National Institute for Health and Care Excellence

Final

Chronic obstructive pulmonary disease in over 16s: diagnosis and management

[B] Oxygen therapy in people with stable COPD

NICE guideline NG115

Evidence reviews

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Final

These evidence reviews were developed by the NICE Guideline Updates Team

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Contents

Ambulatory and short burst oxygen therapy for people not meeting the criteria for long term oxygen therapy 6
Review question 6
Introduction 6
Methods and process 7
Clinical evidence 7
Summary of the systematic review included in the evidence review 8
Quality assessment of clinical studies included in the evidence review 9
Economic evidence 9
Summary of studies included in the economic evidence review 9
Economic model 9
Evidence statements 9
The committee's discussion of the evidence 11
Long-term oxygen therapy 13
Review question 13
Introduction 13
Methods and process 13
Clinical evidence 14
Summary of clinical studies included in the evidence review 15
Quality assessment of clinical studies included in the evidence review 15
Economic evidence 18
Summary of studies included in the economic evidence review 18
Economic model 20
Evidence statements 20
The committee's discussion of the evidence 22
Appendices 27
Appendix A – Review protocols 27
Review protocol for ambulatory and short burst oxygen therapy 27
Review protocol for long term oxygen therapy 30
Appendix B – Methods 36
Priority screening 36
Incorporating published systematic reviews 36
Evidence synthesis and meta-analyses 38
Evidence of effectiveness of interventions 38
Health economics 43
Appendix C – Literature search strategies 45
Cochrane Airways Group Specialised Register (CAGR): Sources and search methods 45

NICE search methods 51
Health Economics search strategy 54
Appendix D – Clinical evidence study selection 57
Ambulatory and short burst oxygen therapy 57
Long term oxygen therapy 57
Appendix E – Clinical evidence tables 58
Ambulatory and short burst oxygen therapy –Systematic review 58
Long term oxygen therapy- Randomised controlled trials 64
Appendix F – Forest plots 78
Ambulatory and short burst oxygen therapy: oxygen versus air 78
Long term oxygen therapy 94
Appendix G – GRADE tables 98
Long term oxygen therapy 102
Appendix H – Economic evidence study selection 111
Ambulatory and short burst oxygen therapy for people not meeting the criteria for long-term oxygen therapy 111
Long-term oxygen therapy 112
Appendix I – Health economic evidence profiles 113
Appendix J – Excluded studies 115
Ambulatory and short burst oxygen therapy 115
Long-term oxygen therapy 115
Economic studies 117
Appendix K – References 118
Clinical evidence - included studies 118
Clinical evidence - excluded studies 118
Economic evidence - included studies 121
Economic evidence - excluded studies 121

Ambulatory and short burst oxygen therapy for people not meeting the criteria for long term oxygen therapy

Review question

What is the effectiveness of oxygen therapy in people with stable COPD who are mildly hypoxaemic or non-hypoxaemic at rest?

Introduction

The aim of this review was to determine whether ambulatory or short burst oxygen therapy are effective at reducing breathlessness and improving quality of life in people with stable COPD who are mildly hypoxaemic or non-hypoxaemic at rest, and do not meet the criteria for long term oxygen therapy (not meeting the criteria was defined as having a mean arterial oxygen (PaO_2) > 7.3 kPa, and not currently receiving long term oxygen therapy).

For the purposes of this question, ambulatory oxygen therapy is defined as the use of supplemental oxygen during exercise and activities of daily living in mobile patients who are not sufficiently hypoxaemic to qualify for long term oxygen therapy but who desaturate on exercise. It has historically been used to optimise saturations and short-term exercise capacity. Ambulatory oxygen is also often supplied to long term oxygen therapy users, either to allow those who are mobile outdoors to optimise their exercise capacity and achieve their recommended hours per day usage, or to enable more immobile patients to leave the house in a wheelchair/scooter on occasion, for example for hospital appointments.

Short burst oxygen therapy is typically given to patients for the relief of breathlessness not relieved by any other treatments. It is used intermittently at home for short periods, for example 10–20 minutes at a time.

These definitions were obtained from the British Thoracic Society Home Oxygen Guidelines (2015).

This review identified studies that fulfilled the conditions specified in Table 1. For full details of the review protocol, see appendix A.

Table 1 PICO table - oxygen therapy for breathlessness

Population	People diagnosed with COPD who are mildly hypoxaemic or non-hypoxaemic at rest[a]
Interventions	• Oxygen therapy
Comparator	• Air delivered by non-invasive method • Optimal medical therapy
Outcomes	• Breathlessness • Health related quality of life • Adverse events

[a] People who are not taking long-term oxygen and who have a mean PaO_2 greater than 7.3k Pa.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A, and the methods section in appendix B. In particular, the minimally important differences (MIDs) used in this review are summarised in Table 8 in appendix B. These were selected based on the literature with input from the committee.

The search strategies used in this review are detailed in appendix C.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

Clinical evidence

Included studies - Oxygen therapy for breathlessness in people with stable COPD

This review was conducted as an update of the 2010 NICE COPD guideline (CG101). A recent systematic review was incorporated and updated to help determine the efficacy of oxygen therapy in people who have stable COPD.

The systematic review was carried out by the Cochrane Airways Group, published in 2016 and included 44 RCTs. The inclusion criteria stated that the participants were 18 years of age or older who had COPD, had mild or no hypoxaemia (mean PaO2 > 7.3 kPa) and did not receive long term oxygen therapy. For studies that also included participants without COPD, the researchers obtained individual participant data for those with COPD and included only that data in the analyses.

Though the Cochrane review was directly applicable and of high quality, the data were reanalysed in line with the methods and processes outlined in appendix B, and therefore the analyses presented in this review may be different from those in the published Cochrane review. The summary of this systematic review is provided in Table 2.

A second set of searches was conducted at the end of the guideline development process for all updated review questions using the original search strategies, to capture papers published whilst the guideline was being developed. These searches, which included articles up to February 2018, returned 3,100 references in total for all the questions included in the update, and these were screened on title and abstract. One additional reference was identified and excluded at full text screening.

The process of study identification is summarised in the diagram in appendix D.

For the full evidence tables and the full GRADE profiles please see appendix E and appendix G. The references of individual included studies are given in appendix K.

Excluded studies

Since this review was based on evidence from a Cochrane review, please refer to this review for the list of studies excluded by the Cochrane group authors. Details of the study excluded at full text from the second search are given in Appendix J.

Summary of the systematic review included in the evidence review

The included systematic review is summarised in Table 2. Please see appendix E for the full evidence table and the characteristics of the included studies from this systematic review.

Table 2 - Oxygen therapy for breathlessness

Short Title	Interventions	Population	Outcomes
Ekstrom (2016)	• Oxygen therapy *(delivered by a non-invasive method, delivered during exertion, continuously or as needed over a defined period, or short-burst oxygen before exertion (defined as therapy given during a short, defined period just before exertion))* • Air *(delivered by a non-invasive method at any inspired dose above that of ambient air (>21%))*	• 44 randomised controlled trials • Update of the 2011 systematic review • Dates searched 2011 - 12 July 2016 • 18 years of age or older who had COPD • Mild or no hypoxaemia (mean PaO2 > 7.3 kPa)	• Level of breathlessness measured on any validated scale • Health related quality of life measured on any validated scale • Adverse events

Quality assessment of clinical studies included in the evidence review

See appendix G for full GRADE tables.

Economic evidence

Included studies

A single search was conducted to cover all review question topics in this guideline update. This search returned 16,299 records, of which 16,295 were excluded on title and abstract. The remaining 4 papers were screened using a review of the full text and 0 were found to be relevant for this review question.

Excluded studies

Details of the studies excluded at full-text review are given in Appendix J.

Summary of studies included in the economic evidence review

No economic evidence as identified for this review question.

Economic model

This topic was not prioritised for health economic modelling and no original analyses were produced.

Evidence statements

The format of the evidence statements is explained in the methods in appendix B.

The evidence statements below only report numbers of participants where this data was available in the Cochrane review.

Oxygen therapy for breathlessness

Breathlessness – all trials

Moderate quality evidence from 32 RCTs reporting data from 865 people with stable COPD who were mildly or non-hypoxaemic at rest found no meaningful difference between people offered oxygen therapy compared to pressurised air. There was also evidence of publication bias, with studies showing more negative results with oxygen therapy being less likely to be published.

Results were consistent across trials with different characteristics as detailed by the subgroup analyses reported below.

Sub group analysis - Type of oxygen therapy - short burst and ambulatory oxygen therapy

Low quality evidence from 4 RCTs reporting data from 90 people with stable COPD who were mildly or non-hypoxaemic at rest found no meaningful difference in breathlessness

between people offered short burst oxygen therapy before exercise compared to pressurised air.

High quality evidence from 28 RCTs reporting data from 775 people with stable COPD who were mildly or non-hypoxaemic at rest found no meaningful difference in breathlessness between people offered ambulatory oxygen during exercise or daily activities compared to pressurised air.

Subgroup analysis – with or without desaturation on exertion

Low quality evidence from 16 RCTs reporting data from people with stable COPD with desaturation (defined as oxygen saturation (SaO_2) <88% at baseline or mean PaO2 < 8 kPa on exertion) during exercise and moderate quality evidence from 15 RCTs reporting data from people with stable COPD without desaturation during exercise found no meaningful difference in breathlessness between people offered oxygen therapy compared to pressurised air.

Sub group analysis – mean arterial oxygen

Low quality evidence from 7 RCTs reporting data from people with stable COPD and a mean arterial oxygen (PaO_2) less than 9.3kpa at baseline and moderate quality evidence from 25 RCTs reporting data from people with stable COPD and a mean arterial oxygen (PaO_2) greater than 9.3kpa at baseline found no meaningful difference in breathlessness between people offered oxygen therapy compared to pressurised air.

Sub group analysis – during exercise and in daily life

Moderate quality evidence from 30 RCTs reporting data from 591 people with stable COPD found no meaningful difference in breathlessness during exercise between people offered oxygen therapy compared to pressurised air.

High quality evidence from 2 RCTs reporting data from people with stable COPD found no meaningful difference in breathlessness in daily life between people offered oxygen therapy compared to pressurised air.

Sub group analysis – short term and long term oxygen training

Moderate quality evidence from 29 RCTs reporting data from people with stable COPD found no meaningful difference in breathlessness during an exercise test between people offered oxygen therapy compared to air.

High quality evidence from 3 RCTs reporting data from people with stable COPD found no meaningful difference in breathlessness with a long training period between people offered oxygen therapy compared to air for the same period.

Sub group analysis – oxygen dose

High quality evidence from 26 RCTs reporting data from people with stable COPD found no meaningful difference in breathlessness between people offered oxygen therapy at a dose greater than 2l/min compared to lower doses.

High quality evidence 5 RCTs reporting data from people with stable COPD found no meaningful difference in breathlessness between people offered oxygen therapy at a dose ≤ 2l/min compared to higher doses.

Health related quality of life

Low-quality evidence from 5 RCTs reporting data from 267 people with stable COPD who were mildly or non-hypoxaemic at rest could not differentiate health-related quality of life between people offered oxygen therapy compared to pressurised air.

Sensitivity analyses

Sensitivity analyses excluding all studies at high risk of bias did not meaningfully change the results compared to when all studies were included.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee agreed that the most relevant outcome for this review question was quality of life, with small improvements in breathlessness likely to be meaningful only if these subsequently led on to improvements in quality of life. It was agreed that since the review focused only on breathlessness in people who were mildly or non-hypoxaemic at rest, it was important to restrict the recommendations made to that population, and that the evidence reviewed would not be relevant to people being considered for ambulatory or short burst oxygen for other indications.

The quality of the evidence

The committee agreed that the evidence presented was from a high quality systematic review containing 44 randomised control trials. Some of the included studies were of low quality with very small sample sizes, however the meta-analyses incorporated over 800 participants, which increased the power and precision of the evidence.

The committee acknowledged that the effect of oxygen therapy on breathlessness was consistent between trials recruiting people with and without desaturation during exercise, studies with differing baseline mean arterial oxygen values, and studies using oxygen doses greater or less than 2 litres per minute. It was therefore not possible to identify specific subgroups of people in which ambulatory or short burst oxygen therapy are more effective.

Evidence of possible publication bias was identified in the studies included in the review; specifically that small, negative studies were less likely to have been published. The committee noted that if these studies had been published, it was likely the estimated effectiveness of ambulatory and short burst oxygen therapy would have been further reduced.

The committee agreed that overall the quality of evidence for the effect of oxygen compared with air on breathlessness was of moderate quality with some variation depending on the subgroup analysis. The consistency of the results across subgroup analysis added confidence to the results observed.

Benefits and harms

Based on the evidence, the committee agreed that ambulatory oxygen therapy is not indicated for the treatment of breathlessness of people who are mildly hypoxaemic or non-hypoxaemic at rest. The evidence from 28 RCTs showed that ambulatory oxygen given

during exercise or daily activities reduced breathlessness when compared to pressurised air, however the reduction was below a level that would be considered clinically meaningful. The committee considered the reduction on breathlessness on the modified Borg scale and noted the published minimal clinically important difference on that scale is 2 points. The evidence presented showed a mean improvement of 0.5, deemed too small to be meaningful to someone experiencing breathlessness, and this was supported by the fact that no improvements in quality of life were found in the studies. In addition, a large number of subgroup analyses were carried out to try to identify subgroups of people that might benefit from the therapy, but none of the subgroups showed an improvement in breathlessness either. As a result, the committee were confident in making a do not offer recommendation that was generalizable across the whole COPD population. The committee noted that although ambulatory oxygen therapy was not effective at managing breathlessness, it could be beneficial under other circumstances, such as during exercise in people with exercise desaturation, but this topic was outside of the scope of the evidence review.

The committee also amended a 2004 ambulatory oxygen recommendation to remove the term dyspnoea (breathlessness) as this was covered by the new recommendation. The rest of the old 2004 recommendation was out of scope of this evidence review.

The committee concluded that short burst oxygen therapy was not indicated for treatment of people who are mildly or non hypoxaemic at rest. Evidence from 4 RCTs, could not find a difference in breathlessness or quality of life between people who were offered short burst oxygen therapy and those offered pressurised air before exertion.

Cost effectiveness and resource use

No economic evidence was identified for this review question, and economic modelling was not prioritised. The committee noted there were costs attached to the provision of oxygen therapy. The evidence indicated that there would be no meaningful benefits arising from its use and agreed that the recommendations not to offer short-burst oxygen therapy or ambulatory oxygen therapy to manage breathlessness in people with COPD who are mildly or non-hypoxaemic at rest were likely to be cost saving.

Other factors the committee took into account

No other factors were discussed.

Long-term oxygen therapy

Review question

In which subgroups of people is long-term oxygen therapy indicated, and is it a clinically and cost effective option for managing stable COPD in these subgroups?

Introduction

The aim of this review question was to determine the subgroups of people in which long term oxygen therapy is indicated, and whether it represents an effective and cost-effective treatment option in those groups.

For the purposes of this question, long term oxygen therapy (LTOT) is defined as oxygen used for at least 15 hours per day. This definition was obtained from the British Thoracic Society Home Oxygen Guidelines (2015), and is based on the original MRC trial of long term oxygen therapy from the 1980s (which is included as part of this review). In UK clinical practice, this is usually delivered by an oxygen concentrator, a machine that draws oxygen from the air and concentrates it to deliver oxygen at higher concentrations to patients, thus reducing the need for oxygen cylinders.

This review identified studies that fulfilled the conditions specified in Table 3. For full details of the review protocol, see appendix A.

Table 3: PICO – Long-term oxygen therapy

Population	People diagnosed with COPD
Interventions	• Long-term oxygen therapy
Comparator	• No intervention • Optimal medical therapy
Outcomes	• Mortality (primary outcome) • Quality of life (primary outcome) • Rates of pulmonary hypertension and cor pulmonale • Exercise capacity/ tolerance • Hospital admissions and readmissions • Exacerbations • Gas transfer (carbon monoxide diffusion capacity and arterial oxygen partial pressure, PaO2) • Change in FEV1, rate of change in FEV1 • Symptoms (including breathlessness) • Adverse events – including trip risk from cables, burns • Resource use and costs

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A, and the methods section in appendix B.

The search strategies used in this review are detailed in appendix C.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

Clinical evidence

Included studies – Long-term oxygen therapy

A systematic literature search for randomised controlled trials (RCTs) and systematic reviews with no date limit identified 5,141 references. No date limit was used as the previous guideline recommendations were not based on a systematic literature search. Additional references were added from the old guideline (33) and the surveillance report (4) to give 5,178 references. Although priority screening was used for this review, all of the abstracts were screened on title and abstract and 43 papers were ordered as potentially relevant systematic reviews or RCTs based on the criteria in the review protocol. In particular, RCTs (including those from identified systematic reviews) were excluded if they did not meet the criteria of enrolling patients with COPD at baseline and did not have long term oxygen therapy (at least 15 hours per day) as an intervention.

Four papers were included after full text screening and all were RCTs. Summaries of the included studies are provided in Table 4.

A second search was conducted at the end of the guideline development process for all updated review questions, to capture papers published whilst the guideline was being developed. This search, which included articles up to February 2018, returned 3,100 references, which were screened on title and abstract. No additional relevant references were found for this review question.

The process of study identification is summarised in the diagram in appendix D.

For the full evidence tables and the full GRADE profiles please see appendix E and appendix G. The references of individual included studies are given in appendix K.

Excluded studies

Details of the studies excluded at full text are given in Appendix J

Summary of clinical studies included in the evidence review

See appendix E for full evidence tables. One of the studies provided evidence on adverse events that could not be analysed in GRADE profiles, and is therefore presented as evidence in appendix E (Table 12).

Table 4: Long-term oxygen therapy

Short Title	Interventions	Population	Outcomes
Albert (2016)	• Long term oxygen therapy - 24hrs/day *Patients were prescribed 24 hour oxygen if their resting SpO2 was 89 - 93% or moderate exercise induced desaturation (during the 6 minute walking test, SpO_2 ≥ 80% for ≥5minutes and <90% for 10 seconds) All patients had stationary and portable oxygen systems and 2 litres of oxygen per minute during sleep and/or at rest. Patients were to use oxygen regardless of increase in the SpO_2 level* • No long term oxygen therapy *Ambulatory dose of oxygen was individually prescribed and reassessed annually - 2 litres of oxygen per minute or adjusted higher to maintain an SpO_2 of 90% or more at least 2 minutes while the patient was walking no supplemental oxygen was to be used unless severe resting desaturation (SpO_2 ≤ 88%) or severe exercise induced desaturation (SpO_2<80% for >/= 1 minute) if either of these happened oxygen was prescribed and reassessed after 1 month*	Sample size 737 Split between study groups Long term oxygen therapy – 368 (220 participants were on 24hour oxygen and 148 were prescribed oxygen during exercise and sleep only) No long term oxygen therapy – 370 participants %female LTOT - 28% No LTOT - 25% Mean age (SD) - LTOT - 68.3+/- 7.5 No LTOT - 69.3+/- 7.4	• Death/Mortality • First readmission to hospital • Incidence of COPD exacerbation • Adherence to the supplemental oxygen • Development of severe resting desaturation • Development of severe exercise - induced desaturation • The distance walked in 6 minutes • St. George's Respiratory Questionnaire

Short Title	Interventions	Population	Outcomes
Gorecka (1996)	• Long term oxygen therapy (*received from an oxygen concentrator at a flow rate adjusted to raise resting PaO2 above 8.7kPa (65mmHg) prescribed for at least 17hrs/day and conventional therapy)* • No long term oxygen therapy *(Conventional treatment was given same as the intervention group)*	Sample size 135 participants Split between study groups *LTOT group - n=68 participants* *Control group - n= 67 participants* Loss to follow-up *No dropouts* %female *32 women (24%)* Mean age (SD) *61.2 years (40-79 years) no S.D* Current smokers *All participants declared to be non-smokers*	• Death/mortality
Medical Research Council working party (1981)	• Long term oxygen therapy at least 15hrs/day (*included sleeping hours, given via nasal prongs, at a flow rate of 2l/minute, or at a higher flow rate if this was necessary to achieve a PaO2>60mmHg. the delivery systems/cylinder varied across the patients.)* • No long term oxygen therapy (*other treatments were given under the direction of a clinician and it included - diuretics, antibiotics and digoxin)*	Sample size *87 patients* Split between study groups *Control group - 102 participants* *Intervention groups - 101 participants* %female *21.2%* *Mean age – 65.7 (no SD)*	• Death/Mortality • Rate of change - forced expiratory volume per second FEV1 • Rates of change - arterial oxygen tension PaO_2

Short Title	Interventions	Population	Outcomes

Nocturnal Oxygen Therapy Trial Group (1980)	• Long term oxygen therapy – (*Average oxygen use of 17.7h/day (SD=4.8hr/day) Oxygen was administered by nasal prongs at a measured flow rate of 1 to 4 l/min. Each patient received the lowest flow in whole litres per minute that demonstrably increased resting semi recumbent arterial pO_2 at least 6 mmHg and maintained resting arterial pO_2 of 60 to 80 mmHg dose was increased by 1l in periods of exercise or sleep oxygen delivery systems varied All patients also treated with oral theophylline and inhaled beta antagonist. Diuretics and antibiotics were used as indicated)*
	• Nocturnal oxygen therapy (*Oxygen therapy only during sleep - averaging 12h/day (SD=2.5hr/day) All patients were treated with oral theophylline and inhaled beta-2-agonists)*
		Sample size
		203 patients
		
		Split between study groups
		Control group - 102 participants
		Intervention groups -101 participants
		
		%female
		21.2%
		
		Mean age (SD)
		65.7years (no S.D)
			• Death/Mortality
			• Several subgroup analysis
			  ○ Comparison of PaO2 more/less than 55mmHg (7.3kPa)
			  ○ Comparison of PaCO2 more/less than 43 mmHg (5.7kPa)
			  ○ FEV1 more/less than 0.69l
			• Comparison of sleep, mean oxygen saturation less/greater than 85%

Quality assessment of clinical studies included in the evidence review

See appendix G for full GRADE tables.

Economic evidence

Included studies

A single search was conducted to cover all review question topics in this guideline update. This search returned 16,299 records, of which 16,295 were excluded on title and abstract. The remaining 4 papers were screened on full test and 2 were found to be relevant for this review question. No UK-based analyses were identified by the review, so inclusion criteria were broadened to allow studies with a non-NHS perspective.

Excluded studies

Details of the studies excluded at full text are given in Appendix J

Summary of studies included in the economic evidence review

Oba (2009) conducted an economic analysis of two different oxygen therapy programmes, long-term continuous (COT) and nocturnal (NOT), compared with no oxygen therapy in patients with COPD. The analysis considered 2 patient cohorts, 1 group with severe resting hypoxaemia who were simulated to receive COT or no therapy, and another with nocturnal desaturation who were simulated to receive either NOT or no therapy. A Markov model was run for 3 and 5 years for both interventions, with a third-party payer perspective on costs (US Medicare). Costs and benefits were discounted at 3% per annum. One-way and probabilistic sensitivity analyses were produced. The model describes 3 disease severity states as defined by FEV1 ranges: stage 1 = FEV1 >50% of predicted; stage 2 = FEV1 of 30–50% of predicted; stage 3 = FEV1 of <30% of predicted. Efficacy data were taken from a study using EQ-5D to measure the HRQoL associated with COPD severity (as measured using FEV1).The model includes an all-cause mortality state, but does not explicitly model COPD exacerbations because no trial evidence was available to suggest a reduction in exacerbation rates in patients who were receiving LTOT.

Table 5 and Table 6 give the base-case results of the incremental cost-effectiveness analyses. During the 3-year ($23,807 [~£16,700] per QALY) and 5-year ($16,124 [£11,300] per QALY) horizons, the ICER for COT in the severe resting hypoxaemia cohort was within commonly accepted thresholds for cost effectiveness in US studies (<$50,000 [~£35,100] per QALY). In the severe resting hypoxaemia cohort, multiple 1-way sensitivity analyses showed that all ICERs for COT were less than $25,000 (~£17,600) per QALY, and the probabilistic analysis showed a >95% probability that COT is associated with an ICER of $50,000 (£35,100)per QALY or better.

Table 5 Base-case cost-effectiveness results – Long-term continuous oxygen therapy compared with no oxygen therapy in people with severe resting hypoxaemia

Strategy	Absolute		Incremental		
	Costs ($)	QALYs	Costs ($)	Effects (QALYs)	ICER ($/QALY)
Three-year horizon					
Control	NR	1.56	-	-	-
Continuous oxygen therapy	NR	1.84	6,567	0.28	23,807 (~£16,700)
Five-year horizon					
Control	NR	2.07	-	-	-
Continuous oxygen therapy	NR	2.66	9,517	0.59	16,124 (~£11,300)

ICER = incremental cost-effectiveness ratio; NR = not reported; QALY = quality-adjusted life-year.

Table 6 Base-case cost-effectiveness results – nocturnal oxygen therapy compared with no oxygen therapy in people with nocturnal desaturation

Strategy	Absolute		Incremental		
	Costs ($)	QALYs	Costs ($)	Effects (QALYs)	ICER ($/QALY)
Three-year horizon					
Control	NR	1.87	-	-	-
Nocturnal oxygen therapy	NR	1.88	5,975	0.0125	477,929 (~£335,800)
Five-year horizon					
Control	NR	2.68	-	-	-
Nocturnal oxygen therapy	NR	2.70	8,615	0.0281	306,356 (~£215,200)

ICER = incremental cost-effectiveness ratio; NR = not reported; QALY = quality-adjusted life-year.

In contrast, the ICER for NOT in the nocturnal desaturation cohort was $477,929 (~£355,800) per QALY during a 3-year horizon and $306,356 (~£215,200) per QALY during a 5-year horizon. Results varied widely when the quarterly rate of death with NOT was varied in 1-way sensitivity analysis. Quantitative results of the probabilistic sensitivity analysis are not reported but, from the cost–utility scatter-plot provided, the probability that NOT is associated with an ICER of $50,000 (~£35,100) per QALY or better appears to be less than 10% at a 3-year time-horizon and less than 25% at the 5-year analysis.

This study was associated with a number of limitations. Firstly, HRQoL scores used were based on FEV1 states for patients with COPD, rather than focussing specifically on patients with hypoxaemia. Secondly, a number of aspects of the methodology are omitted; no cost for the control group is given, usual care is not defined, and distributions for the probabilistic sensitivity analysis are not provided. Finally, there is no grading of evidence of systematic reviews of costs and benefits used to inform the model. The study was classified as being partially applicable, as it was conducted from a non-NHS perspective.

Chandra (2012) conducted a cost-utility analysis of a number of interventions for COPD, of which one was long-term oxygen therapy (LTOT) delivered in an outpatient setting for around 15 hours per day compared to usual care in patients with severe hypoxaemia. The evaluation was conducted from the perspective of the Canadian healthcare system, and used a lifetime time horizon. The authors used a Markov model to simulate patients' progression through four states of severity based on the GOLD classification system. For each annual cycle of the model, patients experienced a number of mild and severe exacerbations, according to their disease severity. The assumption was made that severe hypoxaemia is equivalent to the 'very severe COPD' GOLD state, and so all patients started in this state.

Data on baseline utility for patients in each health state were taken from a previous study of QoL in patients with a variety of COPD disease stages using visual analogue scale and time trade-off methods. Disutilities associated with moderate and severe exacerbations were applied to these as appropriate.

Patients' baseline mortality was assumed to be 3.3 times that of the general population, based on a previous observational study of standardised mortality rates in people with COPD. For patients in the LTOT arm a relative risk for mortality was applied to this value, estimated using data from previous a 'mega-analysis' of chronic disease management conducted in Canada.

An annual cost of CAD $2,261 (~£1,260) for LTOT was used, based on healthcare system data. The model also included annual maintenance costs of COPD and costs per minor and major exacerbation, based on costs from previous economic analyses. However, since the model makes the assumption that LTOT only affects mortality, these costs do not differ between arms for living patients.

Base case results showed that LTOT has an ICER of CAD $38,993 (~£21,700) per QALY compared to usual care. Probabilistic sensitivity analysis indicated that LTOT is associated with a 71% probability of being cost effective at a threshold of CAD $50,000 (~£27,900) QALY.

This evaluation was classified as being partially applicable as it is not conducted from the perspective of the NHS and uses a discount rate of 5% for costs and health benefits. It was categorised as having potentially serious limitations. This was due to the assumption that patients with severe hypoxaemia are identical to those with very severe COPD according to the GOLD staging system. Furthermore, the analysis is potentially simplistic in some aspects – the assumption is made that LTOT only affects mortality, and that, other than the cost of intervention, treatment costs for living patients remain identical between arms.

