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Facial airflow relieves chronic breathlessness in people with advanced disease: an exploratory systematic review and meta-analyses.

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Keywords:	dyspnea, review, self-management, airflow

Abstract:	Background: Chronic breathlessness is a neglected symptom of advanced diseases. Aim: To examine the effect of airflow for chronic breathlessness relief. Design: Exploratory systematic review and meta-analysis. Data sources: Medline, CINAHL, AMED and Cochrane databases were searched (1985 – 2018) for observational studies or randomised controlled trials of airflow as intervention or comparator. Selection against pre-defined inclusion criteria, quality-appraisal and data extraction were conducted by two independent reviewers with access to a third for unresolved differences. "Before and after" breathlessness measures from airflow arms were analysed. Meta-analysis was carried out where possible. Results: 16/78 studies (n=929) were included; 11 randomised controlled trials of oxygen vs medical air, four randomised controlled trials and one fan cohort study. Three meta-analyses were possible: i) Fan at rest in three studies (n=111) offered significant benefit for breathlessness intensity (0-100mm Visual Analogue Scale and 0- 10 Numerical Rating Scale), mean difference -11.17 (95% confidence intervals -16.60 to -5.74), p=0.06 I^2 64%. ii) Medical air via nasal cannulae at rest in two studies (n=89) improved breathlessness intensity (visual analogue scale), mean difference -12.0mm, 95% confidence intervals -7.4 to -

	16.6, P<0.0001 I^2 =0%. iii) Medical airflow during a constant load exercise test before and after rehabilitation (n=29) in two studies improved breathlessness intensity (mBorg, 0-10) mean difference -2.9, 95% confidence intervals -3.2 to -2.7, p<0.0001 I^2 =0%. Conclusion: Airflow appears to offer meaningful relief of chronic breathlessness and should be considered as an adjunct treatment in the management of breathlessness.

Airflow relieves chronic breathlessness in people with advanced disease: an exploratory systematic review and meta-analyses.

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Abstract

Background: Chronic breathlessness is a neglected symptom of advanced diseases.

Aim: To examine the effect of airflow for chronic breathlessness relief.

Design: Exploratory systematic review and meta-analysis.

Data sources: Medline, CINAHL, AMED and Cochrane databases were searched (1985 – 2018) for observational studies or randomised controlled trials of airflow as intervention or comparator. Selection against pre-defined inclusion criteria, quality-appraisal and data extraction were conducted by two independent reviewers with access to a third for unresolved differences. "Before and after" breathlessness measures from airflow arms were analysed. Meta-analysis was carried out where possible.

Results: 16/78 studies (n=929) were included; 11 randomised controlled trials of oxygen *vs* medical air, four randomised controlled trials and one fan cohort study. Three meta-analyses were possible: i) Fan at rest in three studies (n=111) offered significant benefit for breathlessness intensity (0-100mm Visual Analogue Scale and 0- 10 Numerical Rating Scale), mean difference -11.17 (95% confidence intervals -16.60 to -5.74), p=0.06 I^2 64%. ii) Medical air *via* nasal cannulae at rest in two studies (n=89) improved breathlessness intensity (visual analogue scale), mean difference -12.0mm, 95% confidence intervals -7.4 to -16.6, P<0.0001 I^2 =0%. iii) Medical airflow during a constant load exercise test before and after rehabilitation (n=29) in two studies improved breathlessness intensity (mBorg, 0-10) mean difference -2.9, 95% confidence intervals -3.2 to -2.7, p<0.0001 I^2 =0%.

Conclusion: Airflow appears to offer meaningful relief of chronic breathlessness and should be considered as an adjunct treatment in the management of breathlessness.

Keywords:

- dyspnea,
- self-management,
- review,
- airflow (relevant term as the intervention subject heading)

What is already known?

- Randomised Controlled Trials (RCTs) and cohort data have demonstrated that airflow delivered from the fan at rest offers significant relief of breathlessness.
- Systematic review (SR) and RCTs of oxygen *vs* medical air have failed to demonstrate additional benefit from oxygen therapy and suggest that medical air delivery, airflow, is likely to be an active intervention.
- All current evidence available for the effect of airflow for chronic breathlessness relief has not been explored using SR methods.

What this paper adds

This exploratory SR and meta-analyses provide promising data to suggest that:

- airflow from the fan at rest improves breathlessness in people with breathlessness due to a variety of causes
- airflow delivered as cylinder medical air at rest improves breathlessness in advanced cancer
- airflow delivered as cylinder medical air during a constant load exercise test in people with chronic obstructive pulmonary disease and who have completed pulmonary rehabilitation

Implications for practice and theory

- Clinicians should consider the fan as an adjunct to treatment for breathlessness at rest in patients who do not require oxygen-enriched air.
- Airflow may benefit exertion-induced breathlessness, but further work is required to investigate the role of the fan with everyday general activity and in relation to exercise.
- Recovery time from exertion-induced breathlessness, self-efficacy and daily activity are key outcomes to explore in future studies of airflow.

Introduction

Breathlessness is a common, often poorly managed symptom in people with advanced diseases. It is associated with reduced quality of life (1), decreased activities of daily living (2), unplanned emergency hospital attendance and admission. (3-5) Breathlessness inflicts devastating and disabling physical, psychological and social burden on normal daily life for the patient, carers and close family members (6-8). Chronic breathlessness, that is, breathlessness that persists despite optimal treatment for the underlying pathophysiology and causing such disability (9), all too often is left for patients to manage themselves despite a developing evidence base for interventions targeted at the breathlessness itself.

Growing evidence supports complex non-pharmacological interventions to reduce the impact of the symptom and improve quality of life. (10-12) Components target peripheral and central afferent sources of breathlessness sensation, such as facial airflow delivered by the battery-operated hand-held fan (fan). (13-17) Cooling of the facial skin innervated by the 2nd and 3rd branches of the trigeminal nerve, nasal mucosae or the upper airway flow receptors could modulate the central perception of breathlessness leading to decreased neural respiratory drive, thereby reducing the sensation of breathlessness. (18-22) A recent multi-methods secondary analysis of qualitative interview data from three studies found that 80/111 (72%) participants experienced benefit when the fan was used in conjunction with other components of a complex intervention. (23) Airflow delivered from the fan may offer a valuable contribution to the self-management of chronic breathlessness (13, 15, 23), and has been identified as a potentially useful strategy in a variety of situations, e.g. breathlessness crisis (24), a component of pulmonary rehabilitation to assist recovery from exercise, or with general everyday activities. (15)

Systematic reviews (SR) of oxygen in a variety of non-hypoxic patient groups (cancer, chronic heart failure, kyphoscoliosis, COPD and ILD) have not demonstrated additional benefit from oxygen therapy over medical air delivery. (25-30) An updated Cochrane review of COPD found low quality evidence for modest relief of breathlessness. (31) The results from a large, adequately powered trial that randomised 239 participants (COPD 63%, cancer 16%) to receive at least 15 hours a day of oxygen or medical air delivered via home concentrator for seven days reaffirms earlier suggestion that medical air used in the placebo arm may not be an inert comparator as previously thought and points to the likelihood of an

active intervention. (29, 32) Therefore the placebo arm of oxygen studies may provide useful preliminary data regarding the role of airflow for the relief of chronic breathlessness. This systematic review aims to identify and evaluate data from studies of airflow, both from studies of the hand-held fan and the comparator arm data for breathlessness intensity from oxygen studies, analysed as "before and after" airflow exposure cohort data.

Aim

To examine the current evidence for the effectiveness of airflow for the relief of chronic breathlessness.

