P < 0.00001). We observed no significant heterogeneity (I^2 = 0%). Data were available for six studies that focused on both the sensation of breathlessness as well as physical function (Knebel 2000; Jolly 2001 (group 1); Jolly 2001 (group 2); Lewis 2003; McKeon 1988a; Nandi 2003; Woodcock 1981); oxygen improved dyspnoea (SMD -0.32, 95% CI -0.67 to 0.03; P = 0.07). We observed significant heterogeneity (I^2 = 54%).

We performed post-hoc sensitivity analyses for the subgroup focused on function as well as the subgroup focused on both sensation and function after removing the outliers identified in the main analysis. Results were stable following these analyses as follows:

1. Subgroup focused on both sensation and function (SMD -0.15, 95% CI -0.43 to 0.14; P = 0.31, Analysis 1.11).
2. Subgroup focused on function (SMD -0.42, 95% CI -0.58 to -0.25; P < 0.00001, Analysis 1.11).

Studies where exertional desaturation was noted

We divided studies by whether exertional desaturation was noted during the study. Data were available for 15 studies where exertional desaturation was noted (Davidson 1988; Dean 1992; Eaton 2002; Eves 2006; Jolly 2001 (group 2); Killen 2000; Knebel 2000; Kurihara 1989; Laude 2006; Lewis 2003; McDonald 1995; McKeon 1988a; Nandi 2003; O'Donnell 1997; Rooyackers 1997 (group 1); Rooyackers 1997 (group 2)); oxygen improved dyspnoea (SMD -0.33, 95% CI -0.46 to -0.20; P < 0.00001). We observed no significant heterogeneity (I^2 = 8%). Data were available for four studies not noting exertional desaturation (Emtner 2003 (group 1); Emtner 2003 (group 2); Jolly 2001 (group 1), Somfay 2001; Woodcock 1981); oxygen improved dyspnoea when compared to medical air (SMD -0.69, 95% CI -1.04 to -0.34; P < 0.0001, Analysis 1.4). We observed no significant heterogeneity (I^2 = 0%).

We performed post-hoc sensitivity analyses after removing the outliers identified in the main analysis:

1. Subgroup noting exertional desaturation(SMD -0.31, 95% CI -0.43 to -0.18; P < 0.00001).
2. Subgroup not noting exertional desaturation (SMD -0.57, 95% CI -0.95 to -0.19; P = 0.003).

Studies by mean PaO_2

We divided studies into subgroups based on whether participants' mean PaO_2 was greater than or less than 70 mmHg (equivalent to an oxygen saturation of 92.5% based on evaluation of the haemoglobin-oxygen saturation curve). Data were available for 12 studies whose participants had a mean PaO_2 greater than or equal to 70 mmHg (Dean 1992; Eaton 2002; Emtner 2003 (group 1); Emtner 2003 (group 2); Jolly 2001 (group 1); Jolly 2001 (group 2); Killen 2000; Knebel 2000; Lewis 2003; McDonald 1995; O'Donnell 1997; Rooyackers 1997 (group 1); Rooyackers 1997 (group 2); Somfay 2001; Woodcock 1981); oxygen improved dyspnoea when compared to medical air (SMD -0.42, 95% CI -0.60 to -0.24; P < 0.00001, Analysis 1.5). We observed no significant heterogeneity (I^2 = 27%). Data were available for six studies whose participants had a mean PaO_2 of less than 70 mmHg (Davidson 1988; Eves 2006; Kurihara 1989; Laude 2006; McKeon 1988a; Nandi 2003); oxygen improved dyspnoea when compared to medical air (SMD -0.25, 95% CI -0.50 to 0.00; P = 0.05). We observed no significant heterogeneity (I^2 = 28%).

Studies by short-burst oxygen or not

We divided studies into subgroups based on whether or not they provided short-burst oxygen. Data were available for four studies that provided short-burst oxygen (Killen 2000; Lewis 2003; McKeon 1988a; Nandi 2003); short-burst oxygen did not improve dyspnoea when compared to medical air (SMD 0.01, 95% CI -0.26 to 0.28; P = 0.95, Analysis 1.3). We observed no significant heterogeneity (I^2 = 0%). Data were available for 14 studies that provided continuous oxygen (Davidson 1988; Dean 1992; Eaton 2002; Emnter; Eves 2006; Jolly 2001 (group 1); Jolly 2001 (group 2); Knebel 2000; Kurihara 1989; Laude 2006; McDonald 1995; O'Donnell 1997; Rooyackers 1997 (group 1); Rooyackers 1997 (group 2); Somfay 2001; Woodcock 1981); oxygen improved dyspnoea when compared to medical air (SMD -0.46, 95% CI -0.59 to -0.33; P < 0.00001). We observed no significant heterogeneity (I^2 = 0%).

A priori sensitivity analyses

Analysis excluding those trials measuring breathlessness at end of exercise

Only three of the 19 studies included in this meta-analysis reported dyspnoea measurements at the end of exercise (Emtner 2003 (group 1); Emtner 2003 (group 2); Eves 2006; Laude 2006). The remaining studies measured breathlessness at isotime (defined as the end of exercise while receiving medical air) or at the end of a 6MWT. We repeated the analysis of the primary outcome without these three studies. Results were stable following this analysis; oxygen improved dyspnoea when compared to medical air (SMD -0.37, 95% CI -0.54 to -0.21; P < 0.00001, Analysis 1.9). We observed no significant heterogeneity (I^2 = 30%).

Analysis excluding those trials where bias protection was poor

Only seven of 26 included studies provided enough information to conclude that allocation concealment was adequate (Eaton 2006; Emtner 2003 (group 1); Emtner 2003 (group 2); Eves 2006; Killen 2000; Knebel 2000; Laude 2006). Three of these studies were excluded from meta-analysis due to data presentation, leaving only four studies included in this sensitivity analysis (Emtner 2003 (group 1); Emtner 2003 (group 2); Eves 2006; Killen 2000; Knebel 2000; Analysis 1.6). Oxygen did improve breathlessness when compared to medical air, though the effect size was smaller and the upper limit of the 95% CI crossed the null (SMD -0.25, 95% CI -0.55 to 0.06; P = 0.11). We observed no significant heterogeneity (I^2 = 0%).

Analysis excluding trials where imputed quantities were used

Only six of the 26 studies included in this systematic review provided sufficient data to allow calculation of SMD and variance without the use of imputation (Dean 1992; Eaton 2002; Lewis 2003; Nandi 2003; O'Donnell 1997; Woodcock 1981; Analysis 1.7). We repeated the analysis of the primary outcome using only data from these six studies. Results were stable following this analysis; oxygen improved dyspnoea when compared to medical air

(SMD -0.36, 95% CI -0.64 to -0.09; P < 0.00001). We observed significant heterogeneity (I^2 = 59%).

Post-hoc analyses

Review of both the forest plot and a funnel plot of the main analysis revealed the presence of four outlying results. We performed a sensitivity analysis after removing these outliers (Dean 1992; Jolly 2001 (group 1); Jolly 2001 (group 2); Somfay 2001). The benefit of oxygen was preserved (SMD -0.33, 95% CI -0.45 to -0.22, P < 0.00001).

Review of the study design (including inclusion/exclusion criteria), patient characteristics (including baseline measures of pulmonary function as well as baseline oxygen saturation and/or PaO_2), and intervention characteristics of the four studies identified as outliers did not reveal any specific differences from the remaining studies as a whole, nor any differences that could explain the discordant results. As noted above, one additional study (Moore 2009) was not included in meta-analysis due to an order effect. We also noted this study to be an outlier.

After observing that short-burst oxygen did not improve dyspnoea when compared to medical air, we repeated the analysis of the primary outcome without studies providing short-burst oxygen due to the concern that inclusion of these studies could result in underestimation of the benefits of oxygen over medical air. The SMD did change slightly with this analysis(SMD -0.46, 95% CI -0.59 to -0.33; P < 0.00001, Analysis 1.3) versus SMD -0.37, 95% CI -0.50 to -0.24; P < 0.00001).

Secondary outcome: quality of life (QOL)

Three studies in 145 people examined changes in QOL (Eaton 2002; Eaton 2006; McDonald 1995). This outcome could not be combined in meta-analysis due to both data presentation and heterogeneity with respect to measurement of the outcome. Therefore, this outcome is presented in a descriptive fashion.

Two studies examined QOL by both disease-specific (chronic respiratory questionnaire (CRQ)) and generic measures (short form 36 (SF-36)) (Eaton 2006 and Eaton 2002). Additionally, participants filled out the Hospital Anxiety and Depression Scale (HADS). The first study (Eaton 2006) was a randomised, controlled, parallel-group trial that included three arms as follows: oxygen, medical air or usual care. The only domain of the CRQ to show statistical significance (P = 0.045) was emotional function; the greatest improvement was in the usual care group who received neither oxygen nor air. The second study (Eaton 2002) demonstrated statistically significant improvements in all domains of the CRQ (fatigue, P = 0.02; emotional function, P = 0.006; mastery, P = 0.008; total, P = 0.002) and both domains of the HADS (anxiety, P = 0.009; depression, P = 0.05) for oxygen when compared to medical air. Significant improvements in several domains of the SF-36 were also noted. These included role physical (P = 0.01), general health, (P = 0.04), social functioning (P = 0.05) and role emotional (P = 0.02). A third study measured only disease-specific QOL using the CRQ (McDonald 1995). Statistically significant improvements were noted in all domains for the comparison of baseline scores to those after six weeks of oxygen therapy (P < 0.02 for all domains). However, when scores after oxygen therapy were compared to scores after air, no statistically or clinically significant differences were seen.

Secondary outcome: patient preference

Three included studies in 85 patients examined patient preference at a time when participants were still blinded (Eaton 2002; Killen 2000; McDonald 1995). This outcome could not be combined in meta-analysis; a description of results from each trial follows.

The first study (Eaton 2002) simply asked patients if they were interested in the clinical provision of oxygen at study completion. Interestingly, 14 patients (41%) identified as having either an acute or a short-term response to oxygen did not wish to be considered for continued therapy. Eleven of these 14 (76%) cited poor tolerability or acceptability as the reason. The second study (Killen 2000) was a study of short-burst oxygen immediately before and after walking up a flight of steps. Again, patients were asked which gas they preferred. Of 18 patients, five preferred oxygen before ascending the stairs, three preferred air and three had no preference. The remaining seven patients preferred to receive oxygen at the top of the stairs. As a group, there was no significant preference for oxygen therapy (P = 0.119 by binomial theory). The third study (McDonald 1995) included both acute assessments and a domiciliary portion that lasted six weeks with each gas. At the end of the study, patients were asked which six-week period they preferred. Fifty percent preferred the period on oxygen; the remaining 50% either preferred air or had no preference.

DISCUSSION

Oxygen was effective at reducing dyspnoea in mildly and non-hypoxaemic people with chronic obstructive pulmonary disease (COPD) who would not otherwise qualify for home oxygen therapy, with a standardised mean difference (SMD) of -0.37 (95% CI -0.50 to -0.24, P < 0.00001) translating into a reduction of 0.78 cm on a 10 cm visual analogue scale (VAS) and a reduction of 0.9 points on a 0 to 10 numerical rating scale (NRS). This result could also be considered clinically significant as Ries et al (Ries 2005) concluded that a minimally clinically important difference is a change of one point on the Borg scale and a change of 10 to 20 mm on a VAS and a recent consensus statement confirms this recommendation and expands it to cover other aetiologies (Booth 2006). Additionally, emerging data from a population of heart failure patients with chronic breathlessness has suggested that between 0.5 and 1 improvement in a 0 to 10 NRS is symptomatically

meaningful to patients, equating to a one-point change on the global impression of change in breathlessness scale (unpublished data calculation from Oxberry S, Thesis: Opioids in heart failure, University of York 2010).

Interestingly, a subgroup analysis evaluating the effectiveness of oxygen at reducing dyspnoea when the gas was delivered as a short burst prior to exercise failed to show a similar benefit (SMD 0.01, 95% CI -0.26 to 0.28; P = 0.06). The reason for this difference is not clear but there is a possibility that it may be related to a physiologic effect of oxygen that is present during longer-term administration of the gas and that is not generated when oxygen is administered for only a short period. One might argue that there could be an effect resulting from wearing nasal cannulae during continuous gas delivery, but this should have been addressed by the presence of a control arm using medical air. Regardless of the explanation for this finding, it has important implications as it suggests that those individuals demonstrating clinical benefit from oxygen therapy should receive the gas continuously in order to achieve maximum benefit.

Quality of life (QOL) was also evaluated by three of the studies included in this review (Eaton 2002; Eaton 2006; McDonald 1995). Data were conflicting with two (Eaton 2006; McDonald 1995) of three studies demonstrating no improvements in QOL with oxygen versus medical air and a third study demonstrating statistically significant improvements in all domains of the chronic respiratory questionnaire (CRQ), both domains of the Hospital Anxiety and Depression Scale (HADS), and several domains of the short form 36 (SF-36) with oxygen versus medical air. The reason for the conflicting results is not clear. The two studies by Eaton et al included different patient populations, with one study (Eaton 2006) recruiting participants at the time of hospital discharge after an exacerbation and the other (Eaton 2002) enrolling patients with stable disease on an "optimal" medical regimen who had completed a pulmonary rehabilitation programme. Additionally, the positive study (Eaton 2002) was a cross-over trial while the negative study (Eaton 2006) was a parallel trial. Both studies followed patients while they received either oxygen or medical air at home for a six-week period. Based on inclusion criteria alone, the study that failed to show a QOL benefit may have included a more heterogeneous population, making it more difficult to demonstrate a difference between populations. The third study (McDonald 1995) also enrolled stable patients but the study was small (n = 24) so the sample size may not have been large enough to detect a change in QOL. Finally, it is possible that the benefits of oxygen with regard to QOL were overshadowed by the inconveniences and functional restrictions associated with home oxygen therapy. Further research is needed.

The final outcome assessed was patient preference. This is a particularly important outcome given the subjective nature of dyspnoea and general difficulty in quantifying this distressing symptom. Several important issues were highlighted through this review. There were clearly a subset of patients who preferred oxygen, though there was not a statistically significant difference between the preference for oxygen and the preference for medical air. It was not clear whether individuals who reported a decrease in dyspnoea with oxygen were the same individuals who identified oxygen as the preferred gas. One study (Eaton 2002) did report on the preferences of those individuals identified as oxygen "responders", with 41% of these individuals not wishing to be considered for further therapy; the main reason cited was the inconvenience or poor tolerability and is consistent with findings from one other large study of oxygen therapy (Currow 2007). Hence, patient QOL factors such as convenience and adverse consequences should be taken into consideration when trying to decide whether to prescribe oxygen as a treatment for dyspneic palliative care patients who may be already burdened by their illness and other life changes prominent in the advanced-illness setting.

Our systematic review and meta-analysis does have several limitations, in addition to those resulting from limitations in the current body of literature addressing the effect of oxygen on dyspnoea in non-hypoxaemic individuals with COPD. While all of the studies included in this review excluded individuals already qualifying for home oxygen therapy according to current guidelines, the population still included a wide range of baseline oxygen saturation/ PaO_2. This variability could affect the results if there is a relationship between oxygen saturation and response of dyspnoea to oxygen administration. We addressed this issue by performing a subgroup analysis that divided studies by baseline PaO_2 (either greater than or equal to 70 mmHg or less than 70 mmHg). Additionally, few studies provided information regarding baseline dyspnoea and/or baseline functional status (as assessed by six-minute walk test (6MWT) or other standard assessment). As a result, the population likely included patients with varied perceptions of dyspnoea as well as varied functional capacities. Palliative oxygen is most commonly prescribed for seriously ill patients nearing end of life; however, these patients are less likely to be participants in many of the studies reviewed here, especially those with an exercise or exertional component. The applicability of the findings in this review to all COPD patients requiring palliative oxygen is unclear. Finally, we observed significant heterogeneity in most of our analyses. This is likely due to the fact that the studies included in this review, while all comparing oxygen to medical air and evaluating impact on exercise and dyspnoea, were performed with different methodologies. The variability in baseline oxygen saturation/ PaO_2, dyspnoea and functional status may also have contributed to the observed heterogeneity. Importantly, this heterogeneity did not influence the overall results of the meta-analysis as evidenced by the fact that results of all analyses were stable after removal of four outlying studies.

Finally, in considering these results, one needs to be sure not to forget the downsides of administering oxygen. Oxygen is costly and, with current stresses on healthcare systems in many coun-

tries, this needs to be taken into account. The effect of oxygen administration on quality of life also remains unclear. We now have additional therapies, including tiotropium and pulmonary rehabilitation, for dyspnoea that were not available at the time that most of the studies included in this review were ongoing. Future trials should consider a strategy whereby oxygen is evaluated as an add-on to these other measures.

AUTHORS' CONCLUSIONS

Implications for practice

Oxygen can relieve dyspnoea in mildly and non-hypoxaemic people with chronic obstructive pulmonary disease (COPD) who would not otherwise qualify for home oxygen therapy. Impact on quality of life cannot be determined from currently available data.

The small sample sizes and heterogeneity amongst studies included in this review make it difficult to provide general recommendations. Until we have evidence from adequately powered randomised controlled trials addressing this question, decisions regarding the prescription of palliative oxygen to people with COPD and refractory dyspnoea not meeting criteria for long-term oxygen therapy should continue to be made on an individual basis. A larger trial is forthcoming (Currow 2007).