Economic model

This topic was not prioritised for health economic modelling and no original analyses were produced.

Evidence statements

The format of the evidence statements is explained in the methods in appendix B.

Long term oxygen therapy vs no long term oxygen therapy

People with COPD and moderate resting or exercise-induced desaturation

Mortality

Low quality evidence from 1 RCT reporting data from 738 people with COPD and moderate resting or exercise-induced desaturation (SpO_2 89-93% - approximately 7.5kPa – 9.2kPa) could not differentiate mortality rates between people offered long term oxygen therapy compared to no long term oxygen therapy.

Mortality - subgroup analysis

Moderate quality evidence from 1 RCT reporting data from up to 289 people with COPD and moderate resting or exercise-induced desaturation (SpO_2 89-93% - approximately 7.5kPa – 9.2kPa) found reductions in mortality rates in people offered long term oxygen therapy who were aged 71 or over, and in people with a COPD exacerbation in the 3 months prior to the study enrolment, compared to people in the same groups who were not offered long term oxygen therapy.

Low quality evidence from 1 RCT reporting data from 618 people with COPD and moderate resting or exercise-induced desaturation (SpO_2 89-93% - approximately 7.5kPa – 9.2kPa) could not differentiate mortality rates between people offered long term oxygen therapy compared to people not offered long term oxygen therapy in a range of subgroups based on: treatment during sleep and exercise; the number of hours of long term oxygen therapy used per day; desaturation qualifying for long term oxygen therapy at rest or during exercise or under both circumstances; age < 71 years; race; sex; smoking status; levels of FEV1 % predicted; body mass index; minimum oxygen saturations during 6 minute walking test; no COPD exacerbations in the 3 months prior to enrolment or history of anaemia.

Other outcomes

Very low to low quality evidence from 1 RCT reporting data from up to 738 people with COPD and moderate resting or exercise-induced desaturation (SpO_2 89-93% - approximately 7.5kPa – 9.2kPa) could not differentiate quality of life, rates of hospitalisations, room air oxygen saturation levels, room air 6 minute walking distance, post bronchodilator forced expiratory volume or partial arterial oxygen values between people offered long term oxygen therapy compared to no long term oxygen therapy.

Low quality evidence from 1 RCT reporting data from up to 738 people with COPD and moderate resting or exercise-induced desaturation (SpO2 89-93% - approximately 7.5kPa – 9.2kPa) found no meaningful difference between the risk of having an exacerbation between people offered long term oxygen therapy compared to no long term oxygen therapy.

People with COPD and mild hypoxaemia

Mortality

Low quality evidence from 1 RCT reporting data from 135 people with COPD and mild hypoxaemia (arterial oxygen tension (PaO_2) between 56 and 65 mmHg (7.4kPa to 8.7 kPa) could not differentiate the risk of mortality between people offered long term oxygen therapy compared to no long term oxygen therapy.

People with COPD and cor pulmonale

Low quality evidence from 1 RCT reporting data from 59 people with COPD and cor pulmonale where arterial oxygen tensions is between 40 and 60mmHg (5.3kPa to 8kPa) found improvements in partial pressure of arterial oxygen at 3 years follow-up in people offered long term oxygen therapy compared to no long term oxygen therapy.

Very low quality evidence from 1 RCT reporting data from up to 87 people with COPD and cor pulmonale where arterial oxygen tensions is between 40 and 60mmHg (5.3kPa to 8kPa) could not differentiate the rate of change in FEV1 or mortality at 3 years follow-up between people offered long term oxygen therapy compared to no long term oxygen therapy.

Health economic evidence

One partially applicable study with very serious limitations (Oba 2009) suggests that continuous oxygen therapy is cost effective for patients with severe resting hypoxaemia. The same study suggests that, in patients with nocturnal decompensation, the use of nocturnal oxygen is unlikely to be cost effective unless mortality rates are low and the therapy is used over a period of at least 5 years.

One partially applicable study with potentially serious limitations (Chandra 2012) suggests that long-term oxygen therapy delivered in an outpatient setting for around 15 hours a day is potentially cost effective, with an ICER of CAD $38,993 (~£21,700) per QALY. However, there is considerable uncertainty surrounding this finding.

Continuous oxygen therapy vs nocturnal oxygen therapy

People with COPD and moderate to severe hypoxaemia

Moderate quality evidence from 1 RCT reporting data from 203 people with moderate to severe hypoxaemia found a reduced risk of mortality in people with COPD and moderate to severe hypoxaemia (PaO2 of ≤ 55 mmHg (7.3kPa)) offered long term oxygen therapy compared to nocturnal oxygen therapy. This improvement was also observed in moderate quality evidence from subgroups with a baseline mean arterial oxygen ≥ 52 mmHg (6.9 kPa), mean oxygen saturations < 85%, mean pulmonary arterial pressure < 27mmHg (3.6 kPa) and mean arterial carbon dioxide ≥ 43mmHg (5.7 kPa).

Low quality evidence from 1 RCT reporting data from 203 people with moderate to severe hypoxaemia could not differentiate the risk of mortality in people with COPD in the following subgroups: PaO_2 <52 mmHg; FEV1 <0.69L or ≥ 0.69L; mean SaO2 ≥ 85%; mean pulmonary artery pressure ≥27mmHg (3.6kPa) or $PaCO_2$ < 43 mmHg (5.7 kPa).

The committee's discussion of the evidence

Interpreting the evidence – Long term oxygen therapy

The outcomes that matter most

The committee agreed that the critical outcomes for this review were quality of life, mortality and adverse events. Adverse events were defined as any harm incurred as a result of using long term oxygen therapy (including fires, burns, trips and falls). The committee noted that some of the outcomes reported in older studies, such as "the rate of change in arterial

oxygen" as reported in the MRC working group study (1981), were hard to relate to patient experience and therefore difficult to interpret.

The quality of the evidence

The committee agreed that all four studies included were at risk of bias due to lack of blinding of participants and/or investigators. There were variations in the severity of COPD in the included studies and the actual hours spent on oxygen use as all the studies relied on self-reported accounts. The committee was also concerned about the validity of the MRC (1981) and the NOTT (1980) studies as they were carried out over thirty years ago and medical practice has changed considerably since then. However, they acknowledged that this is the best available evidence on long term oxygen therapy in people with moderate to severe hypoxaemia.

The committee agreed that data from the USA (Albert 2016) provided useful evidence on long term oxygen therapy in a modern context. However, it only included people with mild to moderate hypoxaemia. There were concerns about the study design as some people in the control group used oxygen for ambulatory purposes, the lack of blinding could have potentially influenced the participant self-reported outcomes, and adherence to oxygen was self-reported by the participants.

Overall the available evidence was of very low to moderate quality and was drawn from 4 randomised control studies with varying baseline populations in terms of disease severity and administration of long term oxygen therapy. Due to these differences, the committee agreed that it was not appropriate to carry out any meta-analysis and consider each study results in isolation and within context of its baseline population. The committee also agreed that the low quality of the evidence meant that weaker recommendations would need to be made for the use of long term oxygen therapy.

Benefits and harms

Based on the evidence, the committee agreed that continuous long term oxygen therapy can reduce mortality in people with moderate to severe hypoxaemia compared to nocturnal oxygen therapy (NOTT 1980). They noted that this benefit might be even larger if continuous long term oxygen therapy was compared to no oxygen therapy. They concluded that long term oxygen therapy should be considered in those with arterial oxygen pressure of less than 7.3 kPa when stable or arterial oxygen pressure greater than 7.3 and less than 8 kPa when stable and either secondary polycythaemia, peripheral oedema or pulmonary hypertension are present, based on the inclusion criteria for this study.

However, they noted that there is a need for clear risk assessments in those being considered for this therapy, in order to reduce the risk of harms both to the individual and those residing in the same household. The committee's main concern was the increased risk of fires as a result of smoking whilst using oxygen or open flames near the oxygen flames, and risks of tripping over the equipment. The data on the adverse effects of using LTOT presented in the Albert study (2016, please see Table 12 in this evidence review) supports the committee's concerns. 368 people were treated with long term oxygen therapy and there were a total of 51 adverse events attributed to using oxygen therapy. Twenty three reports of people tripping over equipment were made with 2 people requiring hospitalisation. Five people reported 6 cases of fires or burns and 1 of these cases required hospitalisation.

Based on this evidence, the committee agreed on the need for a thorough risk assessment for anyone being considered for oxygen therapy. The committee noted that the increased risk

of fires or burns was not confined to the person with COPD and the assessment should include consideration of the risks for people living with the person on LTOT. The committee were also concerned about the risk posed by others, and agreed it was important to consider whether anyone within the household smokes, not just the person with COPD. They also noted that the risk of fires was not confined to cigarettes and pipes, but that other electronic devices (such as e-cigarettes) could potentially also produce sparks and lead to fires or burns in the presence of oxygen. The committee acknowledged that there were other factors, such as the use of paraffin-based creams, which could pose an additional fire risk to people using oxygen therapy, but agreed that this would be incorporated as part of the risk assessment,

The committee agreed that as per current practice in the NHS, the risk assessment was likely to be performed by the oxygen supplier in conjunction with an oxygen assessment team and that this assessment may also involve a representative from the local fire service. They noted that the BTS oxygen guideline (pages i25-26, 2015) provided information on who should perform the assessment, how to perform the assessment and at what interval. They also noted that the IHORM form summarises the initial risk assessment and that regular follow up is important. This is likely to happen every few months initially, then every 6 months to a year if the person is stable. The committee also noted that the risks for people with COPD (and the people they live with) may change over time, for example, if an ex-smoker with COPD relapses or a smoker with COPD quits and that it is appropriate for the risk assessment to be carried out again under these circumstances.

Based on a discussion about the balance the risks and benefits posed by LTOT to people with COPD and their families, the committee made separate recommendations concerning the use of LTOT for people with COPD who do not smoke, but live with smokers, and for those groups of people with COPD who are current smokers. For the first group of people with COPD, the committee agreed that the presence of smokers in the household still constituted a fire risk, but that this could be potentially mitigated by awareness of the risks. They decided that for these people with COPD and their families the benefits of LTOT could outweigh the risks and as a result, these people with COPD should have access to LTOT if they meet the criteria for this treatment and the results of the structured risk assessment are favourable. However, in an attempt to reduce the fire risk still further, the committee also included a reference to NICE guidance on smoking cessation in another recommendation to ensure that smokers who live in the same household as people with COPD who are being considered for LTOT are offered services to help them quit smoking.

For people with COPD who are still smoking and meet the criteria for LTOT, the committee emphasised the need to explore smoking cessation options to treat tobacco dependency to reduce the risk of fires and burns. They agreed that smoking cessation has been shown to be a highly cost-effective intervention, and does not have the same risks of harm as long term oxygen therapy. However, if the person with COPD is unable or unwilling to stop smoking, the committee decided that it was too dangerous for them and their families to allow them to access to LTOT. They made a do not offer recommendation to reflect the elevated risk of fires caused by people on LTOT who smoke. This recommendation was designed to protect smokers from the risk of injuries that were reported in the literature (Albert, 2016) and was not a result of any evidence suggesting that people who smoke do not benefit from oxygen use. The committee agreed that it is important that clinicians explain fully to patients that the reasons for not prescribing LTOT to people who are still smoking are based solely on the risks to safety of the patients and other household members. The risk of fires in this situation was considered to be far greater than for people on LTOT who do not

smoke, but have family members who smoke, as the oxygen and source of a spark or flame are in much closer proximity in this case.

As the Albert and Gorecka studies did not find mortality benefits from using long term oxygen therapy in populations with less severe hypoxaemia, the committee agreed it would not be appropriate to extend the criteria for long term oxygen therapy to this more severe population. They also noted that, although benefits were seen in a small number of subgroups in that study, results were presented for a sufficiently large number of negative subgroups as well, and therefore they could not be confident these subgroup results represented a real effect.

The committee agreed that to observe benefits, long term oxygen therapy should be administered for at least 15 hours. This was based on the NOTT study (1980) which provided evidence that oxygen therapy for at least 15 hours in people with moderate to severe hypoxaemia reduced the number of deaths when compared to those receiving oxygen therapy just at night. In addition, the committee concluded that long term oxygen therapy should therefore not be offered for treatment of overnight hypoxaemia in the absence of other symptoms. They also considered evidence from the economic review that showed that this oxygen therapy at night did not improve quality of life and did not provide an acceptable balance between benefit and cost.

Cost effectiveness and resource use

The committee agreed that there were very serious limitations to the economic evidence identified, in particular a lack of clarity in the reporting, and the non-systematic way many of the parameters in the model were obtained. However, the committee agreed the results of the paper did support their conclusions that long-term oxygen therapy can be a cost-effective treatment for people with moderate to severe hypoxaemia, and that nocturnal oxygen therapy is unlikely to be a cost-effective alternative.

The committee noted that it is still the case that not all people with COPD who continue to smoke are offered appropriate smoking cessation interventions, which are likely to be the most effective way to improve their COPD. They agreed there might be an additional cost to fully rolling out these services to all people with COPD that smoke, but also agreed that by implementing the cost-effective smoking cessation interventions recommended in the NICE guideline on smoking cessation, this should represent an effective use of NHS resources.

Other factors the committee took into account

The committee discussed potential equalities issues surrounding smoking status. In particular, they noted that smoking status is correlated with low socioeconomic status, and is a factor that is both amenable to change and of particular importance for COPD disease management and progression. They noted that it was inappropriate to make different recommendations for people with COPD treatment based on their smoking status, unless the treatment was less effective for smokers or posed an increased risk to them that outweighed the potential benefits. In this particular review, the committee agreed it was appropriate to make separate recommendations for the use of long term oxygen therapy in smokers and non-smokers, based on the evidence of the elevated risks of fires and burns in people who smoke and their households.

The evidence on long term oxygen for people with COPD and cor pulmonale was also considered in the evidence review on the management of pulmonary hypertension and cor

pulmonale. Recommendations on the management of cor pulmonale are reported in that evidence review.

Appendices

Appendix A – Review protocols

Review protocol for ambulatory and short burst oxygen therapy

Field (based on PRISMA-P)	Content
Review question	What is the effectiveness of oxygen therapy in people with stable COPD who are mildly hypoxaemic or non-hypoxaemic at rest?
Type of review question	Intervention
Objective of the review	To determine whether ambulatory or short burst oxygen therapy are effective at reducing breathlessness and improving quality of life in people with stable COPD who are mildly hypoxaemic or non-hypoxaemic at rest, and do not meet the criteria for long term oxygen therapy.
Eligibility criteria – population	People diagnosed with COPD who are not eligible for long term oxygen therapy.
Eligibility criteria – interventions	• Ambulatory oxygen therapy • Short burst oxygen given before exertion
Eligibility criteria – comparators	• Pressurised air
Outcomes	• Breathlessness • Quality of life • Resource use and costs
Eligibility criteria – study design	• RCTs
Other exclusion criteria	• Short burst oxygen given after exertion • Trials with a follow-up of less than 12 weeks
Proposed sensitivity/sub-group analysis, or meta-regression	Subgroups: • Ambulatory vs short burst oxygen • Level of exertional desaturation • Baseline PaO_2 • Measurement during exertion • Short term vs long term effects

	• Oxygen dose Subgroup analyses will only be conducted if the majority of trials report data for the listed categories in an accessible format.
Selection process – duplicate screening/selection/analysis	The data for this review was obtained from a published Cochrane Review (Ekstrom 2016). The searches conducted for this review were then updated to match the timeline of the other searches conducted for this guideline.
Data management (software)	See Appendix B
Information sources – databases and dates	See Appendix C The searches were undertaken by the Cochrane Airways Group (Ekstrom 2016) using the following databases: Cochrane Airways Group Specialised Register (CAGR): • CENTRAL • MEDLINE (Ovid) • EMBASE (Ovid) • CINAHL (EBSCO) • PSYCINFO (Ovid) • AMED (EBSCO) • Clinicaltrial.gov • World Health Organization (WHO) trials portal • Handsearching of respiratory journals and meeting abstracts All databases were searched from their inception to 12th July 2016. Update searches to 15th June 2017 are covered by the NICE searches for *'In which subgroups of people is long-term oxygen therapy indicated, and is it a clinically and cost effective option for managing stable COPD in these subgroups?'* NICE economic search: • NHS Economic Evaluation Database – NHS EED (Wiley)

	• Health Economic Evaluations Database – HEED (Wiley) • EconLit (Ovid) • Embase (Ovid) • MEDLINE (Ovid) • MEDLINE In-Process (Ovid) The economics search will cover all questions and will be date limited from the previous search January 2009-May 2017
Identify if an update	Update of 2004 COPD guideline question: What is the role of oxygen therapy in patients with stable COPD?
Author contacts	Guideline update
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy – for one database	See Ekstrom 2016
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix E (clinical evidence tables) or I (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix E (clinical evidence tables) or I (economic evidence tables).
Methods for assessing bias at outcome/study level	See Appendix B
Criteria for quantitative synthesis	See Appendix B
Methods for quantitative analysis – combining studies and exploring (in)consistency	See Appendix B
Meta-bias assessment – publication bias, selective reporting bias	See Appendix B
Confidence in cumulative evidence	See Appendix B

Rationale/context – what is known	For details please see the introduction to the evidence review in the main file.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the NICE Guideline Updates Team and chaired by Damien Longson (until September 2017) and Andrew Molyneux (from September 2017) in line with section 3 of Developing NICE guidelines: the manual. Staff from the NICE Guideline Updates Team undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
Sources of funding/support	The NICE Guideline Updates Team is an internal team within NICE.
Name of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
Roles of sponsor	The NICE Guideline Updates Team is an internal team within NICE.

Review protocol for long term oxygen therapy

Field (based on PRISMA-P)	Content
Review question	In which subgroups of people is long-term oxygen therapy indicated, and is it a clinically and cost effective option for managing stable COPD in these subgroups?
Type of review question	Intervention
Objective of the review	To determine the effectiveness of long-term oxygen therapy for people with stable COPD, and to identify which subgroups of people benefit from treatment
Eligibility criteria – population	People diagnosed with COPD (by any means including Global Strategy for the Diagnosis,

	Management and Prevention of COPD, GOLD, guideline; American Thoracic Society criteria for COPD; European Respiratory Society criteria)
Eligibility criteria – interventions	• Long term oxygen therapy (at least 15 hrs/day)
Eligibility criteria – comparators	• No intervention • Routine medical therapy • Placebo
Outcomes	• Mortality • Exacerbations • Hospital admissions, re-admissions and bed days • Symptoms including breathlessness (e.g. Borg dyspnoea score, Modified MRC scale for dyspnoea) and orthopnoea • Pulmonary hypertension and cor pulmonale • Gas transfer (carbon monoxide diffusion capacity and arterial oxygen partial pressure, PaO2) • Exercise capacity/ exercise tolerance (e.g. 6 minute walking distance, 6MWD, treadmill test and the shuttle walk test) • Change in FEV1, rate of change in FEV1 • Adverse events: all, severe, treatment discontinuation (including trip risk from cables, burns) • Quality of life (e.g. St. George's respiratory questionnaire, SGRQ, overall score) • Resource use and costs
Eligibility criteria – study design	• RCTs • Systematic reviews of RCTs
Other exclusion criteria	• Trials with a follow-up of less than 12 weeks • Non-English language publications
Proposed sensitivity/sub-group analysis, or meta-regression	Subgroups:

	• Smoking status (smokers versus non-smokers or, data permitting, never smoked, ex-smokers and current smokers).
	• Multimorbidities (including COPD with asthma, bronchopulmonary dysplasia, bronchiectasis, anxiety or depression)
	• Partial pressure of oxygen dissolved in arterial blood (PaO2):
	  ○ mild hypoxaemia (arterial oxygen tension (PaO2) between 56 and 65 mmHg (7.4kPa to 8.7 kPa)
	  ○ mild to moderate (PaO2 between 40 and 60mmHg (5.3kPa to 8kPa))
	  ○ moderate resting or exercise-induced desaturation (SpO2 89-93% - approximately 7.5kPa – 9.2kPa
	  ○ moderate to severe hypoxaemia (PaO2 of ≤ 55 mmHg (7.3kPa)
	• Secondary polycythaemia
	• Nocturnal hypoxaemia (oxygen saturation of arterial blood (SaO2) < 90% for > 30% of the time)
	• Peripheral oedema
	• Pulmonary hypertension and cor pulmonale
	• Trials that recruited patients with at least one COPD exacerbation in the 12 months before study entry
	
	Subgroup analyses will only be conducted if the majority of trials report data for the listed categories in an accessible format.

Selection process – duplicate screening/selection/analysis	10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. If meaningful disagreements were found between the different reviewers, a further 10% of the abstracts were reviewed by two reviewers, with this process continued until agreement is achieved between the two reviewers. From this point, the remaining abstracts will be screened by a single reviewer.

	This review made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. See Appendix B for more details.
Data management (software)	See Appendix B
Information sources – databases and dates	See Appendix C Main Searches: • Cochrane Database of Systematic Reviews – CDSR (Wiley) • Cochrane Central Register of Controlled Trials – CENTRAL (Wiley) • Database of Abstracts of Reviews of Effects – DARE (Wiley) • Health Technology Assessment Database – HTA (Wiley) • EMBASE (Ovid) • MEDLINE (Ovid) • MEDLINE In-Process (Ovid) • PubMed The search will not be date limited as the previous guideline recommendations were not based on a systematic literature search. Economics: • NHS Economic Evaluation Database – NHS EED (Wiley) • Health Economic Evaluations Database – HEED (Wiley) • EconLit (Ovid) • Embase (Ovid) • MEDLINE (Ovid) • MEDLINE In-Process (Ovid) The economics search will cover all questions and will be date limited from the previous search January 2009-May 2017.
Identify if an update	Update of 2004 COPD guideline question:

	What is the role of oxygen therapy in patients with stable COPD?
Author contacts	Guideline update
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy – for one database	For details please see appendix C
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix E (clinical evidence tables) or I (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix E (clinical evidence tables) or I (economic evidence tables).
Methods for assessing bias at outcome/study level	See Appendix B
Criteria for quantitative synthesis	See Appendix B
Methods for quantitative analysis – combining studies and exploring (in)consistency	See Appendix B
Meta-bias assessment – publication bias, selective reporting bias	See Appendix B
Confidence in cumulative evidence	See Appendix B
Rationale/context – what is known	For details please see the introduction to the evidence review in the main file.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the NICE Guideline Updates Team and chaired by Damien Longson (until September 2017) and Andrew Molyneux (from September 201) in line with section 3 of Developing NICE guidelines: the manual.

	Staff from the NICE Guideline Updates Team undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
Sources of funding/support	The NICE Guideline Updates Team is an internal team within NICE.
Name of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
Roles of sponsor	The NICE Guideline Updates Team is an internal team within NICE.

Appendix B – Methods

Priority screening

The reviews undertaken for this guideline all made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. This uses a machine learning algorithm (specifically, an SGD classifier) to take information on features (1, 2 and 3 word blocks) in the titles and abstract of papers marked as being 'includes' or 'excludes' during the title and abstract screening process, and re-orders the remaining records from most likely to least likely to be an include, based on that algorithm. This re-ordering of the remaining records occurs every time 25 additional records have been screened.

Research is currently ongoing as to what are the appropriate thresholds where reviewing of abstract can be stopped, assuming a defined threshold for the proportion of relevant papers it is acceptable to miss on primary screening. As a conservative approach until that research has been completed, the following rules were adopted during the production of this guideline:

- In every review, at least 50% of the identified abstract (or 1,000 records, if that is a greater number) were always screened.
- After this point, screening was only terminated if a pre-specified threshold was met for a number of abstracts being screened without a single new include being identified. This threshold was set according to the expected proportion of includes in the review (with reviews with a lower proportion of includes needing a higher number of papers without an identified study to justify termination), and was always a minimum of 250.

As an additional check to ensure this approach did not miss relevant studies, the included studies lists of included systematic reviews were searched to identify any papers not identified through the primary search.

Incorporating published systematic reviews

For all review questions where a literature search was undertaken looking for a particular study design, systematic reviews containing studies of that design were also included. All included studies from those systematic reviews were screened to identify any additional relevant primary studies not found as part of the initial search.

Quality assessment

Individual systematic reviews were quality assessed using the ROBIS tool, with each classified into one of the following three groups:

- High quality – It is unlikely that additional relevant and important data would be identified from primary studies compared to that reported in the review, and unlikely that any relevant and important studies have been missed by the review.
- Moderate quality – It is possible that additional relevant and important data would be identified from primary studies compared to that reported in the review, but unlikely that any relevant and important studies have been missed by the review.
- Low quality – It is possible that relevant and important studies have been missed by the review.

Each individual systematic review was also classified into one of three groups for its applicability as a source of data, based on how closely the review matches the specified review protocol in the guideline. Studies were rated as follows:

- Fully applicable – The identified review fully covers the review protocol in the guideline.
- Partially applicable – The identified review fully covers a discrete subsection of the review protocol in the guideline.
- Not applicable – The identified review, despite including studies relevant to the review question, does not fully cover any discrete subsection of the review protocol in the guideline.

Using systematic reviews as a source of data

If systematic reviews were identified as being sufficiently applicable and high quality, they were used as the primary source of data, rather than extracting information from primary studies. The extent to which this was done depended on the quality and applicability of the review, as defined in Table 7. When systematic reviews were used as a source of primary data, any unpublished or additional data included in the review which is not in the primary studies was also included. Data from these systematic reviews was then quality assessed and presented in GRADE/CERQual tables as described below, in the same way as if data had been extracted from primary studies. In questions where data was extracted from both systematic reviews and primary studies, these were cross-referenced to ensure none of the data had been double counted through this process.

Table 7: Criteria for using systematic reviews as a source of data

Quality	Applicability	Use of systematic review
High	Fully applicable	Data from the published systematic review were used instead of undertaking a new literature search or data analysis. Searches were only done to cover the period of time since the search date of the review.
High	Partially applicable	Data from the published systematic review were used instead of undertaking a new literature search and data analysis for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. For other sections not covered by the systematic review, searches were undertaken as normal.
Moderate	Fully applicable	Details of included studies were used instead of undertaking a new literature search. Full-text papers of included studies were still retrieved for the purposes of data analysis. Searches were only done to cover the period of time since the search date of the review.
Moderate	Partially applicable	Details of included studies were used instead of undertaking a new literature search for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. For other sections not covered by the systematic review, searches were undertaken as normal.

Evidence synthesis and meta-analyses

Where possible, meta-analyses were conducted to combine the results of studies for each outcome. For mean differences, where change from baseline data were reported in the trials and were accompanied by a measure of spread (for example standard deviation), these were extracted and used in the meta-analysis. Where measures of spread for change from baseline values were not reported, the corresponding values at study end were used and were combined with change from baseline values to produce summary estimates of effect. All studies were assessed to ensure that baseline values were balanced across the treatment groups; if there were significant differences in important confounding variables at baseline these studies were not included in any meta-analysis and were reported separately.

Evidence of effectiveness of interventions

Quality assessment

Individual RCTs and quasi-randomised controlled trials were quality assessed using the Cochrane Risk of Bias Tool. Cohort studies were quality assessed using the CASP cohort study checklist. Each individual study was classified into one of the following three groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, intervention, comparator and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.
- Partially indirect – Important deviations from the protocol in one of the population, intervention, comparator and/or outcomes.
- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

Methods for combining intervention evidence

Meta-analyses of interventional data were conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011).

Where different studies presented continuous data measuring the same outcome but using different numerical scales (e.g. a 0-10 and a 0-100 visual analogue scale), these outcomes were all converted to the same scale before meta-analysis was conducted on the mean differences. Where outcomes measured the same underlying construct but used different instruments/metrics, data were analysed using standardised mean differences (Hedges' g).

A pooled relative risk was calculated for dichotomous outcomes (using the Mantel–Haenszel method). Both relative and absolute risks were presented, with absolute risks calculated by

applying the relative risk to the pooled risk in the comparator arm of the meta-analysis (all pooled trials). If hazard ratios and relative risks could both be calculated for a given outcome, hazard ratios were used as the preferred outcome for assessing the quality of the evidence.

Fixed- and random-effects models (der Simonian and Laird) were fitted for all syntheses, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models were the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model were clearly not met, even after appropriate pre-specified subgroup analyses were conducted, random-effects results are presented. Fixed-effects models were deemed to be inappropriate if one or both of the following conditions was met:

- Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. This decision was made and recorded before any data analysis was undertaken.
- The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$.