Methods

The SR methods employed an exploratory approach in that only the airflow arm of studies were used and the data analysed as cohort "before and after" treatment.

Study design

The search methods employed are adapted from the Cochrane Handbook of Systematic Reviews (33) and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). (34) A review protocol is not pre-registered but available from the University of Hull Library (Flavia Swan PhD Thesis).

Inclusion and exclusion criteria

Types of studies

Randomised Controlled Trials (RCTs), controlled clinical trials (quasi-randomised experimental trials with or without blinding) and observational cohort studies were included.

Types of participants

Adults with chronic breathlessness from any advanced disease aetiology as shown below:

- Malignancy: advanced primary and metastatic cancer patients, who have undergone disease treatments like chemotherapy, radiotherapy or surgical interventions.
- Chronic Obstructive Pulmonary Disease (COPD) with forced expiratory volume in 1 second (FEV_1) of less than 50% predicted value
- Interstitial lung disease or pulmonary fibrosis where breathlessness is present
- Chronic heart failure: New York Heart Association (NYHA) stage III-IV
- Motor Neurone disease and other neurological disease where breathlessness is present or forced vital capacity (FVC) less than 80% predicted value
- Kyphoscoliosis: a moderate - severe sideways and forwards curvature of the spine Cobb Angle > 50° and FEV_1 of less than 50% predicted value**.**

Studies were included if at least 50% of the study population were classified as advanced, palliative or in the later stages of disease as defined above. These criteria were adapted from the Cochrane review of non-pharmacological interventions for breathlessness. (35)

Studies of participants with mild hypo or normoxaemia, who do not fore-fill the criteria for Long term Oxygen Therapy (LTOT) (36) were included. Studies of hypoxic participants or patients with any condition not assessed as progressive, refractory to treatment and advanced such as asthma were excluded.

Types of exposure

Airflow: i) delivered from either a fan (hand-held or table) or non-oxygen enriched compressed air, or from a non-invasive ventilatory method (nasal cannula, mask or mouthpiece), but not Nasal Intermittent Positive Pressure Ventilation (NIPPV) and ii) directed at the cheek of the face, nasal mucosae or mouth.

Administration: as i) a single dose *during ambulation*, or *at rest* taken as needed (PRN *pro re nata*),(37) ii) placebo short-burst oxygen therapy (SBOT) intermittent use *before* exercise or

after exercise for recovery (36) or iii) continuously over 15hr a day as placebo long-term oxygen therapy (LTOT) studies or during the night as placebo nocturnal oxygen therapy (NOT studies) .(38)

Studies where airflow was directly administered to the trachea, or at sub-zero temperatures were excluded.

Types of outcome measure

Unidimensional breathlessness outcomes

ATS domains of dyspnea measurement (20) including breathlessness severity or intensity rated on uni-dimensional scales as shown below:

- Modified Borg Score, a categorical scale with ratio properties
- Visual Analogue Scale (VAS), 0 - 100mm anchored 0 = no shortness of breath and 100mm = shortness of breath as bad as can be
- Numerical Rating Scales (NRS), 0-10 numbered scale anchored 0 = Not breathless at all and 10 the worst imaginable breathlessness
- Likert scales with verbal responses such as “a bit better”, “much better” or “no difference” or any other validated uni-dimensional scale for measuring breathlessness.

Studies were only included if they reported the breathlessness outcome at baseline and post-treatment measured as either primary or secondary outcomes. If severity or intensity was measured as part of a multi-dimensional or composite scale, e.g. the Chronic Respiratory Questionnaire, that unidimensional measure of breathlessness was *not* extracted and analysed separately. Breathlessness related function/quality of life measures were *not* used as primary breathlessness outcomes in the absence of unidimensional scales.

Other Outcomes

Other outcomes as shown below measured as either primary or secondary outcomes.

- Participant preference and satisfaction with the treatment
- Participant withdrawal and drop-out from the studies
- Adverse effects recorded

Data sources and searches

Medline, CINAHL, AMED and Cochrane databases were searched (1985 – 2015; updated January 2018) for observational or randomised controlled trials (RCTs) of airflow as intervention *vs* control or as comparator *vs* oxygen. Reference lists were scanned. A full search strategy can be seen in Online Supplementary Table 1.

Study selection

Titles, abstracts (and, where unclear, full papers) were screened against the eligibility criteria by two independent reviewers FS and AN, with recourse to MJ as a third reviewer in case of disagreement.

Data extraction and synthesis

Baseline and post-intervention measures of breathlessness intensity were extracted from the fan studies and from the comparator arm of oxygen studies. Data were analysed as "before and after" airflow exposure cohort observational data.

Risk of bias

FS and AN judged the reporting quality and internal validity for each of the included studies. The cohort study was evaluated according to the Cochrane guidelines for assessing bias in a non-randomised study. (39) As there is no tool that is applicable directly to the data extracted from the RCTs control arms, we assessed instead the quality of the parent RCTs as a proxy

marker for quality data. The RCTs were assessed with the Cochrane Risk of bias tool. (33) See online Supplementary Table 2.

Statistical Analysis

Results from the meta-analyses were reported for the primary outcome, breathlessness intensity or severity where heterogeneity allowed, or where not possible these were described narratively. NRS and VAS scales were combined by equating one point on a NRS scale to 10mm on a VAS. (40, 41)

Data calculations for mean difference and SD used STATA Version 12.1, Stata Corp LLC Texas 77845-4512, USA. Breathlessness measurements were analysed as continuous outcomes. Data from the placebo arm of cross-over RCTs were treated as single arm before-after studies. For studies that recorded median values, the mean were calculated from the extracted study data. (42) The I^2 statistic was used to assess heterogeneity. (43) Where the result indicated significant heterogeneity a random effects model was chosen, otherwise a fixed effects model was applied. All analyses were undertaken on Review Manager 5.5. A sensitivity analysis was attempted for any study identified as including a sub-group not fitting the review criteria of mild hypo or normoxaemia to assess for any significant difference in the breathlessness outcome between the hypoxic and non-hypoxic participants.

Results

A total of 403 records were identified for screening. After removal of duplicates, 78 records were reviewed. 14 abstracts were rejected for not meeting inclusion criteria; the remaining 64 full text articles were assessed for eligibility. Of these, 16 studies met the review inclusion criteria and the other 48 studies were excluded (see Figure 1; PRISMA flow chart (34) and Online Supplementary Table 3, eAppendix)**.**

Overall studies represented 929 participants (age median 61.5, range 33 to 90 years; 47% men)