Implications for research

A large trial addressing this issue is needed in order to inform the decision to use palliative oxygen better in this patient population. Consideration should also be given to outcome measures such as health-related quality of life and health care utilisation. Additionally, studies aimed at better defining which specific subgroups of patients with COPD may derive an incremental improvement in their dyspnoea in response to supplemental oxygen are required. Finally, these interesting data from the COPD setting should prompt evaluations in a broader range of illnesses complicated by debilitating breathlessness.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Davidson 1988

Methods	Randomised, double-blind, cross-over (though not explicitly stated in methods)
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 17 patients Gender not specified Mean age 64.4 (SEM 2.1) Mean FEV_1 (L) 0.79 (SEM 0.03) Mean FVC (L) 2.14 (SEM 0.11) Mean PaO_2 (mmHg) 64.51 (SEM 2.25)
Interventions	Compressed air (4 L/min) versus oxygen (2, 4 or 6 L/min) during 6MWT, cycle ergometer test or endurance walk
Outcomes	6MWT: dyspnoea at 1-minute intervals and distance covered as well as recovery time Cycle ergometer test: minute ventilation, heart rate, CO_2 production, oxygen consumption, $HbSaO_2$%, and dyspnoea at 1-minute intervals Endurance walk: endurance time and distance covered as well as recovery time (assessed by asking patients when they were no longer feeling breathless) Dyspnoea measured by 10 cm VAS marked at each end with "not at all breathless" and "extremely breathless"
Notes	Authors only reported outcomes for oxygen at 4 L/min QS (walking) = 2 QS (cycle) = 1

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 (performance bias and detection bias) Breathlessness	Unclear risk	Described as double-blind, other information not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information not available

Dean 1992

Methods	Randomised, double-blind, cross-over
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, orthopedic or neurologic problems that would interfere with cycling; "reduced DLCO" to exclude those with asthma 12 patients All male Age > 50 but specifics not reported Mean FEV_1 (L) 0.89 (SEM 0.09) Mean FVC (L) 2.37 (0.20) Mean DLCO mL/min/mmHg 9.8 (SEM 1.5) Mean PaO_2 (mmHg) 71 (SEM 2.6)
Interventions	Compressed air versus 40% oxygen during incremental and endurance exercise studies
Outcomes	Dyspnoea Duration of exercise Ventilation Heart rate Blood gas RVSP Dyspnoea measured by modified Borg numbered 1 to 10 for which the 2 extremes were "none" and "extremely severe"
Notes	Dyspnoea was the primary limiting symptom in each patient QS = 4

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 (performance bias and detection bias) Breathlessness	Unclear risk	Described as double-blind, other information not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information not available

Eaton 2002

Methods	Randomised, double-blind, controlled
Participants	Inclusion criteria: COPD as defined by ATS criteria, exertional dyspnoea impacting daily activities, not fulfilling criteria for LTOT, exertional desaturation (O_2 saturation <= 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)" 41 patients 70% male Mean age 57.1 (SD 9.3) Mean FEV_1 (% predicted) 25.9 (SD 8) Mean oxygen saturation 94.5 (SD 1.9) Mean PaO_2 (mmHg) 69 (SD 7.5) Mean $PaCO_2$ (mmHg) 43.5 (SD 5.25)
Interventions	Compressed air (4 L/min) versus oxygen (4 L/min) during both 6MWT and 6-week period at home during which patients were instructed "to use flow rate of 4 L/min intranasally for any activity during which they would normally experience dyspnoea."
Outcomes	Physiologic measure: resting, 2-min, and 6-min SaO_2, walk distance, pre- and post-walk modified Borg dyspnoea scores; HRQOL measures: CRQ, HADS, SF-36 scores Domiciliary programme: use of air or oxygen-filled cylinder Dyspnoea measured by modified Borg
Notes	QS = 4

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) Breathlessness	Low risk	"Patients were randomly assigned in a double-blinded manner to cylinder air or O_2 (light weight aluminium: standard 2,000-2,200 psi fill: 145 L, weight 2.04 kg (4.5 lbs) fitted with a conserving demand gas delivery system (Oxymatic; Chad Therapeutics, Inc., Chatsworth, CA, USA). 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."

Eaton 2002 (*Continued*)

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. Treatment and order of treatment (to exclude a carryover effect) were included in the model with the patient as a random effect."

Eaton 2006

Methods	Randomised, double-blind, controlled, parallel-group trial
Participants	Inclusion criteria: 78 hospital inpatients with an acute exacerbation of COPD; moderate or severe COPD as defined by the 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)
Interventions	Cylinder oxygen (2 L/min) versus cylinder air (2 L/min) versus usual care during 6-month domiciliary period. Patients 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	FEV_1 and FVC ABG CRQ, SF-36 and HADS Healthcare utilisation Dyspnoea measured by CRQ
Notes	No improvement in dyspnoea or performance; no improvement in QOL or healthcare utilisation with oxygen QS = 4

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."

Eaton 2006 (*Continued*)

Blinding (performance bias and detection bias) Breathlessness	Low risk	"To ensure double-blinding, cylinders, pre-filled 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."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information not available

Emtner 2003 (group 1)

Methods	Randomised, double-blind, controlled
Participants	Inclusion criteria: COPD that is clinically stable with no recent exacerbations, FEV_1 < 50% predicted, ratio of FEV_1 to VC < 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 15 patients 10 male and 5 female Mean age 67 (SD 10) Mean FEV_1 (L) 1.13 (SD 0.30) Mean FVC (L) 2.74 (SD 0.9) Mean TLC (L) 7.3 (SD 1.4) Mean RV (L) 4.2 (SD 1.2) Mean DLCO mL/min/mmHg 13.1 (SD 5) Mean PaO_2 73.8 (SD 6.2) Mean $PaCO_2$ 42.3 (SD 3.2)
Interventions	Compressed air versus oxygen (30%) during constant work rate exercise
Outcomes	Work rate, heart rate, oxygen saturation, blood pressure, breathlessness and leg fatigue during exercise testing PFTs ABG QOL data with CRDQ and SF-36 Dyspnoea measured by modified Borg
Notes	QS = 5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of generating randomisation schedule not available

Emtner 2003 (group 1) (*Continued*)

Allocation concealment (selection bias)	Low risk	Sealed envelopes used to conceal generated randomisation sequence from study investigators
Blinding (performance bias and detection bias) Breathlessness	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 dyspnoea and fatigue sensations, by blinded therapists."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants withdrew from this arm of treatment

Emtner 2003 (group 2)

Methods	Randomised, double-blind, controlled trial
Participants	Inclusion criteria: COPD that is clinically stable with no recent exacerbations, FEV_1 < 50% predicted, ratio of FEV_1 to VC < 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 14 patients 8 male and 6 female Mean age 65 (SD 11) Mean FEV_1 (L) 1.12 (0.37) Mean FVC (L) 2.9 (0.8) Mean PaO_2 (mmHg) 74.9 (8.7)
Interventions	Compressed air versus oxygen (30%) during constant work rate exercise
Outcomes	Work rate, heart rate, oxygen saturation, blood pressure, breathlessness and leg fatigue during exercise testing PFTs ABG QOL data with CRDQ and SF-36 Dyspnoea measured by modified Borg
Notes	QS = 5

Risk of bias

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

Emtner 2003 (group 2) (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Method of generating randomisation schedule not available
Allocation concealment (selection bias)	Low risk	Sealed envelopes used to conceal generated randomisation sequence from study investigators
Blinding (performance bias and detection bias) Breathlessness	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."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants withdrew from this arm of treatment

Eves 2006

Methods	Randomised, double-blind, cross-over
Participants	Inclusion criteria: clinically stable moderate to severe COPD Exclusion criteria: dependence on supplemental oxygen, cardiovascular disease, and/or musculoskeletal abnormality 10 patients All men Mean age 65 (SD 11) Mean FEV_1 (L) 1.66 (0.59) Mean FVC (L) 3.81 (0.99) Mean PaO_2 (mmHg) 68.3 (6.4)
Interventions	Medial air versus 40% oxygen versus heliox versus heliox/oxygen during constant-load cycling
Outcomes	Exercise time, lung volumes, respiratory mechanics, dyspnoea Dyspnoea measured by modified Borg
Notes	QS = 4

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"
Allocation concealment (selection bias)	Unclear risk	Information on concealment of allocation not available

Eves 2006 (*Continued*)

Blinding (performance bias and detection bias) Breathlessness	Low risk	"Throughout exercise, humidified gases were passed into a reservoir bag and supplied through a low-resistance two-way breathing valve (2700 series, Hans Rudolph, Kansas City, MO). 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."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study

Garrod 1999

Methods	Randomised, single-blind, cross-over (though not explicitly stated in methods)	
Participants	Inclusion criteria: FEV_1 < 1 L, less than 15% and 200 mL reversibility with beta agonists, no exacerbations in the previous 4 weeks, desaturation of at least 4% on baseline walk Exclusion criteria: not stated 15 patients Mean age 66 (range 50 to 75) Mean FEV_1 (L) 0.83 (0.28) Mean PaO_2 (mmHg) 62.86 (9.3)	
Interventions	Oxygen (2 L/min) versus air (2 L/min) versus demand flow oxygen during shuttle walk test	
Outcomes	Distance on shuttle walk test Borg score before and immediately after each shuttle walk test SaO_2 Dyspnoea measured by modified Borg	
Notes	QS = 2	
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)	Low risk	"The codes for randomisation were held in sealed envelopes."
Blinding (performance bias and detection bias) Breathlessness	High risk	Single-blind; participants breathed through identical cylinders

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	One participant failed to complete exercise test

Haidl 2004

Methods	Randomised, controlled, parallel-group trial
Participants	Inclusion criteria: COPD diagnosis (per "current clinical guidelines"), FEV_1/FVC < 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 was >= 90%, peak TR jet < 30 mmHg by ECHO Exclusion criteria: malignant disease, left heart failure or other significant comorbidities (e.g. severe renal failure, severe diabetes) 28 patients (14 in each arm) 13 male and 1 female in each arm Mean age - arm 1 65.7 (6.7) Mean age - arm 2 64.5 (6.4) Mean FEV_1, % predicted - arm 1 38.8 (8.4) Mean FEV_1, % predicted - arm 2 42.7 (11.8) Mean PaO_2 (mmHg) - arm 1 65.6 (6.2) Mean PaO_2 (mmHg) - arm 2 67.3 (6.5)
Interventions	LTOT (2 L/min for at least 15 hours per day) versus control (room air)
Outcomes	Lung function ABG End-exercise dyspnoea score Endurance time every 6 months for 3 years Dyspnoea measured by modified Borg
Notes	QS = 2

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 test
Blinding (performance bias and detection bias) Breathlessness	High risk	Control group received only usual care

Haidl 2004 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Both treatment groups complete at 1 year when assessment was undertaken. Study planned to measure differences at 3 years but attrition rates prevented this

Ishimine 1995

Methods	Randomised, 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) 22 patients All men Mean age 69 (SD 7) Mean FEV_1 (L) 1.02 (0.51) Mean FVC (L) 2.26 (0.57) Mean PaO_2 (mmHg) 75.9 (8.6)
Interventions	Room air versus compressed air (3 L/min) versus oxygen (3 L/min) during 6MWT
Outcomes	Dyspnoea during 6WMT as well as distance walked on 6MWT Dyspnoea measured by a questionnaire involving 8 questions; each question was answered on a 100 mm horizontal line with anchors from the modified Borg
Notes	Translated from Japanese so had to work from translation sheet QS = 2

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 (performance bias and detection bias) Breathlessness	Unclear risk	Placebo controlled; blinding of assessors could not be ascertained
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information not available

Jolly 2001 (group 1)

Methods	Randomised Double-blind Cross-over (though not explicitly stated in methods)
Participants	Inclusion criteria: COPD patients (ATS grade II/III) with at least 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 9 patients Mean age 70 (SEM 3) All male Mean FEV_1 (L) 0.9 (SEM 0.8) Mean FVC (% predicted) 63 (SEM 6) Mean TLC (L) 7.43 (SEM 0.4) Mean RV (L) 4.42 (SEM 0.39) Mean oxygen saturation 95.8 (SEM 0.46) Mean PaO_2 (mmHg) 79 (SEM 3) Mean $PaCO_2$ (mmHg) 40 (SEM 1.6)
Interventions	Room air versus compressed air (3, 6, 9, 12 L/min) versus oxygen (3, 6, 9, 12 L/min) during 6MWT - amount of oxygen increased based upon any desaturation during exercise
Outcomes	Distance walked Oxygen saturation/heart rate during walk Final dyspnoea score Dyspnoea measured by modified Borg
Notes	QS = 3

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 (performance bias and detection bias) Breathlessness	Low risk	"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 end-

Jolly 2001 (group 1) (*Continued*)

		ing in a nasal cannula."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed

Jolly 2001 (group 2)

Methods	Randomised, double-blind, cross-over (though not explicitly stated in methods)
Participants	Inclusion criteria: COPD patients (ATS grade II/III) with at least 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 11 patients Mean age 67 (SEM 2) 10 male and 1 female Mean FEV_1 (L) 0.9 (SEM 0.8) Mean FVC (% predicted) 68 (SEM 8) Mean TLC (L) 7.07 (SEM 0.6) Mean RV (L) 4.19 (SEM 0.45) Mean oxygen saturation 94.7 (SEM 0.27) Mean PaO_2 (mmHg) 74 (SEM 2) Mean $PaCO_2$ (mmHg) 41 (SEM 1.2)
Interventions	Room air versus compressed air (3, 6, 9, 12 L/min) versus oxygen (3, 6, 9, 12 L/min) during 6MWT - amount of oxygen increased based upon any desaturation during exercise
Outcomes	Distance walked Oxygen saturation/heart rate during walk Final dyspnoea score Dyspnoea measured by modified Borg
Notes	QS = 3

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

Jolly 2001 (group 2) (*Continued*)

		which gas was added."
Blinding (performance bias and detection bias) Breathlessness	Low risk	"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."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All participants completed

Killen 2000

Methods	Randomised, single-blind, cross-over (though not explicitly stated in methods)
Participants	Inclusion criteria: COPD predominantly related to smoking and who were being considered for symptomatic oxygen therapy; all had stairs at home and found that ascending these produced dyspnoea; 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 criteria for long-term oxygen therapy 18 patients Mean age 67.5 (IQR 60.5 to 74.3) 8 male and 10 female Median FEV_1 (L) 0.53 (IQR 0.45 to 0.76) Median DLCO (% predicted) 44 (IQR 28 to 64) Median oxygen saturation on room air 94 (IQR 91 to 95)
Interventions	Oxygen (2 L/min) versus compressed air 5 minutes before and/or 5 minutes after ascending 22 steps
Outcomes	Time of ascent Pulse rate, oxygen and dyspnoea at rest, immediately after the ascent, and at 1-minute intervals thereafter Dyspnoea measured by 100 mm VAS with "not at all breathless" at one end and "extremely breathless" at the other end
Notes	QS = 3

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low 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

Killen 2000 (*Continued*)

Blinding (performance bias and detection bias) Breathlessness	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."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed

Knebel 2000

Methods	Randomised, double-blind, cross-over
Participants	Inclusion criteria: adults with OLD due to AAT deficiency; FEV_1 < 70% and FEV_1/FVC ratio < 0.70 Exclusion criteria: FEV_1 < 1 L; hospitalisation in preceding 3 weeks; conditions prohibiting or limited exercise; current use of oxygen; inability to understand English 31 patients Mean age 47 (SD 7) (Range 33-69) 22 male and 13 female Mean FEV_1 (% predicted) 48 (SD 13) (range 27 to 69) Mean TLC (% predicted) 105 (SD 14) (range 73 to 136) Baseline oxygen saturation 97.1% (SD 1.7) (range 92 to 100)
Interventions	Oxygen (4 L/min) versus compressed air (4 L/min) during 6MWT
Outcomes	Distance walked during 6MWT Oxygen sat during walk Heart rate Breathing frequency Dyspnoea measured by 10 cm horizontal VAS with "No shortness of breath" on the left and "Shortness of breath as bad as it can be" on the right
Notes	QS = 5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"A table of random numbers identified the order of administration."
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) Breathlessness	Low risk	"The tanks were covered so neither the patient nor the researcher knew which gas was being used."