In any meta-analyses where some (but not all) of the data came from studies at high risk of bias, a sensitivity analysis was conducted, excluding those studies from the analysis. Results from both the full and restricted meta-analyses are reported. Similarly, in any meta-analyses where some (but not all) of the data came from indirect studies, a sensitivity analysis was conducted, excluding those studies from the analysis.

In situations where subgroup analyses were conducted, pooled results and results for the individual subgroups are reported when there was evidence of between group heterogeneity, defined as a statistically significant test for subgroup interactions (at the 95% confidence level). Where no such evidence as identified, only pooled results are presented.

Meta-analyses were performed in Cochrane Review Manager v5.3.

Minimal clinically important differences (MIDs)

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline. Identified MIDs were assessed to ensure they had been developed and validated in a methodologically rigorous way, and were applicable to the populations, interventions and outcomes specified in this guideline. In addition, the Guideline Committee were asked to prospectively specify any outcomes where they felt a consensus MID could be defined from their experience. In particular, any questions looking to evaluate non-inferiority (that one treatment is not meaningfully worse than another) required an MID to be defined to act as a non-inferiority margin.

MIDs found through this process and used to assess imprecision in the guideline are given in Table 8. For other mean differences where no MID is given below the line of no effect is used.

Table 8: Identified MIDs

Outcome	MID	Source
Borg dyspnoea (breathlessness) score	2 units (-2, +2)	Ries AL. Minimally clinically important difference for the UCSD shortness of breath questionnaire, Borg

Outcome	MID	Source
		Scale, and Visual Analog Scale. J COPD 2005; 2: 105–110.
6 minute walk distance	26m (-26, +26)	Puhan MA, Chandra D, Mosenifar Z, et al. The minimal important difference of exercise tests in severe COPD. Eur Respir J (2011); 37: 784–790.
Total score in St. George's respiratory questionnaire	4 points (-4,+4)	Schünemann HJ, Griffith L, Jaeschke R, et al. Evaluation of the minimal important difference for the feeling thermometer and the St. George's Respiratory Questionnaire in patients with chronic airflow obstruction. J Clin Epidemiol (2003); 56: 1170–1176.
Change in FEV1	100ml (or 0.1L) (-100ml, 100ml)	Cazzola M, MacNee W, Martinez M et al. Outcomes for COPD pharmacological trials: from lung function to biomarkers. Eur Respir J 2008; 31: 416–468.

For standardised mean differences where no other MID was available, an MID of 0.2 was used, corresponding to the threshold for a small effect size initially suggested by Cohen et al. (1988).

For breathlessness, the pooled mean difference was converted back to the Modified Borg scale to allow for meaningful interpretation of the results. This was done by multiplying the calculated standardised mean difference by the pooled standard deviation of all the studies using the Borg scale (estimated standard deviation of 1.385). The resulting mean difference was then used to rate imprecision using the MIDs stated in Table 8 above.

The committee specified that any difference in mortality would be clinically meaningful, and therefore the line of no effect was used as an MID. In this case, a 95% CI boundary of 1.00 for RR, OR and HR is taken as crossing the line of no effect.

For relative risks where no other MID was available, the GRADE default MID interval for dichotomous outcomes of 0.8 to 1.25 was used. The line of no effect was specified as an MID for hazard ratios.

When decisions were made in situations where MIDs were not available, the 'Evidence to Recommendations' section of that review should make explicit the committee's view of the expected clinical importance and relevance of the findings.

GRADE for pairwise meta-analyses of interventional evidence

GRADE was used to assess the quality of evidence for the selected outcomes as specified in 'Developing NICE guidelines: the manual (2014)'. Data from RCTs was initially rated as high quality and the quality of the evidence for each outcome was downgraded or not from this initial point. If non-RCT evidence was included for intervention-type systematic reviews then these were initially rated as either moderate quality (quasi-randomised studies) or low quality (cohort studies) and the quality of the evidence for each outcome was further downgraded or not from this point, based on the criteria given in Table 9.

Table 9: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.
Imprecision	If MIDs (1 corresponding to meaningful benefit; 1 corresponding to meaningful harm) were defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed 1 MID, and twice if it crossed both the upper and lower MIDs. If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e. the outcome was not statistically significant), and twice if the sample size of the study was sufficiently small that it is not plausible any realistic effect size could have been detected. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.

The quality of evidence for each outcome was upgraded if any of the following five conditions were met:

- Data from non-randomised studies showing an effect size sufficiently large that it cannot be explained by confounding alone.
- Data showing a dose-response gradient.
- Data where all plausible residual confounding is likely to increase our confidence in the effect estimate.

Publication bias

Publication bias was assessed in two ways. First, if evidence of conducted but unpublished studies was identified during the review (e.g. conference abstracts, trial protocols or trial records without accompanying published data), available information on these unpublished studies was reported as part of the review. Secondly, where 10 or more studies were included as part of a single meta-analysis, a funnel plot was produced to graphically assess the potential for publication bias.

Evidence statements

For outcomes with a defined MID, evidence statements were divided into 4 groups as follows:

- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), and the magnitude of that effect is most likely to meet or exceed the MID (i.e. the point estimate is not in the zone of equivalence). In such cases, we state that the evidence showed that there is an effect.
- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), but the magnitude of that effect is most likely to be less than the MID (i.e. the point estimate is in the zone of equivalence). In such cases, we state that the evidence showed there is an effect, but it is less than the defined MID.
- Situations where the confidence limits are smaller than the MIDs in both directions. In such cases, we state that the evidence demonstrates that there is no meaningful difference.
- In all other cases, we state that the evidence could not differentiate or detect a difference between the comparators.

For outcomes without a defined MID or where the MID is set as the line of no effect (for example, in the case of mortality), evidence statements are divided into 2 groups as follows:

- We state that the evidence showed that there is an effect if the 95% CI does not cross the line of no effect.
- The evidence could not differentiate between comparators if the 95% CI crosses the line of no effect.

The number of trials and participants per outcome are detailed in the evidence statements, but in cases where there are several outcomes being summarised in a single evidence statement and the numbers of participants and trials differ between outcomes, then the number of trials and participants stated are taken from the outcome with the largest number of trials. This is denoted using the terminology ‘up to’ in front of the numbers of trials and participants.

The evidence statements also cover the quality of the outcome based on the GRADE table entry. These can be included as single ratings of quality or go from one quality level to another if multiple outcomes with different quality ratings are summarised by a single evidence statement.

Health economics

Literature reviews seeking to identify published cost–utility analyses of relevance to the issues under consideration were conducted for all questions. In each case, the search undertaken for the clinical review was modified, retaining population and intervention descriptors, but removing any study-design filter and adding a filter designed to identify relevant health economic analyses. In assessing studies for inclusion, population, intervention and comparator, criteria were always identical to those used in the parallel clinical search; only cost–utility analyses were included. Economic evidence profiles, including critical appraisal according to the Guidelines manual, were completed for included studies.

Economic studies identified through a systematic search of the literature are appraised using a methodology checklist designed for economic evaluations (NICE guidelines manual; 2014). This checklist is not intended to judge the quality of a study per se, but to determine whether an existing economic evaluation is useful to inform the decision-making of the committee for a specific topic within the guideline.

There are 2 parts of the appraisal process. The first step is to assess applicability (that is, the relevance of the study to the specific guideline topic and the NICE reference case); evaluations are categorised according to the criteria in Table 10.

Table 10 Applicability criteria

Level	Explanation
Directly applicable	The study meets all applicability criteria, or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness
Partially applicable	The study fails to meet one or more applicability criteria, and this could change the conclusions about cost effectiveness
Not applicable	The study fails to meet one or more applicability criteria, and this is likely to change the conclusions about cost effectiveness. These studies are excluded from further consideration

In the second step, only those studies deemed directly or partially applicable are further assessed for limitations (that is, methodological quality); see categorisation criteria in Table 11.

Table 11 Methodological criteria

Level	Explanation
Minor limitations	Meets all quality criteria, or fails to meet one or more quality criteria but this is unlikely to change the conclusions about cost effectiveness
Potentially serious limitations	Fails to meet one or more quality criteria and this could change the conclusions about cost effectiveness

Level	Explanation
Very serious limitations	Fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies should usually be excluded from further consideration

Studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available, then other less relevant studies may not have been included. Where selective exclusions were made on this basis, this is noted in the relevant section.

Where relevant, a summary of the main findings from the systematic search, review and appraisal of economic evidence is presented in an economic evidence profile alongside the clinical evidence

Appendix C – Literature search strategies

Cochrane Airways Group Specialised Register (CAGR): Sources and search methods

Review question search strategy

- What is the effectiveness of oxygen therapy in people with stable COPD who are mildly hypoxaemic or non-hypoxaemic at rest?

Electronic searches: core databases

Database	Frequency of search
CENTRAL (the Cochrane Library)	Monthly
MEDLINE (Ovid)	Weekly
Embase (Ovid)	Weekly
PsycINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly
AMED (EBSCO)	Monthly

Clinicaltrial.gov

World Health Organization (WHO) trials portal

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards

European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify trials for the CAGR

COPD search

1. Lung Diseases, Obstructive/
2. exp Pulmonary Disease, Chronic Obstructive/
3. emphysema$.mp.
4. (chronic$ adj3 bronchiti$).mp.
5. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp.
6. COPD.mp.
7. COAD.mp.
8. COBD.mp.
9. AECB.mp.
10. or/1-9

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)

12. 8 not 11

The MEDLINE strategy and RCT filter were adapted to identify trials in other electronic databases.

Airways Group Specialised Register search strategy

#1 MeSH DESCRIPTOR Pulmonary Disease, Chronic Obstructive Explode All

#2 MeSH DESCRIPTOR Bronchitis, Chronic

#3 (obstruct*) near3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)

#4 COPD:MISC1

#5 (COPD OR COAD OR COBD):TI,AB,KW

#6 #1 OR #2 OR #3 OR #4 OR #5

#7 MeSH DESCRIPTOR Oxygen Inhalation Therapy

#8 MeSH DESCRIPTOR Oxygen

#9 oxygen*

#10 O2:ti,ab

#11 LTOT:ti,ab

#12 inhalation* NEXT therap*

#13 #7 or #8 or #9 or #10 or #11 or #12

#14 #6 and #13

CENTRAL search strategy:

Search 1: COPD + oxygen

#1 MESH DESCRIPTOR Pulmonary Disease, Chronic Obstructive EXPLODE ALL TREES

#2 ((obstruct*) near3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)):TI,AB,KY

#3 (COPD OR COAD OR COBD):TI,AB,KY

#4 #1 OR #2 OR #3

#5 MESH DESCRIPTOR Oxygen Inhalation Therapy EXPLODE ALL TREES

#6 MESH DESCRIPTOR Oxygen EXPLODE ALL TREES

#7 oxygen*:TI,AB,KY

#8 O2:TI,AB

#9 LTOT:TI,AB,KY

#10 (inhalation* NEXT therap*):TI,AB,KY

#11 #5 OR #6 OR #7 OR #8 OR #9 OR #10

#12 #4 AND #11

Search 2: Dyspnoea + oxygen

#1 MESH DESCRIPTOR Dyspnea EXPLODE ALL TREES

#2 (dyspnoea* or dyspnoea*):TI,AB,KY

#3 breathless*:TI,AB,KY

#4 ((shortness* or difficult*) NEAR2 (breath*)):TI,AB,KY

#5 #1 OR #2 OR #3 OR #4

#6 MESH DESCRIPTOR Oxygen EXPLODE ALL TREES

#7 MESH DESCRIPTOR Oxygen Inhalation Therapy EXPLODE ALL TREES

#8 LTOT:TI,AB,KY

#9 ((inhalation* NEXT therap*)):TI,AB,KY

#10 ((oxygen*) NEAR (therap* or palliative* or inhal* or long-term*)):TI,AB,KY

#11 #6 OR #7 OR #8 OR #9 OR #10

#12 #5 AND #11

MEDLINE search strategy:

1. exp Dyspnea/

2. (dyspnoea$ or dyspnoea$).ti,ab.

3. breathless$.ti,ab.

4. ((shortness$ or difficult$) adj2 breath$).ti,ab.

5. or/1-4

6. Oxygen/ad, tu [Administration & Dosage, Therapeutic Use]

7. exp Oxygen Inhalation Therapy/

8. LTOT.ti,ab.

9. (inhalation$ adj3 therap$).ti,ab.

10. (oxygen$ adj3 (therap$ or palliative$ or inhal$ or long-term$)).ti,ab.

11. or/6-10

12. 5 and 11

13. (controlled clinical trial or randomized controlled trial).pt.

14. (randomized or randomised).ab,ti.

15. placebo.ab,ti.

16. dt.fs.

17. randomly.ab,ti.

18. trial.ab,ti.

19. groups.ab,ti.

20. or/13-19

21. Animals/

22. Humans/

23. 21 not (21 and 22)

24. 20 not 23

25. 12 and 24

Embase search strategy:

1. exp dyspnoea/

2. (dyspnoea$ or dyspnoea$).ti,ab.

3. breathless$.ti,ab.

4. ((shortness$ or difficult$) adj2 breath$).ti,ab.

5. or/1-4

6. oxygen/ad, cm, dt, ih [Drug Administration, Drug Comparison, Drug Therapy, Inhalational Drug Administration]

7. oxygen therapy/

8. LTOT.ti,ab.

9. (inhalation$ adj3 therap$).ti,ab.

10. (oxygen$ adj3 (therap$ or palliative$ or inhal$ or long-term$)).ti,ab.

11. or/6-10

12. 5 and 11

13. Randomized Controlled Trial/

14. randomization/

15. controlled clinical trial/

16. Double Blind Procedure/

17. Single Blind Procedure/

18. Crossover Procedure/

19. (clinica$ adj3 trial$).tw.

20. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (mask$ or blind$ or method$)).tw.

21. exp Placebo/

22. placebo$.ti,ab.

23. random$.ti,ab.

24. ((control$ or prospectiv$) adj3 (trial$ or method$ or stud$)).tw.

25. (crossover$ or cross-over$).ti,ab.

26. or/13-25

27. exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/

28. human/ or normal human/ or human cell/

29. 27 and 28

30. 27 not 29

31. 26 not 30

32. 12 and 31

Further information on the CAGR can be found: http://airways.cochrane.org/sites/airways.cochrane.org/files/public/uploads/Search%20strategies%20document_2013_0.pdf

NICE search methods

Main searches

Sources searched for this review question:

- Cochrane Database of Systematic Reviews – CDSR (Wiley)
- Cochrane Central Register of Controlled Trials – CENTRAL (Wiley)
- Database of Abstracts of Reviews of Effects – DARE (Wiley)
- Health Technology Assessment Database – HTA (Wiley)
- EMBASE (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)

Identification of evidence

The population terms have been updated from the original guideline to include potential co-morbidities such as asthma, bronchopulmonary dysplasia and bronchiectasis. These were excluded in the original strategy.

In this update, several lines of the strategy have been focused with the use of the term 'chronic' to reduce retrieval of articles focusing on acute signs or symptoms.

Additional acronyms for COPD have been included and on recommendation from the guideline committee, terms around 'breathlessness' have been added.

Searches were re-run in February 2018 and also included searching Medline epub ahead of print.

Review question search strategy

- In which subgroups of people is long-term oxygen therapy indicated, and is it a clinically and cost effective option for managing stable COPD in these subgroups?

The MEDLINE search strategy is presented below. This was translated for use in all of the other databases.

Search strategy

Medline Strategy, searched 15th June 2017
Database: Ovid MEDLINE(R) 1946 to June Week 1 2017
Search Strategy:

Strategy used:

1 lung diseases, obstructive/
2 exp pulmonary disease, chronic obstructive/
3 (copd or coad or cobd or aecb).tw.
4 emphysema*.tw.
5 (chronic* adj4 bronch*).tw.
6 (chronic* adj3 (airflow* or airway* or bronch* or lung* or respirat* or pulmonary) adj3 obstruct*).tw.
7 (pulmonum adj4 (volumen or pneumatosis)).tw.
8 pneumonectasia.tw.
9 *Dyspnea/
10 (chronic* adj3 (breath* or respirat*) adj3 (difficult* or labor* or labour* or problem* or short*)).tw.
11 (chronic* adj3 (dyspnea* or dyspnoea* or dyspneic or breathless*)).tw.
12 or/1-11
13 Oxygen Inhalation Therapy/
14 Respiratory Therapy/
15 Oxygen/
16 ((oxygen* or o2) adj4 (long* or prolong* or indefinit* or contin* or ongoing or timespan or duration or length*)).tw.
17 ((inhalation* or respiratory) adj4 therap*).tw.
18 LTOT.tw.
19 or/13-18
20 12 and 19
21 animals/ not humans/
22 20 not 21

Medline Strategy, searched 15th June 2017 Database: Ovid MEDLINE(R) 1946 to June Week 1 2017 Search Strategy:	
23	limit 22 to english language
24	limit 23 to (letter or historical article or comment or editorial or news or case reports)
25	23 not 24

Note: In-house RCT and systematic review filters were appended

Study design filters and limits

The MEDLINE systematic review (SR) and Randomized Controlled Trial (RCT) filters were appended to the review question above and are presented below. They were translated for use in the MEDLINE In-Process and Embase databases.

Study design filters

The MEDLINE SR and RCT filters are presented below. They were translated for use in the MEDLINE In-Process and Embase databases.	
Systematic Review	
1. Meta-Analysis.pt.	
2. Meta-Analysis as Topic/	
3. Review.pt.	
4. exp Review Literature as Topic/	
5. (metaanaly$ or metanaly$ or (meta adj3 analy$)).tw.	
6. (review$ or overview$).ti.	
7. (systematic$ adj5 (review$ or overview$)).tw.	
8. ((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw.	
9. ((studies or trial$) adj2 (review$ or overview$)).tw.	
10. (integrat$ adj3 (research or review$ or literature)).tw.	
11. (pool$ adj2 (analy$ or data)).tw.	
12. (handsearch$ or (hand adj3 search$)).tw.	
13. (manual$ adj3 search$).tw.	
14. or/1-13	
15. animals/ not humans/	
16. 14 not 15	
RCT	
1	Randomized Controlled Trial.pt.
2	Controlled Clinical Trial.pt.
3	Clinical Trial.pt.
4	exp Clinical Trials as Topic/
5	Placebos/
6	Random Allocation/
7	Double-Blind Method/
8	Single-Blind Method/
9	((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw.
10	(random$ adj3 allocat$).tw.
11	placebo$.tw.

The MEDLINE SR and RCT filters are presented below. They were translated for use in the MEDLINE In-Process and Embase databases.	
12	((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.
13	or/1-12
14	animals/ not humans/
15	13 not 14
Note: analysts requested cross-over studies to be removed.	

An English language limit has been applied. Animal studies and certain publication types (letters, historical articles, comments, editorials, news and case reports) have been excluded.

No date limit was used as the previous guideline recommendations were not based on a systematic literature search.

Health Economics search strategy

Economic evaluations and quality of life data

Sources searched:

- NHS Economic Evaluation Database – NHS EED (Wiley) (legacy database)
- Health Technology Assessment (HTA Database)
- EconLit (Ovid)
- Embase (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)

Search filters to retrieve economic evaluations and quality of life papers were appended to population search terms in MEDLINE, MEDLINE In-Process and EMBASE to identify relevant evidence and can be seen below. Searches were carried out on 5th May 2017 with a date limit from the previous search of January 2009 – May 2017. Searches were re-run in February 2018.

An English language limit has been applied. Animal studies and certain publication types (letters, historical articles, comments, editorials, news and case reports) have been excluded.

Health economics filters

The MEDLINE economic evaluations and quality of life search filters are presented below. They were translated for use in the MEDLINE In-Process and Embase databases. Economic evaluations	
1	Economics/
2	exp "Costs and Cost Analysis"/
3	Economics, Dental/
4	exp Economics, Hospital/
5	exp Economics, Medical/
6	Economics, Nursing/
7	Economics, Pharmaceutical/
8	Budgets/

The MEDLINE economic evaluations and quality of life search filters are presented below. They were translated for use in the MEDLINE In-Process and Embase databases.
Economic evaluations
9 exp Models, Economic/
10 Markov Chains/
11 Monte Carlo Method/
12 Decision Trees/
13 econom$.tw.
14 cba.tw.
15 cea.tw.
16 cua.tw.
17 markov$.tw.
18 (monte adj carlo).tw.
19 (decision adj3 (tree$ or analys$)).tw.
20 (cost or costs or costing$ or costly or costed).tw.
21 (price$ or pricing$).tw.
22 budget$.tw.
23 expenditure$.tw.
24 (value adj3 (money or monetary)).tw.
25 (pharmacoeconomic$ or (pharmaco adj economic$)).tw.
26 or/1-25
Quality of life
1 "Quality of Life"/
2 quality of life.tw.
3 "Value of Life"/
4 Quality-Adjusted Life Years/
5 quality adjusted life.tw.
6 (qaly$ or qald$ or qale$ or qtime$).tw.
7 disability adjusted life.tw.
8 daly$.tw.
9 Health Status Indicators/
10 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
11 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
12 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
13 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
14 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
15 (euroqol or euro qol or eq5d or eq 5d).tw.
16 (qol or hql or hqol or hrqol).tw.
17 (hye or hyes).tw.
18 health$ year$ equivalent$.tw.
19 utilit$.tw.
20 (hui or hui1 or hui2 or hui3).tw.
21 disutili$.tw.
22 rosser.tw.

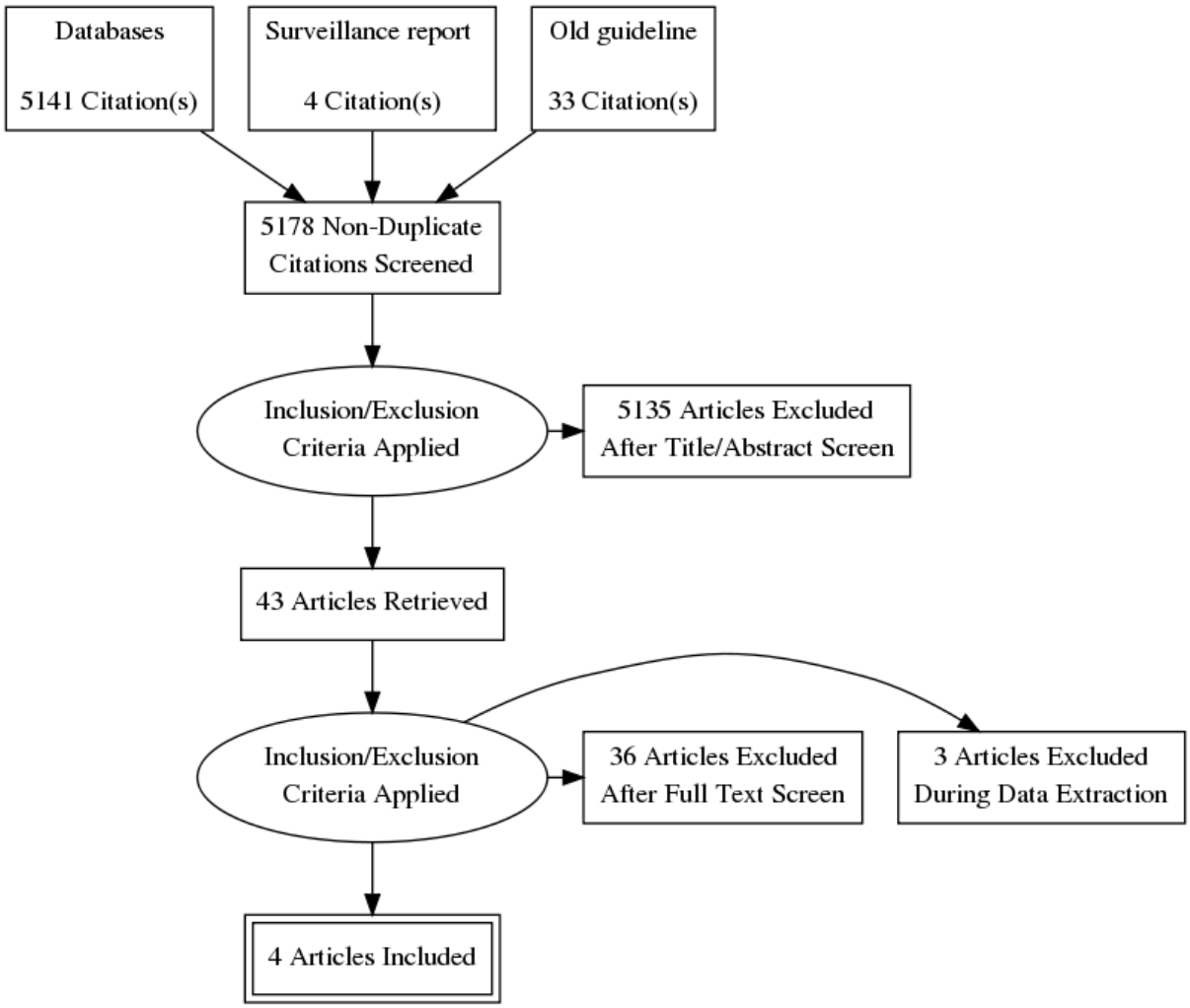
The MEDLINE economic evaluations and quality of life search filters are presented below. They were translated for use in the MEDLINE In-Process and Embase databases.	
Economic evaluations	
23	quality of wellbeing.tw.
24	quality of well-being.tw.
25	qwb.tw.
26	willingness to pay.tw.
27	standard gamble$.tw.
28	time trade off.tw.
29	time tradeoff.tw.
30	tto.tw.
31	or/1-30

Appendix D – Clinical evidence study selection

Ambulatory and short burst oxygen therapy

This question was answered by using a recently published Cochrane review (Ekstrom 2016). Details of the search can be found in the published Cochrane review. One additional reference was found during the re-run process, but excluded at full text screening.