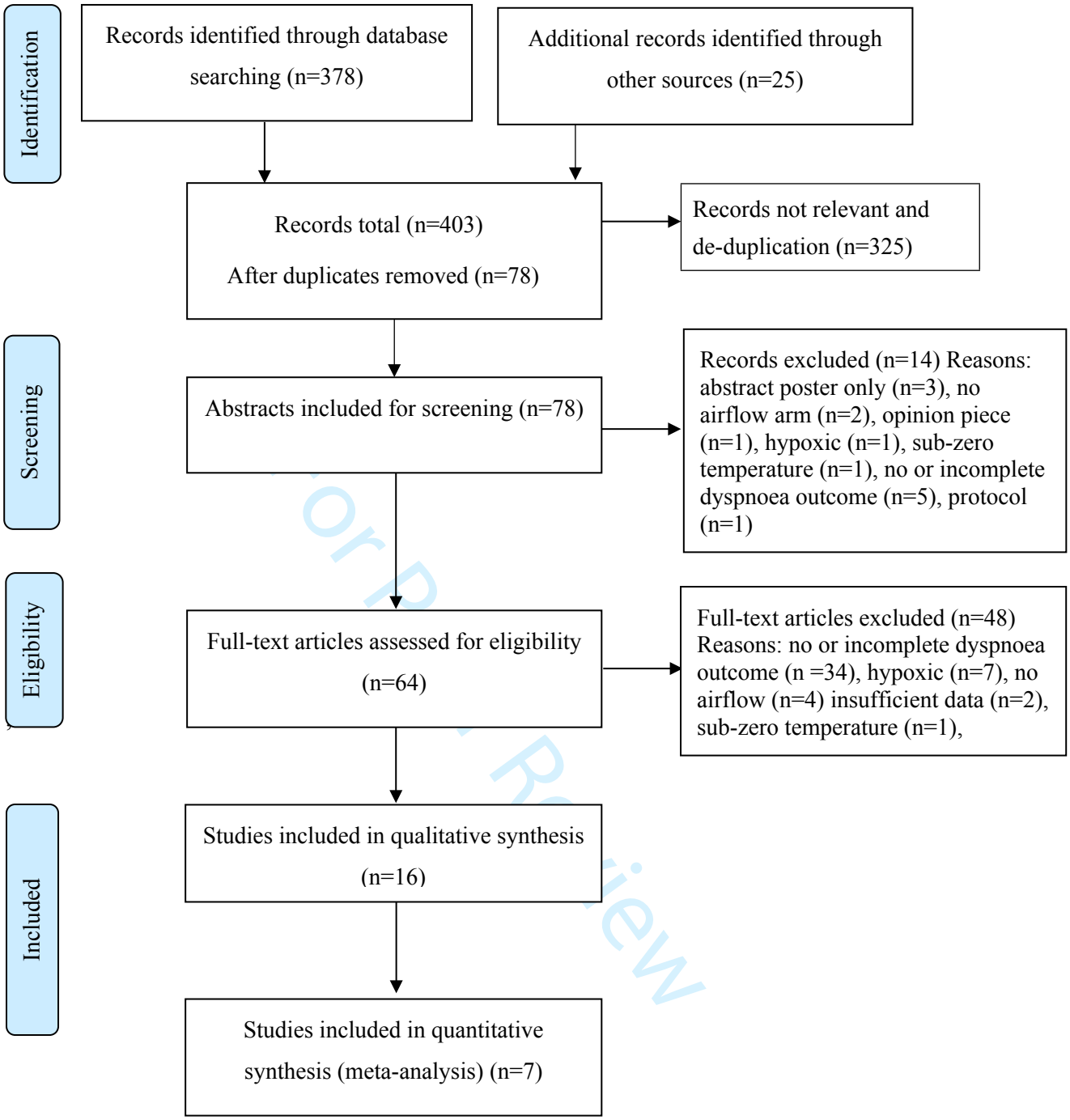

Figure 1 PRISMA 2009 Flow-diagram of study selection and retrieval (34)

Airflow was delivered by fan (13, 14, 16, 17, 44) or as medical air. (29, 32, 45-53) See Table 1 for study characteristics

Description of fan studies

Design: five studies (n=230) used the fan. Two feasibility RCTs; (n =49), (13) and (n=30), (44), a feasibility cohort study (n=31), (14), a feasibility longitudinal RCT (n=70), (16) and a phase III cross-over RCT (n=50), (17).

Patient characteristics: Four studies recruited a mixed population of people with breathlessness due to a variety of advanced conditions including COPD (n=101), cancer (n=55), heart failure (n=23) and other causes (n=21), (13, 14, 16, 17), and one study recruited advanced cancer only (n=30). (44)

Intervention and comparator characteristics: three studies used the fan to face at rest (14, 17, 44), two with comparator groups; fan to leg (17), or no fan use and carer support (44), and the other was a cohort design. (14) One study assessed acceptability of the fan when used with general activity over 6 months compared with an acupressure wristband (16), and the remaining study assessed the fan when used with exercise advice over 4 weeks. (13)

Breathlessness Outcome: Three studies focused on the sensory-perceptual domain of dyspnea measurement and used breathlessness intensity as the primary outcome (17) or main outcome (14, 44). These studies selected the VAS (17), the NRS (44), or both VAS and NRS (14). The other two studies assessed symptom impact as well as the sensory-perceptual domain. These studies selected the NRS breathlessness intensity (13) and the Modified Borg Scale of breathlessness severity. (16)

Other outcomes: All of the fan studies reported participant withdrawals (13, 14, 16, 17, 44). These ranged from 0 to 6 participants. (13, 14, 44) One study reported that there were no Adverse Events (AE) (13) and the other fan studies did not include any AE details. (14, 16, 17, 44) Airflow preferences were described in four fan studies (13, 16, 17, 44) and not in one study. (14) In addition, one study quantified the experience of fan use at 2 months. (16)

Description of medical air studies

Design: eleven RCT's (n=699) used oxygen, helium hyperoxia or both gases for the intervention compared with medical air. (29, 32, 45-53) Study size ranged from 16 to 239

participants. (29, 48) Four were cross-over (32, 48, 49, 51) and seven used a parallel group design. (29, 45-47, 50, 52, 53) Nine studies were double blind (29, 45-52), and two were single blind. (32, 53)

Patient characteristics: the eleven studies represent; COPD n=537, cancer n=109, other lung diseases n=21, cardiac disease n=14 and other causes n=18. Inclusion criteria required moderate to severe COPD (45-50, 52, 53), advanced cancer (51), or were a mixed population with no specific stipulation of severity. (29, 32)

Intervention Characteristics: the source of airflow was an oxygen cylinder (32, 45-50), a sham concentrator (29), and a Douglas bag. (52) Two studies did not state the airflow source. (51, 53) Medical air or compressed air was delivered through nasal cannulae (29, 32, 45, 47, 49-51, 53), face-mask and nasal cannula (48), a non-rebreathing face-mask (46) and through a mouthpiece. (52) The flow rates varied widely in the studies; 2l/minute (29, 45), 3l/minute (47), 4l/minute (32, 49, 51), 5l/minute (53), 6l/minute (50) and 8l/minute *via* nasal cannula or 15l/minute with face mask. (48) Two studies did not report flow rate details. (46, 52) The timing of airflow delivery was; 15 minutes at rest (32, 51), with daily activity over 3 (50), or 6 months (45), 15 hours a day over one week (29), or in conjunction with exertion-induced breathlessness during pulmonary rehabilitation (PR), (46, 52, 53) or a walking test. (47-49) The PR programme parameters for airflow delivery were with treadmill exercise 3 times a week for 30 minutes over two months (53), a cycle ergometer used 3 times a week for 30 minutes over 6 weeks (46), or 3 times a week for 20 minutes over two months. (52) The 6MWT test parameters for airflow delivery were; i) three same day 6MWTs with 45 minutes washout, using room air for the basal walk and compressed air for the subsequent walks (47), ii) five 6MWTs performed over three visits, (timing not stated) using room air for the practice walk on visit one and cylinder air for the two 6MWTs with 60 minute washout on visits two and three (48), and iii) three same day 6MWTs using cylinder air with 20 minutes washout between tests at baseline, 6 and 12 weeks as well as short burst use at home with daily activity during the study period. (49)