Incomplete outcome data (attrition bias) All outcomes	High risk	"Two patients were unable to complete all of the walks because of unrelated problems". Data on remaining participants analysed in the study

Kurihara 1989

Methods	Randomised, single-blind, cross-over
Participants	Inclusion criteria: "COPD" Exclusion criteria: none mentioned (working from Cochrane translation) 14 patients 11 male and 3 female Mean age 62 (10.2) Mean FEV_1 (L) 0.67 (0.23) Mean FVC, % predicted 58.3 (6.2) Mean PaO_2 (mmHg) 68.8 (8.9)
Interventions	Dyspnoea by modified Borg scale and distance walked on treadmill
Outcomes	Dyspnoea by modified Borg scale and distance walked on treadmill Dyspnoea measured by modified Borg scale numbered 1 to 10 for which the two extremes were "none" and "extremely severe"
Notes	Translated from Japanese so had to work from translation sheet as opposed to reading entire article QS = 1

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 (performance bias and detection bias) Breathlessness	High risk	Single-blind study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information not available

Laude 2006

Methods	Randomised, controlled, cross-over study (though not explicitly stated in methods)
Participants	Inclusion criteria: COPD confirmed by an FEV_1 /FVC ratio < 80% predicted and limited bronchodilator reversibility; exertion dyspnoea defined by Borg ? 3 after exercise; no history of recent exacerbation Exclusion criteria: not explicitly stated 82 patients Gender not specified Mean age 69.7 (range 46 to 84) Mean FEV_1 (L) 1.1 (0.4) Mean FVC (L) 2.6 (0.8) Baseline oxygen saturation 93.9% (2.3)
Interventions	Heliox 28 (72%He/28%O_2) versus heliox 21 (79%He/21%O_2) versus oxygen 28 (72%N2/28%O_2) versus medical air (79%N2/21%O_2) during treadmill exercise
Outcomes	Dyspnoea at rest and on exercise SaO_2 Heart rate Dyspnoea measured by 100 mm VAS and modified Borg
Notes	QS = 1

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; no other information presented
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) Breathlessness	Unclear 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."
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

Leach 1992

Methods	Randomised, double-blind, cross-over (though not explicitly stated in methods)
Participants	Inclusion criteria: severely reduced exercise tolerance secondary to chronic respiratory disease; no previous experience of exercise testing Exclusion criteria: angina, impaired LV function, locomotor disability 20 patients Gender not specified Mean age 63.4 Mean FEV_1 (L) 0.74 (0.25) Mean FVC (L) 1.94 (0.51) Mean PaO_2 (mmHg) 65.5 (17.6)
Interventions	Oxygen (2, 4 or 6 L/min) versus compressed air (4 L/min) during 6MWT and endurance walk (walk as far as possible and stop when unable to go further)
Outcomes	Distance walked in metres (both 6MWT and endurance walk) Dyspnoea score by 10 cm VAS (both 6MWT and endurance walk at end exercise) Dyspnoea measured by 10 cm VAS with "not at all breathless" at one end and "extremely breathless" at the other
Notes	QS = 3

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 (performance bias and detection bias) Breathlessness	Unclear 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."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed

Lewis 2003

Methods	Randomised, single-blind, placebo-controlled, cross-over trial (though not explicitly stated in methods)
Participants	Inclusion criteria: moderate to severe COPD according to BTS criteria, significant self-reported dyspnoea, on optimal treatment, no exacerbation of disease for >= 4 weeks prior to study with exacerbation defined as "a deterioration in respiratory symptoms requiring treatment with corticosteroids or antibiotics or both" Exclusion criteria: significant limiting or unstable co morbidities 18 patients 16 male and 2 female Mean age 68.7 (SD 10.1) Mean FEV_1 (L) 0.91 (SD 0.36) Baseline oxygen saturation 94.4 (SD 1.6)
Interventions	Oxygen (2 L/min) versus air (2 L/min) prior to 6MWT
Outcomes	Baseline heart rate, saturation and dyspnoea HR and saturation every minute during 6MWT Dyspnoea at end of 6MWT Distances in metres HR, saturation and dyspnoea every 30 seconds during recovery until patient returned to baseline
Notes	QS = 2

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 (performance bias and detection bias) Breathlessness	High risk	"...identical cylinders in a single-blind fashion."
Incomplete outcome data (attrition bias) All outcomes	High risk	2 withdrawals: "All completed walks were included for analysis."

Maltais 2001

Methods	Randomised, double-blind, cross-over (though not explicitly stated in methods)
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

Maltais 2001 (*Continued*)

	the capacity to perform an exercise test according to medical history, physical exam, resting and exercise electrocardiogram and chest x-ray 14 patients Gender not specified Mean age 63 (SEM 3) Mean FEV_1 (L) 1.04 (SEM 0.07) Mean FVC (L) 2.64 (SEM 0.15) Mean PaO_2 (mmHg) 85 (SEM 4)
Interventions	Room air versus oxygen (75%) during exercise testing
Outcomes	Single leg blood flow Respiratory rate (RR), tidal volume (TV), minute ventilation (MV), oxygen uptake Dyspnoea and leg fatigue perception Arterial and venous PO_2 and PCO_2 and pH Dyspnoea measured by modified Borg
Notes	QS = 2

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"
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) Breathlessness	Low risk	"Patients and the physician supervising the exercise tests were blinded as to which inspiratory gas was used."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study

McDonald 1995

Methods	Randomised, double-blind, cross-over
Participants	Inclusion criteria: stable severe COPD, resting PaO_2 > 60 mmHg, exertional dyspnoea sufficient to interfere with daily activities, non-smoker, no exacerbations in preceding 3 months, use of maximal bronchodilator and/or corticosteroid therapy Exclusion criteria: symptomatic cardiac dysfunction; angina pectoris; locomotor disability 26 patients 24 male and 2 female Mean age 73 (SD 6) Mean FEV_1 (L) 0.9 (SD 0.4)

McDonald 1995 (*Continued*)

	Mean DLCO (mL/min/mmHg) 10.6 (SD 2.4) Mean oxygen saturation 94 (SD 2.1) Mean PaO_2 (mmHg) 69 (SD 8.5) and range 58 to 82 Mean $PaCO_2$ (mmHg) 41 (SD 3.3)
Interventions	Oxygen (4 L/min) versus compressed air (4 L/min) over long-term (successive 6-week periods during which patients were instructed to use portable gas cylinder during "any activity that would normally induce dyspnea") as well as in acute setting (6MWT and step test)
Outcomes	Acute: 6-minute walk distance and step test at study beginning as well as beginning of each 6-week period plus modified Borg dyspnoea score at the end of each exercise test Chronic: QOL by CRDQ and symptom scores from patient diaries Dyspnoea measured by modified Borg
Notes	QS = 4

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 (performance bias and detection bias) Breathlessness	Low risk	Cylinders had identical appearance
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study

McKeon 1988a

Methods	Randomised, double-blind, cross-over (though not explicitly stated in methods)
Participants	COPD with "significant disability with exertional dyspnoea despite treatment with inhaled and oral bronchodilators"; "stable condition" at the time of the study 20 patients 13 male and 7 female Mean age 63.2 (SD 10) Mean FEV_1 (L) 0.79 (SD 0.29) 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 oxygen saturation 90 (SD 3) (range 84 to 96)

McKeon 1988a (*Continued*)

	Mean PaO_2 (mmHg) 58 (SD 9) (range 43 to 82) Mean $PaCO_2$ (mmHg) 44 (SD 9) (range 31 to 62) Baseline PaO_2 (mmHg) on room air 58 (SD 9) and range 43 to 82
Interventions	Compressed air versus oxygen via nasal prongs at 2.5 L/min for 10 minutes prior to treadmill test (gradient flat with starting speed 1.5 km/hr with increments of 0.5 km/hr every minute)
Outcomes	Heart rate Oxygen saturation Breathlessness before and each minute during exercise Maximum distance walked Dyspnoea measured by 300 mm VAS
Notes	QS = 2

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 (performance bias and detection bias) Breathlessness	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."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study

McKeon 1988b

Methods	Double-blind, randomised, controlled, cross-over trial
Participants	COPD with "significant disability with exertional dyspnoea despite treatment with inhaled and oral bronchodilators"; "stable condition" at the time of the study 21 patients 11 women and 10 men Mean age 62 (SD 9) Mean FEV_1 (L) 0.77 (SD 0.40) Mean FEV_1 (% predicted) 29 (SD 13) Mean FVC (L) 2.00 (SD 0.89) Mean FVC (% predicted) 58 (SD 20) Mean RV (L) 3.53 (SD 0.94)

McKeon 1988b (*Continued*)

	Mean TLC (L) 5.97 (SD 1.34) Mean baseline PaO_2 (mmHg) 66.4 (SD 11) Mean baseline $PaCO_2$ (mmHg) 43.9 (SD 8.8)
Interventions	Oxygen (4 L/min) versus air (4 L/min) during treadmill test
Outcomes	Heart rate, arterial oxygen saturation, breathlessness, maximum walking distance Dyspnoea measured by 300 mm VAS
Notes	QS = 5

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)	Low risk	Cylinders prepared by technician not involved in study
Blinding (performance bias and detection bias) Breathlessness	Low risk	Identical cylinders used in the study
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study

Moore 2009

Methods	Double-blind, randomised, controlled, cross-over (though not explicitly stated in methods)
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 52 (51 included in analysis) 40 male and 11 female 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 FVC (L) 2.82 (SD 1.03) Mean FVC (% predicted) 86.3 (SD 21.0) Mean FEV_1/FVC (%) 44 (SD 14.5) Baseline oxygen saturation (%) 94.6 (SD 3.2)
Interventions	Oxygen (44%) versus medical air via mouthpiece

Moore 2009 (*Continued*)

Outcomes	Breathing frequency, cardiac frequency, oxygen saturation, dyspnoea Dyspnoea measured by modified Borg	
Notes	QS = 3	
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 (performance bias and detection bias) Breathlessness	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All participants completed the study

Nandi 2003

Methods	Randomised, double-blind, controlled trial
Participants	Inclusion criteria: FEV_1 < 60% predicted with less than 15% reversibility to inhaled salbutamol, a smoking history of more than 20 pack-years, exertional desaturation of at least 4% on pulse oximetry during submaximal exertion (corridor walking) Exclusion criteria: any other complicating medical condition 34 patients 18 male and 16 female Mean age 68 (SD 5.98) Mean FEV_1 (L) 0.88 (SD 0.34) Mean oxygen saturation 91.9 (5.2) with range 76 to 97 Mean PaO_2 (mmHg) 57.83 (10.88)* with range 38.56 to 78.76 *22 patients Baseline oxygen saturation on room air 91.9 (SD 5.2) with range 76 to 97
Interventions	Oxygen (28% at 4 L/min) versus compressed air (4 L/min) before exercise
Outcomes	Physiologic measure: resting, 2-min and 6-min SaO_2, walk distance, pre- and post-walk modified Borg dyspnoea scores; HRQOL measures: CRQ, HADS, SF-36 scores Domiciliary programme: use of air or oxygen-filled cylinder Dyspnoea measured by 100 mm VAS with end points of "not breathless at all" and "the most breathless I have ever been"
Notes	QS = 3

Nandi 2003 (*Continued*)

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 (performance bias and detection bias) Breathlessness	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."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study

O'Donnell 1997

Methods	Double-blind, randomised, cross-over, placebo-controlled trial
Participants	Inclusion criteria: advanced chronic airway limitation (FEV_1 < 60% predicted), mild hypoxaemia (did not meet criteria for home oxygen, referred to an exercise programme because they were sedentary/had poor exercise tolerance/experienced severe activity-related breathlessness with a modified dyspnoea index of 6 or less* Exclusion criteria: clinical evidence of significant cardiovascular disease, other pulmonary disease (including cor pulmonale), or other disorders that could contribute to dyspnoea or exercise limitation 11 patients 7 male and 4 female Mean age 68 (SEM 2) Mean FEV_1 (% predicted) 0.97 (SEM 0.13) Mean FVC (% predicted) 2.27 (SEM 0.25) Mean TLC (% predicted) 6.98 (SEM 0.5) Mean RV (% predicted) 4.39 (SEM 0.33) Mean DLCO (mL/min/mmHg) 8.8 (SEM 1.1) Mean PaO_2 (mmHg) 74 (SEM 3) Mean $PaCO_2$ (mmHg) 41 (SEM 2)
Interventions	Room air versus 60% O_2 (L/min not provided) on endurance cycle exercise test
Outcomes	Subjective ratings of breathlessness (defined as "the sensation of labored or difficult breathing") and perceived leg effort (defined as "the level of difficulty experienced during pedaling") by modified Borg scale at rest, every minute during exercise, and at peak exercise Objective measures of cardiovascular function, ventilatory function, gas exchange (via ABG) Measurements were taken during steady-state rest and during constant-load exercise

O'Donnell 1997 (*Continued*)

	Dyspnoea measured by modified Borg with zero indicating "no breathlessness" and 10 representing "the most severe breathlessness that had ever been experienced or that they could imagine experiencing"
Notes	QS = 3

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 (performance bias and detection bias) Breathlessness	Low risk	Identical breathing apparatus used in the study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All participants completed

Rooyackers 1997 (group 1)

Methods	Randomised, blinded study
Participants	Inclusion criteria: hypoxaemia (SaO_2 < 90%) at maximal exercise and an increase in alveolar-arterial difference in oxygen tension of at least 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, and neuromuscular or cardiovascular 12 patients 10 male and 2 female Mean age 59 (SD 13) Mean FEV_1 (L) 1.2 (SD 0.5) Mean TLC (% predicted) 110 (SD 11) Mean DLCO (% predicted) 40 (SD 15) Mean PaO_2 (mmHg) 76.5 (SD 9.0) Mean $PaCO_2$ (mmHg) 36.8 (4.5)
Interventions	Room air (RA) versus oxygen (4 L/min) during maximal incremental cycle exercise test, single-stage exercise test and 6MWT
Outcomes	PFTs (spirometry and DLCO) Maximal incremental exercise - ABG, minute ventilation, carbon dioxide production, breathlessness every 3 minutes and at end of exercise

Rooyackers 1997 (group 1) (*Continued*)

	Single-stage cycle exercise test - endurance cycling time, minute ventilation, carbon dioxide production, breathlessness every 3 minutes and at end of exercise Activities of daily life - 6MWT distance with continuous SaO_2 measurement and dyspnoea score at end; stair-climbing in 5 minutes; weightlifting during 3 minutes Dyspnoea measured by modified Borg
Notes	QS = 1

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer random number generator (see Nonoyama 2007)
Allocation concealment (selection bias)	Unclear risk	Central randomisation (see Nonoyama 2007)
Blinding (performance bias and detection bias) Breathlessness	High risk	Room air compared with compressed oxygen
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study

Rooyackers 1997 (group 2)

Methods	Randomised
Participants	Inclusion criteria: hypoxaemia (SaO_2 < 90%) at maximal exercise and an increase in alveolar-arterial difference in oxygen tension of at least 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, and neuromuscular or cardiovascular 12 patients 10 male and 2 female Mean age 63 (SD 5) Mean FEV_1 (L) 1.0 (SD 0.4) Mean TLC (% predicted) 110 (SD 22) Mean DLCO (% predicted) 30 (SD 15) Mean PaO_2 (mmHg) 71.3 (SD 15) Mean $PaCO_2$ (mmHg) 39.8 (8.3)
Interventions	Room air (RA) versus oxygen (4 L/min) during maximal incremental cycle exercise test, single-stage exercise test, and 6MWT

Rooyackers 1997 (group 2) (*Continued*)

Outcomes	PFTs (spirometry and DLCO) Maximal incremental exercise - ABG, minute ventilation, carbon dioxide production, breathlessness every 3 minutes and at end of exercise Single-stage cycle exercise test - endurance cycling time, minute ventilation, carbon dioxide production, breathlessness every 3 minutes and at end of exercise Activities of daily life - 6MWT distance with continuous SaO_2 measurement and dyspnoea score at end; stair-climbing in 5 minutes; weightlifting during 3 minutes Dyspnoea measured by modified Borg
Notes	QS = 1

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer random number generator (see Nonoyama 2007)
Allocation concealment (selection bias)	Low risk	Central randomisation (see Nonoyama 2007)
Blinding (performance bias and detection bias) Breathlessness	High risk	Room air compared with compressed oxygen.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study

Somfay 2001

Methods	Randomised, single-blind, controlled, cross-over trial (though not explicitly stated in methods)
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 dyspnoea or exercise limitation 10 patients 6 male and 4 female 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) Baseline oxygen saturation 95.7 % (SD 0.8)
Interventions	Compressed air versus oxygen (30%, 50%, 75% or 100%) during constant work rate test (with constant work rate determined by 75% of peak work rate in incremental test at study beginning)

Somfay 2001 (*Continued*)

Outcomes	Endurance time Dyspnoea score Lung volumes Respiratory flows Minute ventilation Gas exchange Heart rate Oxygen saturation Dyspnoea measured by modified Borg
Notes	QS = 1

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 (performance bias and detection bias) Breathlessness	High risk	Single-blind study
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study

Swinburn 1984

Methods	Randomised, single-blind, cross-over trial
Participants	Inclusion criteria: advanced obstructive airways disease but in "stable clinical state" 5 patients Exclusion criteria: not explicitly stated
Interventions	Room air (RA) versus oxygen (60%) during incremental cycle exercise test
Outcomes	Breathlessness Maximum ventilation reached on exercise Duration of exercise
Notes	QS = 1

Risk of bias

Bias	Authors' judgement	Support for judgement

Swinburn 1984 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Described as randomised; other information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) Breathlessness	High risk	Single-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study

Wadell 2001

Methods	Randomised, single-blind, controlled trial
Participants	Inclusion criteria: under the age of 75 years, stopped smoking at least 6 months before entering the study, hypoxaemia during exercise (<= 92% in 6MWT), FEV_1 < 70% predicted, PaO_2 > 60 mmHg at rest, no infection in the 3 weeks preceding study enrolment, no change in medical treatment in the month preceding enrolment Exclusion criteria: any past or present major illness, such as cardiac, orthopedic or neurological disease that might have interfered with exercise performance 20 patients 10 in air group and 10 in oxygen group Median age - air group 69 (60 to 72) and oxygen group 65 (52 to 73) Median FEV_1, % predicted - air group 51.6 (24 to 65.7) and oxygen group 39.3 (23.3 to 59.1) Median PaO_2 (mmHg) - air group 69.8 (59.3 to 85.5) and oxygen group 71.3 (64.5 to 87)
Interventions	Oxygen (5 L/min) versus air (5 L/min) during 6MWT on treadmill - baseline effect of 2 interventions as complete study involved training over an 8-week period
Outcomes	6MWT distance modified Borg dyspnoea score HR Borg perceived exertion score Dyspnoea measured by modified Borg
Notes	QS = 3

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Picking allocation from container (see Nonoyama 2007)

Wadell 2001 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Not enough information available to determine how order of treatment group assignment was concealed from investigators
Blinding (performance bias and detection bias) Breathlessness	High risk	Single-blind study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information not available

Woodcock 1981

Methods	Randomised, double-blind, cross-over
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 10 patients 9 male and 1 female Mean age 62 (range 43 to 70) Mean FEV_1 (L) 0.71 (SD 0.29) Mean FVC (L) 2.65 (SD 1.041) Mean PaO_2 (mmHg) 72 (SD 11.3) Mean $PaCO_2$ (mmHg) 34.1 (SD 4.5)
Interventions	Compressed air (4 L/min) versus oxygen (100% delivered at 4 L/min) during treadmill test and 6MWT
Outcomes	Dyspnoea at end exercise 6-minute walk distance Treadmill test distance Dyspnoea measured by 10 cm VAS
Notes	QS = 3