Long term oxygen therapy



Appendix E – Clinical evidence tables

Ambulatory and short burst oxygen therapy –Systematic review

Short Title	Title	Study Characteristics	Risk of Bias and directness
Ekstrom (2016)	Oxygen for breathlessness in patients with chronic obstructive pulmonary disease who do not qualify for home oxygen therapy	**Study type** Systematic review **Study details** Dates searched *2011 - 12 July 2016* Databases searched *Cochrane Airways Group Specialised Register Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 6), MEDLINE (to 12 July 2016) and Embase (to 12 July 2016).* Sources of funding *National Institute for Health Research (NIHR) via Cochrane Infrastructure funding to the Cochrane Airways Group* **Study exclusion criteria** Studies of participants already	**Study eligibility criteria** Low risk of bias *Objectives, eligibility criteria for both studies and participants were clearly stated* **Identification and selection of studies** Low risk of bias *No concerns regarding identification and selection of studies.* **Data collection and study appraisal** Low risk of bias *No concerns* **Synthesis and findings** Low risk of bias

Short Title	Title	Study Characteristics	Risk of Bias and directness
		qualifying for home oxygen therapy according to guidelines Based on sensitive analysis authors also excluded studies with any of the following - *1.measurement at peak exertion (compared with iso-time); 2. High risk of bias for any bias category; 3. Any participant without COPD; and 4. Outlier findings (based on forest and funnel plots).* **Participant inclusion criteria** had mild or no hypoxaemia (mean PaO2 > 7.3 kPa) not receiving LTOT 18 years of age or older who had COPD **Participant exclusion criteria** Eligible for LTOT **Interventions** Oxygen therapy *delivered by a non-invasive method,*	*No concerns* **Overall quality** High **Applicability as a source of data** Fully applicable

Short Title	Title	Study Characteristics	Risk of Bias and directness
		delivered during exertion, continuously or as needed over a defined period, or short-burst oxygen before exertion (defined as therapy given during a short, defined period just before exertion) Air *delivered by a non-invasive method at any inspired dose above that of ambient air (>21%)* **Outcome measures** Level of breathlessness measured on any validated scale Health related quality of life measured on any validated scale	

Characteristics of the included studies

Study	O2 delivery	O2 dose	Baseline PaO2 (kPa)	Baseline SaO2 (%)	Baseline Breathlessness	Breathlessness outcome measure	Sample size	HRQOL outcome measure
Abernethy 2010	NC	2 L/min	10.0 (SD 1.5)	NA	4.8 (SD 2.1)	NRS	211	10-cm VAS
Bruni 2012a	Mouthpiece	50%	9.5 (SD 1.2)	NA	NA	Modified Borg	10	-
Bruni 2012b	Mouthpiece	50%	10.3 (SD 0.9)	NA	NA	Modified Borg	6	-

Study	O2 delivery	O2 dose	Baseline PaO2 (kPa)	Baseline SaO2 (%)	Baseline Breathlessness	Breathlessness outcome measure	Sample size	HRQOL outcome measure
Davidson 1988	NC or valve	4 L/min	8.6 (SE 0.3)	NA	NA	10-cm VAS	17	-
Dean 1992	Mouthpiece	40%	9.5 (SE 0.3)	NA	NA	Modified Borg	12	-
Dyer 2012	NC	2-6 L/min	NA	94 (SD 2)	3 (SD 1)	CRQ dyspnoea	55	CRQ subdomains
Eaton 2002	NC	4 L/min	9.2 (SD 1.0)	94 (SD 1.9)	0.7 (SD 1.0)	Modified Borg	50	CRQ total CRQ subdomains SF-36
Eaton 2006	NC	2 L/min	Oxygen: 9.6 (SD 1.3) Air: 10.1 (SD 1.7)	Oxygen: 95 (SD 1.9) Air: 95 (SD 1.6)	Oxygen: 17.8 (SD 5.0) Air: 17.5 (SD 4.2)	CRQ dyspnoea	51	CRQ total CRQ subdomains SF-36
Emtner 2003a	Mouthpiece	30%	9.8 (SD 0.8)	NA	5.8 (SD 1.8)	Modified Borg	30	CRQ total CRQ subdomains SF-36
Emtner 2003b	Mouthpiece	30%	10.0 (SD 1.2)	NA	6.3 (2.5)	Modified Borg	30	CRQ total CRQ subdomains SF-36
Eves 2006	Mouthpiece	40%	9.1 (SD 0.9)	NA	NA	Modified Borg	10	-
Haidl 2004	NC	2 L/min	Oxygen: 9.0 (SD 0.9) Controls: 8.7 (SD 0.8)	NA	Oxygen: 5.0 (SD 2.1) Controls: 5.0 (SD 1.5)	Modified Borg	28	-

Study	O2 delivery	O2 dose	Baseline PaO2 (kPa)	Baseline SaO2 (%)	Baseline Breathlessness	Breathlessness outcome measure	Sample size	HRQOL outcome measure
Ishimine 1995	Unknown	3 L/min	10.1 (SD 1.1)	NA	NA	Dyspnoea questionnaire	22	-
Jolly 2001a	NC	3 L/min	10.5 (SE 0.4)	95.8 (SE 0.46)	0.56 (SE 0.34)	Modified Borg	9	-
Jolly 2001b	NC	3 L/min	9.9 (SE 0.3)	94.7 (SE 0.27)	1.27 (SE 0.43)	Modified Borg	11	-
Killen 2000	Mask	2 L/min	NA	Median 94 (IQR 91, 95)	NA	100-mm VAS	18	-
Knebel 2000	NC	4 L/min	NA	97.1 (SD 1.7) (range 92-100)	0.5 (SD 0.9)	10-cm VAS	33	-
Kurihara 1989	NC	3 L/min	9.2 (SD 1.2)	NA	NA	Modified Borg	14	-
Laude 2006	Mask/valve	28%	NA	93.9 (SD 2.3)	VAS 24.2 (19.0) Borg 1.8 (1.1)	100-mm VAS modified Borg	82	-
Leach 1992	Mask	2 L/min	8.7 (SD 2.3)	NA	NA	10-cm VAS	20	-
Lewis 2003	NC	2 L/min	NA	94.4 (1.6)	0.4 (0.5)	Modified Borg	22	-
Maltais 2001	Mouthpiece	75%	11.3 (SEM 0.5)	NA	NA	Modified Borg	14	-
McDonald 1995	NC	4 L/min	9.2 (SD 1.1) (range 7.7-10.9)	94 (SD 2.1)	NA	Modified Borg	33	CRQ subdomains
McKeon 1988a	NC	2.5 L/min	7.7 (SD 1.2) (range 5.7-10.9)	90 (SD 3) (range 84-96)	NA	300-mm VAS	20	-
McKeon 1988b	NC	4 L/min	8.9 (SD 1.5)	NA	NA	300-mm VAS	21	-

Study	O2 delivery	O2 dose	Baseline PaO2 (kPa)	Baseline SaO2 (%)	Baseline Breathlessness	Breathlessness outcome measure	Sample size	HRQOL outcome measure
Miki 2012	Mask/valve	24%	10.1 (SD 1.3)	NA	Oxygen: 0.1 (SD 0.2) Air: 0.1 (SD 0.4)	Modified Borg	35	-
Moore 2009	Mouthpiece	44%	NA	95 (SD 3.2)	NA	Modified Borg	55	-
Moore 2011	NC	6 L/min	9.5 (SD 1.1)	NA	Oxygen: 17.6 (SD 5.2) Air: 17.5 (SD 4.9)	CRQ dyspnoea	143	CRQ total CRQ subdomains
Nandi 2003	Mask	4 L/min	7.7 (SD 1.5)	91.9 (SD 5.2) (range 76 to 97)	NA	100-mm VAS	34	-
Nonoyama 2007	NC	1-3 L/min	NA	NA	3.7 (SD 1.1)	Modified Borg	38	CRQ subdomains SQRQ total
O'Donnell 1997	Mouthpiece	60%	9.9 (SEM 0.4)	NA	5.1 (SD 0.3)a	Modified Borg	11	-
O'Driscoll 2011	Mask	4 L/min	NA	95.0 (SD, 1.3)	1.5 (SD 1.1)	Modified Borg	39	-
Oliveira 2012a	Mask	40%	8.5 (SD 1.1)	NA	NA	Modified Borg	8	-
Oliveira 2012b	Mask	40%	10.0 (SD 1.3)	NA	NA	Modified Borg	12	-
Ringbaek 2013	NC	2 L/min	NA	93.6 (SD 2.0)	5.3 (SD 1.8)	Modified Borg	45	SQRQ total
Rooyackers 1997a	NC	4 L/min	10.2 (SD 1.2)	NA	NA	Modified Borg	12	CRQ total CRQ subdomains
Rooyackers 1997b	NC	4 L/min	9.5 (SD 2.0)	NA	NA	Modified Borg	12	CRQ total

Study	O2 delivery	O2 dose	Baseline PaO2 (kPa)	Baseline SaO2 (%)	Baseline Breathlessness	Breathlessness outcome measure	Sample size	HRQOL outcome measure
								CRQ subdomains
Scorsone 2010	Mouthpiece	40%	Oxygen: 9.9 (SD 1.0) Air: 10.2 (SD 1.2)	NA	7 (SD 3)	Modified Borg	20	
Somfay 2001	Mouthpiece	30%	NA	95.7 (0.8)	NA	Modified Borg	10	-
Spielmanns 2014	NC	4 L/min	NA	> 90%	NA	-	85	SF-36 total
Swinburn 1984	Mouthpiece	60%	NA	93.2 (SD 0.8)	NA	10-cm VAS	5	-
Voduc 2010	Mask	50%	NA	97.1 (SD 1.9)	NA	Modified Borg	24	-
Wadell 2001	NC	5 L/min	Median 9.3 (range 7.9-11.4)	Median 94.6 (range 90.7-97.2)	Median 1.5 (range 0-3)	Modified Borg	22	-
Woodcock 1981	NC	4 L/min	9.6 (SD 1.5)	NA	4 (SD 0.94)b	10-cm VAS	10	-

Long term oxygen therapy- Randomised controlled trials

Short Title	Title	Study Characteristics	Risk of Bias and directness
Albert (2016)	A Randomized Trial of Long-Term Oxygen for COPD with Moderate Desaturation.	**Study type** Randomised controlled trial **Study details** Study location	**Random sequence generation** Low risk of bias *The randomization schedule was stratified by regional clinical centre with randomly permuted blocks of*

Short Title	Title	Study Characteristics	Risk of Bias and directness
		USA Study setting *14 regional clinical centres (a total of 47 centres)* Study dates *January 2009 to August 2014* Duration of follow-up *1 to 6 years (median follow up 18.4 months)* Sources of funding *National Heart, Lung and Blood Institute, National Institutes of Health and Department of Health and Human services, Centres of Medicare and Medicaid Services, Department of Health and Human Services.* **Inclusion criteria** All must be met Age at least 40 At least 10 pack/day cigarette smoking history Modified Medical Research Council (MMRC)* dyspnoea (breathlessness) score ≥ 1 (short of breath when hurrying on Post-bronchodilator FEV1 / FVC < 0.70 Post-bronchodilator FEV1 <70% of the predicted normal value or > 70% of the predicted normal value and Study Physician determines that there is radiologic evidence of emphysema Resting SpO2 89-93% (moderate resting hypoxemia) OR resting SpO2 94% or greater and desaturation during exercise defined as SpO2 below 90% for at least 10 seconds during the 6-minute walk test	*sizes 2, 4, and 6. The data system generated the treatment assignment only if the electronic checks for conformance with the eligibility criteria were passed.* **Allocation concealment** High risk of bias *The trial-group assignment was not masked* **Blinding of outcome assessment** Unclear risk of bias **Incomplete outcome data** Low risk of bias **Selective reporting** Low risk of bias **Other sources of bias** Moderate risk of bias

Short Title	Title	Study Characteristics	Risk of Bias and directness
		(normal resting saturation but hypoxemia with exercise) Medicare Part A and Part B beneficiary, insurance willing to pay costs of treatment and costs of study procedures and visits, or willing to self-pay costs Approval by study physician for randomization to either treatment group No exacerbation requiring antibiotics or new/ increased dose of systemic corticosteroids in the 30 days prior to screening At least 30 days post-discharge from an acute care hospital for COPD or other condition prior to screening If patient regularly uses supplemental oxygen prior to screening, all of the following must be met before randomisation: *- Patient agrees to stop using supplemental oxygen if randomized to no supplemental oxygen - Patient's physician agrees in writing to rescind order for supplemental oxygen if patient is randomized to no supplemental oxygen - Patient must not use supplemental oxygen for the 4 calendar days prior to randomization and must report that he/she had no problems doing without the oxygen* Signature of written contract agreeing not to smoke while using supplemental oxygen **Exclusion criteria** None may be met	*self-reported adherence may have been an over/underestimate of the participants actual oxygen use in both groups hospitalisation was recorded from self-reported accounts every 4 months - possibility of underestimating the number of hospitalisations. Excluded participants who were not able to pay for costs of treatment and study procedure* **Overall risk of bias** Moderate risk – *due to lack of blinding and self-reported adherence of oxygen* **Directness** Fully applicable - *potential excluded the equivalent of the UK population that is most likely to smoke, as only included those who could pay for treatment – this was downgraded in the risk of bias section*

Short Title	Title	Study Characteristics	Risk of Bias and directness
		COPD exacerbation requiring antibiotics, new or increased dose of systemic corticosteroids, or New prescription of supplemental oxygen after screening starts and before randomization Thoracic surgery or other procedure in the 6 months prior to evaluation likely to cause instability of pulmonary status Non-COPD lung disease that would affect oxygenation or survival Epworth Sleepiness Scale† score greater than 15 Desaturation below 80% for at least 1 minute during the 6-minute walk Disease or condition expected to cause death or inability to perform procedures for the trial or inability to comply with therapy within 6 months of randomisation, as judged by study physician Participation in another intervention study **Sample characteristics** Sample size *737* Split between study groups *Long term oxygen therapy - 368(220 patients were on 24hour oxygen and 148 were prescribed oxygen during exercise and sleep only) No long term oxygen therapy - 370* %female *LTOT - 28% No LTOT - 25%* Mean age (SD)	

Short Title	Title	Study Characteristics	Risk of Bias and directness
		LTOT - 68.3+/- 7.5 No LTOT - 69.3+/- 7.4 **Interventions** Long term oxygen therapy - 24hrs/day *Patients were prescribed 24 hour oxygen if their resting SpO2 was 89 - 93% or moderate exercise induced desaturation (during the 6 minute walking test, Spo2 >/= 80% for >/=5minutes and <90% for 10 seconds) All patients had stationary and portable oxygen systems and 2 litres of Oxygen per minute during sleep and/or at rest. Patients were to use oxygen regardless of increase in the SpO2 level. Ambulatory dose of oxygen was individually prescribed and reassessed annually - 2 litres of oxygen per minute or adjusted high to maintain and SpO2 of 90% or more at least 2 minutes while the patient was walking.* **Control** No long term oxygen therapy *No supplemental oxygen was to be used unless severe resting desaturation (SpO2 </= 88%) or severe exercise induced desaturation (SpO2<80% for >/= 1 minute) if either of these happened oxygen was prescribed and reassessed after 1 month* **Outcome measure(s)** Death/Mortality First readmission to hospital	

Short Title	Title	Study Characteristics	Risk of Bias and directness
		incidence of COPD exacerbation Adherence to the supplemental oxygen Development of severe resting desaturation Development of severe exercise -induced desaturation The distance walked in 6 minutes St. George's Respiratory Questionnaire	
Nocturnal Oxygen Therapy Trial group (1980)	Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group	**Study details** Randomised control trial Study location *USA* Study setting *6 treatment centres* Study dates *unclear - before 1980* Duration of follow-up *at least 1 year* Sources of funding *Nocturnal Oxygen Therapy Trial Group* **Inclusion criteria** Post-bronchodilator FEV1 / FVC < 0.70 PaO2 </= to 55mmHg (7.3 kpa) PaO2 </= 59 mmHg (7.85 kPa) plus one of the following:	**Random sequence generation** Low risk of bias *Randomisation schedules were developed separately for each investigative centre. Treatment assignments were present in blocks of four with an equal number of patients receiving nocturnal oxygen and continuous oxygen therapy in each block. The order of treatment assignment was randomly computer generated within each block of four.* **Allocation concealment** Unclear risk of bias *No information provided* **Blinding of outcome assessment** Unclear risk of bias

Short Title	Title	Study Characteristics	Risk of Bias and directness
		Exclusion criteria Previous oxygen therapy, 12h/day for 30 days during previous 2 months, other disease that might be expected to influence mortality, morbidity, compliance with therapy, or ability to give informed consent **Sample characteristics** Sample size *203 participants* Split between study groups *LTOT group - n=101 participants nocturnal group - n= 102 participants* %female *21.2%*Mean age (SD) *65.7years (no S.D)* **Interventions** Long term oxygen therapy *Average oxygen use of 17.7h/day (SD=4.8hr/day) Oxygen was administered by nasal prongs at a measured flow rate of 1 to 4 l/min. Each patient received the lowest flow in whole litres per minute that demonstrably increased resting semi recumbent arterial Po2 at least 60 mmHg (7.98kPa) and*	*No information provided* **Selective reporting** Low risk of bias **Other sources of bias** High risk of bias *Self-reported use of oxygen in especially continuous oxygen therapy compared to nocturnal oxygen therapy. Only stationary oxygen cylinders had timers recording use of oxygen, therefore nocturnal oxygen therapy was recorded accurately but possible underestimating of continuous oxygen therapy.* **Overall risk of bias** Moderate risk of bas *due to uncertainties regarding blinding and allocation concealment and the bias surrounding self-reported outcomes*

Short Title	Title	Study Characteristics	Risk of Bias and directness
		maintained resting arterial Po2 of 60 to 80 mmHg (7.98 – 10.6kPa) dose was increased by 1l in periods of exercise or sleep oxygen delivery systems varied All patients also treated with oral theophylline and inhaled beta antagonist. Diuretics and antibiotics were used as indicated **Control** Nocturnal oxygen therapy *oxygen therapy only during sleep - averaging 12h/day (SD=2.5hr/day) All patients were treated with oral theophylline and inhaled beta-2- agonists* **Outcome measure(s)** Mortality *Several subgroup analysis PaO2 less/more than 55mmHg(7.3 kPa) PaCO2 less/more than 43 mmHg (5.7kPa) PH less/more than 7.40 FEV1 less/more than 0.69l Sleep, mean oxygen saturation less/greater than 85%*	**Directness** Directly applicable
Medical Research Council working party (1981)	Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party.	**Study type** Randomised controlled trial	**Random sequence generation** Low risk of bias

Short Title	Title	Study Characteristics	Risk of Bias and directness
		Study details Study location *UK* Study setting *Centres in Edinburgh, Birmingham and Sheffield.* Study dates *1973- unknown end date* Duration of follow-up *3 years* Sources of funding *Medical Research Council* **Inclusion criteria** Chronic bronchitis or emphysema with irreversible airways obstruction *FEV1 <1.2 litres* Arterial oxygen tension between 40 and 60 mmHg (5.3 and 7.98 kPa) when breathing air at rest One of more episodes of heart failure with ankle oedema. *Resting pulmonary arterial hypertension was not used as an entry criterion.* Arterial blood gas, FEV1 and body weight stable over 2 measurements at least 3 weeks apart.	**Allocation concealment** Unclear risk of bias *No information provided* **Blinding of participants and personnel** High risk of bias *Absence of a placebo* **Blinding of outcome assessment** Unclear risk of bias *No information provided* **Incomplete outcome data** High risk of bias *the author only analysed data from male participants for physiological factors.* **Selective reporting** High risk of bias *Data for rates of change of physiological variables is not presented for the whole data set, just males.*

Short Title	Title	Study Characteristics	Risk of Bias and directness
		Exclusion criteria History of ischaemic heart disease Other concomitant life threatening diseases Fibrotic or infiltrative lung disease Pneumoconiosis (category 2 or more), severe kyphoscoliosis, overt episodes of pulmonary embolism Systemic hypertension *diastolic pressure >100 mmHg under 60 years of age, or > 110 mmHg over 65 years of age.* **Sample characteristics** Sample size *87* Split between study groups *Intervention: 42 Control: 45* Loss to follow up *86/87 (98.9%) completed the trial.* % female *24.1%* Mean age: years (SD) *57.7 (no SD data provided)* **Interventions** No intervention- routine treatment for COPD Oxygen	**Other sources of bias** Low risk of bias **Overall risk of bias** High *Due to the lack of information regarding allocation concealment and outcome assessor blinding, the absence of a placebo and selective reporting of data* **Directness** Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias and directness
		For at least 15hrs a day. Included sleeping hours, given via nasal prongs, at a flow rate of 2l/minute, or at a higher flow rate if this was necessary to achieve a PaO2>60mmHg. The delivery systems/cylinder varied across the patients. **Outcome measure(s)** Mortality Rate of change in FEV1 Rate of change in PaO_2	
Gorecka (1996)	Long-term oxygen therapy in COPD patients with moderate hypoxemia	**Study type** Randomised controlled trial **Study details** Study location *Poland* Study setting *Nine regional LTOT centres* Study dates *participants recruited 1987-1992 and followed up until 1994* Duration of follow-up *For at least 3 years or until death (on average patients were observed for 40.9 months, range 2-*	**Random sequence generation** Low risk of bias *"Randomisation schedules were generated electronically, treatment assignments were computer generated by random numbers, with an equal number of patients in the control/treatment groups"* **Allocation concealment** Low risk of bias *as above* **Blinding of outcome assessment** Unclear risk of bias

Short Title	Title	Study Characteristics	Risk of Bias and directness
		85months) **Inclusion criteria** Diagnosed with COPD Post-bronchodilator FEV1 / FVC < 0.70 Aged between 40 and 80 years **Exclusion criteria** Patients with a malignant disease, left heart failure or other significant comorbidities (e.g. severe renal failure, severe diabetes) **Sample characteristics** Sample size *135 participants* Split between study groups *LTOT group - n=68 participants Control group - n= 67 participants* Loss to follow-up *No dropouts* %female *32 women (24%)* Mean age (SD) *61.2 years (40-79 years) no S.D* Current smokers	*No details mentioned on blinding of outcomes* **Incomplete outcome data** Low risk of bias *No concerns* **Selective reporting** High risk of bias *outcomes to be reported were not included in the methods section.* **Overall risk of bias** Moderate risk of bias *due to uncertainties regarding blinding and selective reporting* **Directness** Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias and directness
		All participants declared to be non-smokers **Interventions** Long term oxygen therapy *received from an oxygen concentrator at a flow rate adjusted to raise resting PaO2 above 8.7kPa (65mmHg) prescribed for at least 17hrs/day* **Control** No long term oxygen therapy *Conventional treatment was given same as the intervention group* **Outcome** Mortality	

Table 12: Evidence on adverse events (Albert 2016)

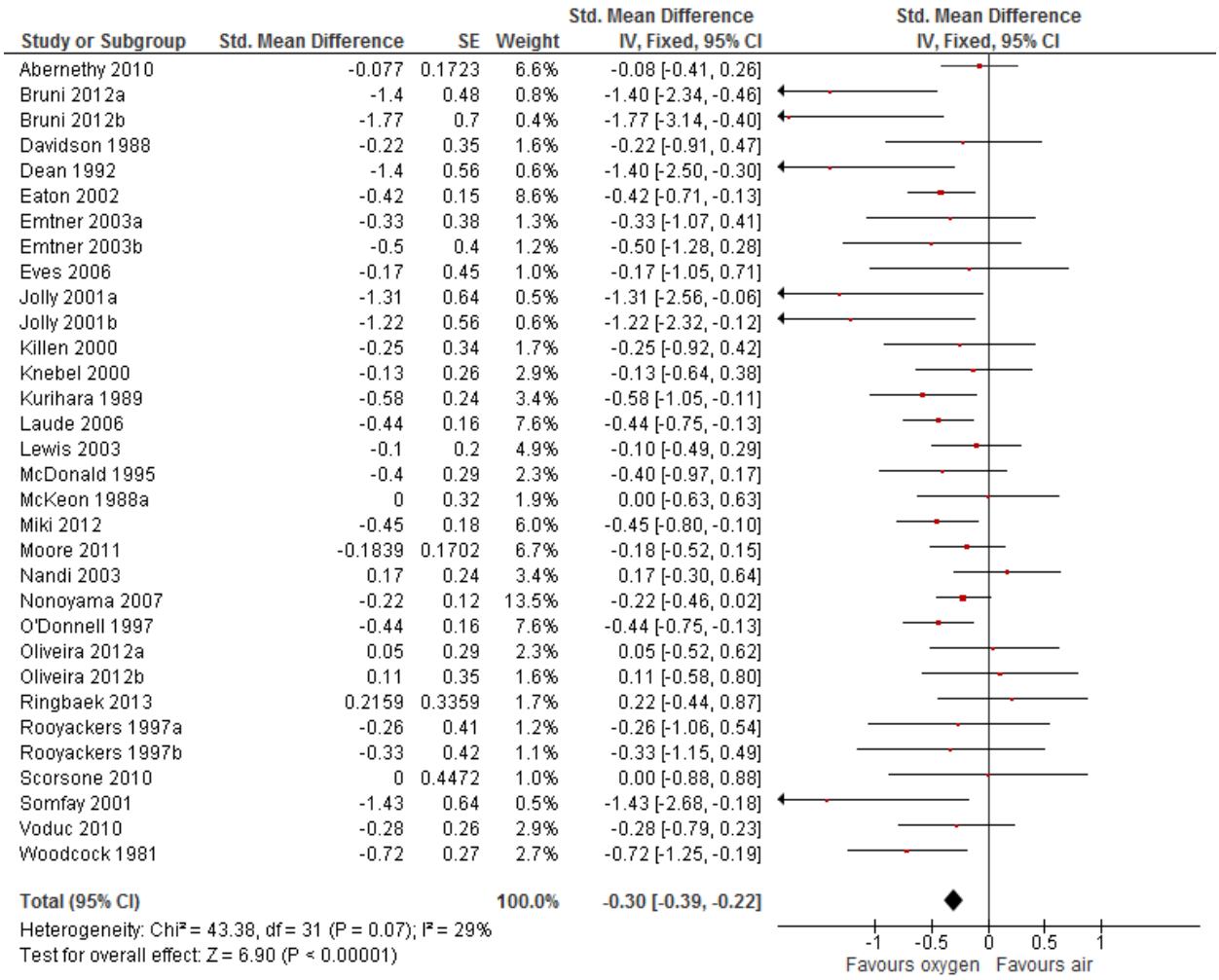
Expected, related events	No. of reports	Reports per 100 person years	Unexpected, related events	No. of reports	Reports per 100 person years
Fires related to oxygen use	2	0.08	Blisters, ear pain	3	0.12
Burns from smoking around oxygen equipment	3	0.12	Dry eyes	1	0.04
Burns from using oxygen equipment around open flame	1	0.04	Funny feeling in sinus area	1	0.04
Burns from liquid oxygen	4	0.16	Increased intestinal gas	1	0.04
Nosebleed	9	0.35	Headache	2	0.08
Tripping/falling over oxygen equipment	23	0.90	Nausea	1	0.04
Total no of expected events, related events	42	1.64	Total no, of all related events	9	0.35

Expected, related events	No. of reports	Reports per 100 person years	Unexpected, related events	No. of reports	Reports per 100 person years
Total no. of all related events				**52**	
Total no of patients ever using supplemental oxygen during follow-up				**490**	
Number (%) reporting at least 1 related adverse event				42 (8.6%)	