Breathlessness outcome: two studies focused on the sensory-perceptual domain of dyspnea measurement and recorded breathlessness intensity as a primary outcome with the VAS and Borg scale (32) or the VAS only. (51) All of the other studies focused on symptom impact as well as the sensory-perceptual domain. (29, 45-50, 52, 53) Of these, three studies measured

breathlessness intensity as a primary outcome with the NRS (29) or the CRQ dyspnea domain. (45, 50) The remaining six studies identified the modified Borg scale as one of the main outcomes (47-49, 52, 53) or a secondary measure. (46) One study in addition selected the CRQ. (49)

Other outcomes: participant withdrawals were reported in all of the studies (29, 32, 45-51, 53), apart from one. (52) Five studies reported no withdrawals (32, 46-48, 51) and in the other five studies withdrawals ranged from 2 to 21 participants. (45, 53) AE were poorly reported with only two studies including details; "few" or "no AE". (29, 46) All of the other studies omitted reporting AE. (32, 45, 47-53) Airflow preferences were only reported in one study. (51) The remaining studies did not report airflow preferences (29, 32, 45-48, 50, 52, 53), although one study did quantify side-effects (29) and a second study examined preference for cylinder delivery of airflow. (50)

Table 1 Characteristics of included studies (fan)

Study author	Study Design	Population	Intervention	Comparator	Mode of gas delivery	Dyspnea Outcome measure(s)	Other Outcomes: withdrawals, Adverse Events (AE), airflow preferences	Timing of measurement	Results airflow arm only (before and after treatment)	Improvement with airflow Yes/No
Booth (2016) [14]	Feasibility observational cohort	n= 31 Males: 20 Age mean: 74.8 SD 11.49 Mixed population, non-malignant, cardiorespiratory disease: 8 (26%) Baseline dyspnoea score: Mean VAS 48mm SD 27.4	Hand-held fan to face	No comparator group	Airflow from hand-held fan to face for 5 minutes	VAS (mm), NRS	Withdrawals = 6 AE and airflow preferences not reported	After 5 minutes at rest	VAS = Mean 35mm SD 25.7 after 5min air Mean change = 12mm SD 21.2	Yes
Bausewein (2010) [16]	Feasibility longitudinal phase II RCT	n = 70 Males: 36 Age mean: 65.6yrs SD 8.80 COPD = 45, cancer = 25 Baseline dyspnoea score: 3.7 (1.83)	Hand-held fan to face	Wristband	Airflow from hand-held fan	Modified Borg score	Withdrawals at 2 months =16/33 (48%) AE not reported Airflow preferences: Positive = 13/38 Negative = 7/38	Monthly over 6 months	Mean Borg score change over 2 months = 0.6 (SD 2.1), p = 0.90	No, phase II not powered to test
Galbraith (2010) [17]	Cross-over RCT	n = 50 Males: 23 Age mean: 71.3, range 33-90yrs Mixed population; COPD = 26, lung cancer = 11, heart disease = 15 Baseline dyspnoea score: VAS Fan/face 1st group = 31mm (SD 12-61mm)	Hand-held fan to face	Hand-held fan to leg	Airflow from hand-held fan to face for 5 minutes	VAS (mm)	Withdrawals = 1 AE not reported Airflow preferences: positive patient comments, numbers not reported	After 5 minutes at rest and after 10 minute washout	VAS = -7.0mm Median change after 5 minutes Fan/face 1st group (IRQ 1.5 - 14.5) VAS = -10.0mm Median change incl 10 minute washout Fan/face 1st group (IRQ 3.5 – 17), P=0.003	Yes

Table 1 Characteristics of included studies (fan)

Study author	Study Design	Population	Intervention	Comparator	Mode of gas delivery	Dyspnea Outcome measure(s)	Other Outcomes: withdrawals, AE, airflow preferences	Timing of measurement	Results: airflow arm only (before and after treatment)	Improvement with airflow Yes/No
Johnson (2016) [13]	Feasibility phase II RCT	n =49 Males: 26 Age mean: 68 (range 46-88) Mixed population; COPD = 28, cancer =9, heart disease = 5, others = 7 Baseline dyspnoea score Mean NRS = 5.7 (SD 1.5)	Hand-held fan to face at high or low flow rate	Usual care: verbal and written exercise and breathlessness management advice	Airflow from hand-held fan	NRS	Withdrawals = 6 No AE Airflow preference: positive patient comments, numbers not reported	After 4 weeks	NRS = 6.0 (2.0) at 4 weeks Mean change 0.0 (3.0)	No, phase II not powered to test
Wong (2017) [44]	Feasibility phase II RCT	n=30 Males: 14 Age: NR Lung cancer = 13, other cancers = 17 Baseline dyspnoea score Control group: NRS mean 5.6 (SD 1.55) Intervention group: NRS mean 6.13 (SD 2.48)	Table fan with low flow rate	Placebo accompanied by carer	Airflow from table fan to face for 5 minutes	NRS	No withdrawals AE not reported Airflow preference: mixed patient comments, numbers not reported	After 5 minutes at rest	NRS = 4.60 after 5 minutes fan to face Mean change -1.53 (1.06) p< 0.001	Yes

Table 1 Characteristics of included studies (medical air)

Study author	Study Design	Population	Intervention	Comparator	Mode of gas delivery	Dyspnea Outcome measure(s)	Other Outcomes: withdrawals, AE, airflow preferences	Timing of measurement	Results airflow arm only (before and after treatment)	Improvement with airflow Yes/No
Abernethy (2010) [29]	Double-blind RCT	n = 239 Males: 63% Age mean: Air = 74yrs (SD 10) Mixed: COPD = 152, Primary lung cancer = 33 Baseline dyspnoea score: Am air = 4.6 (SD 2.4) Pm air = 4.7 (SD 2.3)	Oxygen	Room air via concentrator	2l/min via nasal cannula for at least 15hrs a day (LTOT)	NRS 1-10	Withdrawals = 15 Few AE, number not reported Side-effects reported Airflow preferences not reported, oxygen only	Am and pm each day, within 30 minutes of waking and bedtime for 7 days	Am = -0.7 NRS point change Pm = -0.5 NRS point change, (p = 0.5)	Yes
Booth (1996) [32]	Single-blind cross-over RCT	n = 38 Males: 22 Age Median: 71 Range: 54-90yrs Lung Cancer 20, COPD 13, Cardiac 4 Baseline dyspnoea score: VAS 59mm	Oxygen	Cylinder air	4l/minute for 15 minutes via nasal cannula	VAS (mm) Modified Borg Scale	No withdrawals AE and airflow preferences not reported	After 15 minutes of breathing oxygen or air at rest.	VAS = -11mm change after air 48mm, p<0.001	Yes
Eaton (2006) [45]	Double-blind parallel RCT	n = 78 Males: 36 Age mean: 77.3yrs (7.06) Moderate/severe COPD Baseline CRQ score: Air = 17.5 (SD 4.2)	Oxygen	Cylinder air	2l/minute via nasal cannula over 6 months (SBOT)	CRQ	Withdrawals = 21 AE and airflow preferences not reported	Monthly over 6 months	CRQ = Average change over 6 months: air group = -3.6	No

Table 1 Characteristics of included studies (medical air)