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) Breathlessness	Low risk	Compressed air versus oxygen delivered via coded unmarked cylinders

Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study

6MWT: six-minute walk test; AAT: Alpha 1 anti-trypsin; ABG: Arterial blood gas; ATS: American Thoracic Society; BTS: British Thoracic Society; CAD: Coronary artery disease; CO: Carbon monoxide; COPD: chronic obstructive pulmonary disease; CRDQ : Chronic respiratory disease questionnaire; CRQ: chronic respiratory questionnaire; DLCO: Diffusing capacity of the lung for carbon monoxide; ECHO; Echocardiogram; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; HAD: Hospital Anxiety and Depression Scale; hr: hour; HR: Heart rate; HRQOL: health-related quality of life; IQR: interquartile range; LTOT: long-term oxygen relief therapy; LV: Left ventricle; OLD: Obstructive lung disease; PaO2: partial pressure of oxygen in arterial blood; pCO2: Partial pressure of carbon dioxide; PFT: Pulmonary function test; pO2: Partial pressure of oxygen; QS: quality score; RV: Right ventricle; RVSP:- RV systolic pressure; SBOT: short-burst oxygen therapy; SD: standard deviation; SEM: standard error of the mean; SF-36: Short Form 36; SPO2: 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
Balkissoon 2006	Other - review of another manuscript
Bradley 1978	No suitable outcome
Bye 1985	No suitable outcome
Criner 1987	No suitable outcome
Cuvelier 2002	Patients already on home oxygen
Edvardsen 2007	Patients already on home oxygen
Evans 1986	No suitable outcome
Fujimoto 2002	No suitable outcome
Garrod 2000	Patients already on home oxygen
Gosselin 2004	No suitable outcome
King 1973	Mean PaO_2 < 55 mmHg
Lane 1987	Not a randomised controlled trial
Leggett 1977	Mean PaO_2 < 55 mmHg No suitable outcome

(*Continued*)

Light 1989	No suitable outcome
Liss 1988	Patients already on home oxygen
Lock 1992	Mean PaO_2 < 55 mmHg No placebo or control arm
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 on home oxygen
Nguyen 2008	Intervention not oxygen versus medical air
Noseda 1997	Intervention not oxygen versus medical air
O'Donnell 2001	Patients already on home oxygen
O'Driscoll 2003	Other - editorial
O'Driscoll 2007	No suitable outcome
O'Neill 2006	No suitable outcome
Ouyang 2006	Intervention not oxygen versus medical air
Peters 2006	Intervention not oxygen versus medical air
Raimondi 1970	No suitable outcome
Roberts 1996	Mean PaO_2 < 55 mmHg Patients already on home oxygen
Sandland 2008a	Patients hypoxic at rest
Sandland 2008b	Patients already on home oxygen or PRN oxygen No dyspnoea outcome
Stein 1982	No suitable outcome
Stevenson 2004	No suitable outcome
Swinburn 1991	Mean PaO_2 < 55 mmHg

(*Continued)*

Vyas 1971	No suitable outcome
Waterhouse 1983	No suitable outcome
Wedzicha 2006	Other - editorial

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	21		Std. Mean Difference (Random, 95% CI)	-0.37 [-0.50, -0.24]
2 Breathlessness - subgroup analysis - study focus	21		SMD (Random, 95% CI)	Subtotals only
2.1 Studies with primary focus = sensation	2		SMD (Random, 95% CI)	-0.39 [-0.66, -0.12]
2.2 Studies with primary focus = function	12		SMD (Random, 95% CI)	-0.45 [-0.61, -0.30]
2.3 Studies with primary focus = both	7		SMD (Random, 95% CI)	-0.32 [-0.67, 0.03]
3 Breathlessness - subgroup analysis - short burst or not	21		SMD (Random, 95% CI)	Subtotals only
3.1 Studies not using short-burst oxygen	17		SMD (Random, 95% CI)	-0.46 [-0.59, -0.33]
3.2 Studies using short-burst oxygen	4		SMD (Random, 95% CI)	0.01 [-0.26, 0.28]
4 Breathlessness - subgroup analysis - saturation on exertion	21		SMD (Random, 95% CI)	Subtotals only
4.1 Studies with exertional desaturation	16		SMD (Random, 95% CI)	-0.33 [-0.46, -0.20]
4.2 Studies with no exertional desaturation	5		SMD (Random, 95% CI)	-0.69 [-1.04, -0.34]
5 Breathlessness - subgroup analysis - mean PaO2	21		SMD (Random, 95% CI)	Subtotals only
5.1 Studies with mean PaO2 >= 70mmHg	15		SMD (Random, 95% CI)	-0.42 [-0.60, -0.24]
5.2 Studies with mean PaO2 < 70mmHg	6		SMD (Random, 95% CI)	-0.25 [-0.50, -0.00]
6 Breathlessness - sensitivity analysis - quality	5		SMD (Random, 95% CI)	-0.25 [-0.55, 0.06]
7 Breathlessness - sensitivity analysis - no imputed quantities	6		SMD (Random, 95% CI)	-0.36 [-0.64, -0.09]
8 Breathlessness - sensitivity - no outliers	17		SMD (Random, 95% CI)	-0.33 [-0.45, -0.22]
9 Breathlessness - sensitivity analysis - no end exercise	17		SMD (Random, 95% CI)	-0.37 [-0.54, -0.21]
10 Breathlessness - subgroup analysis - short-burst or not - post hoc - no outliers	17		SMD (Random, 95% CI)	-0.33 [-0.45, -0.22]
10.1 Studies not using short-burst oxygen	13		SMD (Random, 95% CI)	-0.42 [-0.55, -0.28]
10.2 Studies using short-burst oxygen	4		SMD (Random, 95% CI)	-0.03 [-0.28, 0.22]

11 Breathlessness - subgroup analysis - study focus - post-hoc - no outliers	17	SMD (Random, 95% CI)	-0.33 [-0.45, -0.22]
11.1 Studies with primary focus = function	10	SMD (Random, 95% CI)	-0.42 [-0.58, -0.25]
11.2 Studies with primary focus = sensation	2	SMD (Random, 95% CI)	-0.39 [-0.66, -0.12]
11.3 Studies with primary focus = both	5	SMD (Random, 95% CI)	-0.15 [-0.43, 0.14]
12 Breathlessness - subgroup analysis - saturation on exertion - post-hoc - no outliers	17	SMD (Random, 95% CI)	-0.33 [-0.45, -0.22]
12.1 Studies with exertional desaturation	14	SMD (Random, 95% CI)	-0.31 [-0.43, -0.18]
12.2 Studies with no exertional desaturation	3	SMD (Random, 95% CI)	-0.57 [-0.95, -0.19]
13 Breathlessness - subgroup analysis - mean PaO2 - post-hoc - no outliers	17	SMD (Random, 95% CI)	-0.33 [-0.45, -0.22]
13.1 Studies with mean PaO2 >= 70mmHg	11	SMD (Random, 95% CI)	-0.36 [-0.51, -0.22]
13.2 Studies with mean PaO2 < 70mmHg	6	SMD (Random, 95% CI)	-0.25 [-0.50, -0.00]
14 Breathlessness - post-hoc - no short-burst studies	17	SMD (Random, 95% CI)	-0.46 [-0.59, -0.33]
15 Breathlessness - post-hoc - subgroup analysis - saturation on exertion - no short burst	17	SMD (Random, 95% CI)	-0.46 [-0.59, -0.33]
15.1 Studies with exertional desaturation	12	SMD (Random, 95% CI)	-0.43 [-0.57, -0.29]
15.2 Studies with no exertional desaturation	5	SMD (Random, 95% CI)	-0.69 [-1.04, -0.34]
16 Breathlessness - post-hoc - subgroup analysis - study focus - no short-burst	17	SMD (Random, 95% CI)	-0.53 [-0.69, -0.36]
16.1 Studies with primary focus = sensation	1	SMD (Random, 95% CI)	-0.42 [-0.71, -0.13]
16.2 Studies with primary focus = function	12	SMD (Random, 95% CI)	-0.53 [-0.74, -0.33]
16.3 Studies with primary focus = both	4	SMD (Random, 95% CI)	-0.67 [-1.19, -0.14]
17 Breathlessness - post-hoc - subgroup analysis - mean PaO2 - no short-burst	17	SMD (Random, 95% CI)	-0.46 [-0.58, -0.33]
17.1 Studies with mean PaO2 >= 70mmHg	13	SMD (Random, 95% CI)	-0.47 [-0.62, -0.32]
17.2 Studies with mean PaO2 < 70mmHg	4	SMD (Random, 95% CI)	-0.43 [-0.67, -0.19]
18 Breathlessness - post-hoc - sensitivity analysis - quality - no short-burst	4	SMD (Random, 95% CI)	-0.25 [-0.59, 0.09]

19 Breathlessness - post-hoc - no outliers and no short-burst	13	SMD (Random, 95% CI)	-0.42 [-0.55, -0.28]
20 Breathlessness - post-hoc - sensitivity analysis - no imputed quantities and no outliers	5	SMD (Random, 95% CI)	-0.31 [-0.56, -0.05]
21 Breathlessness - post-hoc - sensitivity analysis - no end exercise and no outliers	13	SMD (Random, 95% CI)	-0.31 [-0.44, -0.18]
22 Breathlessness - subgroup analysis - dyspnoea measure	21	Std. Mean Difference (Random, 95% CI)	-0.37 [-0.50, -0.24]
22.1 modified Borg	14	Std. Mean Difference (Random, 95% CI)	-0.44 [-0.58, -0.29]
22.2 VAS	7	Std. Mean Difference (Random, 95% CI)	-0.25 [-0.48, -0.02]

Analysis 1.1. Comparison 1 Oxygen versus air, Outcome 1 Breathlessness - all trials.

Review: Symptomatic oxygen for non-hypoxaemic chronic obstructive pulmonary disease

Comparison: 1 Oxygen versus air

Outcome: 1 Breathlessness - all trials

Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Davidson 1988	-0.22 (0.35)		3.3 %	-0.22 [-0.91, 0.47]
Dean 1992	-1.4 (0.56)		1.4 %	-1.40 [-2.50, -0.30]
Eaton 2002	-0.42 (0.15)		12.7 %	-0.42 [-0.71, -0.13]
Emtner 2003 (group 1)	-0.33 (0.38)		2.8 %	-0.33 [-1.07, 0.41]
Emtner 2003 (group 2)	-0.5 (0.4)		2.6 %	-0.50 [-1.28, 0.28]
Eves 2006	-0.17 (0.45)		2.1 %	-0.17 [-1.05, 0.71]
Jolly 2001 (group 1)	-1.31 (0.64)		1.0 %	-1.31 [-2.56, -0.06]
Jolly 2001 (group 2)	-1.22 (0.56)		1.4 %	-1.22 [-2.32, -0.12]
Killen 2000	-0.25 (0.34)		3.5 %	-0.25 [-0.92, 0.42]
Knebel 2000	-0.13 (0.26)		5.5 %	-0.13 [-0.64, 0.38]
Kurihara 1989	-0.58 (0.24)		6.3 %	-0.58 [-1.05, -0.11]
Laude 2006	-0.44 (0.16)		11.6 %	-0.44 [-0.75, -0.13]
Lewis 2003	-0.1 (0.2)		8.4 %	-0.10 [-0.49, 0.29]
McDonald 1995	-0.4 (0.29)		4.6 %	-0.40 [-0.97, 0.17]
McKeon 1988a	0 (0.32)		3.9 %	0.0 [-0.63, 0.63]

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Study or subgroup	Std. Mean Difference (SE)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Nandi 2003	0.17 (0.24)		6.3 %	0.17 [-0.30, 0.64]
O'Donnell 1997	-0.44 (0.16)		11.6 %	-0.44 [-0.75, -0.13]
Rooyackers 1997 (group 1)	-0.26 (0.41)		2.5 %	-0.26 [-1.06, 0.54]
Rooyackers 1997 (group 2)	-0.33 (0.42)		2.3 %	-0.33 [-1.15, 0.49]
Somfay 2001	-1.43 (0.64)		1.0 %	-1.43 [-2.68, -0.18]
Woodcock 1981	-0.72 (0.27)		5.2 %	-0.72 [-1.25, -0.19]
Total (95% CI)			**100.0 %**	**-0.37 [-0.50, -0.24]**

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 23.31$, df = 20 (P = 0.27); $I^2 = 14\%$

Test for overall effect: Z = 5.60 (P < 0.00001)

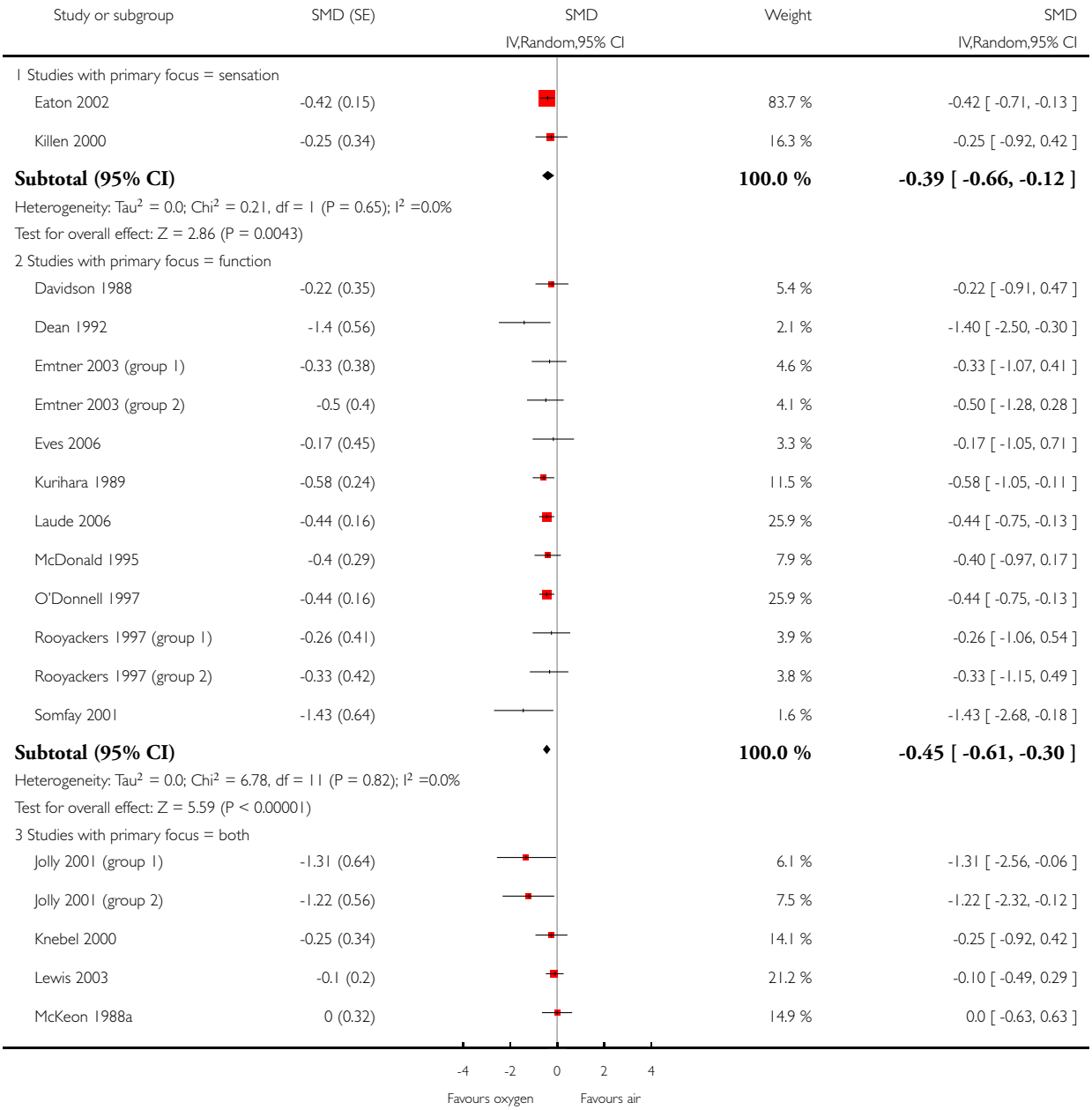
Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Oxygen versus air, Outcome 2 Breathlessness - subgroup analysis - study focus.

Review: Symptomatic oxygen for non-hypoxaemic chronic obstructive pulmonary disease

Comparison: 1 Oxygen versus air

Outcome: 2 Breathlessness - subgroup analysis - study focus



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Study or subgroup	SMD (SE)	SMD IV,Random,95% CI	Weight	SMD IV,Random,95% CI
Nandi 2003	0.17 (0.24)		18.9 %	0.17 [-0.30, 0.64]
Woodcock 1981	-0.72 (0.27)		17.3 %	-0.72 [-1.25, -0.19]
Subtotal (95% CI)			**100.0 %**	**-0.32 [-0.67, 0.03]**
Heterogeneity: Tau² = 0.11; Chi² = 12.99, df = 6 (P = 0.04); I² =54%				
Test for overall effect: Z = 1.80 (P = 0.072)				

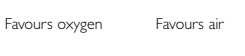
Analysis 1.3. Comparison 1 Oxygen versus air, Outcome 3 Breathlessness - subgroup analysis - short burst or not.