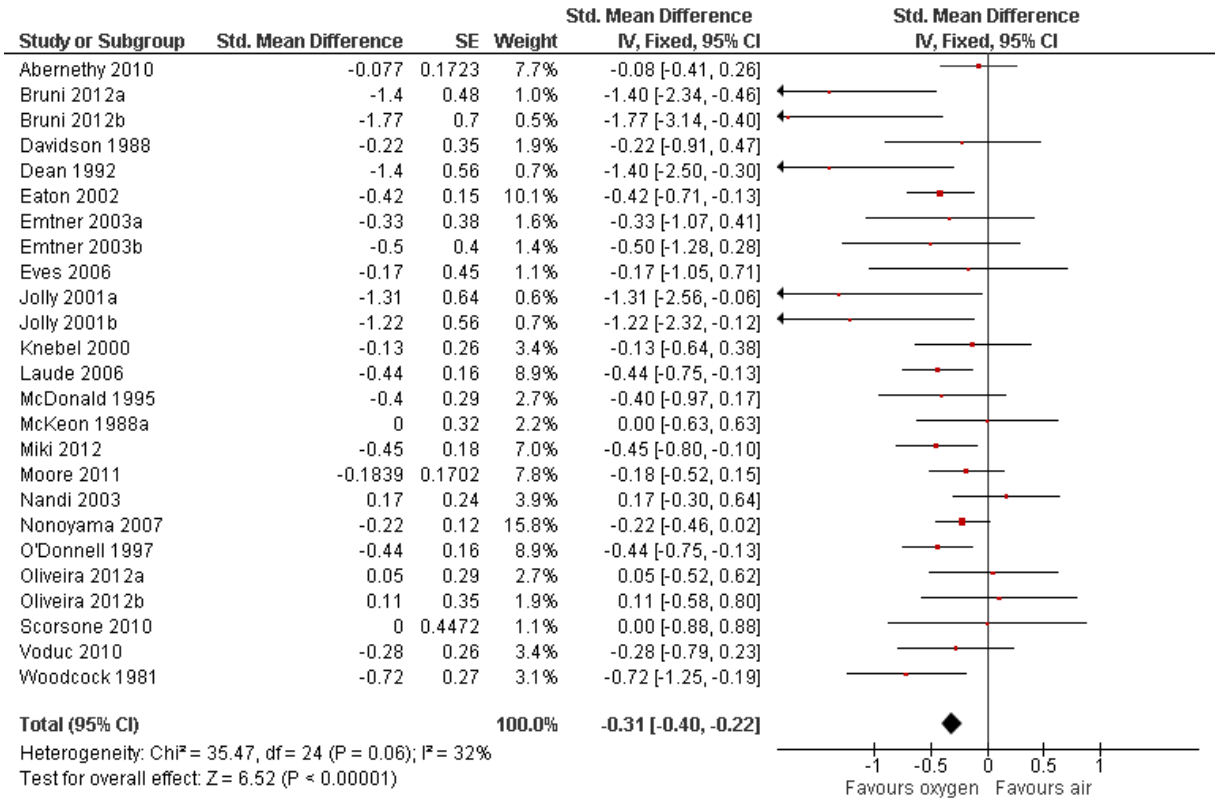
Appendix F – Forest plots

Ambulatory and short burst oxygen therapy: oxygen versus air

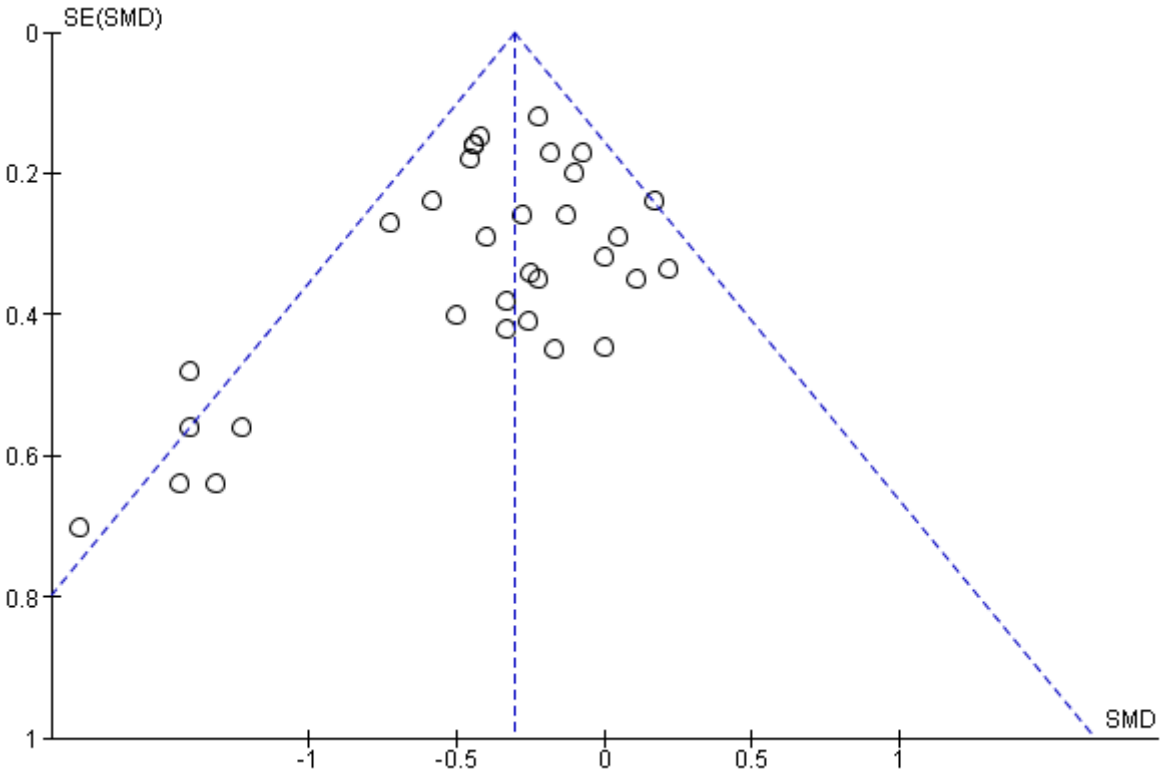
Breathlessness - all trials



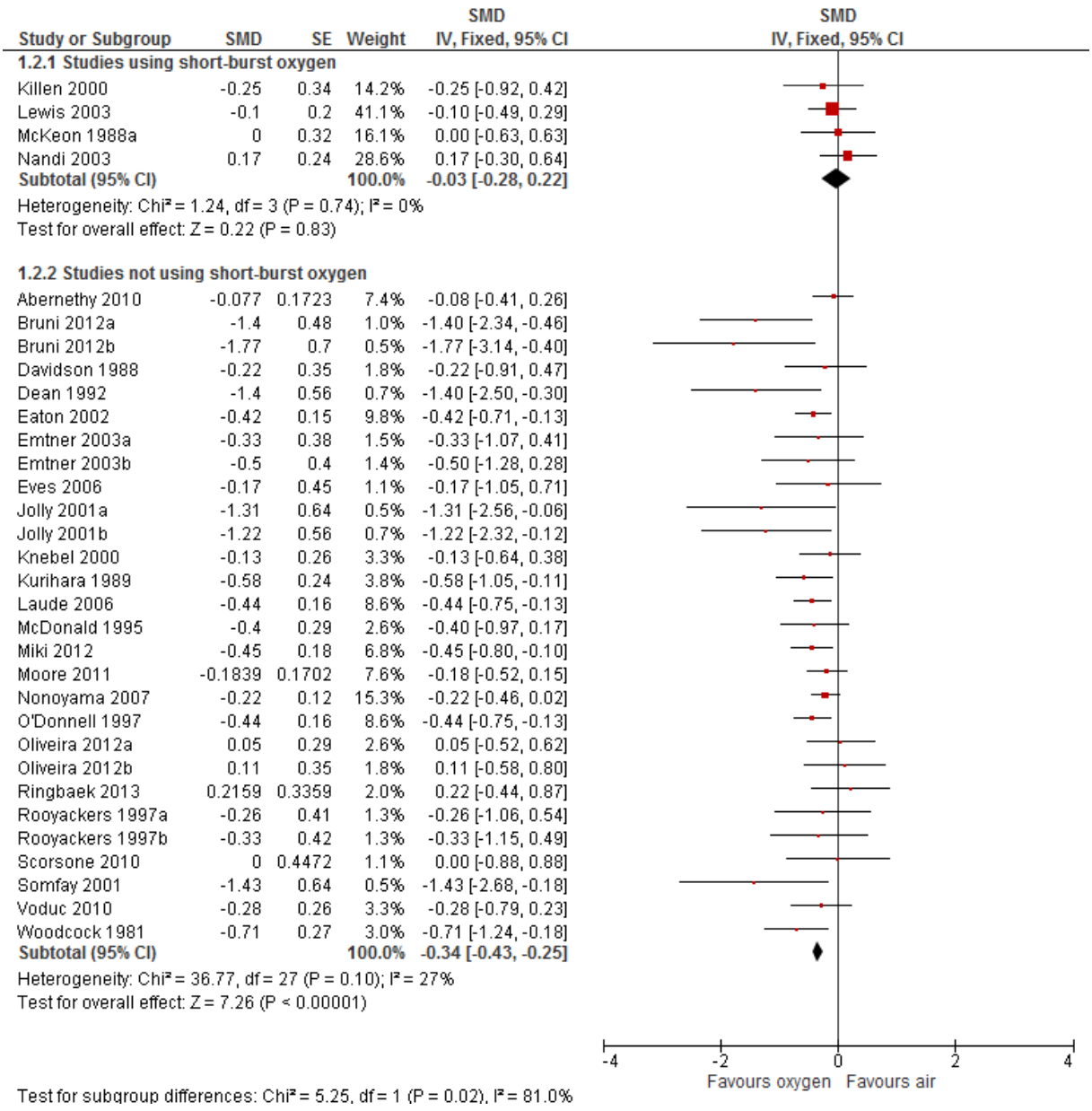
Sensitivity analysis – breathlessness



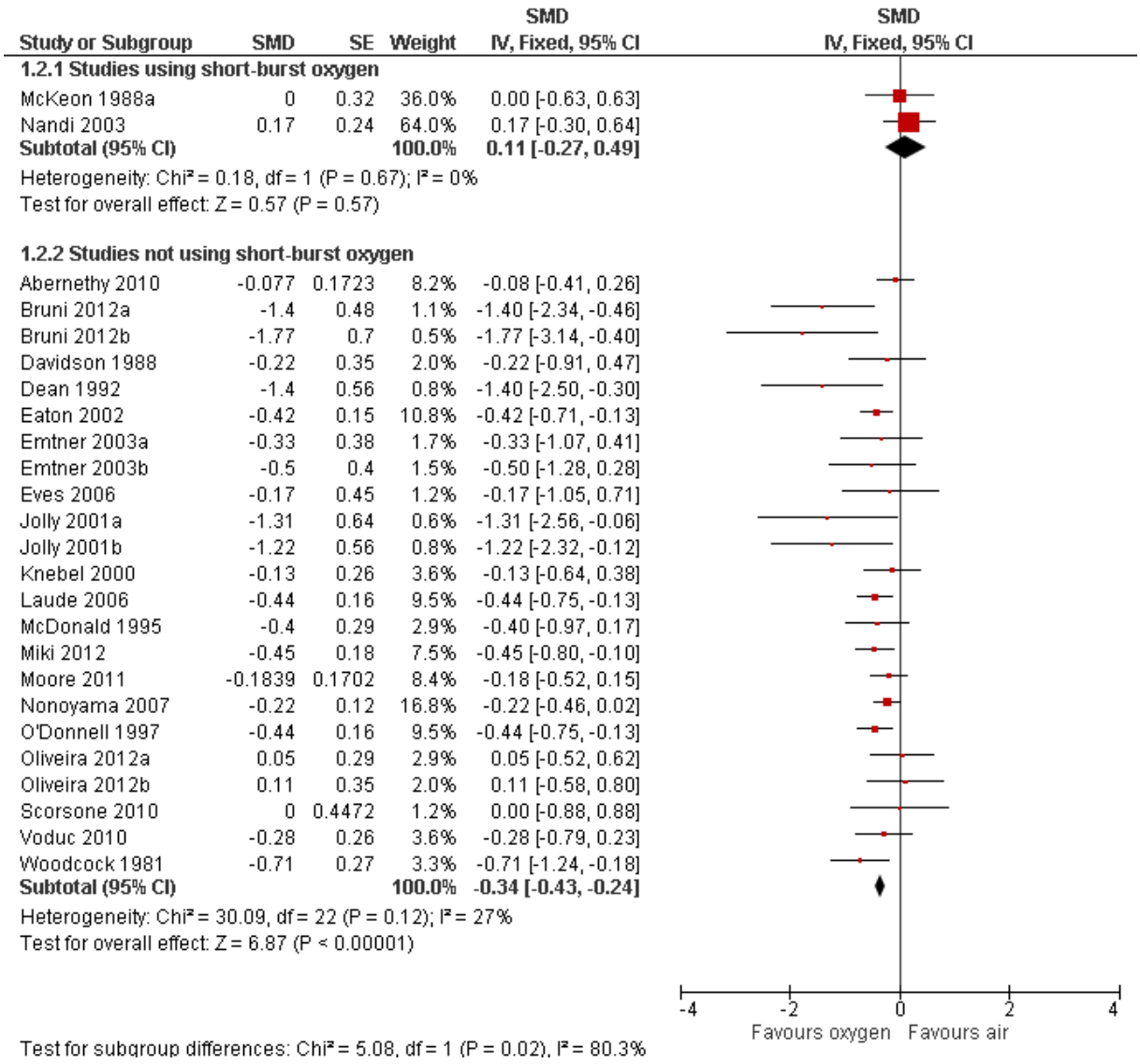
Funnel plot to assess publication bias – breathlessness



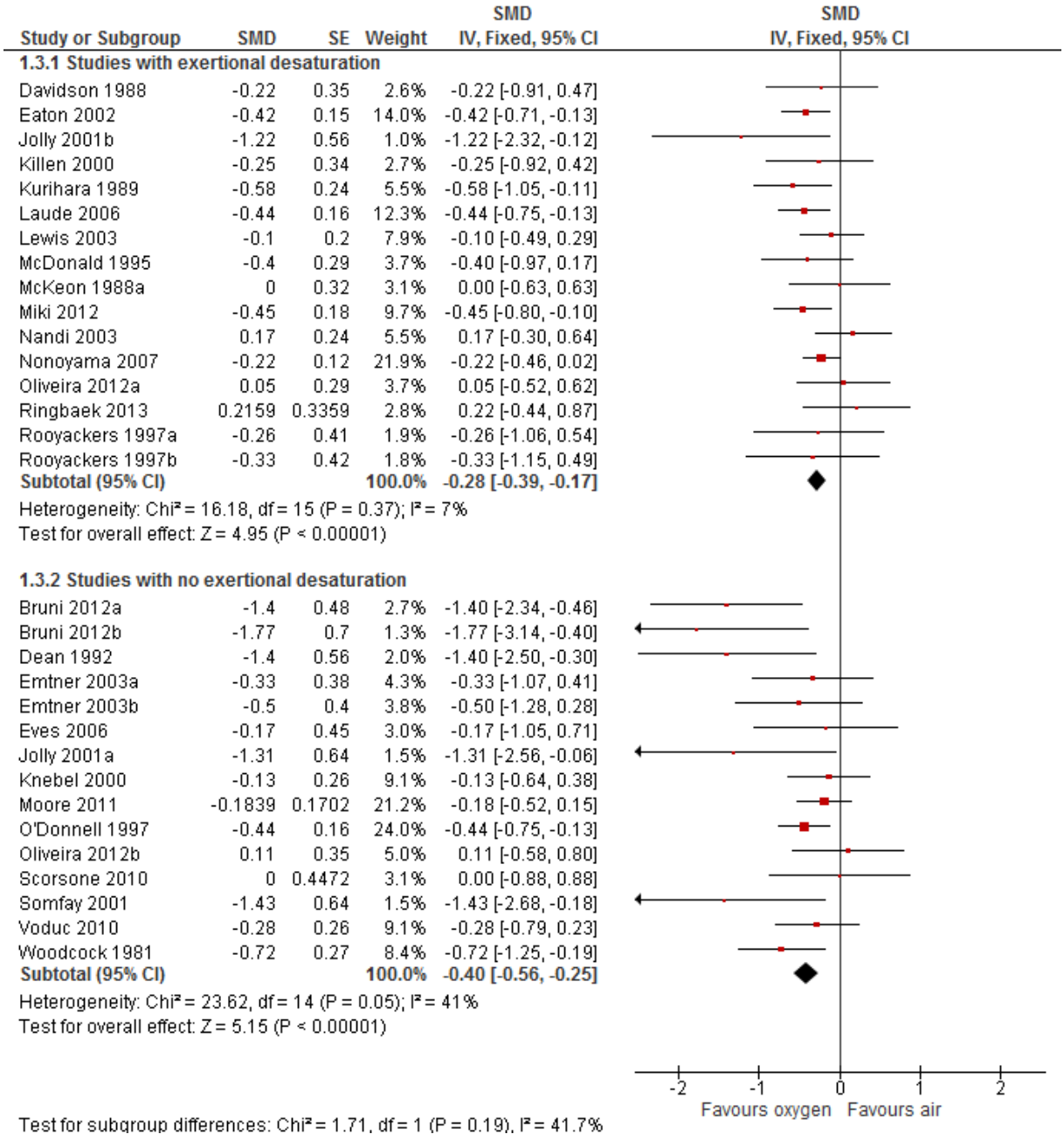
Breathlessness - subgroup analysis - short-burst oxygen or not using short burst oxygen



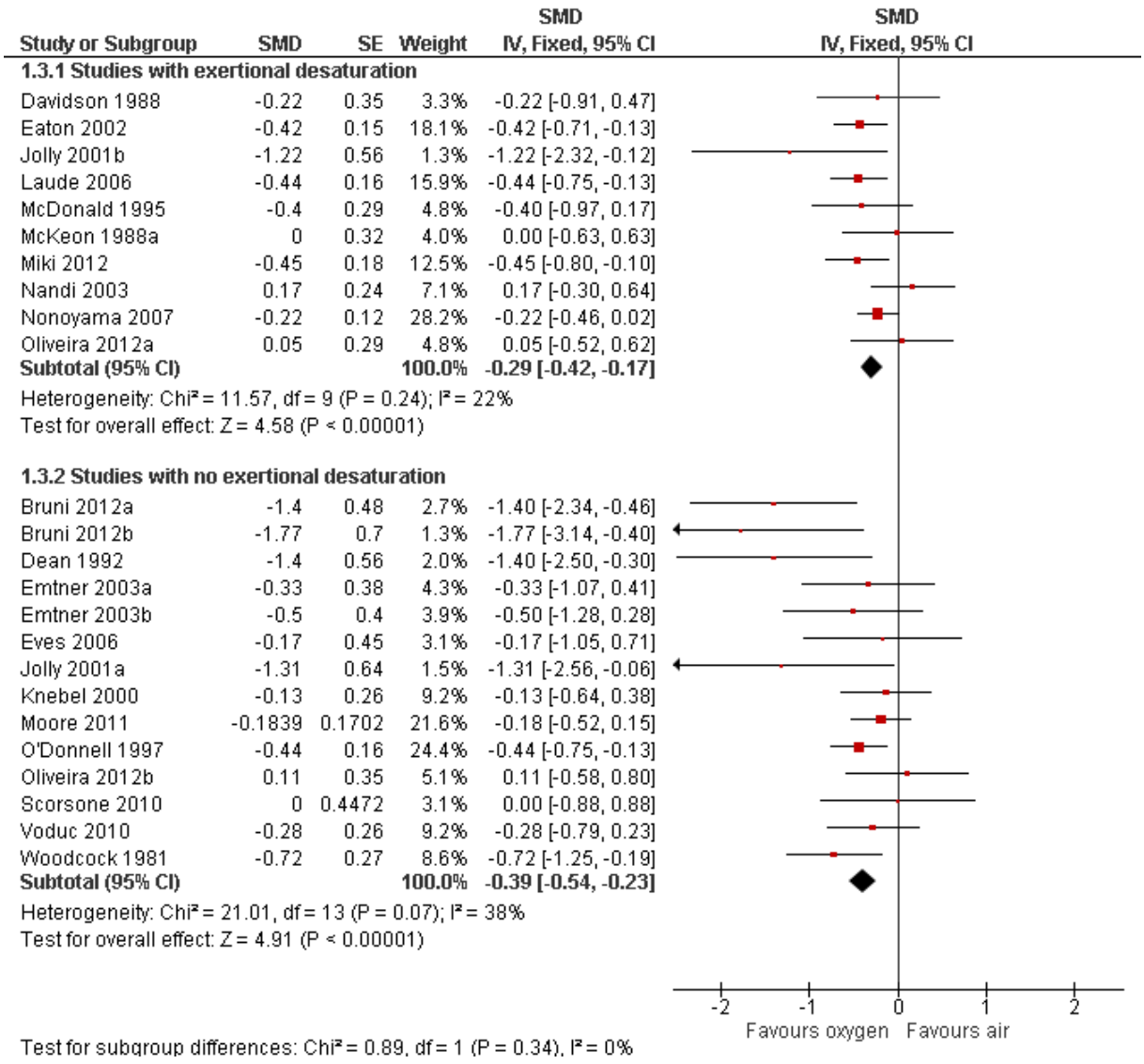
Sensitivity analysis- short-burst oxygen or not using short burst oxygen



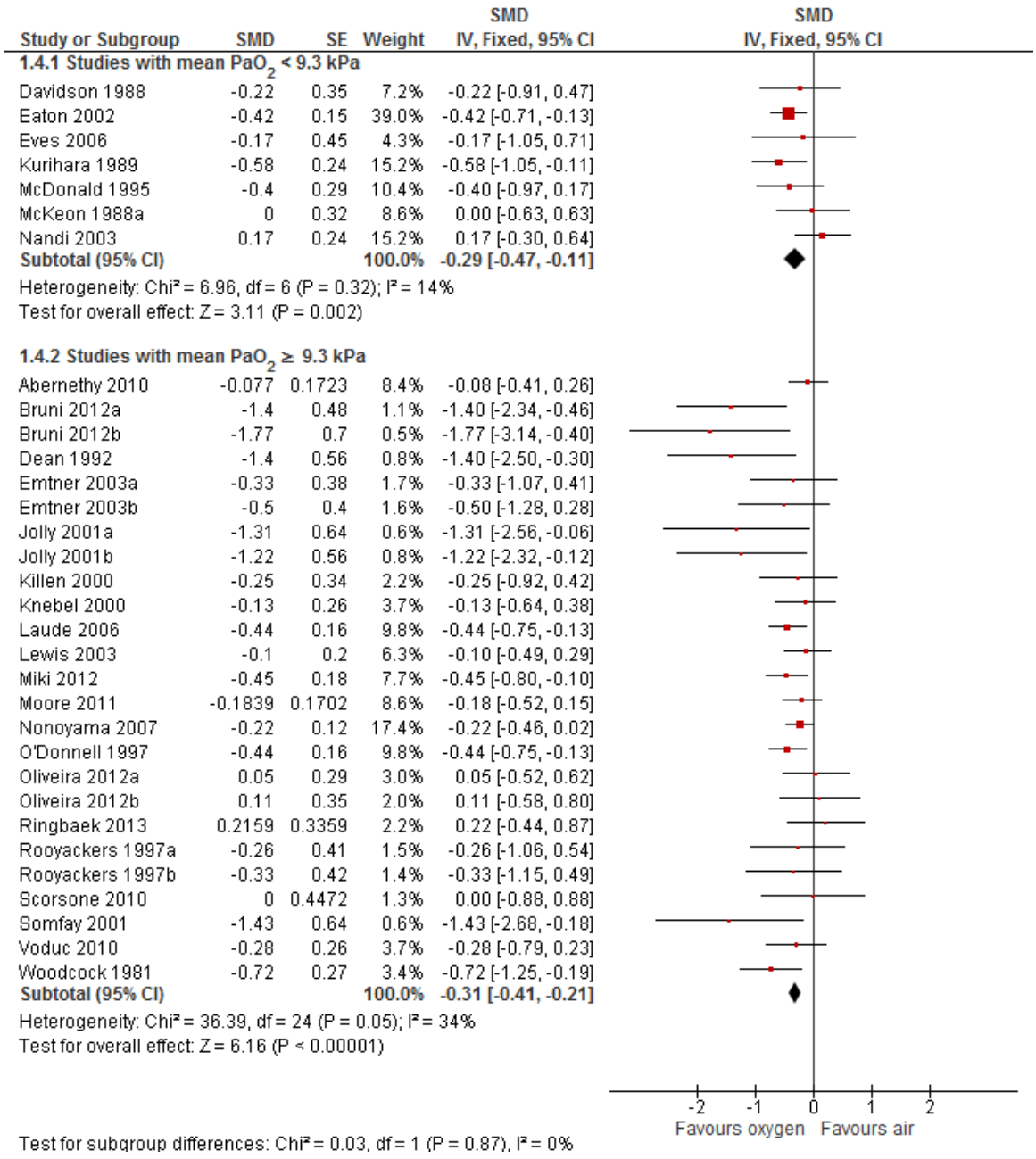
Breathlessness - subgroup analysis - exertional desaturation or no exertional desaturation



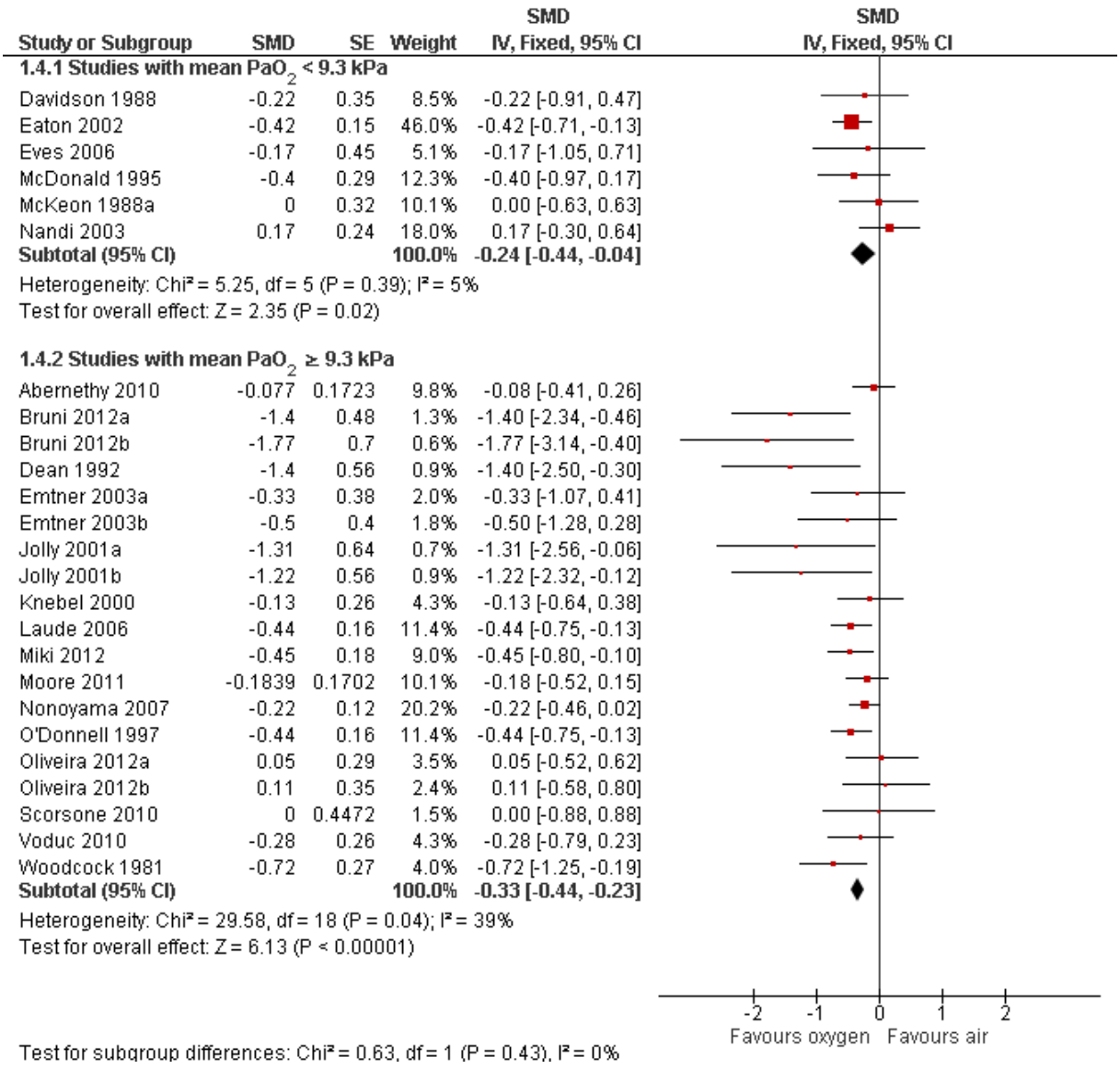
Sensitivity analysis- exertional desaturation or no exertional desaturation



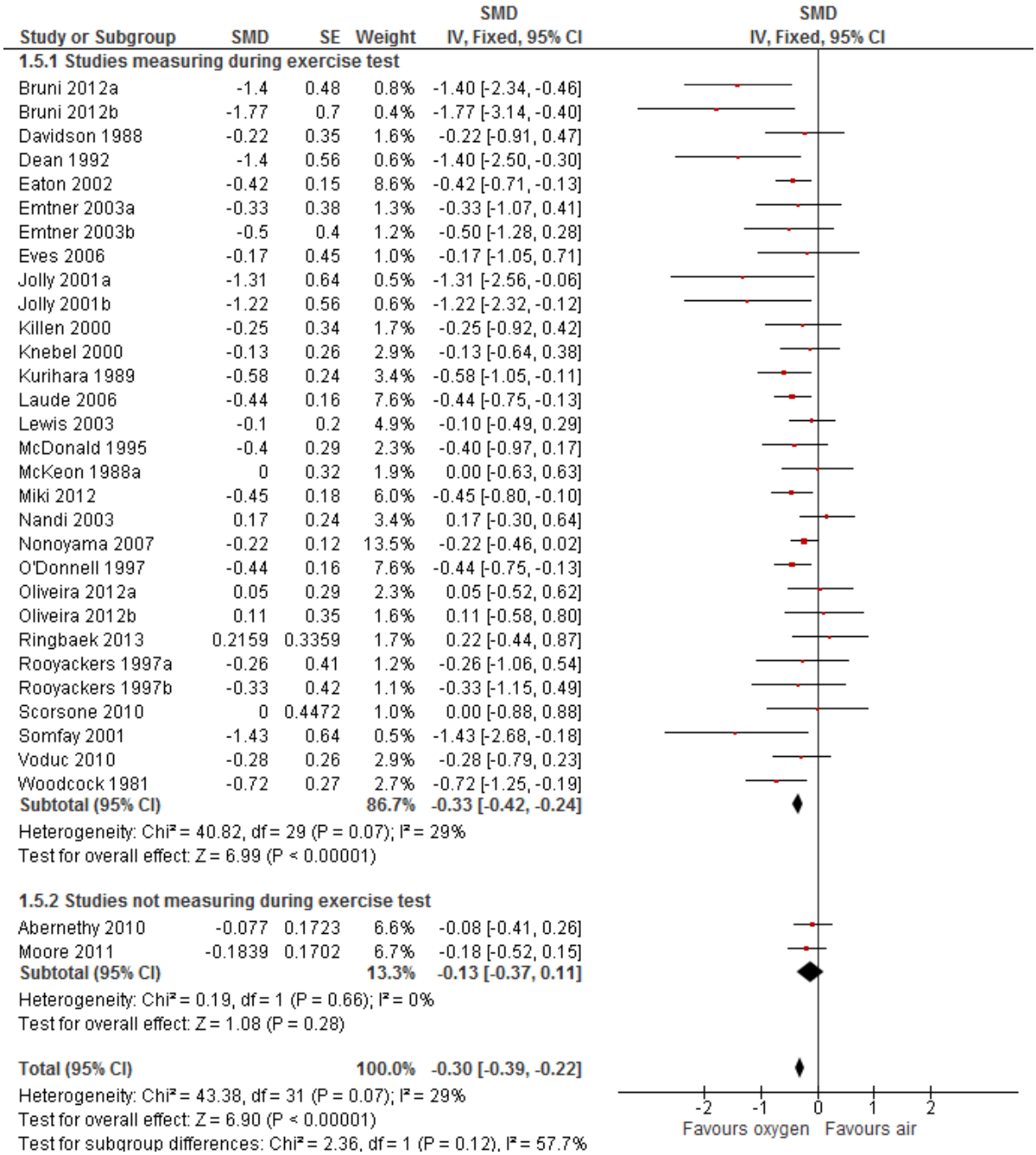
Breathlessness - subgroup analysis - mean PaO2 < 9.3 kPa or ≥ 9.3kPa