Study author	Study Design	Population	Intervention	Comparator	Mode of gas delivery	Dyspnea Outcome measure(s)	Other Outcomes: withdrawals, AE, airflow preferences	Timing of measurement	Results airflow comparator arm only (before and after treatment)	Improvement with airflow Yes/No
Eves (2009) [46]	Double-blind RCT	n = 38 Males: 23 Age mean: 65.5yrs (SD 8) Stable COPD Baseline dyspnoea score: constant load exercise Borg mean: Air = 6.0 (SD 2.2) incremental load exercise Borg mean: Air = 5.6 (SD2.0)	Helium-hyperoxia (60% HE: 40% O^2)	Cylinder air	Face mask (non-rebreathing)	Modified Borg score	No withdrawals No AE Airflow preferences not reported	During exercise test before and after 6 weeks pulmonary rehabilitation programme, 3 times a week for 30 minutes on cycle ergometer	constant load exercise Borg mean: Air = 4.2 (SD 2.1) mean change = -1.8 (95% CI -3.1 to -0.2), $p < 0.05$ incremental load exercise Borg mean: Air = 5.6 (SD 2.1) No change (95% CI -0.7 to 0.7)	Yes
Jolly (2001) [47]	Double-blind RCT	n = 20 Males: 19 Age mean: 68.5yrs (SEM 2.5) Stable COPD Baseline dyspnoea score: Borg mean score Desat group Baseline 6MWT = 5.82 (SEM 0.46) Non-desat group Baseline 6MWT = 4.22 (SEM 0.46)	Oxygen	Cylinder air	3l/minute via nasal cannula	Modified Borg score	No withdrawals AE and airflow preferences not reported	Before and after 3 x 6 MWTs with at least 45minutes washout between walks	Borg mean score: Desat group Air 6MWT = 5.82 (SEM 0.42) No change Non-desat group Air 6MWT = 4.44 (SEM 0.73) No change	No
Marciniuk (2007) [48]	Double-blind crossover RCT	n = 16 Males: 7 Age mean: 67 (SD 8) Moderate to severe COPD Baseline dyspnoea score: Borg mean score Baseline 6MWT = 5 (SD 2)	100% Oxygen or Helium-hyperoxia (70% HE: 30% O^2)	Cylinder air	15l/minute via face mask 8l/minute via nasal cannula	Modified Borg score	No withdrawals AE and airflow preferences not reported	Before and after each 6 MWTs on visit 1,2 and 3 with 60 minutes washout between walks	Borg mean score After 6MWT Air = 3.5 mean Borg score change = -1.5 decrease	Yes

Table 1 Characteristics of included studies (medical air)

Study author	Study Design	Population	Intervention	Comparator	Mode of gas delivery	Dyspnea Outcome measure(s)	Other outcomes: withdrawals, AE, airflow preferences	Timing of measurement	Results airflow comparator arm only (before and after treatment)	Improvement with airflow Yes/No
McDonald (1995) [49]	Double-blind crossover RCT	n = 26 Males: 24 Age mean: 73 (SD 6) Stable severe COPD Baseline dyspnoea score 6MWT: Air group = 3.8 (SD 1.4) CRQ = 14 (SD 5)	Oxygen	Cylinder air	4l/minute via nasal cannula	Modified Borg score CRQ	Withdrawals = 7 AE and airflow preferences not reported	After 6 and 12 weeks of home cylinder air using 6MWT exercise test with 20 minute washout between walks	Borg Mean score Home air: 6MWT with cylinder air = 3.8 (SD 1.5) No change CRQ score Home air = 17 (SD 6)3 point change	No with 6MWT Yes with CRQ
Moore (2011) [50]	Double-blind RCT	n = 143 Males: 99 Age mean: 71.8yrs (SD 9.8) Range: 43-78 Stable COPD Baseline dyspnoea score: Air = 17.5 (SD 4.9)	Oxygen	Cylinder air	6l/minute via nasal cannula at home for 12 weeks with activity (SBOT)	CRQ	Withdrawals = 4 AE not reported Airflow preferences 45% prefer no cylinder	At 4 weeks and 12 weeks	Air: 4 weeks = 18.4 (SD5.8) 12 weeks = 18.4 (SD 5.8) Air: CRQ = Mean change at 4 and 12 weeks = 0.9	Yes
Philip (2006) [51]	Double-blind cross-over RCT	n = 51 Males: 31 Age median: 65 Range: 33-82yrs NSCLC = 22, Small cell lung cancer = 6, Breast = 8, Colorectal = 4 Others = 11 Baseline dyspnoea score: VAS median Air 1st = 52mm (range 23-92) VAS median Air 2nd = 42mm (range 10-70)	Oxygen	Medical Air	4l/minute for 15 minutes via nasal cannula	VAS (mm)	No withdrawals AE not reported Airflow preferences: Positive: n=15 (29%)	Before and after 15 minutes of gas	VAS median After air 1st = -3mm change (range -19 to 7) VAS median After air 2nd = -11.5mm change (range -20 to 45) VAS mean change = -13.4mm	Yes

Table 1 Characteristics of included studies (medical air)

Study author	Study Design	Population	Intervention	Comparator	Mode of gas delivery	Dyspnea Outcome measure(s)	Other Outcomes: withdrawals, AE, airflow preferences	Timing of measurement	Results airflow comparator arm only (before and after treatment)	Improvement with airflow Yes/No
Scorsone (2010) [52]	Double-blind RCT	n = 30 Males: 23 Age mean: 67.3yrs (SD 8.3) Moderate to severe COPD Baseline dyspnoea score: Before training incremental load exercise Borg: Air = 7 (SD 3) Before training constant load exercise Borg: Air = 8 (SD 3)	40% Oxygen or Helium - hyperoxia (60% HE: 40% O^2)	Humidified room air	Mouthpiece from a Douglas bag	Modified Borg score	No withdrawals AE and airflow preferences not reported	During exercise before and after a 2 months pulmonary rehabilitation programme, 3 times a week for 20 minutes on cycle ergometer	After training incremental load exercise Borg: Air = 4 (SD 2) After training constant load exercise Borg = 5 (SD 3) Borg change = -3 point decrease both exercise tests	Yes
Wadell (2001) [53]	Single-blind crossover RCT	n = 20 Males: 10 Age mean: 67yrs Range: 52-73 Stable COPD Baseline dyspnoea median score: Test A (Air) At rest; Pre-training Borg: Air group = 1.5 (0-3) Test A (Air) After 6MWT, Pre-training Borg: Air group = 6.5 (4-9)	Oxygen	Air	5l/minute via nasal cannula	Modified Borg score	Withdrawals =2 AE and patient preferences not reported	During exercise using 2 x 6MWT (air/O^2 or O^2/air) with 1hour washout before and after a 2 months pulmonary rehabilitation programme, 3 times a week for 30 minutes on a treadmill	Test A (Air) At rest; Post-training Borg: Air group = 1 (0-3) Test A (Air) After 6MWT, Post-training Borg: Air group = 6 (1-7) Borg change = -0.5 point at rest and after exercise test	Yes

Risk of Bias

The quality appraisal is summarised in Online Supplementary Table 2 and described below.