Review: Symptomatic oxygen for non-hypoxaemic chronic obstructive pulmonary disease

Comparison: 1 Oxygen versus air

Outcome: 3 Breathlessness - subgroup analysis - short burst or not

Study or subgroup	SMD (SE)	SMD IV,Random,95% CI	Weight	SMD IV,Random,95% CI
1 Studies not using short-burst oxygen				
Davidson 1988	-0.22 (0.35)		3.6 %	-0.22 [-0.91, 0.47]
Dean 1992	-1.4 (0.56)		1.4 %	-1.40 [-2.50, -0.30]
Eaton 2002	-0.42 (0.15)		19.4 %	-0.42 [-0.71, -0.13]
Emtner 2003 (group 1)	-0.33 (0.38)		3.0 %	-0.33 [-1.07, 0.41]
Emtner 2003 (group 2)	-0.5 (0.4)		2.7 %	-0.50 [-1.28, 0.28]
Eves 2006	-0.17 (0.45)		2.2 %	-0.17 [-1.05, 0.71]
Jolly 2001 (group 1)	-1.31 (0.64)		1.1 %	-1.31 [-2.56, -0.06]
Jolly 2001 (group 2)	-1.22 (0.56)		1.4 %	-1.22 [-2.32, -0.12]
Knebel 2000	-0.13 (0.26)		6.4 %	-0.13 [-0.64, 0.38]
Kurihara 1989	-0.58 (0.24)		7.6 %	-0.58 [-1.05, -0.11]
Laude 2006	-0.44 (0.16)		17.0 %	-0.44 [-0.75, -0.13]



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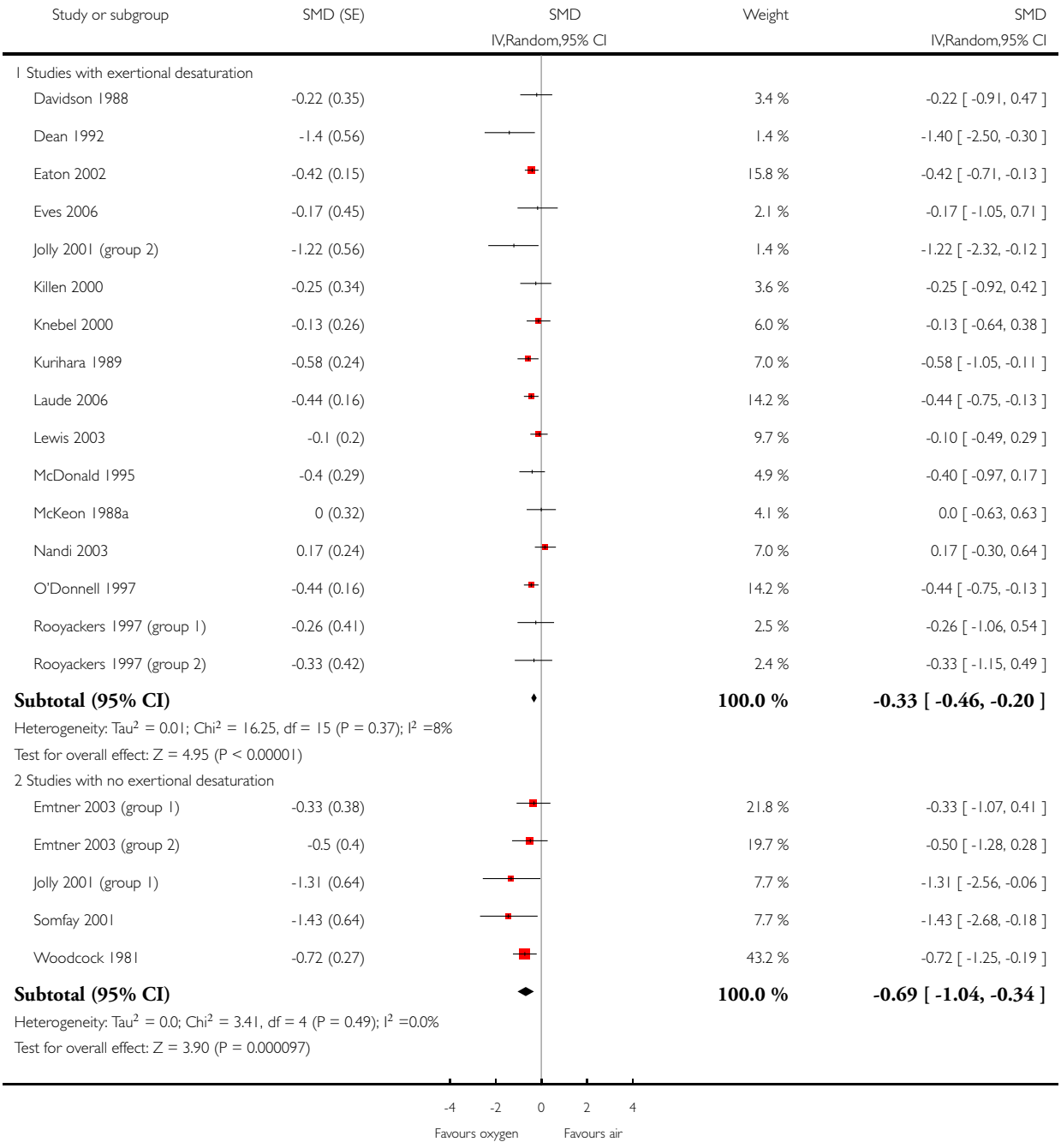
Study or subgroup	SMD (SE)	SMD IV,Random,95% CI	Weight	SMD IV,Random,95% CI
McDonald 1995	-0.4 (0.29)		5.2 %	-0.40 [-0.97, 0.17]
O'Donnell 1997	-0.44 (0.16)		17.0 %	-0.44 [-0.75, -0.13]
Rooyackers 1997 (group 1)	-0.26 (0.41)		2.6 %	-0.26 [-1.06, 0.54]
Rooyackers 1997 (group 2)	-0.33 (0.42)		2.5 %	-0.33 [-1.15, 0.49]
Somfay 2001	-1.43 (0.64)		1.1 %	-1.43 [-2.68, -0.18]
Woodcock 1981	-0.71 (0.27)		6.0 %	-0.71 [-1.24, -0.18]
Subtotal (95% CI)			**100.0 %**	**-0.46 [-0.59, -0.33]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 12.93, df = 16 (P = 0.68); I^2 =0.0%				
Test for overall effect: Z = 7.00 (P < 0.00001)				
2 Studies using short-burst oxygen				
Killen 2000	-0.25 (34)		0.0 %	-0.25 [-66.89, 66.39]
Lewis 2003	-0.1 (0.2)		48.0 %	-0.10 [-0.49, 0.29]
McKeon 1988a	0 (0.32)		18.7 %	0.0 [-0.63, 0.63]
Nandi 2003	0.17 (0.24)		33.3 %	0.17 [-0.30, 0.64]
Subtotal (95% CI)			**100.0 %**	**0.01 [-0.26, 0.28]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.75, df = 3 (P = 0.86); I^2 =0.0%				
Test for overall effect: Z = 0.06 (P = 0.95)				

Analysis 1.4. Comparison 1 Oxygen versus air, Outcome 4 Breathlessness - subgroup analysis - saturation on exertion.

Review: Symptomatic oxygen for non-hypoxaemic chronic obstructive pulmonary disease

Comparison: 1 Oxygen versus air

Outcome: 4 Breathlessness - subgroup analysis - saturation on exertion



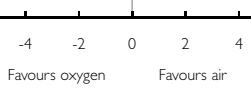
Analysis 1.5. Comparison 1 Oxygen versus air, Outcome 5 Breathlessness - subgroup analysis - mean PaO2.

Review: Symptomatic oxygen for non-hypoxaemic chronic obstructive pulmonary disease

Comparison: 1 Oxygen versus air

Outcome: 5 Breathlessness - subgroup analysis - mean PaO2

Study or subgroup	SMD (SE)	SMD IV,Random,95% CI	Weight	SMD IV,Random,95% CI
1 Studies with mean PaO2 >= 70mmHg				
Dean 1992	-1.4 (0.56)		2.5 %	-1.40 [-2.50, -0.30]
Eaton 2002	-0.42 (0.15)		16.0 %	-0.42 [-0.71, -0.13]
Emtner 2003 (group 1)	-0.33 (0.38)		4.9 %	-0.33 [-1.07, 0.41]
Emtner 2003 (group 2)	-0.5 (0.4)		4.5 %	-0.50 [-1.28, 0.28]
Jolly 2001 (group 1)	-1.31 (0.64)		1.9 %	-1.31 [-2.56, -0.06]
Jolly 2001 (group 2)	-1.22 (0.56)		2.5 %	-1.22 [-2.32, -0.12]
Killen 2000	-0.25 (0.34)		5.8 %	-0.25 [-0.92, 0.42]
Knebel 2000	-0.13 (0.26)		8.7 %	-0.13 [-0.64, 0.38]
Lewis 2003	0.1 (0.2)		12.1 %	0.10 [-0.29, 0.49]
McDonald 1995	-0.4 (0.29)		7.4 %	-0.40 [-0.97, 0.17]
O'Donnell 1997	-0.44 (0.16)		15.1 %	-0.44 [-0.75, -0.13]
Rooyackers 1997 (group 1)	-0.26 (0.41)		4.3 %	-0.26 [-1.06, 0.54]
Rooyackers 1997 (group 2)	-0.33 (0.42)		4.1 %	-0.33 [-1.15, 0.49]
Somfay 2001	-1.43 (0.64)		1.9 %	-1.43 [-2.68, -0.18]
Woodcock 1981	-0.72 (0.27)		8.2 %	-0.72 [-1.25, -0.19]
Subtotal (95% CI)			**100.0 %**	**-0.42 [-0.60, -0.24]**
Heterogeneity: Tau² = 0.03; Chi² = 19.18, df = 14 (P = 0.16); I² =27%				
Test for overall effect: Z = 4.52 (P < 0.00001)				
2 Studies with mean PaO2 < 70mmHg				
Davidson 1988	-0.22 (0.35)		10.9 %	-0.22 [-0.91, 0.47]
Eves 2006	-0.17 (0.45)		7.1 %	-0.17 [-1.05, 0.71]
Kurihara 1989	-0.58 (0.24)		19.2 %	-0.58 [-1.05, -0.11]
Laude 2006	-0.44 (0.16)		31.0 %	-0.44 [-0.75, -0.13]



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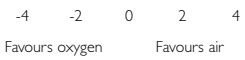
Study or subgroup	SMD (SE)	SMD IV,Random,95% CI	Weight	SMD IV,Random,95% CI
McKeon 1988a	0 (0.32)		12.6 %	0.0 [-0.63, 0.63]
Nandi 2003	0.17 (0.24)		19.2 %	0.17 [-0.30, 0.64]
Subtotal (95% CI)			**100.0 %**	**-0.25 [-0.50, 0.00]**
Heterogeneity: Tau² = 0.03; Chi² = 6.93, df = 5 (P = 0.23); I² =28%				
Test for overall effect: Z = 1.98 (P = 0.048)				



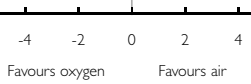
Analysis 1.6. Comparison 1 Oxygen versus air, Outcome 6 Breathlessness - sensitivity analysis - quality.

Review: Symptomatic oxygen for non-hypoxaemic chronic obstructive pulmonary disease

Comparison: 1 Oxygen versus air

Outcome: 6 Breathlessness - sensitivity analysis - quality

Study or subgroup	SMD (SE)	SMD IV,Random,95% CI	Weight	SMD IV,Random,95% CI
Emtner 2003 (group 1)	-0.33 (0.38)		16.7 %	-0.33 [-1.07, 0.41]
Emtner 2003 (group 2)	-0.5 (0.4)		15.0 %	-0.50 [-1.28, 0.28]
Eves 2006	-0.17 (0.45)		11.9 %	-0.17 [-1.05, 0.71]
Killen 2000	-0.25 (0.34)		20.8 %	-0.25 [-0.92, 0.42]
Knebel 2000	-0.13 (0.26)		35.6 %	-0.13 [-0.64, 0.38]
Total (95% CI)			**100.0 %**	**-0.25 [-0.55, 0.06]**
Heterogeneity: Tau² = 0.0; Chi² = 0.68, df = 4 (P = 0.95); I² =0.0%				
Test for overall effect: Z = 1.60 (P = 0.11)				
Test for subgroup differences: Not applicable				



Analysis 1.7. Comparison 1 Oxygen versus air, Outcome 7 Breathlessness - sensitivity analysis - no imputed quantities.

Review: Symptomatic oxygen for non-hypoxaemic chronic obstructive pulmonary disease

Comparison: 1 Oxygen versus air

Outcome: 7 Breathlessness - sensitivity analysis - no imputed quantities

Study or subgroup	SMD (SE)	SMD IV,Random,95% CI	Weight	SMD IV,Random,95% CI
Dean 1992	-1.4 (0.56)		5.3 %	-1.40 [-2.50, -0.30]
Eaton 2002	-0.42 (0.15)		22.8 %	-0.42 [-0.71, -0.13]
Lewis 2003	-0.1 (0.2)		19.0 %	-0.10 [-0.49, 0.29]
Nandi 2003	0.17 (0.24)		16.3 %	0.17 [-0.30, 0.64]
O'Donnell 1997	-0.44 (0.16)		22.1 %	-0.44 [-0.75, -0.13]
Woodcock 1981	-0.72 (0.27)		14.5 %	-0.72 [-1.25, -0.19]
Total (95% CI)			**100.0 %**	**-0.36 [-0.64, -0.09]**

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 12.18$, df = 5 (P = 0.03); $I^2 = 59\%$

Test for overall effect: Z = 2.56 (P = 0.010)

Test for subgroup differences: Not applicable

Analysis 1.8. Comparison 1 Oxygen versus air, Outcome 8 Breathlessness - sensitivity - no outliers.

Review: Symptomatic oxygen for non-hypoxaemic chronic obstructive pulmonary disease

Comparison: 1 Oxygen versus air

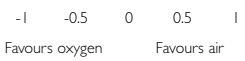
Outcome: 8 Breathlessness - sensitivity - no outliers

Study or subgroup	SMD (SE)	SMD IV,Random,95% CI	Weight	SMD IV,Random,95% CI
Davidson 1988	-0.22 (0.35)		2.9 %	-0.22 [-0.91, 0.47]
Eaton 2002	-0.42 (0.15)		15.9 %	-0.42 [-0.71, -0.13]
Emtner 2003 (group 1)	-0.33 (0.38)		2.5 %	-0.33 [-1.07, 0.41]
Emtner 2003 (group 2)	-0.5 (0.4)		2.2 %	-0.50 [-1.28, 0.28]
Eves 2006	-0.17 (0.45)		1.8 %	-0.17 [-1.05, 0.71]
Killen 2000	-0.25 (0.34)		3.1 %	-0.25 [-0.92, 0.42]
Knebel 2000	-0.13 (0.26)		5.3 %	-0.13 [-0.64, 0.38]
Kurihara 1989	-0.58 (0.24)		6.2 %	-0.58 [-1.05, -0.11]
Laude 2006	-0.44 (0.16)		14.0 %	-0.44 [-0.75, -0.13]
Lewis 2003	-0.1 (0.2)		9.0 %	-0.10 [-0.49, 0.29]
McDonald 1995	-0.4 (0.29)		4.3 %	-0.40 [-0.97, 0.17]
McKeon 1988a	0 (0.32)		3.5 %	0.0 [-0.63, 0.63]
Nandi 2003	0.17 (0.24)		6.2 %	0.17 [-0.30, 0.64]
O'Donnell 1997	-0.44 (0.16)		14.0 %	-0.44 [-0.75, -0.13]
Rooyackers 1997 (group 1)	-0.26 (0.41)		2.1 %	-0.26 [-1.06, 0.54]
Rooyackers 1997 (group 2)	-0.33 (0.42)		2.0 %	-0.33 [-1.15, 0.49]
Woodcock 1981	-0.72 (0.27)		4.9 %	-0.72 [-1.25, -0.19]
Total (95% CI)			**100.0 %**	**-0.33 [-0.45, -0.22]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 12.34$, df = 16 (P = 0.72); $I^2 = 0.0\%$

Test for overall effect: Z = 5.56 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 1.9. Comparison 1 Oxygen versus air, Outcome 9 Breathlessness - sensitivity analysis - no end exercise.