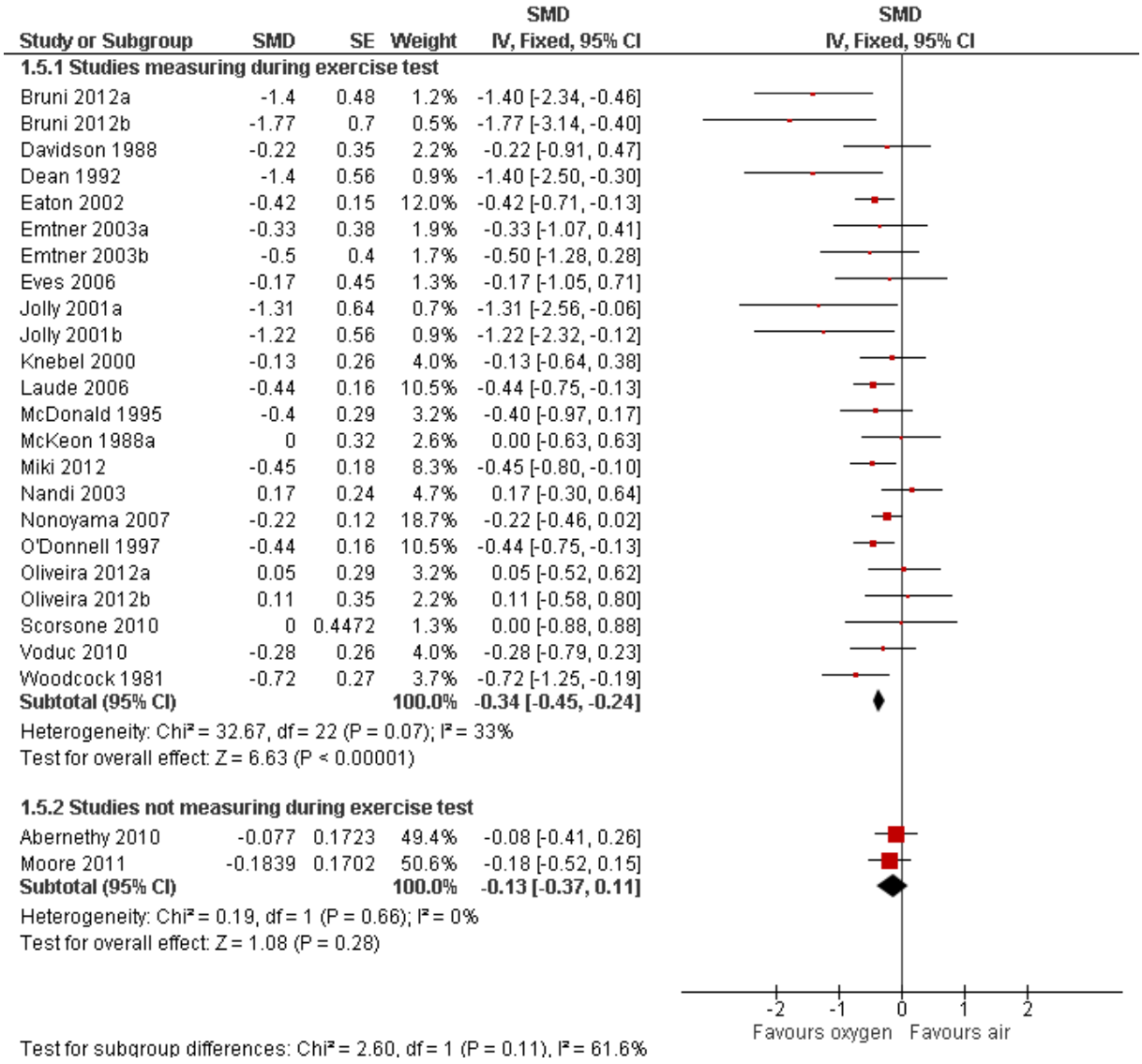
Sensitivity analysis- mean PaO2 < 9.3 kPa or ≥ 9.3kPa



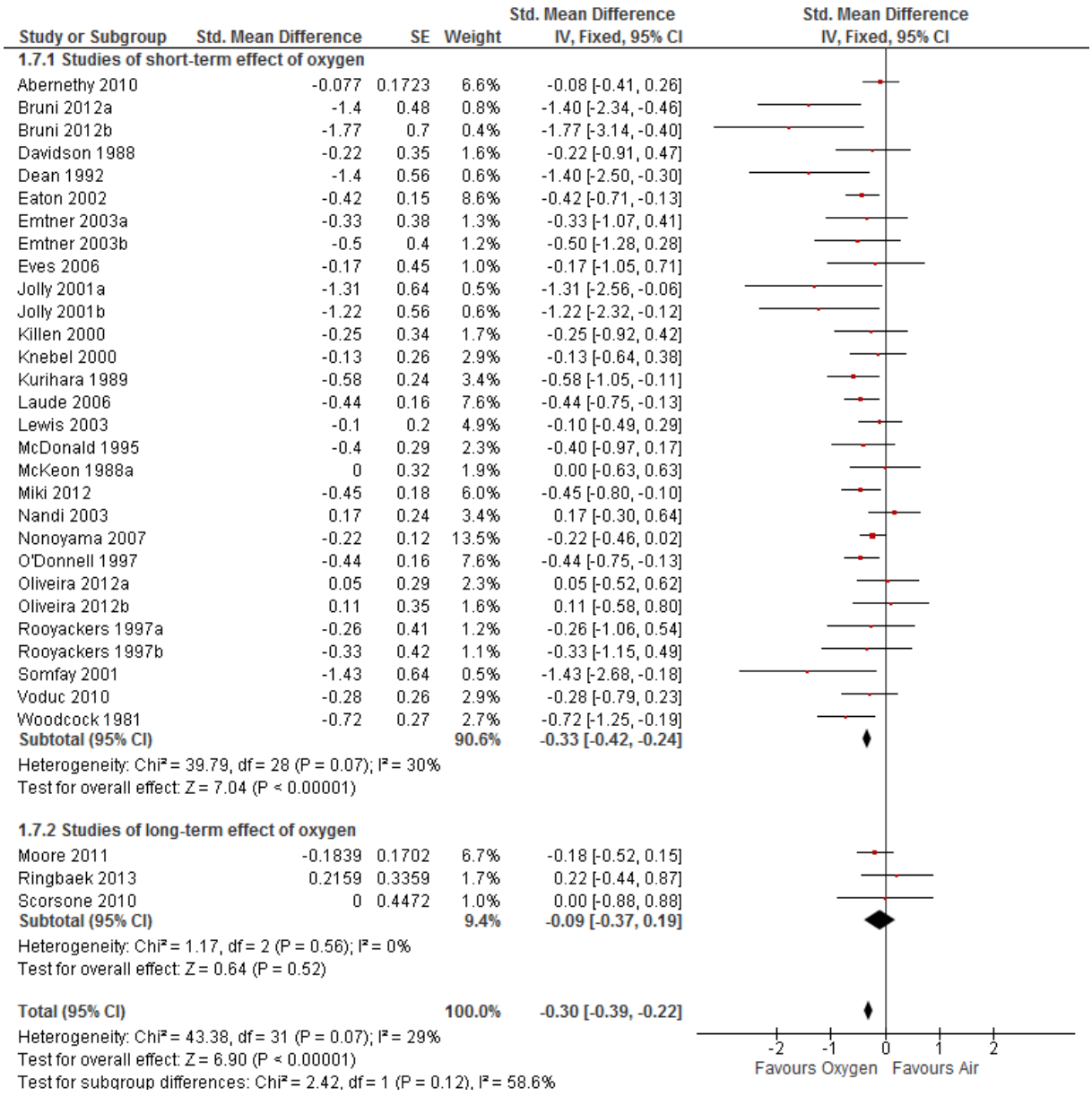
Breathlessness - subgroup analysis - measured during exercise test or not measured during exercise test



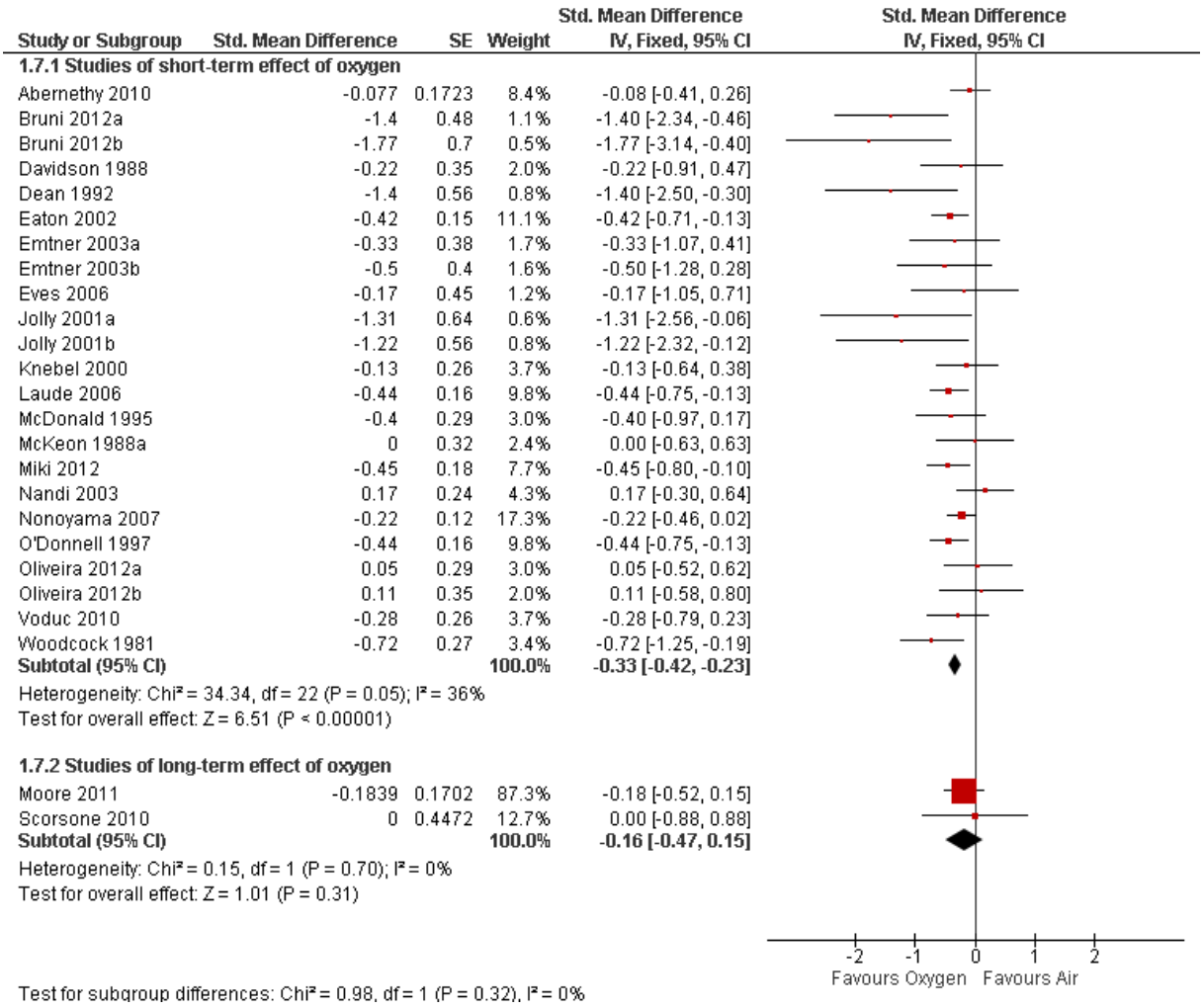
Sensitivity analysis- measured during an exercise test or not measured during an exercise test



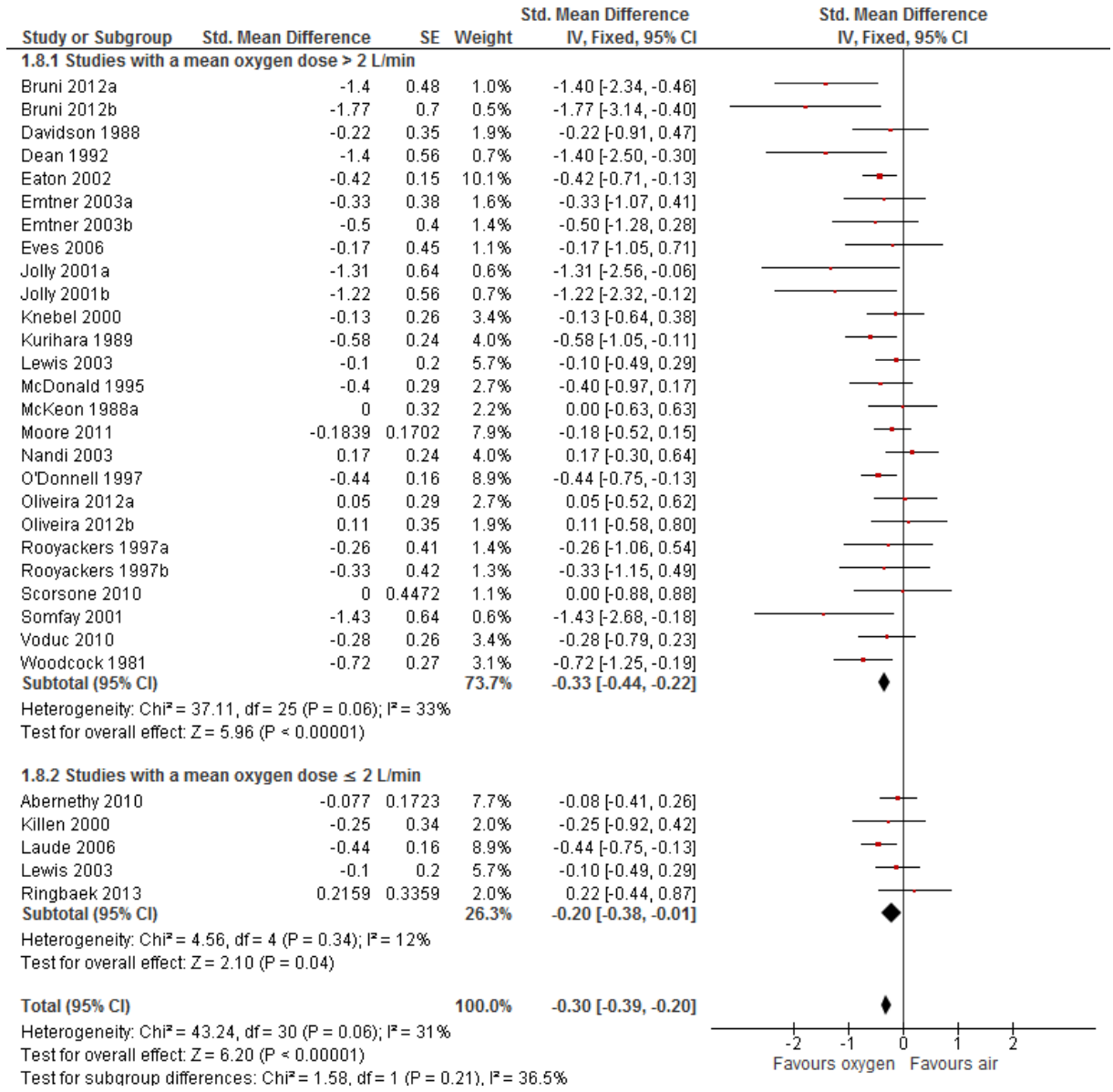
Breathlessness - subgroup analysis - short-term or long-term (training) effect of oxygen



Sensitivity analysis- short-term or long-term (training) effect of oxygen

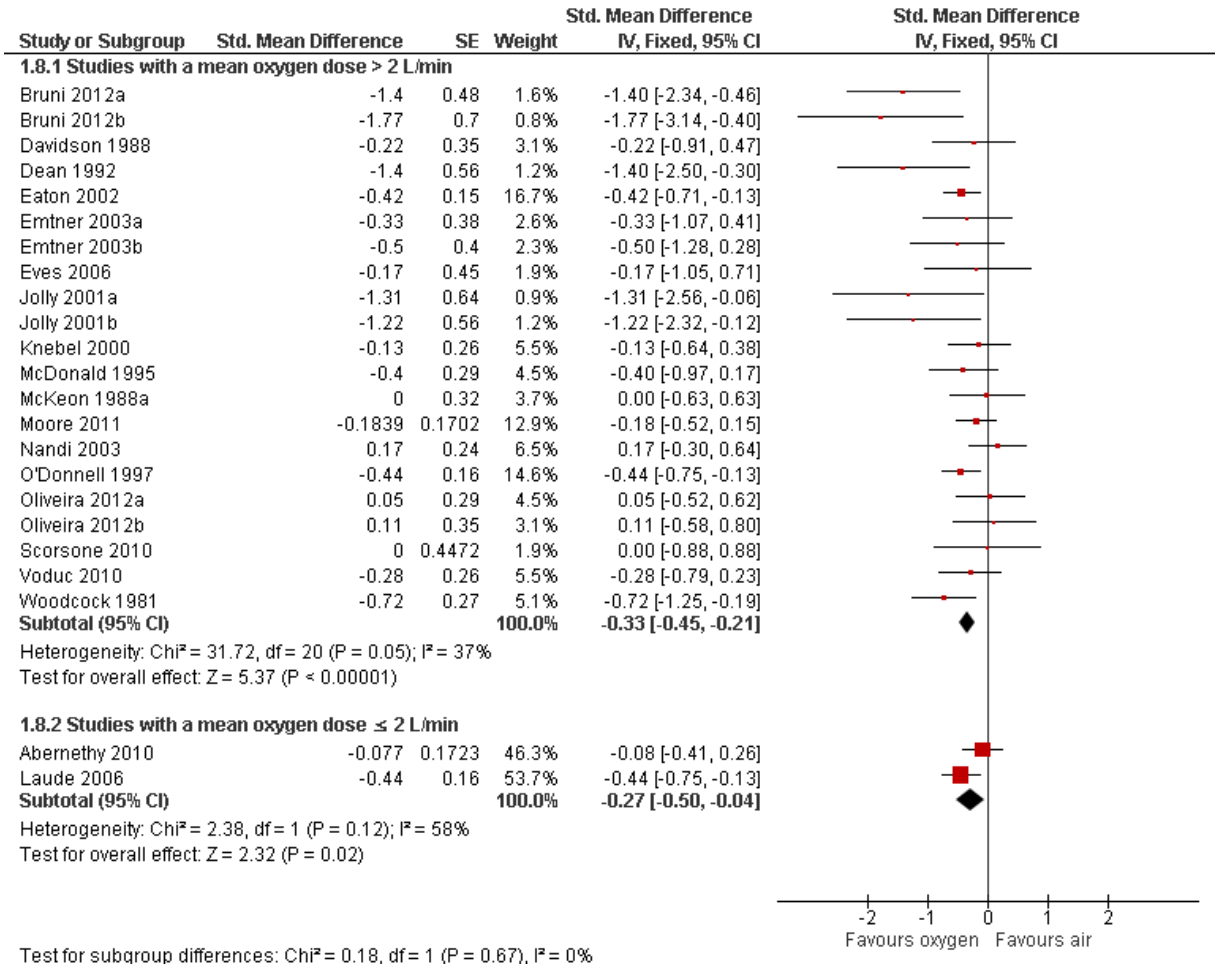


Breathlessness - subgroup analysis - mean oxygen dose > 2 L/min or ≤ 2L /min



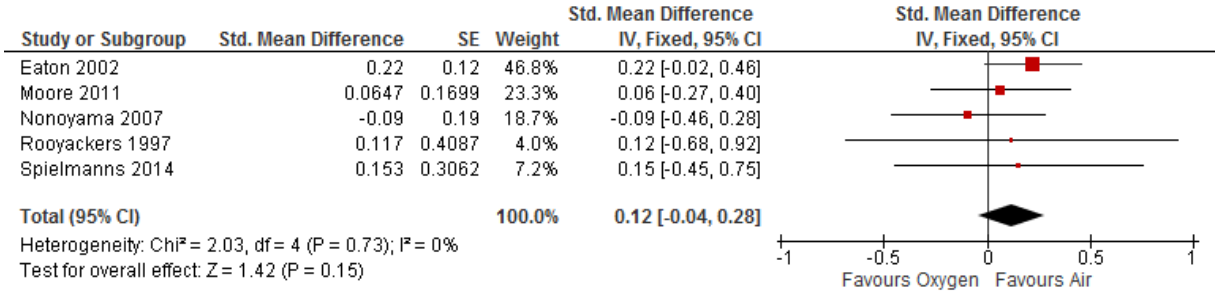
Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Fixed, 95% CI
1.8.1 Studies with a mean oxygen dose > 2 L/min				
Bruni 2012a	-1.4	0.48	1.0%	-1.40 [-2.34, -0.46]
Bruni 2012b	-1.77	0.7	0.5%	-1.77 [-3.14, -0.40]
Davidson 1988	-0.22	0.35	1.9%	-0.22 [-0.91, 0.47]
Dean 1992	-1.4	0.56	0.7%	-1.40 [-2.50, -0.30]
Eaton 2002	-0.42	0.15	10.1%	-0.42 [-0.71, -0.13]
Emtner 2003a	-0.33	0.38	1.6%	-0.33 [-1.07, 0.41]
Emtner 2003b	-0.5	0.4	1.4%	-0.50 [-1.28, 0.28]
Eves 2006	-0.17	0.45	1.1%	-0.17 [-1.05, 0.71]
Jolly 2001a	-1.31	0.64	0.6%	-1.31 [-2.56, -0.06]
Jolly 2001b	-1.22	0.56	0.7%	-1.22 [-2.32, -0.12]
Knebel 2000	-0.13	0.26	3.4%	-0.13 [-0.64, 0.38]
Kurihara 1989	-0.58	0.24	4.0%	-0.58 [-1.05, -0.11]
Lewis 2003	-0.1	0.2	5.7%	-0.10 [-0.49, 0.29]
McDonald 1995	-0.4	0.29	2.7%	-0.40 [-0.97, 0.17]
McKeon 1988a	0	0.32	2.2%	0.00 [-0.63, 0.63]
Moore 2011	-0.1839	0.1702	7.9%	-0.18 [-0.52, 0.15]
Nandi 2003	0.17	0.24	4.0%	0.17 [-0.30, 0.64]
O'Donnell 1997	-0.44	0.16	8.9%	-0.44 [-0.75, -0.13]
Oliveira 2012a	0.05	0.29	2.7%	0.05 [-0.52, 0.62]
Oliveira 2012b	0.11	0.35	1.9%	0.11 [-0.58, 0.80]
Rooyackers 1997a	-0.26	0.41	1.4%	-0.26 [-1.06, 0.54]
Rooyackers 1997b	-0.33	0.42	1.3%	-0.33 [-1.15, 0.49]
Scorsone 2010	0	0.4472	1.1%	0.00 [-0.88, 0.88]
Somfay 2001	-1.43	0.64	0.6%	-1.43 [-2.68, -0.18]
Voduc 2010	-0.28	0.26	3.4%	-0.28 [-0.79, 0.23]
Woodcock 1981	-0.72	0.27	3.1%	-0.72 [-1.25, -0.19]
Subtotal (95% CI)			**73.7%**	**-0.33 [-0.44, -0.22]**
Heterogeneity: Chi² = 37.11, df = 25 (P = 0.06); I² = 33%				
Test for overall effect: Z = 5.96 (P < 0.00001)				
1.8.2 Studies with a mean oxygen dose ≤ 2 L/min				
Abernethy 2010	-0.077	0.1723	7.7%	-0.08 [-0.41, 0.26]
Killen 2000	-0.25	0.34	2.0%	-0.25 [-0.92, 0.42]
Laude 2006	-0.44	0.16	8.9%	-0.44 [-0.75, -0.13]
Lewis 2003	-0.1	0.2	5.7%	-0.10 [-0.49, 0.29]
Ringbaek 2013	0.2159	0.3359	2.0%	0.22 [-0.44, 0.87]
Subtotal (95% CI)			**26.3%**	**-0.20 [-0.38, -0.01]**
Heterogeneity: Chi² = 4.56, df = 4 (P = 0.34); I² = 12%				
Test for overall effect: Z = 2.10 (P = 0.04)				
Total (95% CI)			**100.0%**	**-0.30 [-0.39, -0.20]**
Heterogeneity: Chi² = 43.24, df = 30 (P = 0.06); I² = 31%				
Test for overall effect: Z = 6.20 (P < 0.00001)				
Test for subgroup differences: Chi² = 1.58, df = 1 (P = 0.21), I² = 36.5%				

Sensitivity analysis- mean oxygen dose > 2 L/min or ≤ 2L /min



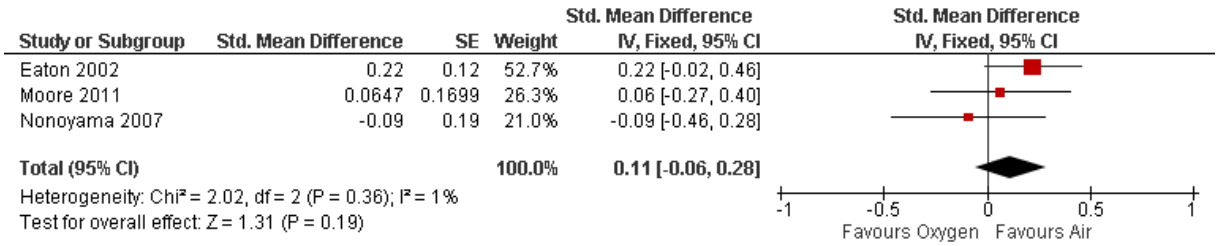
Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Fixed, 95% CI
1.8.1 Studies with a mean oxygen dose > 2 L/min				
Bruni 2012a	-1.4	0.48	1.6%	-1.40 [-2.34, -0.46]
Bruni 2012b	-1.77	0.7	0.8%	-1.77 [-3.14, -0.40]
Davidson 1988	-0.22	0.35	3.1%	-0.22 [-0.91, 0.47]
Dean 1992	-1.4	0.56	1.2%	-1.40 [-2.50, -0.30]
Eaton 2002	-0.42	0.15	16.7%	-0.42 [-0.71, -0.13]
Emtner 2003a	-0.33	0.38	2.6%	-0.33 [-1.07, 0.41]
Emtner 2003b	-0.5	0.4	2.3%	-0.50 [-1.28, 0.28]
Eves 2006	-0.17	0.45	1.9%	-0.17 [-1.05, 0.71]
Jolly 2001a	-1.31	0.64	0.9%	-1.31 [-2.56, -0.06]
Jolly 2001b	-1.22	0.56	1.2%	-1.22 [-2.32, -0.12]
Knebel 2000	-0.13	0.26	5.5%	-0.13 [-0.64, 0.38]
McDonald 1995	-0.4	0.29	4.5%	-0.40 [-0.97, 0.17]
McKeon 1988a	0	0.32	3.7%	0.00 [-0.63, 0.63]
Moore 2011	-0.1839	0.1702	12.9%	-0.18 [-0.52, 0.15]
Nandi 2003	0.17	0.24	6.5%	0.17 [-0.30, 0.64]
O'Donnell 1997	-0.44	0.16	14.6%	-0.44 [-0.75, -0.13]
Oliveira 2012a	0.05	0.29	4.5%	0.05 [-0.52, 0.62]
Oliveira 2012b	0.11	0.35	3.1%	0.11 [-0.58, 0.80]
Scorsone 2010	0	0.4472	1.9%	0.00 [-0.88, 0.88]
Voduc 2010	-0.28	0.26	5.5%	-0.28 [-0.79, 0.23]
Woodcock 1981	-0.72	0.27	5.1%	-0.72 [-1.25, -0.19]
Subtotal (95% CI)			**100.0%**	**-0.33 [-0.45, -0.21]**
Heterogeneity: Chi² = 31.72, df = 20 (P = 0.05); I² = 37%				
Test for overall effect: Z = 5.37 (P < 0.00001)				
1.8.2 Studies with a mean oxygen dose ≤ 2 L/min				
Abernethy 2010	-0.077	0.1723	46.3%	-0.08 [-0.41, 0.26]
Laude 2006	-0.44	0.16	53.7%	-0.44 [-0.75, -0.13]
Subtotal (95% CI)			**100.0%**	**-0.27 [-0.50, -0.04]**
Heterogeneity: Chi² = 2.38, df = 1 (P = 0.12); I² = 58%				
Test for overall effect: Z = 2.32 (P = 0.02)				
Test for subgroup differences: Chi² = 0.18, df = 1 (P = 0.67), I² = 0%				