Allocation: all of the studies, apart from one, a cohort design (14), were described as RCTs. It was possible to verify the randomisation process in eight studies. (13, 16, 17, 29, 32, 45, 46, 50). There was insufficient information to determine the risk of allocation bias in the other RCTs. (44, 47-49, 51-53)

Blinding: two of the fan studies attempted to blind the participants (16, 17); a placebo wristband was used as a comparator (16) and participants were not told if the fan to face or fan to leg was the active intervention. (17) There was no blinding in two studies, a cohort and phase II RCT (13, 14), and the fifth study stated single blinding that could not be verified from the methods described. (44) All five were judged high risk of bias due to incomplete blinding or limited description. Nine medical air RCTs were described as double blind. (29, 45-52) All were judged low risk of bias (29, 45, 46, 48-50, 52), apart from one study that was unclear due to the lack of detail reported. (51) Two RCTs were single blind (32, 53); one was judged low risk of bias (32) and the other was regarded as unclear risk due to the inadequate description. (53)

Incomplete outcome data: 13 studies adequately addressed withdrawals and incomplete outcome data; these were considered low risk of bias.(13, 14, 17, 29, 32, 46-53) Three studies were uncertain risk (16, 45); one due to the proportion of attrition (16) and the other two lacked description of how any missing data were statistically managed. (44, 45)

Selective Outcome reporting: all of the studies reported the pre-specified outcomes and were judged as low risk of bias. (13, 14, 16, 17, 29, 32, 44-53) Study protocols were available for eight studies. (13, 14, 16, 17, 29, 46, 50, 51)

Other issues of bias: twelve studies appeared free from other bias and were judged low risk. (13, 16, 17, 29, 44-46, 48, 50-53) Three studies reported insufficient information to adequately assess risk (32, 47, 49), and one study, a cohort design was judged high risk. (14)

Effect of interventions

The airflow was delivered, i) at rest (14, 17, 32, 44, 51) ii) over days or weeks (either intermittently or as periods of continuous flow) whilst the participant continued with usual general activities (13, 16, 29, 45, 50) or iii) during specific episodes of exertion induced breathlessness. (46-49, 52, 53)

i) At rest

Five studies demonstrated improvement with airflow delivery at rest.

Results from 5 minutes fan use to the face in three studies were VAS breathlessness intensity difference from baseline mean -7mm (CI -11.5 to -2.5) (17), and mean -12mm (CI -19.3 to -4.4) (14), and for the NRS mean change -1.53 (-9.6 to -6.5).(44)

Cylinder medical air delivery for 15 minutes demonstrated improvement VAS breathlessness intensity mean -11mm (CI -17.0 to -5.0) (32), and mean -13mm (CI -20.5 to-6.3). (51) Four studies were sub-divided into two groups and included in meta-analyses.

Fan

Airflow from the fan at rest improved breathlessness in a mixed population (n=111; 58% cancer) VAS (mm) mean difference (MD), -11.17 (CI -16.60 to -5.74), p=0.06. Significant heterogeneity was observed, Chi² p-value = 0.2, (I^2 = 64%) (See Figure 2).

<<insert Figure 2 Meta-analysis of fan at rest >>

Medical air

Airflow delivered as cylinder medical air at rest improved breathlessness in advanced cancer (n=89) VAS (mm) MD -12.0, (CI -16.6 to -7.4), P<0.0001. No evidence of heterogeneity was observed, Chi² P value = 0.6, (I^2 =0%).

<<insert Figure 3 Meta-analysis of cylinder air at rest >>

ii) General activity

Six studies used airflow at home with everyday general activity. A narrative description was used for these due to study diversity. Breathlessness points change from four cylinder air studies were mixed (29, 45, 49, 50), with CRQ -3.6 after 6 months (45), 3.0 after 12 weeks (49), or 0.9 at 12 weeks (50), or NRS -0.7 (am) and -0.5 NRS (pm) after 7 days. (29) In the two fan studies a modified Borg score of -0.6 (SD 2.1) was found after 2 months (16), but there was no NRS score change after 4 weeks of fan use with exercise advice. (13)

iii) Exertion-induced breathlessness

Six studies examined airflow delivery with exertion-induced breathlessness. Results for mean Borg breathlessness score during a walking test for three studies varied; no change during a 6MWT repeated on the same day (47), or at 12 weeks (49), and improvement -1.5 for a 6MWT repeated on 3 separate visits. (48) Airflow delivered during a constant load exercise test after PR in three studies also demonstrated variable improvement in mean Borg breathlessness scores; -1.8 points (46), and -3 point (52) using a cycle ergometer, and -0.5 point from a treadmill test. (53) Two studies were suitable to include in a meta-analysis (See Figure 4). (46, 52)

Medical air

Airflow delivered as cylinder medical air during a constant load exercise test after PR in COPD (n=29) significantly improved breathlessness Borg score MD -2.9, (CI -3.2 to -2.7), $p<0.0001$. No evidence of heterogeneity was observed, Chi^2 p-value = 0.7, (I^2 =0%), (Figure 4).

<< insert Figure 4 Meta-analysis of cylinder medical air for exertion-induced breathlessness>>

Discussion

These exploratory data support that facial and nasal airflow delivery at rest offers relief of breathlessness intensity consistent with a moderate clinically important difference, (54, 55) and during exertion. (46, 52) All participants in the cylinder medical air delivery at rest studies had advanced cancer, but nearly half of those in the fan "at rest" studies had other conditions indicating that airflow for breathlessness at rest is of benefit irrespective of cause.

In a recent pooled qualitative data study of facial airflow use from the fan in 133 people with chronic breathlessness (56), over 80% patients reported some or substantial benefit.(57) However, the data presented here varied with regard to relief of breathlessness intensity when facial or nasal airflow delivery was used with everyday general activity or with exertion induced breathlessness. This may reflect the use of outcome measures that do not reliably capture change in breathlessness intensity in the context of exertion. Studies that used a 6MWT (47-49) highlight the problem of a self-paced test that allows patients to control their walking speed and thus limit the maximal level of exertion–induced breathlessness experienced. In contrast, studies that used an externally paced test, such as the cycle ergometer, identified relief of breathlessness intensity. (46, 52) The relationship between exercise and breathlessness intensity is complex, and measuring one without taking the other into account may miss relevant improvement. Scores are likely to remain static after the introduction of an intervention as patients are able to exert themselves to the same level of breathlessness without noticing an increase in their exercise tolerance (58), or indeed the outcome may be of little value to the patient. (57)

A previous study of recovery time after an ISWT in people with thoracic cancer (n=57) reported a rapid reduction in breathlessness intensity with a return to baseline time of median 4 (IQR 2-5) minutes. (59) The analysis of 133 patient interviews found that a faster recovery time was a key patient-reported benefit of airflow delivered from the fan, irrespective of breathlessness intensity. (57) Even though recovery time may only be a matter of minutes, interventions which shorten this further are clearly welcomed and give the patient a sense of self-control that may help prevent a breathlessness-anxiety spiral. The ability to recover quickly and predictably from bouts of exertion is likely to encourage further activity and prevent the deconditioning cycle.

The fan therefore seems suitable as a patient-delivered intervention to target the recovery time from exertion-induced breathlessness. Preliminary magnetoencephalography (MEG) imaging data suggests airflow delivery during recovery from exercise may modulate central perception of breathlessness by modifying sensory attention. (60) Cooling of the facial skin innervated by the 2nd and 3rd branches of the trigeminal nerve and/or stimulation of nasal mucosa and upper airway 'flow' receptors are reported to improve breathlessness intensity and exercise tolerance (18, 19, 61, 62) and could "fool" the brain into thinking that the respiratory status is adequate. (22)

Unpleasant respiratory sensations associated with exercise are known to adversely influence adherence to an exercise regime. (63) Therefore, use of airflow as part of PR may help the problems of low patient attendance and poor maintenance of long term outcomes. (64-67) Facial airflow from fan use during a cycle ergometer test in COPD patients resulted in significant breathlessness reduction and a longer total exercise time. (68) Likewise, the meta-analysis result from this SR suggest significant relief of breathlessness when airflow is delivered during exercise. These data highlight the potential value of using airflow delivery with PR or home based exercise programmes. In addition, intervention preference and AE data support the role of the fan in this context as a portable device that is unlikely to harm and therefore appropriate for the majority of patients to try.