Review: Symptomatic oxygen for non-hypoxaemic chronic obstructive pulmonary disease

Comparison: 1 Oxygen versus air

Outcome: 9 Breathlessness - sensitivity analysis - no end exercise

Study or subgroup	SMD (SE)	SMD IV,Random,95% CI	Weight	SMD IV,Random,95% CI
Davidson 1988	-0.22 (0.35)		4.6 %	-0.22 [-0.91, 0.47]
Dean 1992	-1.4 (0.56)		2.1 %	-1.40 [-2.50, -0.30]
Eaton 2002	-0.42 (0.15)		13.0 %	-0.42 [-0.71, -0.13]
Jolly 2001 (group 1)	-1.31 (0.64)		1.6 %	-1.31 [-2.56, -0.06]
Jolly 2001 (group 2)	-1.22 (0.56)		2.1 %	-1.22 [-2.32, -0.12]
Killen 2000	-0.25 (0.34)		4.8 %	-0.25 [-0.92, 0.42]
Knebel 2000	-0.13 (0.26)		7.1 %	-0.13 [-0.64, 0.38]
Kurihara 1989	-0.58 (0.24)		7.9 %	-0.58 [-1.05, -0.11]
Lewis 2003	-0.1 (0.2)		9.8 %	-0.10 [-0.49, 0.29]
McDonald 1995	-0.4 (0.29)		6.1 %	-0.40 [-0.97, 0.17]
McKeon 1988a	0 (0.32)		5.3 %	0.0 [-0.63, 0.63]
Nandi 2003	0.17 (0.24)		7.9 %	0.17 [-0.30, 0.64]
O'Donnell 1997	-0.44 (0.16)		12.3 %	-0.44 [-0.75, -0.13]
Rooyackers 1997 (group 1)	-0.26 (0.41)		3.6 %	-0.26 [-1.06, 0.54]
Rooyackers 1997 (group 2)	-0.33 (0.42)		3.4 %	-0.33 [-1.15, 0.49]
Somfay 2001	-1.43 (0.64)		1.6 %	-1.43 [-2.68, -0.18]
Woodcock 1981	-0.72 (0.27)		6.8 %	-0.72 [-1.25, -0.19]
Total (95% CI)			**100.0 %**	**-0.37 [-0.54, -0.21]**

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 22.80$, df = 16 (P = 0.12); $I^2 = 30\%$

Test for overall effect: Z = 4.43 (P < 0.00001)

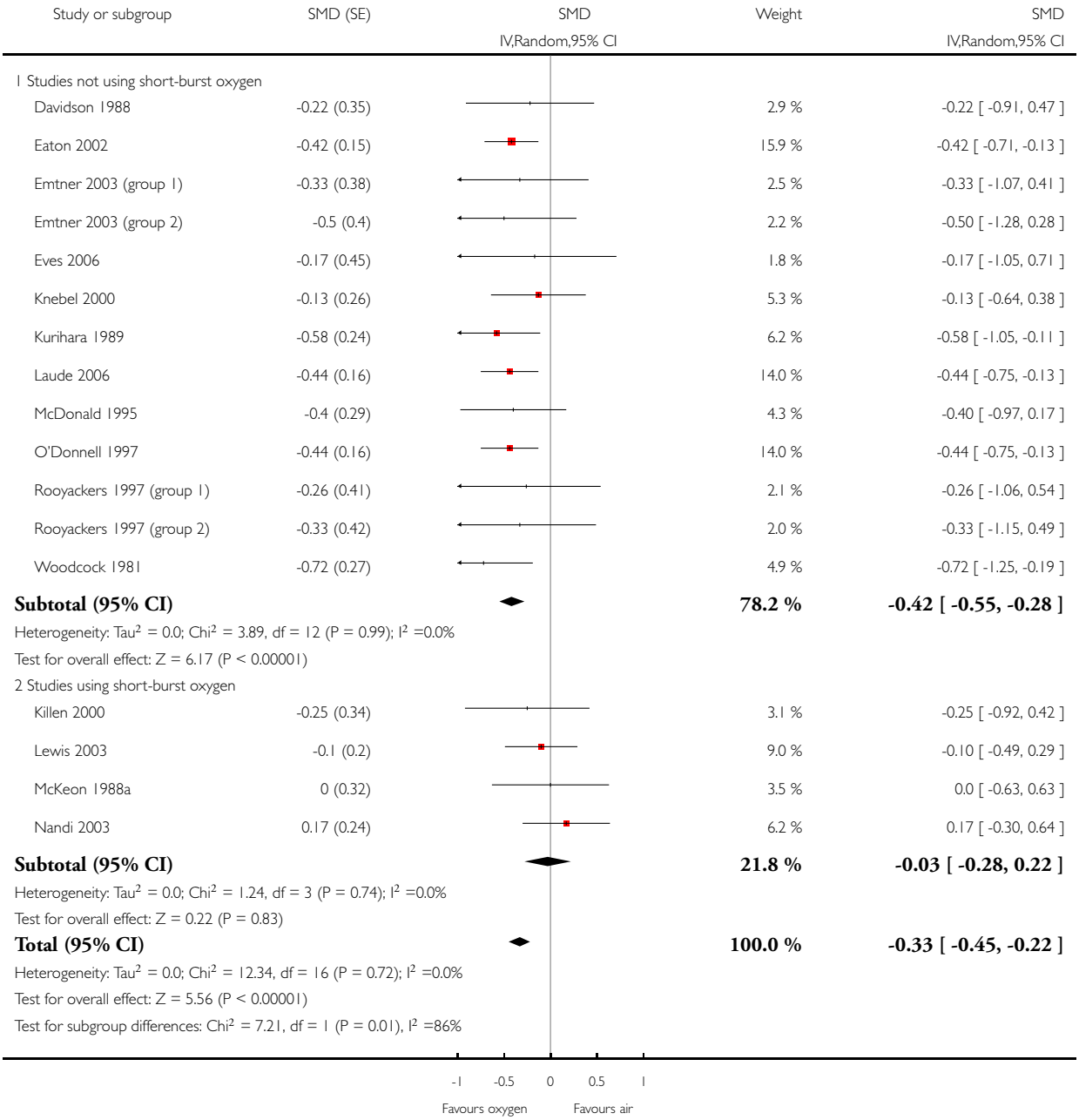
Test for subgroup differences: Not applicable

Analysis 1.10. Comparison 1 Oxygen versus air, Outcome 10 Breathlessness - subgroup analysis - short-burst or not - post hoc - no outliers.

Review: Symptomatic oxygen for non-hypoxaemic chronic obstructive pulmonary disease

Comparison: 1 Oxygen versus air

Outcome: 10 Breathlessness - subgroup analysis - short-burst or not - post hoc - no outliers

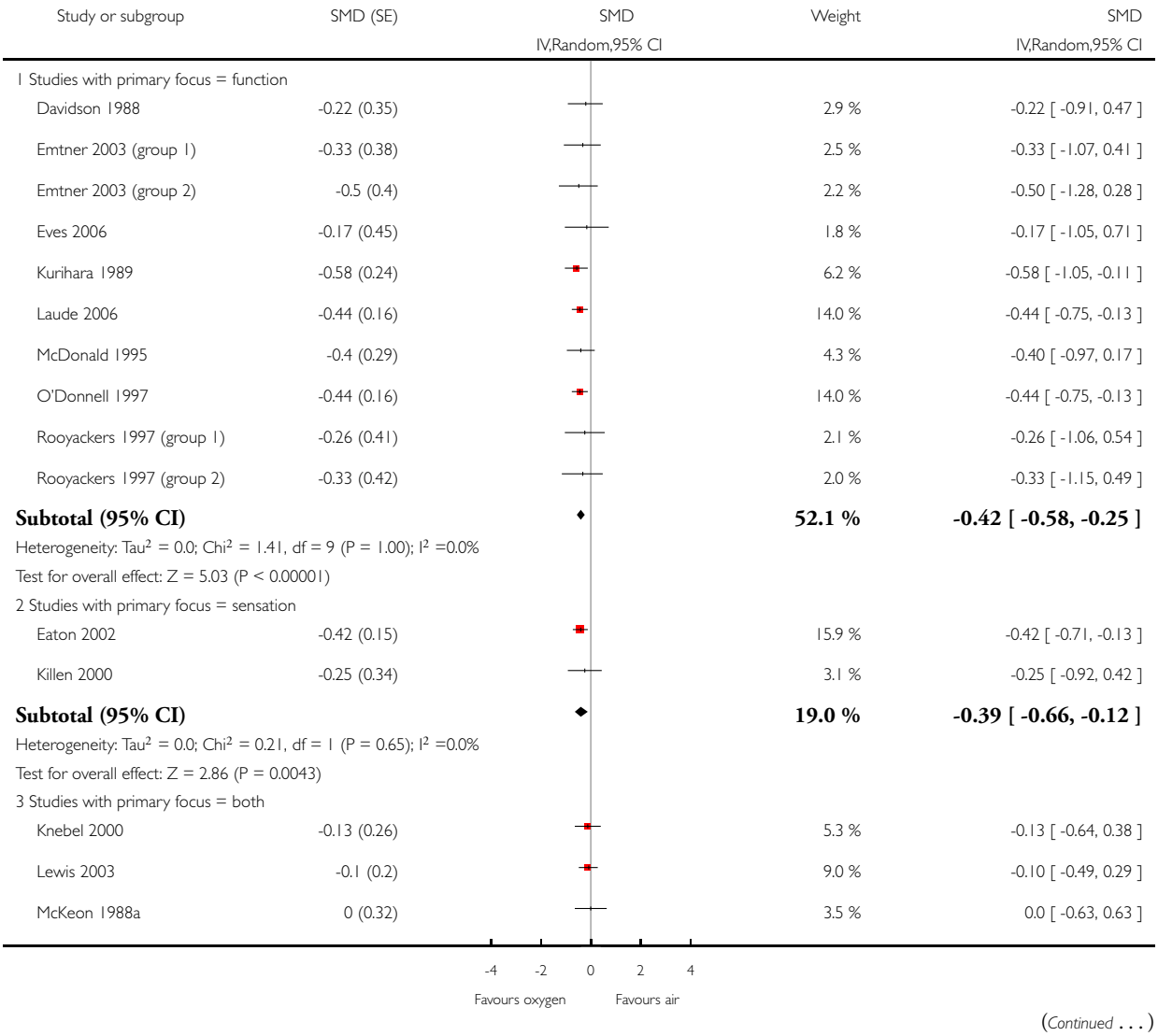


Analysis 1.11. Comparison 1 Oxygen versus air, Outcome 11 Breathlessness - subgroup analysis - study focus - post-hoc - no outliers.

Review: Symptomatic oxygen for non-hypoxaemic chronic obstructive pulmonary disease

Comparison: 1 Oxygen versus air

Outcome: 11 Breathlessness - subgroup analysis - study focus - post-hoc - no outliers



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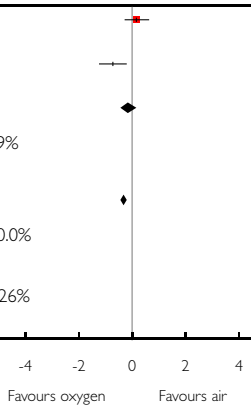
Study or subgroup	SMD (SE)	SMD IV,Random,95% CI	Weight	SMD IV,Random,95% CI
Nandi 2003	0.17 (0.24)		6.2 %	0.17 [-0.30, 0.64]
Woodcock 1981	-0.72 (0.27)		4.9 %	-0.72 [-1.25, -0.19]
Subtotal (95% CI)			**28.9 %**	**-0.15 [-0.43, 0.14]**
Heterogeneity: Tau^2 = 0.04; Chi^2 = 6.52, df = 4 (P = 0.16); I^2 =39%				
Test for overall effect: Z = 1.02 (P = 0.31)				
Total (95% CI)			**100.0 %**	**-0.33 [-0.45, -0.22]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 12.34, df = 16 (P = 0.72); I^2 =0.0%				
Test for overall effect: Z = 5.56 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 2.69, df = 2 (P = 0.26), I^2 =26%				



Analysis 1.12. Comparison 1 Oxygen versus air, Outcome 12 Breathlessness - subgroup analysis - saturation on exertion - post-hoc - no outliers.

Review: Symptomatic oxygen for non-hypoxaemic chronic obstructive pulmonary disease

Comparison: 1 Oxygen versus air

Outcome: 12 Breathlessness - subgroup analysis - saturation on exertion - post-hoc - no outliers

Study or subgroup	SMD (SE)	SMD IV,Random,95% CI	Weight	SMD IV,Random,95% CI
1 Studies with exertional desaturation				
Davidson 1988	-0.22 (0.35)		2.9 %	-0.22 [-0.91, 0.47]
Eaton 2002	-0.42 (0.15)		15.9 %	-0.42 [-0.71, -0.13]
Eves 2006	-0.17 (0.45)		1.8 %	-0.17 [-1.05, 0.71]
Killen 2000	-0.25 (0.34)		3.1 %	-0.25 [-0.92, 0.42]
Knebel 2000	-0.13 (0.26)		5.3 %	-0.13 [-0.64, 0.38]
Kurihara 1989	-0.58 (0.24)		6.2 %	-0.58 [-1.05, -0.11]
Laude 2006	-0.44 (0.16)		14.0 %	-0.44 [-0.75, -0.13]
Lewis 2003	-0.1 (0.2)		9.0 %	-0.10 [-0.49, 0.29]

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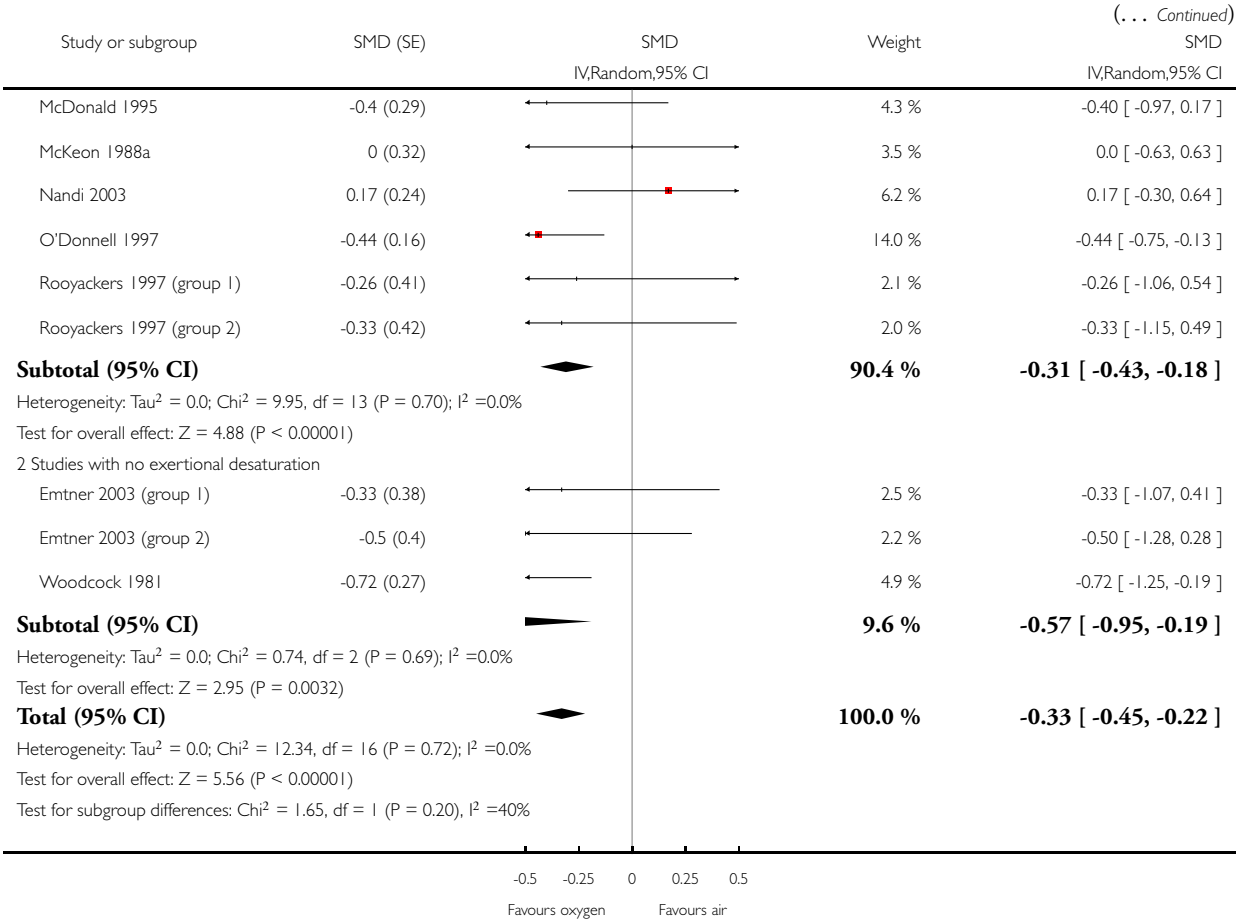
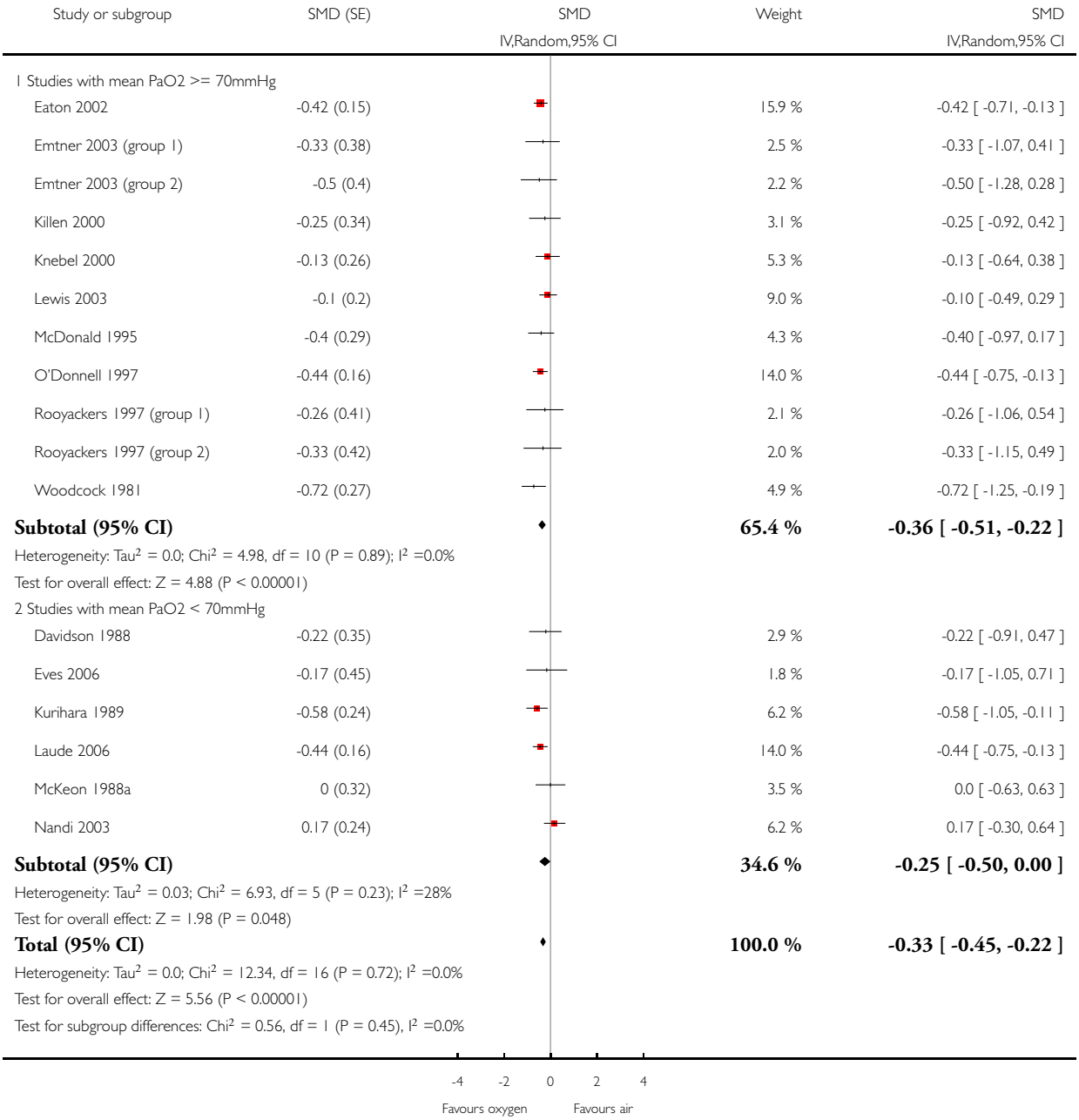


Analysis 1.13. Comparison 1 Oxygen versus air, Outcome 13 Breathlessness - subgroup analysis - mean PaO2 - post-hoc - no outliers.