Health-related quality of life – all trials



Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Fixed, 95% CI
Eaton 2002	0.22	0.12	46.8%	0.22 [-0.02, 0.46]
Moore 2011	0.0647	0.1699	23.3%	0.06 [-0.27, 0.40]
Nonoyama 2007	-0.09	0.19	18.7%	-0.09 [-0.46, 0.28]
Rooyackers 1997	0.117	0.4087	4.0%	0.12 [-0.68, 0.92]
Spielmanns 2014	0.153	0.3062	7.2%	0.15 [-0.45, 0.75]
Total (95% CI)			**100.0%**	**0.12 [-0.04, 0.28]**
Heterogeneity: Chi² = 2.03, df = 4 (P = 0.73); I² = 0%				
Test for overall effect: Z = 1.42 (P = 0.15)				

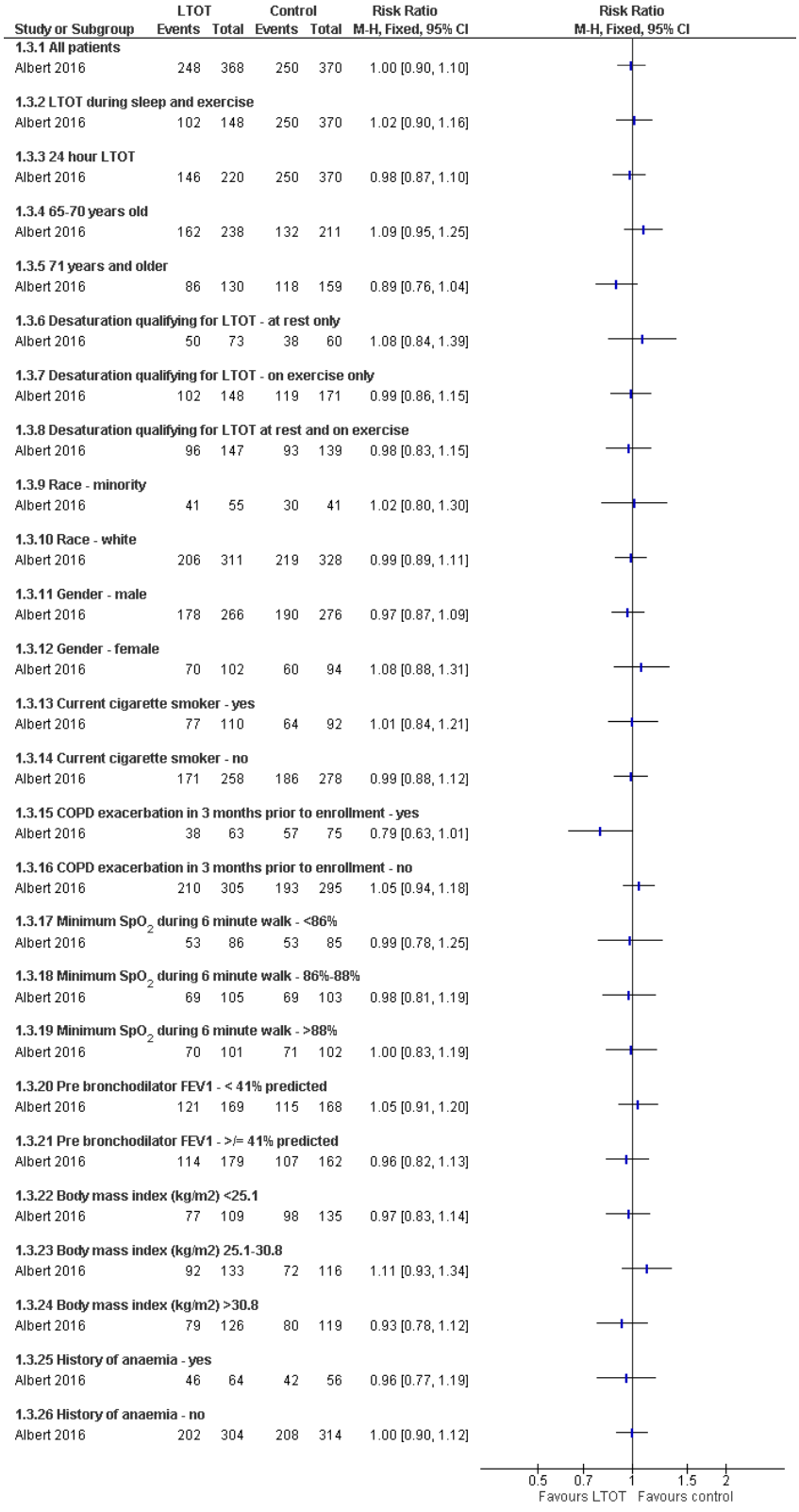
Sensitivity analysis- Health-related quality of life



Long term oxygen therapy

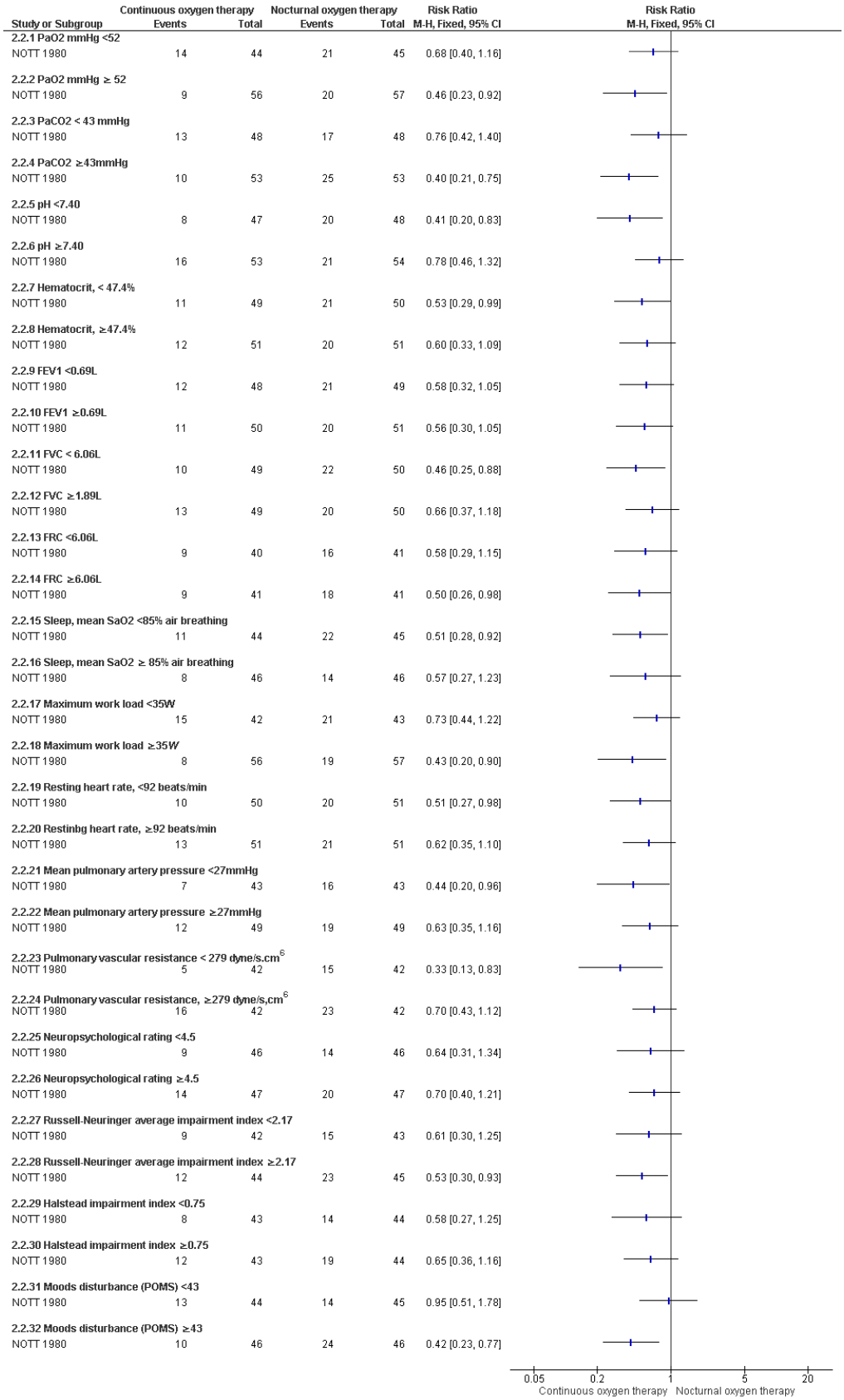
Long term oxygen therapy vs no long term oxygen therapy

Mortality – subgroup analyses


LTOT
Control
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
1.3.1 All patients
Albert 2016 248 368 250 370 1.00 [0.90, 1.10]
1.3.2 LTOT during sleep and exercise
Albert 2016 102 148 250 370 1.02 [0.90, 1.16]
1.3.3 24 hour LTOT
Albert 2016 146 220 250 370 0.98 [0.87, 1.10]
1.3.4 65-70 years old
Albert 2016 162 238 132 211 1.09 [0.95, 1.25]
1.3.5 71 years and older
Albert 2016 86 130 118 159 0.89 [0.76, 1.04]
1.3.6 Desaturation qualifying for LTOT - at rest only
Albert 2016 50 73 38 60 1.08 [0.84, 1.39]
1.3.7 Desaturation qualifying for LTOT - on exercise only
Albert 2016 102 148 119 171 0.99 [0.86, 1.15]
1.3.8 Desaturation qualifying for LTOT at rest and on exercise
Albert 2016 96 147 93 139 0.98 [0.83, 1.15]
1.3.9 Race - minority
Albert 2016 41 55 30 41 1.02 [0.80, 1.30]
1.3.10 Race - white
Albert 2016 206 311 219 328 0.99 [0.89, 1.11]
1.3.11 Gender - male
Albert 2016 178 266 190 276 0.97 [0.87, 1.09]
1.3.12 Gender - female
Albert 2016 70 102 60 94 1.08 [0.88, 1.31]
1.3.13 Current cigarette smoker - yes
Albert 2016 77 110 64 92 1.01 [0.84, 1.21]
1.3.14 Current cigarette smoker - no
Albert 2016 171 258 186 278 0.99 [0.88, 1.12]
1.3.15 COPD exacerbation in 3 months prior to enrollment - yes
Albert 2016 38 63 57 75 0.79 [0.63, 1.01]
1.3.16 COPD exacerbation in 3 months prior to enrollment - no
Albert 2016 210 305 193 295 1.05 [0.94, 1.18]
1.3.17 Minimum SpO2 during 6 minute walk - <86%
Albert 2016 53 86 53 85 0.99 [0.78, 1.25]
1.3.18 Minimum SpO2 during 6 minute walk - 86%-88%
Albert 2016 69 105 69 103 0.98 [0.81, 1.19]
1.3.19 Minimum SpO2 during 6 minute walk - >88%
Albert 2016 70 101 71 102 1.00 [0.83, 1.19]
1.3.20 Pre bronchodilator FEV1 - < 41% predicted
Albert 2016 121 169 115 168 1.05 [0.91, 1.20]
1.3.21 Pre bronchodilator FEV1 - >/= 41% predicted
Albert 2016 114 179 107 162 0.96 [0.82, 1.13]
1.3.22 Body mass index (kg/m2) <25.1
Albert 2016 77 109 98 135 0.97 [0.83, 1.14]
1.3.23 Body mass index (kg/m2) 25.1-30.8
Albert 2016 92 133 72 116 1.11 [0.93, 1.34]
1.3.24 Body mass index (kg/m2) >30.8
Albert 2016 79 126 80 119 0.93 [0.78, 1.12]
1.3.25 History of anaemia - yes
Albert 2016 46 64 42 56 0.96 [0.77, 1.19]
1.3.26 History of anaemia - no
Albert 2016 202 304 208 314 1.00 [0.90, 1.12]
0.5 0.7 1 1.5 2
Favours LTOT Favours control

Continuous oxygen therapy vs nocturnal oxygen therapy

Mortality- subgroup analysis


Continuous oxygen therapy
Nocturnal oxygen therapy
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
2.2.1 PaO2 mmHg <52
NOTT 1980 14 44 21 45 0.68 [0.40, 1.16]
2.2.2 PaO2 mmHg ≥ 52
NOTT 1980 9 56 20 57 0.46 [0.23, 0.92]
2.2.3 PaCO2 < 43 mmHg
NOTT 1980 13 48 17 48 0.76 [0.42, 1.40]
2.2.4 PaCO2 ≥43mmHg
NOTT 1980 10 53 25 53 0.40 [0.21, 0.75]
2.2.5 pH <7.40
NOTT 1980 8 47 20 48 0.41 [0.20, 0.83]
2.2.6 pH ≥7.40
NOTT 1980 16 53 21 54 0.78 [0.46, 1.32]
2.2.7 Hematocrit, < 47.4%
NOTT 1980 11 49 21 50 0.53 [0.29, 0.99]
2.2.8 Hematocrit, ≥47.4%
NOTT 1980 12 51 20 51 0.60 [0.33, 1.09]
2.2.9 FEV1 <0.69L
NOTT 1980 12 48 21 49 0.58 [0.32, 1.05]
2.2.10 FEV1 ≥0.69L
NOTT 1980 11 50 20 51 0.56 [0.30, 1.05]
2.2.11 FVC < 6.06L
NOTT 1980 10 49 22 50 0.46 [0.25, 0.88]
2.2.12 FVC ≥1.89L
NOTT 1980 13 49 20 50 0.66 [0.37, 1.18]
2.2.13 FRC <6.06L
NOTT 1980 9 40 16 41 0.58 [0.29, 1.15]
2.2.14 FRC ≥6.06L
NOTT 1980 9 41 18 41 0.50 [0.26, 0.98]
2.2.15 Sleep, mean SaO2 <85% air breathing
NOTT 1980 11 44 22 45 0.51 [0.28, 0.92]
2.2.16 Sleep, mean SaO2 ≥ 85% air breathing
NOTT 1980 8 46 14 46 0.57 [0.27, 1.23]
2.2.17 Maximum work load <35W
NOTT 1980 15 42 21 43 0.73 [0.44, 1.22]
2.2.18 Maximum work load ≥35W
NOTT 1980 8 56 19 57 0.43 [0.20, 0.90]
2.2.19 Resting heart rate, <92 beats/min
NOTT 1980 10 50 20 51 0.51 [0.27, 0.98]
2.2.20 Restinbg heart rate, ≥92 beats/min
NOTT 1980 13 51 21 51 0.62 [0.35, 1.10]
2.2.21 Mean pulmonary artery pressure <27mmHg
NOTT 1980 7 43 16 43 0.44 [0.20, 0.96]
2.2.22 Mean pulmonary artery pressure ≥27mmHg
NOTT 1980 12 49 19 49 0.63 [0.35, 1.16]
2.2.23 Pulmonary vascular resistance < 279 dyne/s.cm6
NOTT 1980 5 42 15 42 0.33 [0.13, 0.83]
2.2.24 Pulmonary vascular resistance, ≥279 dyne/s,cm6
NOTT 1980 16 42 23 42 0.70 [0.43, 1.12]
2.2.25 Neuropsychological rating <4.5
NOTT 1980 9 46 14 46 0.64 [0.31, 1.34]
2.2.26 Neuropsychological rating ≥4.5
NOTT 1980 14 47 20 47 0.70 [0.40, 1.21]
2.2.27 Russell-Neuringer average impairment index <2.17
NOTT 1980 9 42 15 43 0.61 [0.30, 1.25]
2.2.28 Russell-Neuringer average impairment index ≥2.17
NOTT 1980 12 44 23 45 0.53 [0.30, 0.93]
2.2.29 Halstead impairment index <0.75
NOTT 1980 8 43 14 44 0.58 [0.27, 1.25]
2.2.30 Halstead impairment index ≥0.75
NOTT 1980 12 43 19 44 0.65 [0.36, 1.16]
2.2.31 Moods disturbance (POMS) <43
NOTT 1980 13 44 14 45 0.95 [0.51, 1.78]
2.2.32 Moods disturbance (POMS) ≥43
NOTT 1980 10 46 24 46 0.42 [0.23, 0.77]
0.05
0.2
1
5
20
Continuous oxygen therapy
Nocturnal oxygen therapy

Appendix G – GRADE tables

Ambulatory and short burst oxygen therapy

Oxygen vs. air

No. of studies	Study design	Sample size	Effect size (95% CI)	Equivalent mean difference on the modified Borg Scale*	Risk of bias	Inconsistency	Indirectness	Imprecision**	Quality
Breathlessness – all trials (lower numbers favour oxygen therapy)									
32	RCTs	865	SMD -0.30 (-0.39, -0.22)	MD -0.42 (-0.54,-0.30)	Serious[1]	Not serious	Not serious	Not serious	Moderate
Subgroup analyses - breathlessness									
Breathlessness – short burst oxygen before exercise (lower numbers favour oxygen therapy)									
4	RCTs	90	SMD -0.03 (-0.28, 0.22)	MD -0.04 (-0.39, 0.30)	Very serious[4]	Not serious	Not serious	Not serious	Low
Breathlessness – ambulatory oxygen (lower numbers favour oxygen therapy)									
28	RCTs	775	SMD -0.34 (-0.43, -0.25)	MD -0.47 (-0.56, -0.35)	Not serious	Not serious	Not serious	Not serious	High
Breathlessness – desaturation during exercise (baseline SaO_2 <88% or mean <8kPa on exertion) (lower numbers favour oxygen therapy)									
16	RCTs	Not reported[5]	SMD -0.28 (-0.39, -0.17)	MD -0.39 (-0.5, -0.24)	Very Serious[4]	Not serious	Not serious	Not serious	Low
Breathlessness – no desaturation during exercise (SaO_2 ≥88% or mean ≥8kPa on exertion) (lower numbers favour oxygen therapy)									
15	RCTs	Not reported[5]	SMD -0.40 (-0.56, -0.25)	MD -0.55 (-0.78, -0.35)	Not serious	Serious[3]	Not serious	Not serious	Moderate
Breathlessness – mean arterial oxygen PaO_2 <9.3kPa at baseline (lower numbers favour oxygen therapy)									
7	RCTs	Not reported[5]	SMD -0.29 (-0.47, -0.11)	MD -0.40 (-0.65, -0.15)	Very serious[4]	Not serious	Not serious	Not serious	Low
Breathlessness – mean arterial oxygen PaO_2 ≥9.3kPa at baseline (lower numbers favour oxygen therapy)									

No. of studies	Study design	Sample size	Effect size (95% CI)	Equivalent mean difference on the modified Borg Scale*	Risk of bias	Inconsistency	Indirectness	Imprecision**	Quality
25	RCTs	Not reported[5]	SMD -0.31 (-0.41, -0.21)	MD -0.43 (-0.57, -0.29)	Not serious	Serious[3]	Not serious	Not serious	Moderate
Breathlessness - measured during exercise test (lower numbers favour oxygen therapy)									
30	RCTs	591	SMD -0.33 (-0.42, -0.24)	MD -0.46 (-0.58, -0.33)	Serious[1]	Not serious	Not serious	Not serious	Moderate
Breathlessness – measured in daily life (lower numbers favour oxygen therapy)									
2	RCTs	274	SMD -0.13 (-0.37, 0.11)	MD -0.18 (-0.51, 0.15)	Not serious	Not serious	Not serious	Not serious	High
Breathlessness - short term effects of oxygen (lower numbers favour oxygen therapy)									
29	RCTs	Not reported[5]	SMD -0.33 (-0.42, -0.24)	MD -0.46 (-0.58, -0.33)	Serious[1]	Not serious	Not serious	Not serious	Moderate
Breathlessness - long term effects of oxygen (lower numbers favour oxygen therapy)									
3	RCTs	Not reported[5]	SMD -0.09 (-0.37, 0.19)	MD -0.12 (-0.51, 0.26)	Not serious	Not serious	Not serious	Not serious	High
Breathlessness - mean oxygen dose > 2 L/min (lower numbers favour oxygen therapy)									
26	RCTs	Not reported[5]	SMD -0.33 (-0.44, -0.22)	MD -0.46 (-0.61, -0.30)	Not serious	Not serious	Not serious	Not serious	High
Breathlessness - mean oxygen dose ≤ 2 L/min (lower numbers favour oxygen therapy)									
5	RCTs	Not reported[5]	SMD -0.20 (-0.38, -0.01)	MD -0.28 (-0.53, -0.01)	Not serious	Not serious	Not serious	Not serious	High
Health related quality of life (higher numbers favour oxygen therapy)									
5	RCTs	267	SMD -0.12 (-0.04, 0.28)	N/A	Serious[1]	Not serious	Not serious	Serious[2]	Low

*Estimated based on a standard deviation of 1.385 for the modified Borg Scale, the pooled standard deviation in this dataset.

** MD data used for estimation of imprecision using MID for Borg scale.

PaO_2 at baseline ranged from 7.7 to 11.3 kPa in 30/42 studies. The remaining 12 studies provided baseline oxygen saturation ranging from 90% to 97%

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

1. >33% of weighted data from studies at moderate or high risk of bias
2. 95% confidence interval crosses one end of a defined MID interval

No. of studies	Study design	Sample size	Effect size (95% CI)	Equivalent mean difference on the modified Borg Scale*	Risk of bias	Inconsistency	Indirectness	Imprecision**	Quality

3. I^2 between 33.3% and 66.7%
4. >33% of weighted data from studies at high risk of bias
5. Numbers not reported in the Cochrane review.

Oxygen vs. air (sensitivity analysis excluding studies at high risk of bias)

No. of studies	Study design	Sample size	Effect size (95% CI)	Equivalent mean difference on the modified Borg Scale*	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Breathlessness – all trials (lower numbers favour oxygen therapy)									
25	RCTs	Not reported	SMD -0.31 (-0.40, -0.22)	MD -0.43 (-0.54, -0.30)	Serious[1]	Not serious	Not serious	Not serious	Moderate
Subgroup analyses									
Breathlessness – studies using short burst oxygen before exercise (lower numbers favour oxygen therapy)									
2	RCTs	Not reported	SMD 0.11 (-0.27, 0.49)	MD 0.15 (-0.37, 0.67)	Very serious[4]	Not serious	Not serious	Not serious	Low
Breathlessness – studies not using short burst oxygen (lower numbers favour oxygen therapy)									
28	RCTs	Not reported	SMD -0.34 (-0.43, -0.24)	MD -0.47 (-0.60, -0.33)	Not serious	Not serious	Not serious	Not serious	High
Breathlessness – studies with desaturation during exercise (SaO_2 <88% or mean <8kPa on exertion) (lower numbers favour oxygen therapy)									
10	RCTs	Not reported	SMD -0.29 (-0.42, -0.17)	MD -0.40 (-0.58, -0.24)	Not serious	Not serious	Not serious	Not serious	High
Breathlessness – studies without desaturation during exercise (lower numbers favour oxygen therapy)									
14	RCTs	Not reported	SMD -0.39 (-0.54, -0.22)	MD -0.54 (-0.75, -0.30)	Not serious	Serious[3]	Not serious	Not serious	Moderate
Breathlessness – studies with mean PaO_2 <9.3kPa at baseline (lower numbers favour oxygen therapy)									

No. of studies	Study design	Sample size	Effect size (95% CI)	Equivalent mean difference on the modified Borg Scale*	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
6	RCTs	Not reported	SMD -0.24 (-0.44, -0.04)	MD -0.33 (-0.61, -0.06)	Not serious	Not serious	Not serious	Not serious	High
Breathlessness – mean arterial oxygen PaO_2 >9.3kPa at baseline (lower numbers favour oxygen therapy)									
19	RCTs	Not reported	SMD -0.33 (-0.44, -0.23)	MD -0.45 (-0.6, -0.31)	Not serious	Serious[3]	Not serious	Not serious	Moderate
Studies measuring breathlessness during exercise test (lower numbers favour oxygen therapy)									
23	RCTs	Not reported	SMD -0.34 (-0.45, -0.24)	MD -0.47 (-0.63, -0.33)	Serious[1]	Not serious	Not serious	Not serious	Moderate
Studies measuring breathlessness in daily life (lower numbers favour oxygen therapy)									
2	RCTs	Not reported	SMD -0.13 (-0.37, 0.11)	MD -0.18 (-0.51, 0.15)	Not serious	Not serious	Not serious	Not serious	High
Studies of short term effects of oxygen (lower numbers favour oxygen therapy)									
23	RCTs	Not reported	SMD -0.33 (-0.42, -0.23)	MD -0.46 (-0.58, -0.33)	Serious[1]	Not serious	Not serious	Not serious	Moderate
Studies of long term effects of oxygen (lower numbers favour oxygen therapy)									
2	RCTs	Not reported	SMD -0.16 (-0.47, 0.15)	MD -0.22 (-0.65, 0.21)	Not serious	Not serious	Not serious	Not serious	High
Studies with a mean oxygen dose > 2 L/min (lower numbers favour oxygen therapy)									
20	RCTs	Not reported	SMD -0.33 (-0.45, -0.22)	MD -0.46 (-0.62, -0.30)	Not serious	Not serious	Not serious	Not serious	High
Studies with a mean oxygen dose ≤ 2 L/min (lower numbers favour oxygen therapy)									
2	RCTs	Not reported	SMD -0.27 (-0.50, -0.04)	MD -0.37 (-0.69, -0.01)	Not serious	Not serious	Not serious	Not serious	High
Health related quality of life (higher numbers favour oxygen therapy)									
4	RCTs	Not reported	SMD -0.11 (-0.06, 0.28)	N/A	Serious[1]	Not serious	Not serious	Serious[2]	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Equivalent mean difference on the modified Borg Scale*	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality

*Estimated based on a standard deviation of 1.385 for the modified Borg Scale, the pooled standard deviation in this dataset

PaO_2 at baseline ranged from 7.7 to 11.3 kPa in 30/42 studies. The remaining 12 studies provided baseline oxygen saturation ranging from 90% to 97%

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

1. >33% of weighted data from studies at moderate or high risk of bias
2. 95% confidence interval crosses one end of a defined MID interval
3. I^2 between 33.3% and 66.7%
4. >33% of weighted data from studies at high risk of bias