Finally, it is likely that any positive benefits of airflow delivery from fan use with everyday general activity and at rest were not captured in the review data. The lack of signal from the results may in part reflect the complexity and the nuances of when, where and how this intervention is used by patients. (57) Current breathlessness management is modelled on a complex intervention, of which the fan is identified as a valuable therapeutic component alongside other interventions and strategies that are tailored to the patient's breathlessness needs. (11, 69)

Limitation of methods

Data were analysed as cohort "before and after" design, and no adjustments were made to control for confounding bias. The pre-post comparison increases the potential risk of bias and it is possible that results may be influenced by the timing of "before and after" measures. For example, studies of longer duration (up to 6 months) may not be representative of the

immediate benefits of airflow, but rather reflect more complex use and mechanism of any observed benefit may be related to reconditioning, facilitated by airflow, over time. Risk of bias was assessed using a tool designed for RCTs therefore it is possible that this assessment may not capture potential sources of bias associated with the observational methods used in this SR.

Overall, the qualitative synthesis represents findings from 929 participants the largest to date, however the meta-analyses pertain to a small number of participants and only provide a preliminary indication of the pooled effect estimate of airflow. The meta-analyses involve few studies therefore heterogeneity is difficult to estimate and the accuracy of the I^2 value is less certain. (70) The number of studies that fulfilled the review criteria was restricted by the need for baseline breathlessness measures. Some of the included studies (32, 51) did not report repeated measurements in a format suitable for meta-analysis necessitating statistical assumptions. (42)

Implications for practice and further research

Airflow is safe and should be used as an adjunct to treatment for breathlessness at rest in those who do not require oxygen-enriched air. Clinicians should consider airflow an important intervention to use as part of a breathlessness management programme in breathlessness at rest irrespective of cause. The relief of breathlessness during exertion in those with COPD may provide a useful intervention during pulmonary rehabilitation where breathlessness is a reason for poor adherence.

The fan, when taught by an appropriately trained clinician, offers patients an inexpensive and portable source of airflow likely to benefit exertion-induced breathlessness. Recovery time from exertion induced breathlessness is an important patient-reported outcome and further work is needed to explore the role of airflow in recovery, self-efficacy and increased daily activity as part of complex breathlessness intervention programmes including rehabilitation.

Conclusion

These data support facial or nasal airflow for clinically meaningful relief of breathlessness at rest. This SR pulls together the growing evidence to support airflow as an effective self-management option for people with chronic breathlessness and identifies airflow as an intervention for future study.

Declarations.

Authorship: Concept - FS; Design - FS, MJJ, CB, SB, JY; Data collection - FS, AN; Data analysis - FS, VA, MB; Data interpretation- All; Draft manuscript FS; critical revision of manuscript for intellectual content – All; approval final manuscript – All.

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Data management and sharing: The full search strategy is found in the Online Supplementary materials and included and excluded papers are presented.

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Airflow relieves chronic breathlessness in people with advanced disease: an exploratory systematic review and meta-analyses.

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Abstract

Background: Chronic breathlessness is a neglected symptom of advanced diseases.

Aim: To examine the effect of airflow for chronic breathlessness relief.

Design: Exploratory systematic review and meta-analysis.

Data sources: Medline, CINAHL, AMED and Cochrane databases were searched (1985 – 2018) for observational studies or randomised controlled trials of airflow as intervention or comparator. Selection against pre-defined inclusion criteria, quality-appraisal and data extraction were conducted by two independent reviewers with access to a third for unresolved differences. "Before and after" breathlessness measures from airflow arms were analysed. Meta-analysis was carried out where possible.

Results: 16/78 studies (n=929) were included; 11 randomised controlled trials of oxygen *vs* medical air, four randomised controlled trials and one fan cohort study. Three meta-analyses were possible: i) Fan at rest in three studies (n=111) offered significant benefit for breathlessness intensity (0-100mm Visual Analogue Scale and 0- 10 Numerical Rating Scale), mean difference -11.17 (95% confidence intervals -16.60 to -5.74), p=0.06 I^2 64%. ii) Medical air *via* nasal cannulae at rest in two studies (n=89) improved breathlessness intensity (visual analogue scale), mean difference -12.0mm, 95% confidence intervals -7.4 to -16.6, P<0.0001 I^2 =0%. iii) Medical airflow during a constant load exercise test before and after rehabilitation (n=29) in two studies improved breathlessness intensity (mBorg, 0-10) mean difference -2.9, 95% confidence intervals -3.2 to -2.7, p<0.0001 I^2 =0%.

Conclusion: Airflow appears to offer meaningful relief of chronic breathlessness and should be considered as an adjunct treatment in the management of breathlessness.

Keywords:

- dyspnea,
- self-management,
- review,
- airflow (relevant term as the intervention subject heading)

What is already known?

- Randomised Controlled Trials (RCTs) and cohort data have demonstrated that airflow delivered from the fan at rest offers significant relief of breathlessness.
- Systematic review (SR) and RCTs of oxygen *vs* medical air have failed to demonstrate additional benefit from oxygen therapy and suggest that medical air delivery, airflow, is likely to be an active intervention.
- All current evidence available for the effect of airflow for chronic breathlessness relief has not been explored using SR methods.

What this paper adds

This exploratory SR and meta-analyses provide promising data to suggest that:

- airflow from the fan at rest improves breathlessness in people with breathlessness due to a variety of causes
- airflow delivered as cylinder medical air at rest improves breathlessness in advanced cancer
- airflow delivered as cylinder medical air during a constant load exercise test in people with chronic obstructive pulmonary disease and who have completed pulmonary rehabilitation

Implications for practice and theory

- Clinicians should consider the fan as an adjunct to treatment for breathlessness at rest in patients who do not require oxygen-enriched air.
- Airflow may benefit exertion-induced breathlessness, but further work is required to investigate the role of the fan with everyday general activity and in relation to exercise.
- Recovery time from exertion-induced breathlessness, self-efficacy and daily activity are key outcomes to explore in future studies of airflow.

Introduction

Breathlessness is a common, often poorly managed symptom in people with advanced diseases. It is associated with reduced quality of life (1), decreased activities of daily living (2), unplanned emergency hospital attendance and admission. (3-5) Breathlessness inflicts devastating and disabling physical, psychological and social burden on normal daily life for the patient, carers and close family members (6-8). Chronic breathlessness, that is, breathlessness that persists despite optimal treatment for the underlying pathophysiology and causing such disability (9), all too often is left for patients to manage themselves despite a developing evidence base for interventions targeted at the breathlessness itself.

Growing evidence supports complex non-pharmacological interventions to reduce the impact of the symptom and improve quality of life. (10-12) Components target peripheral and central afferent sources of breathlessness sensation, such as facial airflow delivered by the battery-operated hand-held fan (fan). (13-17) Cooling of the facial skin innervated by the 2nd and 3rd branches of the trigeminal nerve, nasal mucosae or the upper airway flow receptors could modulate the central perception of breathlessness leading to decreased neural respiratory drive, thereby reducing the sensation of breathlessness. (18-22) A recent multi-methods secondary analysis of qualitative interview data from three studies found that 80/111 (72%) participants experienced benefit when the fan was used in conjunction with other components of a complex intervention. (23) Airflow delivered from the fan may offer a valuable contribution to the self-management of chronic breathlessness (13, 15, 23), and has been identified as a potentially useful strategy in a variety of situations, e.g. breathlessness crisis (24), a component of pulmonary rehabilitation to assist recovery from exercise, or with general everyday activities. (15)

Systematic reviews (SR) of oxygen in a variety of non-hypoxic patient groups (cancer, chronic heart failure, kyphoscoliosis, COPD and ILD) have not demonstrated additional benefit from oxygen therapy over medical air delivery. (25-30) An updated Cochrane review of COPD found low quality evidence for modest relief of breathlessness. (31) The results from a large, adequately powered trial that randomised 239 participants (COPD 63%, cancer 16%) to receive at least 15 hours a day of oxygen or medical air delivered via home concentrator for seven days reaffirms earlier suggestion that medical air used in the placebo arm may not be an inert comparator as previously thought and points to the likelihood of an

active intervention. (29, 32) Therefore the placebo arm of oxygen studies may provide useful preliminary data regarding the role of airflow for the relief of chronic breathlessness. This systematic review aims to identify and evaluate data from studies of airflow, both from studies of the hand-held fan and the comparator arm data for breathlessness intensity from oxygen studies, analysed as "before and after" airflow exposure cohort data.