Review: Symptomatic oxygen for non-hypoxaemic chronic obstructive pulmonary disease

Comparison: 1 Oxygen versus air

Outcome: 13 Breathlessness - subgroup analysis - mean PaO2 - post-hoc - no outliers



Analysis 1.14. Comparison 1 Oxygen versus air, Outcome 14 Breathlessness - post-hoc - no short-burst studies.

Review: Symptomatic oxygen for non-hypoxaemic chronic obstructive pulmonary disease

Comparison: 1 Oxygen versus air

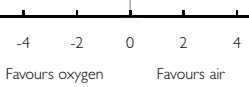
Outcome: 14 Breathlessness - post-hoc - no short-burst studies

Study or subgroup	SMD (SE)	SMD IV,Random,95% CI	Weight	SMD IV,Random,95% CI
Davidson 1988	-0.22 (0.35)		3.6 %	-0.22 [-0.91, 0.47]
Dean 1992	-1.4 (0.56)		1.4 %	-1.40 [-2.50, -0.30]
Eaton 2002	-0.42 (0.15)		19.4 %	-0.42 [-0.71, -0.13]
Emtner 2003 (group 1)	-0.33 (0.38)		3.0 %	-0.33 [-1.07, 0.41]
Emtner 2003 (group 2)	-0.5 (0.4)		2.7 %	-0.50 [-1.28, 0.28]
Eves 2006	-0.17 (0.45)		2.2 %	-0.17 [-1.05, 0.71]
Jolly 2001 (group 1)	-1.31 (0.64)		1.1 %	-1.31 [-2.56, -0.06]
Jolly 2001 (group 2)	-1.22 (0.56)		1.4 %	-1.22 [-2.32, -0.12]
Knebel 2000	-0.13 (0.26)		6.4 %	-0.13 [-0.64, 0.38]
Kurihara 1989	-0.58 (0.24)		7.6 %	-0.58 [-1.05, -0.11]
Laude 2006	-0.44 (0.16)		17.0 %	-0.44 [-0.75, -0.13]
McDonald 1995	-0.4 (0.29)		5.2 %	-0.40 [-0.97, 0.17]
O'Donnell 1997	-0.44 (0.16)		17.0 %	-0.44 [-0.75, -0.13]
Rooyackers 1997 (group 1)	-0.26 (0.41)		2.6 %	-0.26 [-1.06, 0.54]
Rooyackers 1997 (group 2)	-0.33 (0.42)		2.5 %	-0.33 [-1.15, 0.49]
Somfay 2001	-1.43 (0.64)		1.1 %	-1.43 [-2.68, -0.18]
Woodcock 1981	-0.72 (0.27)		6.0 %	-0.72 [-1.25, -0.19]
Total (95% CI)			**100.0 %**	**-0.46 [-0.59, -0.33]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 13.00$, df = 16 (P = 0.67); $I^2 = 0.0\%$

Test for overall effect: Z = 7.01 (P < 0.00001)

Test for subgroup differences: Not applicable

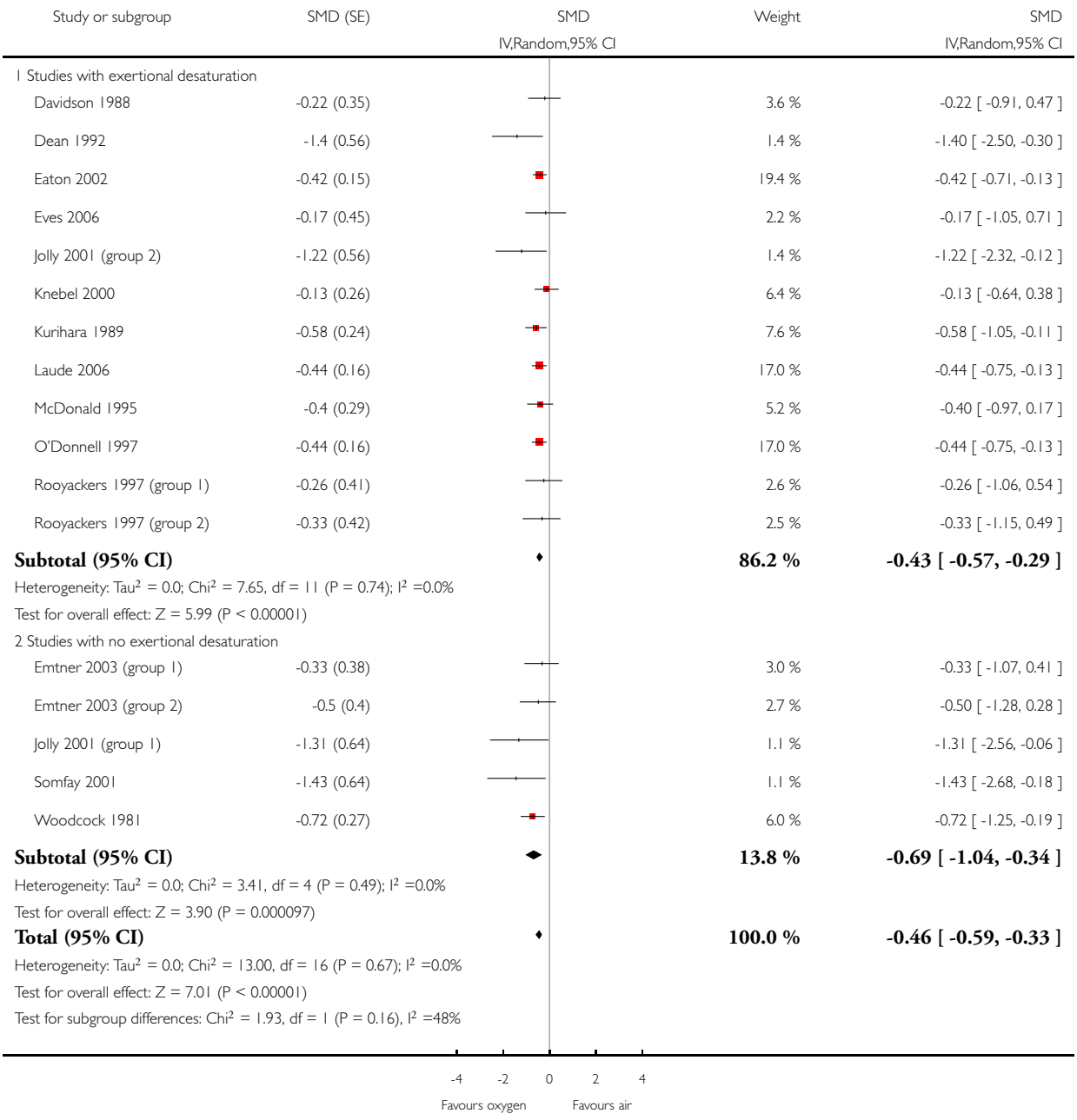


Analysis 1.15. Comparison 1 Oxygen versus air, Outcome 15 Breathlessness - post-hoc - subgroup analysis - saturation on exertion - no short burst.

Review: Symptomatic oxygen for non-hypoxaemic chronic obstructive pulmonary disease

Comparison: 1 Oxygen versus air

Outcome: 15 Breathlessness - post-hoc - subgroup analysis - saturation on exertion - no short burst



Analysis 1.16. Comparison 1 Oxygen versus air, Outcome 16 Breathlessness - post-hoc - subgroup analysis - study focus - no short-burst.

Review: Symptomatic oxygen for non-hypoxaemic chronic obstructive pulmonary disease

Comparison: 1 Oxygen versus air

Outcome: 16 Breathlessness - post-hoc - subgroup analysis - study focus - no short-burst

Study or subgroup	SMD (SE)	SMD IV,Random,95% CI	Weight	SMD IV,Random,95% CI
1 Studies with primary focus = sensation				
Eaton 2002	-0.42 (0.15)		12.9 %	-0.42 [-0.71, -0.13]
Subtotal (95% CI)			**12.9 %**	**-0.42 [-0.71, -0.13]**
Heterogeneity: not applicable				
Test for overall effect: Z = 2.80 (P = 0.0051)				
2 Studies with primary focus = function				
Davidson 1988	-0.22 (0.35)		4.6 %	-0.22 [-0.91, 0.47]
Dean 1992	-1.4 (0.56)		2.1 %	-1.40 [-2.50, -0.30]
Emtner 2003 (group 1)	-0.33 (0.38)		4.0 %	-0.33 [-1.07, 0.41]
Emtner 2003 (group 2)	-0.5 (0.4)		3.7 %	-0.50 [-1.28, 0.28]
Eves 2006	-0.17 (0.45)		3.0 %	-0.17 [-1.05, 0.71]
Kurihara 1989	-0.58 (0.24)		7.9 %	-0.58 [-1.05, -0.11]
Laude 2006	-0.44 (0.16)		12.2 %	-0.44 [-0.75, -0.13]
McDonald 1995	-0.4 (0.29)		6.1 %	-0.40 [-0.97, 0.17]
O'Donnell 1997	-0.44 (0.16)		12.2 %	-0.44 [-0.75, -0.13]
Rooyackers 1997 (group 1)	-0.26 (0.41)		3.6 %	-0.26 [-1.06, 0.54]
Rooyackers 1997 (group 2)	-0.33 (0.42)		3.4 %	-0.33 [-1.15, 0.49]
Somfay 2001	-1.43 (0.27)		6.8 %	-1.43 [-1.96, -0.90]
Subtotal (95% CI)			**69.6 %**	**-0.53 [-0.74, -0.33]**
Heterogeneity: Tau^2 = 0.04; Chi^2 = 16.76, df = 11 (P = 0.12); I^2 =34%				
Test for overall effect: Z = 5.04 (P < 0.00001)				
3 Studies with primary focus = both				
Jolly 2001 (group 1)	-1.31 (0.64)		1.6 %	-1.31 [-2.56, -0.06]
Jolly 2001 (group 2)	-1.22 (0.56)		2.1 %	-1.22 [-2.32, -0.12]
Knebel 2000	-0.13 (0.26)		7.1 %	-0.13 [-0.64, 0.38]
Woodcock 1981	-0.72 (0.27)		6.8 %	-0.72 [-1.25, -0.19]

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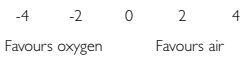
Study or subgroup	SMD (SE)	SMD IV,Random,95% CI	Weight	SMD IV,Random,95% CI
Subtotal (95% CI)			**17.5 %**	**-0.67 [-1.19, -0.14]**
Heterogeneity: Tau² = 0.13; Chi² = 5.85, df = 3 (P = 0.12); I² =49%				
Test for overall effect: Z = 2.50 (P = 0.013)				
Total (95% CI)			**100.0 %**	**-0.53 [-0.69, -0.36]**
Heterogeneity: Tau² = 0.03; Chi² = 23.06, df = 16 (P = 0.11); I² =31%				
Test for overall effect: Z = 6.26 (P < 0.00001)				
Test for subgroup differences: Chi² = 0.75, df = 2 (P = 0.69), I² =0.0%				



Analysis 1.17. Comparison 1 Oxygen versus air, Outcome 17 Breathlessness - post-hoc - subgroup analysis - mean PaO2 - no short-burst.

Review: Symptomatic oxygen for non-hypoxaemic chronic obstructive pulmonary disease

Comparison: 1 Oxygen versus air

Outcome: 17 Breathlessness - post-hoc - subgroup analysis - mean PaO2 - no short-burst

Study or subgroup	SMD (SE)	SMD IV,Random,95% CI	Weight	SMD IV,Random,95% CI
1 Studies with mean PaO2 >= 70mmHg				
Dean 1992	-1.4 (0.56)		1.3 %	-1.40 [-2.50, -0.30]
Eaton 2002	-0.42 (0.15)		17.9 %	-0.42 [-0.71, -0.13]
Emtner 2003 (group 1)	-0.33 (0.38)		2.8 %	-0.33 [-1.07, 0.41]
Emtner 2003 (group 2)	-0.5 (0.4)		2.5 %	-0.50 [-1.28, 0.28]
Jolly 2001 (group 1)	-1.31 (0.64)		1.0 %	-1.31 [-2.56, -0.06]
Jolly 2001 (group 2)	-1.22 (0.56)		1.3 %	-1.22 [-2.32, -0.12]
Knebel 2000	-0.13 (0.26)		6.0 %	-0.13 [-0.64, 0.38]
McDonald 1995	-0.4 (0.18)		12.4 %	-0.40 [-0.75, -0.05]
O'Donnell 1997	-0.44 (0.16)		15.7 %	-0.44 [-0.75, -0.13]
Rooyackers 1997 (group 1)	-0.26 (0.41)		2.4 %	-0.26 [-1.06, 0.54]

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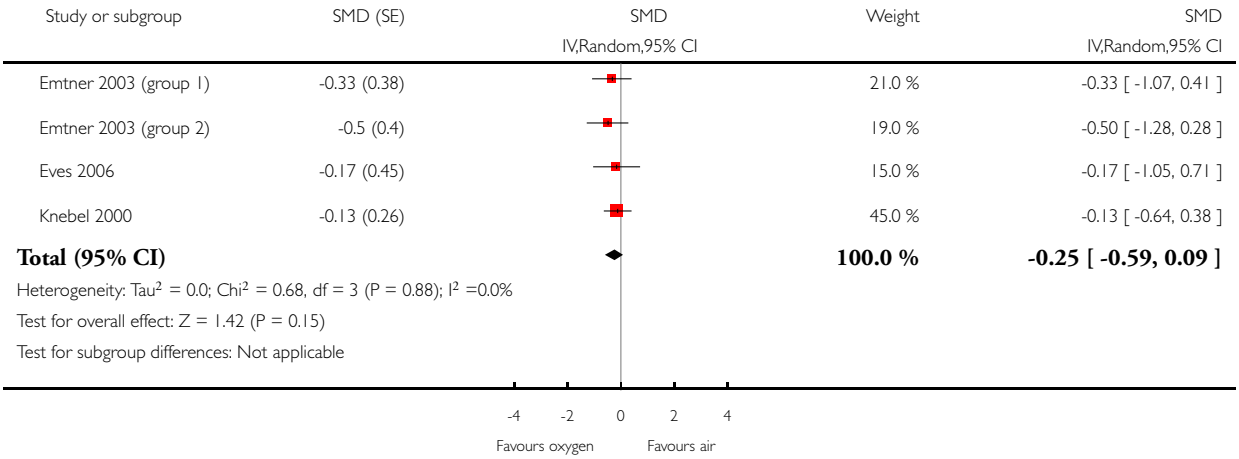
Study or subgroup	SMD (SE)	SMD IV,Random,95% CI	Weight	SMD IV,Random,95% CI
Rooyackers 1997 (group 2)	-0.33 (0.42)		2.3 %	-0.33 [-1.15, 0.49]
Somfay 2001	-1.43 (0.64)		1.0 %	-1.43 [-2.68, -0.18]
Woodcock 1981	-0.72 (0.27)		5.5 %	-0.72 [-1.25, -0.19]
Subtotal (95% CI)			**72.0 %**	**-0.47 [-0.62, -0.32]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 11.90, df = 12 (P = 0.45); I^2 =0.0%				
Test for overall effect: Z = 6.27 (P < 0.00001)				
2 Studies with mean PaO2 < 70mmHg				
Davidson 1988	-0.22 (0.35)		3.3 %	-0.22 [-0.91, 0.47]
Eves 2006	-0.17 (0.45)		2.0 %	-0.17 [-1.05, 0.71]
Kurihara 1989	-0.58 (0.24)		7.0 %	-0.58 [-1.05, -0.11]
Laude 2006	-0.44 (0.16)		15.7 %	-0.44 [-0.75, -0.13]
Subtotal (95% CI)			**28.0 %**	**-0.43 [-0.67, -0.19]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.09, df = 3 (P = 0.78); I^2 =0.0%				
Test for overall effect: Z = 3.59 (P = 0.00034)				
Total (95% CI)			**100.0 %**	**-0.46 [-0.58, -0.33]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 13.07, df = 16 (P = 0.67); I^2 =0.0%				
Test for overall effect: Z = 7.22 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.08, df = 1 (P = 0.78), I^2 =0.0%				

Analysis 1.18. Comparison 1 Oxygen versus air, Outcome 18 Breathlessness - post-hoc - sensitivity analysis - quality - no short-burst.