Long term oxygen therapy

Long term oxygen therapy vs no long term oxygen therapy

People with COPD and moderate resting or exercise-induced desaturation (SpO_2 89-93% - approximately 7.5kPa – 9.2kPa), (Albert 2016)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Mortality – lower numbers favour LTOT										
1 (Albert 2016)	RCT	738	HR 0.90 (0.64, 1.25) RR 0.91 (0.67, 1.23)	5.7 per 100 person years	5.1 (3.6, 7.1)	Serious[1]	N/A	Not serious	Serious[2]	Low
Mortality - subgroup analyses – lower numbers favour LTOT										
LTOT during sleep and exercise only (estimated reported 11.3 (±5.0) hours per day)										
1 (Albert 2016)	RCT	513	HR 1.05 (0.83, 1.32)	36.4 per 100 person years	38.2 (30.2, 48.0)	Serious[1]	N/A	Not serious	Serious[2]	Low
24 hours/day LTOT (estimated reported 15.1 (±6.2) hours per day)										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (Albert 2016)	RCT	590	HR 0.88 (0.72, 1.08)	36.4 per 100 person years	32.0 (26.2, 39.3)	Serious[1]	N/A	Not serious	Serious[2]	Low
Desaturation qualifying for LTOT at rest only										
1 (Albert 2016)	RCT	133	HR 0.96 (0.63, 1.47)	34.4 per 100 person years	33.0 (21.6, 50.7)	Serious[1]	N/A	Not serious	Serious[2]	Low
Desaturation qualifying for LTOT during exercise only										
1 (Albert 2016)	RCT	319	HR 0.95 (0.73, 1.24)	39.3 per 100 person years	37.3 (28.7, 48.7)	Serious[1]	N/A	Not serious	Serious[2]	Low
Desaturation qualifying for LTOT at rest and during exercise										
1 (Albert 2016)	RCT	286	HR 0.95 (0.72, 1.27)	34 per 100 person years	32.3 (24.5, 43.2)	Serious[1]	N/A	Not serious	Serious[2]	Low
Age – 65-70 years old										
1 (Albert 2016)	RCT	449	HR 1.11 (0.88, 1.40)	31.7 per 100 person years	35.2 (27.9, 44.4)	Serious[1]	N/A	Not serious	Serious[2]	Low
Age – 71 or older										
1 (Albert 2016)	RCT	289	HR 0.75 (0.57, 0.99)	43.6 per 100 person years	32.7 (24.9, 43.2)	Serious[1]	N/A	Not serious	Not serious	Moderate
Race – non-white										
1 (Albert 2016)	RCT	96	HR 0.86 (0.53, 1.37)	44.2 per 100 person years	38.0 (23.4, 60.6)	Serious[1]	N/A	Not serious	Serious[2]	Low
Race – white										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (Albert 2016)	RCT	639	HR 0.95 (0.78, 1.15)	35.5 per 100 person years	33.7 (27.7, 40.8)	Serious[1]	N/A	Not serious	Serious[2]	Low
Gender – male										
1 (Albert 2016)	RCT	542	HR 0.87 (0.71, 1.07)	39.1 per 100 person years	34.0 (27.8, 41.8)	Serious[1]	N/A	Not serious	Serious[2]	Low
Gender female										
1 (Albert 2016)	RCT	104	HR 1.15 (0.82, 1.63)	29.9 per 100 person years	34.4 (24.5, 48.7)	Serious[1]	N/A	Not serious	Serious[2]	Low
Current cigarette smoker – yes										
1 (Albert 2016)	RCT	202	HR 0.96 (0.69, 1.33)	39.9 per 100 person years	38.3 (27.5, 53.1)	Serious[1]	N/A	Not serious	Serious[2]	Low
Current cigarette smoker – no										
1 (Albert 2016)	RCT	536	HR 0.93 (0.75, 1.14)	35.4 per 100 person years	32.9 (26.6, 40.4)	Serious[1]	N/A	Not serious	Serious[2]	Low
COPD exacerbation in 3 months prior to enrolment										
1 (Albert 2016)	RCT	138	HR 0.58 (0.39, 0.88)	51.1 per 100 person years	29.6 (19.9, 45.0)	Serious[1]	N/A	Not serious	Not Serious	Moderate
No COPD exacerbation in 3 months prior to enrolment										
1 (Albert 2016)	RCT	600	HR 1.07 (0.88, 1.30)	33.6 per 100 person years	36.0 (29.6, 43.7)	Serious[1]	N/A	Not serious	Serious[2]	Low
Minimum SpO_2 during 6 minute walk - <86%										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (Albert 2016)	RCT	171	HR 1.10 (0.75, 1.63)	31.8 per 100 person years	35.0 (23.9, 51.8)	Serious[1]	N/A	Not serious	Serious[2]	Low
Minimum SpO_2 during 6 minute walk 86% - 88%										
1 (Albert 2016)	RCT	208	HR 0.92 (0.66, 1.28)	37.9 per 100 person years	34.9 (25.0, 48.5)	Serious[1]	N/A	Not serious	Serious[2]	Low
Minimum SpO_2 during 6 minute walk >88%										
1 (Albert 2016)	RCT	203	HR 0.88 (0.63, 1.23)	42.4 per 100 person years	37.3 (26.7, 52.2)	Serious[1]	N/A	Not serious	Serious[2]	Low
Forced expiratory volume per second (FEV1) <41% predicted										
1 (Albert 2016)	RCT	337	HR 0.93 (0.72, 1.20)	39.2 per 100 person years	36.5 (28.2, 47.0)	Serious[1]	N/A	Not serious	Serious[2]	Low
Forced expiratory volume per second (FEV1) ≥41% predicted										
1 (Albert 2016)	RCT	341	HR 1.00 (0.77, 1.31)	32.4 per 100 person years	32.4 (24.9, 42.4)	Serious[1]	N/A	Not serious	Serious[2]	Low
BMI <25.1 kg/m^2										
1 (Albert 2016)	RCT	244	HR 0.82 (0.61, 1.11)	43.1 per 100 person years	35.3 (26.3, 47.0)	Serious[1]	N/A	Not serious	Serious[2]	Low
BMI 25.1-30.8kg/m^2										
1 (Albert 2016)	RCT	249	HR 1.28 (0.94, 1.75)	30.1 per 100 person years	38.5 (28.3, 52.7)	Serious[1]	N/A	Not serious	Serious[2]	Low
BMI >30.8 kg/m^2										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (Albert 2016)	RCT	245	HR 0.81 (0.60, 1.12)	36.3 per 100 person years	29.5 (21.8, 40.7)	Serious[1]	N/A	Not serious	Serious[2]	Low
History of anaemia										
1 (Albert 2016)	RCT	120	HR 1.00 (0.66, 1.53)	41.3 per 100 person years	41.3 (27.3, 63.2)	Serious[1]	N/A	Not serious	Serious[2]	Low
No history of anaemia										
1 (Albert 2016)	RCT	618	HR 0.93 (0.76, 1.12)	35.6 per 100 person years	33.1 (27.1, 39.9)	Serious[1]	N/A	Not serious	Serious[2]	Low
Other outcomes										
Hospitalisation for any cause – lower numbers favours LTOT										
1 (Albert 2016)	RCT	738	HR 0.92 (0.77, 1.10) RR 0.97 (0.87, 1.08)	64 per 100 people	59 per 100 (49, 70)	Serious[1]	N/A	Not serious	Serious[2]	Low
Proportion of people having an exacerbation – lower numbers favour LTOT										
1 (Albert 2016)	RCT	738	RR 1.08 (0.98, 1.19)	67.7 per 100 people	73.1 (66.3, 80.6)	Serious[1]	N/A	Not serious	Not serious	Moderate
St George's Respiratory Questionnaire – lower numbers favour LTOT										
1 (Albert 2016)	RCT	236	MD -0.30 (-4.63, 4.03)	-	-	Serious[1]	N/A	Not serious	Very serious[4]	Very low
Quality of Wellbeing score - higher numbers favour LTOT										
1 (Albert 2016)	RCT	307	MD -0.01 (-0.04, 0.02)	-	-	Serious[1]	N/A	Not serious	Serious[2]	Low
Post bronchodilator FEV1 (litres) – higher numbers favour LTOT										
1 (Albert 2016)	RCT	176	MD -0.05 (-0.11, 0.00)	-	-	Serious[1]	N/A	Not serious	Serious[2]	Low
Room air resting oxygen saturation (%) - higher numbers favour LTOT										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (Albert 2016)	RCT	217	MD 0.00 (-0.52, 0.52)	-	-	Serious[1]	N/A	Not serious	Serious[2]	Low
Room air 6 minute walk distance - higher numbers favour LTOT										
1 (Albert 2016)	RCT	191	MD -35.00 (-84.71, 14.71)	-	-	Serious[1]	N/A	Not serious	Serious[3]	Low

1. Moderate risk of bias due to self-reported outcomes and a lack of blinding
2. Non-significant result
3. 95% confidence interval crosses one end of a defined MID interval
4. 95% confidence interval crosses both ends of a defined MID interval

People with COPD and mild hypoxaemia (arterial oxygen tension (PaO_2) between 56 and 65 mmHg (7.4kPa to 8.7 kPa)) (Gorecka, 1996)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Mortality – lower numbers favours LTOT										
1 (Gorecka 1996)	RCT	135	RR 1.17 (0.84, 1.62)	48 per 100 people	56 per 100 (40, 77)	Serious[1]	N/A	Not serious	Serious[2]	Low

1. Moderate risk of bias - lack of blinding
2. Non-significant result

People with COPD and cor pulmonale (PaO_2 between 40 and 60mmHg (5.3kPa to 8kPa)) (MRC working group (1981)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Rate of change in partial pressure of arterial oxygen (PaO_2) on air (higher numbers favour LTOT)										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (MRC 1981)	RCT	59	MD 2.69 (0.49, 4.90)	-	-	Very Serious[1]	N/A	Not serious	Not serious	Low
Rate of change in Forced expiratory volume in 1 second (FEV1) (higher numbers favour LTOT)										
1 (MRC 1981)	RCT	61	MD 0.02 (-0.02, 0.07)	-	-	Very Serious[1]	N/A	Not serious	Serious[2]	Very Low
Mortality – lower numbers favours LTOT										
1 (MRC 1981)	RCT	87	RR 0.68 (0.46, 1.00)	66 per 100 people	45 per 100 (31, 66)	Very serious[1]	NA	Not serious	Serious[2]	Very low

1. High risk of bias – lack of blinding, selective reporting
2. Non-significant result

*rate – mean rate of change of individuals in either FEV1 and PaO_2 (MRC authors)

Continuous oxygen therapy vs nocturnal oxygen therapy

People with COPD and moderate to severe hypoxaemia (PaO_2 of ≤ 55 mmHg (7.3kPa)) (NOTT Study, 1980)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Mortality – (lower deaths favours LTOT)										
1 (NOTT 1980)	RCT	203	RR 0.57 (0.37, 0.87)	40 per 100 people	23 per 100 (15, 35)	Serious[1]	N/A	Not serious	Not serious	Moderate
Mortality - subgroup analyses – lower numbers favour LTOT										
PaO_2 <52 mmHg (6.9 kPa)										
1 (NOTT 1980)	RCT	89	RR 0.68 (0.40, 1.16)	47 per 100 people	32 per 100 (19, 37)	Serious[1]	N/A	Not serious	Serious[2]	Low
PaO_2 ≥ 52 mmHg (6.9 kPa)										

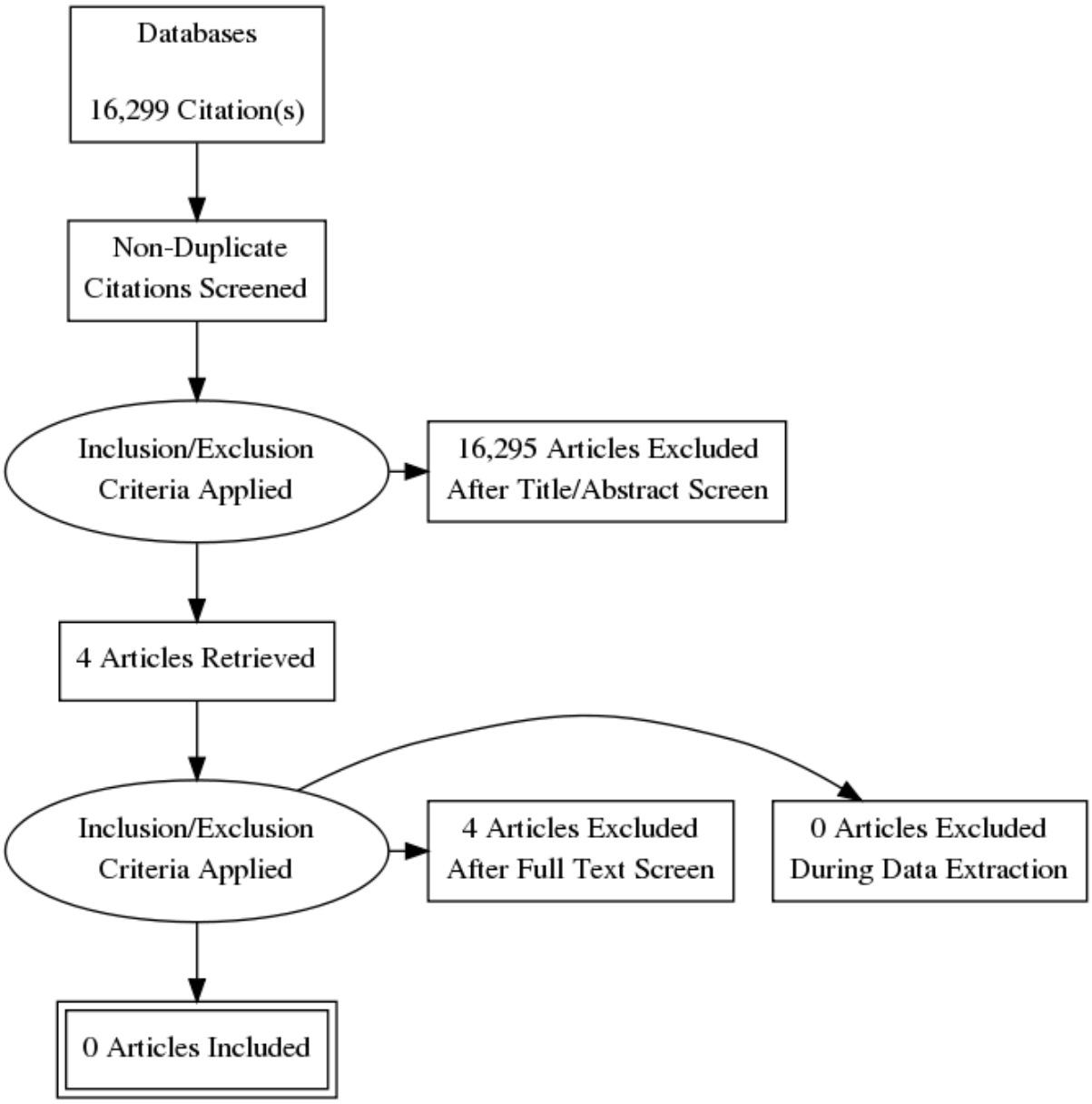
No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (NOTT 1980)	RCT	113	RR 0.46 (0.23, 0.92)	35 per 100 people	16 per 100 (8, 32)	Serious[1]	N/A	Not serious	Not serious	Moderate
Forced expiratory volume FEV1 <0.69L										
1 (NOTT 1980)	RCT	97	RR 0.58 (0.32, 1.05)	43 per 100 people	25 per 100 (14, 45)	Serious[1]	N/A	Not serious	Serious[2]	Low
Forced expiratory volume FEV1 ≥0.69l										
1 (NOTT 1980)	RCT	101	RR 0.56 (0.30, 1.05)	39 per 100 people	22 per 100 (12, 41)	Serious[1]	N/A	Not serious	Serious[2]	Low
Sleep, mean SaO_2 <85% air breathing										
1 (NOTT 1980)	RCT	89	RR 0.51 (0.28, 0.92)	49 per 100 people	25 per 100 (14, 15)	Serious[1]	N/A	Not serious	Not serious	Moderate
Sleep, mean SaO_2 ≥ 85% air breathing										
1 (NOTT 1980)	RCT	92	RR 0.57 (0.27, 1.23)	30 per 100 people	17 per 100 (8, 37)	Serious[1]	N/A	Not serious	Serious[2]	Low
Mean pulmonary artery pressure <27mmHg (3.6kPa)										
1 (NOTT 1980)	RCT	86	RR 0.44 (0.20, 0.96)	37 per 100 people	16 per 100 (7, 36)	Serious[1]	N/A	Not serious	Not serious	Moderate
Mean pulmonary artery pressure ≥27mmHg (3.6kPa)										
1 (NOTT 1980)	RCT	98	RR 0.63 (0.35, 1.16)	39 per 100 people	24 per 100 (14, 45)	Serious[1]	N/A	Not serious	Serious[2]	Low
$PaCO_2$ < 43 mmHg (5.7 kPa)										
1 (NOTT 1980)	RCT	96	RR 0.76 (0.42, 1.40)	35 per 100 people	27 per 100 (15, 50)	Serious[1]	N/A	Not serious	Serious[2]	Low
$PaCO_2$ ≥43mmHg (5.7 kPa)										
1 (NOTT 1980)	RCT	106	RR 0.40 (0.21, 0.75)	47 per 100 people	19 per 100 (10, 35)	Serious[1]	N/A	Not serious	Not serious	Moderate

1. Moderate risk of bias – unclear of blinding and allocation concealment

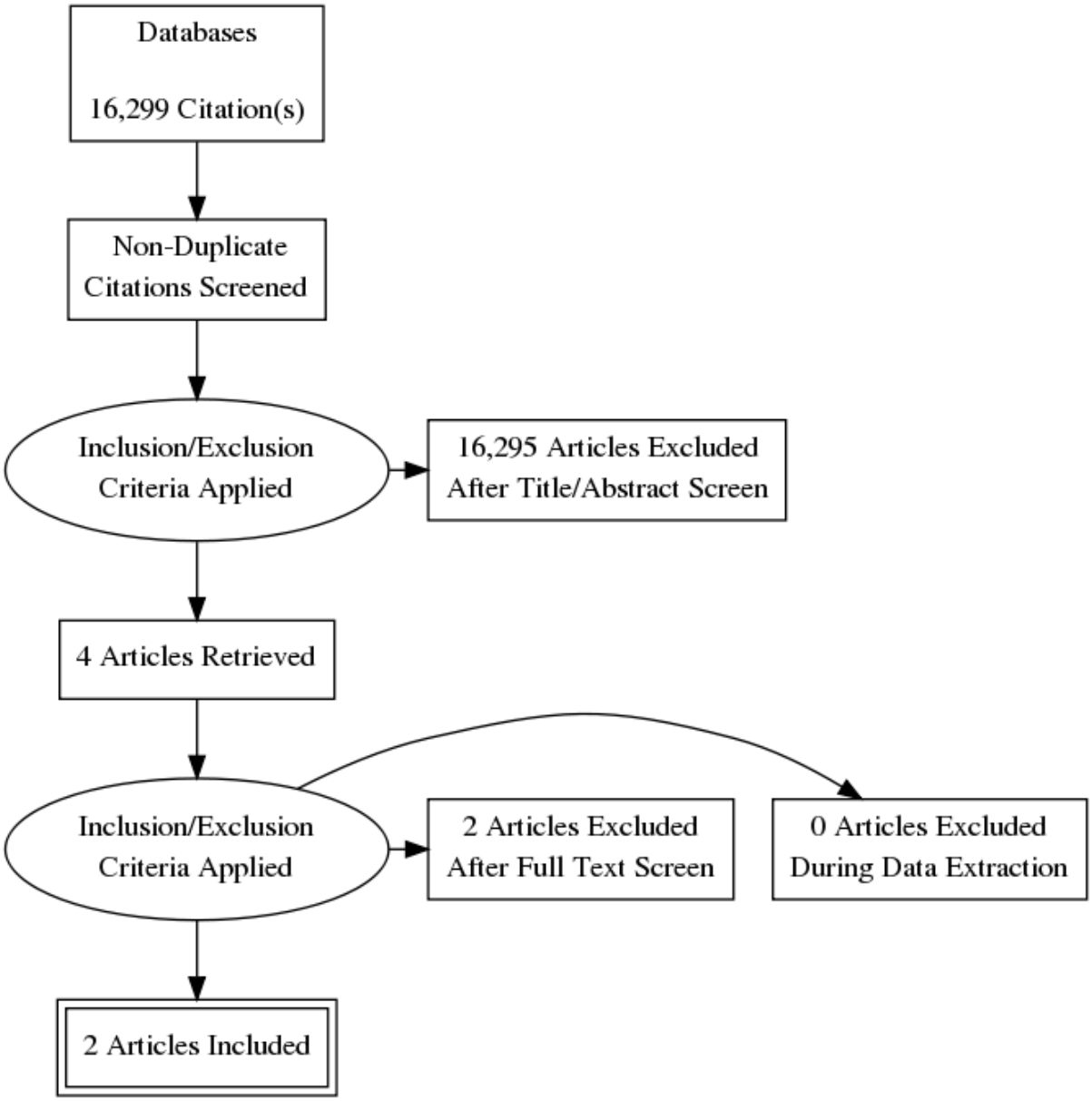
No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
2. Non-significant result										

Appendix H – Economic evidence study selection

Ambulatory and short burst oxygen therapy for people not meeting the criteria for long-term oxygen therapy



Long-term oxygen therapy



Appendix I – Health economic evidence profiles

Study	1. Applicability 2. Limitations	Comparison(s)	Setting	Duration Discount rate(s)	Results / conclusion	Uncertainty
Oba (2009)	1. Partially applicable 2. Very serious limitations [a,b,c,d,e]	COT vs Control NOT vs Control	USA	3 & 5 years 3% (costs, QALYs)	COT ICER 3yrs $23,807 (~£16,700) COT ICER 5yrs $16,124 (~£11,300) NOT ICER 3yrs $477,929 (~£335,800) NOT ICER 5yrs $306,356 (~£215,200)	In the SRH cohort, the multiple 1-way sensitivity analyses showed that all ICERs for COT were less than $25,000 (~£17,600) per QALY, and the probabilistic analysis showed that the 95% CI elliptical of COT was below the $50,000 (~£35,100) per QALY line. In the ND cohort, the ICER for NOT was sensitive to the quarterly mortality rate varying from $18,267 (~£12,800) per QALY to being dominated by no oxygen therapy. The ICER for NOT also varied widely in the probabilistic sensitivity analysis. The estimated ICER was more than $100,000 (~£70,300) per QALY in a large portion of the 95% CI elliptical

(a) No cost for the control group was reported
(b) Usual care/alternatives to O_2 therapy not defined or explored
(c) No grading of evidence taken from systematic reviews of costs and benefits, and therefore lack of transparency in uncertainty
(d) PSA reported, but no detail of distributions fitted to parameters
(e) Model used a short time horizon (5 years)

Study	1. Applicability 2. Limitations	Comparison(s)	Setting	Duration Discount rate(s)	Results / conclusion	Uncertainty
Chandra (2012)	1. Partially applicable [a] 2. Potentially serious limitations [b]	Long-term oxygen therapy versus usual care in patients with severe hypoxaemia	Canada	Lifetime time horizon 5% (costs and QALYs)	ICER for long-term oxygen therapy versus usual care: CAD$38,993 (~£21,799) per QALY	Probabilistic sensitivity analysis showed that long-term oxygen therapy is associated with a 71% probability of being cost-effective at a threshold of CAD$50,000 (~£27,900).

(a) Analysis was conducted in a non-UK setting
(b) The analysis makes the assumptions that patients with severe hypoxaemia are equivalent to patients with very severe COPD according to GOLD staging and that LTOT only affects mortality. The analysis only considers the cost of the LTOT intervention; other healthcare resource usage is not included in the model.

Appendix J – Excluded studies

Ambulatory and short burst oxygen therapy

Short Title	Title	Reason for exclusion
Neunhauserer (2016)	Supplemental Oxygen During High-Intensity Exercise Training in Nonhypoxemic Chronic Obstructive Pulmonary Disease	Crossover study with treatment duration of < 12 weeks

Long-term oxygen therapy

Short Title	Title	Reason for exclusion
Bailey (2004)	Home oxygen therapy for treatment of patients with chronic obstructive pulmonary disease	Study not a randomised control trial
Cooper (1987)	Twelve year clinical study of patients with hypoxic cor pulmonale given long term domiciliary oxygen therapy.	Study not a randomised control trial
Crockett (2000)	Domicilary oxygen for chronic obstructive pulmonary disease	More recent systematic review included that covers the same topic
Deng (2001)	(The effects of long-term domiciliary oxygen therapy on patients of chronic obstructive pulmonary disease with hypoxaemia)	Study not reported in English
Dikensoy (2002)	Comparison of non-invasive ventilation and standard medical therapy in acute hypercapnic respiratory failure: a randomised controlled study at a tertiary health centre in SE Turkey	Study not reported in English
Edvardsen (2007)	Effect of high dose oxygen on dyspnea and exercise tolerance in patients with COPD given LTOT	Not a peer-reviewed publication
Ekstrom (2016)	Oxygen for breathlessness in patients with chronic obstructive pulmonary disease who do not qualify for home oxygen therapy	Systematic review – population excludes those eligible for long term oxygen therapy
Fichter (1997)	Comparison of the efficacy of demand oxygen delivery systems with continuous oxygen in patients with COPD	All groups prescribed LTOT however different delivery methods
Fletcher (1992)	A double-blind trial of nocturnal supplemental oxygen for sleep desaturation in patients with chronic obstructive pulmonary disease and a daytime PaO2 above 60 mm Hg	Nocturnal oxygen therapy – different type of therapy out of scope
Gautier (2002)	Home rehabilitation in COPD patients on long term oxygen therapy (LTOT): a multi-centre randomized controlled study	Conference abstract

Short Title	Title	Reason for exclusion
Gorecka (1997)	Effect of long-term oxygen therapy on survival in patients with chronic obstructive pulmonary disease with moderate hypoxaemia	Conference abstract
Gorzelak (1994)	LTOT does not improve survival in COPD patients with moderate hypoxaemia (PaO2 56-65 mm Hg)	Conference abstract
Haidl (2002)	Long term oxygen therapy enhances endurance in patients with severe COPD, but moderate hypoxaemia and intermittent hypercapnia	Conference abstract
Haidl (2004)	Long-term oxygen therapy stops the natural decline of endurance in COPD patients with reversible hypercapnia	Baseline characteristics suggested the participants were healthy
Hanaford (1993)	Long-term oxygen therapy in patients with chronic obstructive pulmonary disease	Review article but not a systematic review
Hernandez (2016)	Effect of Post extubation High-Flow Nasal Cannula vs Conventional Oxygen Therapy on Reintubation in Low-Risk Patients: A Randomized Clinical Trial	All groups prescribed LTOT however different delivery methods
Klein (1986)	Long-term oxygen therapy vs. IPPB therapy in patients with COLD and respiratory insufficiency: survival and pulmonary hemodynamics	LTOT only for 12 hours
Levin (1980)	Effect of 15 hours per day oxygen therapy on patients with chronic airways obstruction	Conference abstract
Meecham (1995)	Nasal pressure support ventilation plus oxygen compared with oxygen therapy alone in hypercapnic COPD	Randomised crossover study with no control group
Paramelle (1981)	Evolution of chronic respiratory disease with or without long term oxygen therapy. Preliminary study	Study not reported in English
Petty (1999)	Controversial indications for long-term respiratory care: long-term oxygen therapy	Review article but not a systematic review
Radulovic (2006)	The importance of the application long-term oxygen therapy (LTOT) in COPD treatment	Conference abstract
Re (2011)	A highly complex home care service for COPD in LTOT may reduce the exacerbations and the hospitalizations	Conference abstract
Sadoul (1988)	Long term oxygen therapy (LTOT) for chronic respiratory insufficiency	Review article but not a systematic review
Schulz (1981)	Pulmonary haemodynamics in long-term oxygen treatment at home of patients with chronic bronchitis	Study not reported in English
Stuart-Harris (1981)	Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale	Same study as the NOTT study

Short Title	Title	Reason for exclusion
	complicating chronic bronchitis and emphysema	
Timms (1985)	Hemodynamic response to oxygen therapy in chronic obstructive pulmonary disease	Duplicate reference
Turkoglu (2015)	Evaluating the efficiency of long term oxygen therapy and mortality in chronic obstructive pulmonary disease	Not a randomised control trial
Vergeret (1989)	Portable oxygen therapy: use and benefit in hypoxaemic COPD patients on long-term oxygen therapy	All groups prescribed LTOT, but with different delivery methods
Vivodtzev (2016)	Automatically adjusted oxygen flow rates to stabilize oxygen saturation during exercise in O2-dependent and hypercapnic COPD	All groups prescribed LTOT, but with different delivery methods
Wedzicha (2000)	Long-term oxygen therapy vs long-term ventilatory assistance	Review article but not a systematic review
Weitzenblum (1999)	Results of a randomized multicenter study on nocturnal oxygen therapy in chronic obstructive lung disease not justifying conventional oxygen therapy	Study not reported in English
Xu (2012)	(Effect of long-term home oxygen therapy combined with rehabilitation training on life quality in chronic obstructive pulmonary disease patients)	Study not reported in English
Zielinski (1984)	Effects of oxygen therapy on pulmonary arterial hypertension in chronic obstructive lung disease	Study not reported in English
Zielinski (1997)	Causes of death in patients with COPD and chronic respiratory failure.	Study not reported in English

Economic studies

Short Title	Title	Reason for exclusion
Blissett (2014)	An economic evaluation of domiciliary non-invasive ventilation (NIV) in patients with end-stage COPD in the UK	Incorrect intervention
Jurisevic (2014)	Cost effectiveness of portable oxygen concentrators compared to portable oxygen cylinders: A multi-centre RCT	Incorrect comparator – not compared to usual care

Appendix K – References

Clinical evidence - included studies

Ambulatory and short burst oxygen therapy

Ekstrom Magnus, Ahmadi Zainab, Bornefalk-Hermansson Anna, Abernethy Amy, and Currow David (2016) Oxygen for breathlessness in patients with chronic obstructive pulmonary disease who do not qualify for home oxygen therapy. The Cochrane database of systematic reviews 11, CD006429

Long term oxygen therapy

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