Review: Symptomatic oxygen for non-hypoxaemic chronic obstructive pulmonary disease

Comparison: 1 Oxygen versus air

Outcome: 18 Breathlessness - post-hoc - sensitivity analysis - quality - no short-burst



Analysis 1.19. Comparison 1 Oxygen versus air, Outcome 19 Breathlessness - post-hoc - no outliers and no short-burst.

Review: Symptomatic oxygen for non-hypoxaemic chronic obstructive pulmonary disease

Comparison: 1 Oxygen versus air

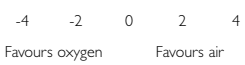
Outcome: 19 Breathlessness - post-hoc - no outliers and no short-burst

Study or subgroup	SMD (SE)	SMD IV,Random,95% CI	Weight	SMD IV,Random,95% CI
Davidson 1988	-0.22 (0.35)		3.7 %	-0.22 [-0.91, 0.47]
Eaton 2002	-0.42 (0.15)		20.4 %	-0.42 [-0.71, -0.13]
Emtner 2003 (group 1)	-0.33 (0.38)		3.2 %	-0.33 [-1.07, 0.41]
Emtner 2003 (group 2)	-0.5 (0.4)		2.9 %	-0.50 [-1.28, 0.28]
Eves 2006	-0.17 (0.45)		2.3 %	-0.17 [-1.05, 0.71]
Knebel 2000	-0.13 (0.26)		6.8 %	-0.13 [-0.64, 0.38]
Kurihara 1989	-0.58 (0.24)		8.0 %	-0.58 [-1.05, -0.11]
Laude 2006	-0.44 (0.16)		17.9 %	-0.44 [-0.75, -0.13]
McDonald 1995	-0.4 (0.29)		5.4 %	-0.40 [-0.97, 0.17]
O'Donnell 1997	-0.44 (0.16)		17.9 %	-0.44 [-0.75, -0.13]
Rooyackers 1997 (group 1)	-0.26 (0.41)		2.7 %	-0.26 [-1.06, 0.54]
Rooyackers 1997 (group 2)	-0.33 (0.42)		2.6 %	-0.33 [-1.15, 0.49]
Woodcock 1981	-0.72 (0.27)		6.3 %	-0.72 [-1.25, -0.19]
Total (95% CI)			**100.0 %**	**-0.42 [-0.55, -0.28]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.89$, df = 12 (P = 0.99); $I^2 = 0.0\%$

Test for overall effect: Z = 6.17 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 1.20. Comparison 1 Oxygen versus air, Outcome 20 Breathlessness - post-hoc - sensitivity analysis - no imputed quantities and no outliers.

Review: Symptomatic oxygen for non-hypoxaemic chronic obstructive pulmonary disease

Comparison: 1 Oxygen versus air

Outcome: 20 Breathlessness - post-hoc - sensitivity analysis - no imputed quantities and no outliers

Study or subgroup	SMD (SE)	SMD IV,Random,95% CI	Weight	SMD IV,Random,95% CI
Eaton 2002	-0.42 (0.15)		25.3 %	-0.42 [-0.71, -0.13]
Lewis 2003	-0.1 (0.2)		19.9 %	-0.10 [-0.49, 0.29]
Nandi 2003	0.17 (0.24)		16.4 %	0.17 [-0.30, 0.64]
O'Donnell 1997	-0.44 (0.16)		24.1 %	-0.44 [-0.75, -0.13]
Woodcock 1981	-0.72 (0.27)		14.3 %	-0.72 [-1.25, -0.19]
Total (95% CI)			**100.0 %**	**-0.31 [-0.56, -0.05]**

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 8.58$, df = 4 (P = 0.07); $I^2 = 53\%$

Test for overall effect: Z = 2.39 (P = 0.017)

Test for subgroup differences: Not applicable

Analysis 1.21. Comparison 1 Oxygen versus air, Outcome 21 Breathlessness - post-hoc - sensitivity analysis - no end exercise and no outliers.

Review: Symptomatic oxygen for non-hypoxaemic chronic obstructive pulmonary disease

Comparison: 1 Oxygen versus air

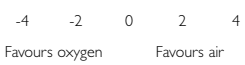
Outcome: 21 Breathlessness - post-hoc - sensitivity analysis - no end exercise and no outliers

Study or subgroup	SMD (SE)	SMD IV,Random,95% CI	Weight	SMD IV,Random,95% CI
Davidson 1988	-0.22 (0.35)		3.7 %	-0.22 [-0.91, 0.47]
Eaton 2002	-0.42 (0.15)		20.0 %	-0.42 [-0.71, -0.13]
Killen 2000	-0.25 (0.34)		3.9 %	-0.25 [-0.92, 0.42]
Knebel 2000	-0.13 (0.26)		6.7 %	-0.13 [-0.64, 0.38]
Kurihara 1989	-0.58 (0.24)		7.8 %	-0.58 [-1.05, -0.11]
Lewis 2003	-0.1 (0.2)		11.3 %	-0.10 [-0.49, 0.29]
McDonald 1995	-0.4 (0.29)		5.4 %	-0.40 [-0.97, 0.17]
McKeon 1988a	0 (0.32)		4.4 %	0.0 [-0.63, 0.63]
Nandi 2003	0.17 (0.24)		7.8 %	0.17 [-0.30, 0.64]
O'Donnell 1997	-0.44 (0.16)		17.6 %	-0.44 [-0.75, -0.13]
Rooyackers 1997 (group 1)	-0.26 (0.41)		2.7 %	-0.26 [-1.06, 0.54]
Rooyackers 1997 (group 2)	-0.33 (0.42)		2.6 %	-0.33 [-1.15, 0.49]
Woodcock 1981	-0.72 (0.27)		6.2 %	-0.72 [-1.25, -0.19]
Total (95% CI)			**100.0 %**	**-0.31 [-0.44, -0.18]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 11.50$, df = 12 (P = 0.49); $I^2 = 0.0\%$

Test for overall effect: Z = 4.66 (P < 0.00001)

Test for subgroup differences: Not applicable

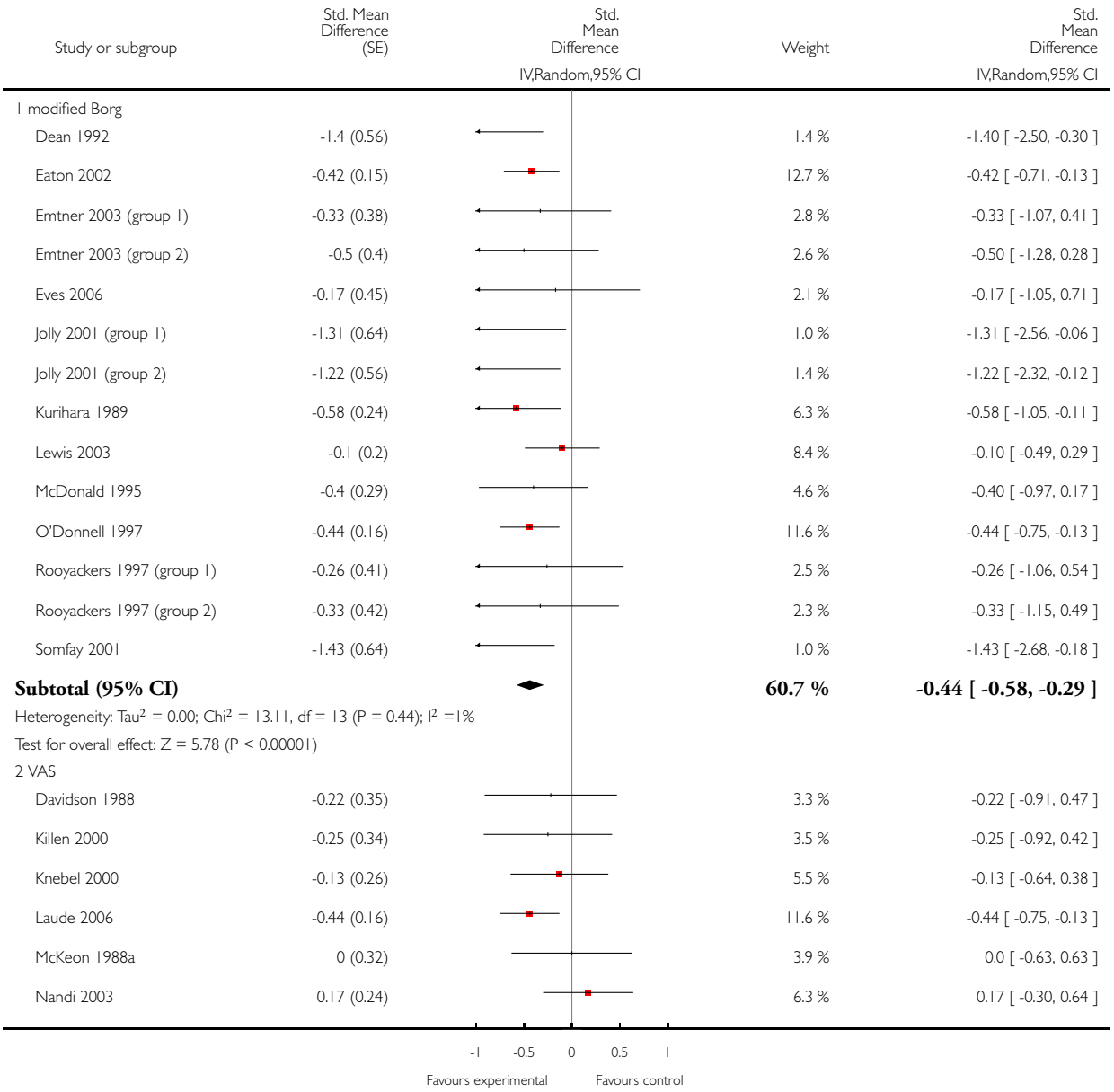


Analysis 1.22. Comparison 1 Oxygen versus air, Outcome 22 Breathlessness - subgroup analysis - dyspnoea measure.

Review: Symptomatic oxygen for non-hypoxaemic chronic obstructive pulmonary disease

Comparison: 1 Oxygen versus air

Outcome: 22 Breathlessness - subgroup analysis - dyspnoea measure



(*Continued* . . .)

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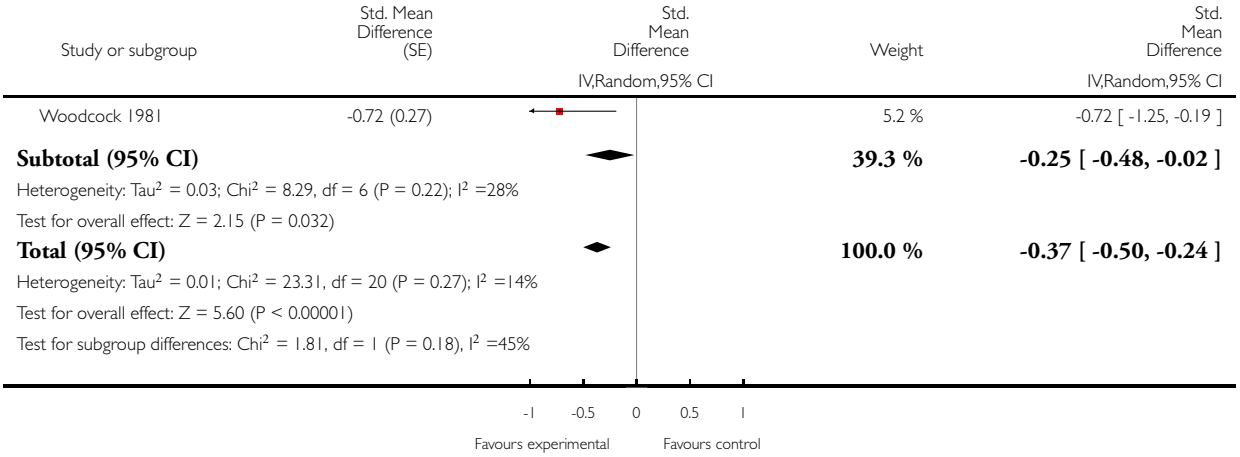

ADDITIONAL TABLES

Table 1. Overview of characteristics of included studies

Study	Focus	BL PaO_2 (mmHg)	BL SaO_2 (%)	Dyspnoea measure	BL dyspnoea	O_2 delivery	O_2 dose	Jadad score
Moore 2009	Function	NA	94.6 (SD 3.2)	Modified Borg	NA	Mouthpiece	44%	3
Eaton 2006	Function	75	NA	CRQ	17.1	NC	2 L/min	4
Eves 2006	Function	68.3 (SD 6.4)	NA	Modified Borg	NA	Mouthpiece	40%	4
Laude 2006	Function	NA	93.9 (SD 2.3)	100 mm VAS and modified Borg	VAS 24.2 (SD 19) or Borg 1.8 (SD 1.1)	Mask/valve	28%	1
Haidl 2004	Function	66.5	NA	Modified Borg	NA	NC	2 L/min	1
Emtner 2003 (group 1)	Function	73.8 (SD 6.2)	NA	Modified Borg	NA	Mouthpiece	30%	5

Table 1. Overview of characteristics of included studies *(Continued)*

Emtner 2003 (group 2)	Function	74.9 (SD 8.7)	NA	Modified Borg	NA	Mouthpiece	30%	5
Lewis 2003	Both	NA	94.4 (SD 1.6)	Modified Borg	0.4 (SD 0.5)	NC	2 L/min	2
Nandi 2003	Both	NA	91.9 (SD 5.2) (range 76 to 97)	100 mm VAS	NA	Mask	4 L/min	3
Eaton 2002	Sensation	69 (SD 7.5)	NA	Modified Borg	0.7 (SD 1.0)	NC	4 L/min	4
Jolly 2001 (group 1)	Both	79 (SE 3)	95.8 (SE 0.46)	Modified Borg	0.56 (SE 0.34)	NC	3 L/min	3
Emtner 2003 (group 2)	Both	74 (SE 2)	94.7 (SE 0.27)	Modified Borg	1.27 (SE 0.43)	NC	3 L/min	2
Maltais 2001	Function	85 (SD 4)	NA	Modified Borg	NA	Mouthpiece	75%	2
Wadell 2001	Both	Median 69.8 (range 59.3 to 85.5)	Median 94.6 (range 90.7 to 97.2)	Modified Borg	Median 1.5 (range 0 to 3)	NC	5 L/min	3
Somfay 2001	Function	NA	95.7 (SD 0.8)	Modified Borg	NA	Mouthpiece	30%	1
Killen 2000	Sensation	NA	Median 94 (quartiles 91, 95)	100 mm VAS	NA	Mask	2 L/min	3
Knebel 2000	Both	NA	97.1 (SD 1.7) (range 92 to 100)	10 cm VAS	0.5 (SD 0.9) (range 0 to 4.7)	NC	4 L/min	5
Garrod 1999	Function	62.86 (SD 9.3)	NA	Modified Borg	NA	NC	2 L/min	2
O'Donnell 1997	Function	74 (SEM 3)	NA	Modified Borg	5.1 (SD 0.3) *	Mouthpiece	60%	3
Rooyackers 1997 (group 1)	Function	76.5 (SD 9.0)	NA	Modified Borg	NA	NC	4 L/min	1

Table 1. Overview of characteristics of included studies *(Continued)*

Rooyackers 1997 (group 2)	Function	71.3 (SD 15)	NA	Modified Borg	NA	NC	4 L/min	1
Ishimine 1995	Both	75.9 (SD 8.6)	NA	Dyspnoea questionnaire	NA	Unknown	3 L/min	2
McDonald 1995	Function	69 (SD 8.5) (range 58 to 82)	94 (SD 2.1)	Modified Borg	NA	NC	4 L/min	4
Dean 1992	Function	71 (SE 2.6)	NA	Modified Borg	NA	Mouthpiece	40%	4
Leach 1992	Function	65.5 (SD 17.6)	NA	10 cm VAS	NA	Mask	2 L/min	3
Kurihara 1989	Function	68.8 (SD 8.9)	NA	Modified Borg	NA	NC	3 L/min	1
Davidson 1988	Function	64.51 (SE 2.25)	NA	10 cm VAS	NA	NC or valve	4 L/min	2
McKeon 1988a	Both	58 (SD 9) (range 43 to 82)	90 (SD 3) (range 84 to 96)	300 mm VAS	NA	NC	2.5 L/min	2
McKeon 1988b	Function	66.4 (SD 11)	NA	300 mm VAS	NA	NC	4 L/min	5
Swinburn 1984	Function	NA	93.2 (SD 0.8)	10 cm VAS	NA	Mouthpiece	60%	1
Woodcock 1981	Both	72 (SD 11.3)	NA	10 cm VAS	4 (SD 0.94) **	NC	4 L/min	3
Data presented as mean (standard deviation (SD)) unless otherwise specified					* by dyspnoea index ** by MRC dyspnoea grade			

BL = baseline; NA = Not available; VAS = visual analogue scale; CRQ = chronic respiratory questionnaire; SD = standard deviation; SE = standard error; LTOT = long term oxygen therapy; NC = nasal canula

CONTRIBUTIONS OF AUTHORS

APA conceived, designed and co-ordinated the review and is the guarantor of the review.

HEU collected and managed data for the review. All of her efforts were duplicated by APA in order to ensure accuracy.

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

GPS contributed to the development of the analysis plan and provided guidance in interpretation of results.

DCM contributed to the design of the review protocol and the development of the analysis plan.

All authors contributed to generation of the review manuscript.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Agency for Healthcare Research and Quality (5 T32 HS000079), USA.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have incorporated a 'Risk of bias' table into this review, with assessments made of four sources of bias in clinical trials (allocation sequence generation, allocation concealment, blinding and handling of withdrawals). We removed exercise capacity as a secondary outcome, following peer review.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Humans