Aim

To examine the current evidence for the effectiveness of airflow for the relief of chronic breathlessness.

Methods

The SR methods employed an exploratory approach in that only the airflow arm of studies were used and the data analysed as cohort "before and after" treatment.

Study design

The search methods employed are adapted from the Cochrane Handbook of Systematic Reviews (33) and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). (34) A review protocol is not pre-registered but available from the University of Hull Library (Flavia Swan PhD Thesis).

Inclusion and exclusion criteria

Types of studies

Randomised Controlled Trials (RCTs), controlled clinical trials (quasi-randomised experimental trials with or without blinding) and observational cohort studies were included.

Types of participants

Adults with chronic breathlessness from any advanced disease aetiology as shown below:

- Malignancy: advanced primary and metastatic cancer patients, who have undergone disease treatments like chemotherapy, radiotherapy or surgical interventions.
- Chronic Obstructive Pulmonary Disease (COPD) with forced expiratory volume in 1 second (FEV_1) of less than 50% predicted value
- Interstitial lung disease or pulmonary fibrosis where breathlessness is present
- Chronic heart failure: New York Heart Association (NYHA) stage III-IV
- Motor Neurone disease and other neurological disease where breathlessness is present or forced vital capacity (FVC) less than 80% predicted value
- Kyphoscoliosis: a moderate - severe sideways and forwards curvature of the spine Cobb Angle > 50° and FEV_1 of less than 50% predicted value**.**

Studies were included if at least 50% of the study population were classified as advanced, palliative or in the later stages of disease as defined above. These criteria were adapted from the Cochrane review of non-pharmacological interventions for breathlessness. (35)

Studies of participants with mild hypo or normoxaemia, who do not fore-fill the criteria for Long term Oxygen Therapy (LTOT) (36) were included. Studies of hypoxic participants or patients with any condition not assessed as progressive, refractory to treatment and advanced such as asthma were excluded.

Types of exposure

Airflow: i) delivered from either a fan (hand-held or table) or non-oxygen enriched compressed air, or from a non-invasive ventilatory method (nasal cannula, mask or mouthpiece), but not Nasal Intermittent Positive Pressure Ventilation (NIPPV) and ii) directed at the cheek of the face, nasal mucosae or mouth.

Administration: as i) a single dose *during ambulation*, or *at rest* taken as needed (PRN *pro re nata*),(37) ii) placebo short-burst oxygen therapy (SBOT) intermittent use *before* exercise or

after exercise for recovery (36) or iii) continuously over 15hr a day as placebo long-term oxygen therapy (LTOT) studies or during the night as placebo nocturnal oxygen therapy (NOT studies) .(38)

Studies where airflow was directly administered to the trachea, or at sub-zero temperatures were excluded.

Types of outcome measure

Unidimensional breathlessness outcomes

ATS domains of dyspnea measurement (20) including breathlessness severity or intensity rated on uni-dimensional scales as shown below:

- Modified Borg Score, a categorical scale with ratio properties
- Visual Analogue Scale (VAS), 0 - 100mm anchored 0 = no shortness of breath and 100mm = shortness of breath as bad as can be
- Numerical Rating Scales (NRS), 0-10 numbered scale anchored 0 = Not breathless at all and 10 the worst imaginable breathlessness
- Likert scales with verbal responses such as “a bit better”, “much better” or “no difference” or any other validated uni-dimensional scale for measuring breathlessness.

Studies were only included if they reported the breathlessness outcome at baseline and post-treatment measured as either primary or secondary outcomes. If severity or intensity was measured as part of a multi-dimensional or composite scale, e.g. the Chronic Respiratory Questionnaire, that unidimensional measure of breathlessness was *not* extracted and analysed separately. Breathlessness related function/quality of life measures were *not* used as primary breathlessness outcomes in the absence of unidimensional scales.

Other Outcomes

Other outcomes as shown below measured as either primary or secondary outcomes.

- Participant preference and satisfaction with the treatment
- Participant withdrawal and drop-out from the studies
- Adverse effects recorded

Data sources and searches

Medline, CINAHL, AMED and Cochrane databases were searched (1985 – 2015; updated January 2018) for observational or randomised controlled trials (RCTs) of airflow as intervention *vs* control or as comparator *vs* oxygen. Reference lists were scanned. A full search strategy can be seen in Online Supplementary Table 1.

Study selection

Titles, abstracts (and, where unclear, full papers) were screened against the eligibility criteria by two independent reviewers FS and AN, with recourse to MJ as a third reviewer in case of disagreement.

Data extraction and synthesis

Baseline and post-intervention measures of breathlessness intensity were extracted from the fan studies and from the comparator arm of oxygen studies. Data were analysed as "before and after" airflow exposure cohort observational data.

Risk of bias

FS and AN judged the reporting quality and internal validity for each of the included studies. The cohort study was evaluated according to the Cochrane guidelines for assessing bias in a non-randomised study. (39) As there is no tool that is applicable directly to the data extracted from the RCTs control arms, we assessed instead the quality of the parent RCTs as a proxy

marker for quality data. The RCTs were assessed with the Cochrane Risk of bias tool. (33) See online Supplementary Table 2.

Statistical Analysis

Results from the meta-analyses were reported for the primary outcome, breathlessness intensity or severity where heterogeneity allowed, or where not possible these were described narratively. NRS and VAS scales were combined by equating one point on a NRS scale to 10mm on a VAS. (40, 41)

Data calculations for mean difference and SD used STATA Version 12.1, Stata Corp LLC Texas 77845-4512, USA. Breathlessness measurements were analysed as continuous outcomes. Data from the placebo arm of cross-over RCTs were treated as single arm before-after studies. For studies that recorded median values, the mean were calculated from the extracted study data. (42) The I^2 statistic was used to assess heterogeneity. (43) Where the result indicated significant heterogeneity a random effects model was chosen, otherwise a fixed effects model was applied. All analyses were undertaken on Review Manager 5.5. A sensitivity analysis was attempted for any study identified as including a sub-group not fitting the review criteria of mild hypo or normoxaemia to assess for any significant difference in the breathlessness outcome between the hypoxic and non-hypoxic participants.

Results

A total of 403 records were identified for screening. After removal of duplicates, 78 records were reviewed. 14 abstracts were rejected for not meeting inclusion criteria; the remaining 64 full text articles were assessed for eligibility. Of these, 16 studies met the review inclusion criteria and the other 48 studies were excluded (see Figure 1; PRISMA flow chart (34) and Online Supplementary Table 3, eAppendix)**.**

Overall studies represented 929 participants (age median 61.5, range 33 to 90 years; 47% men)

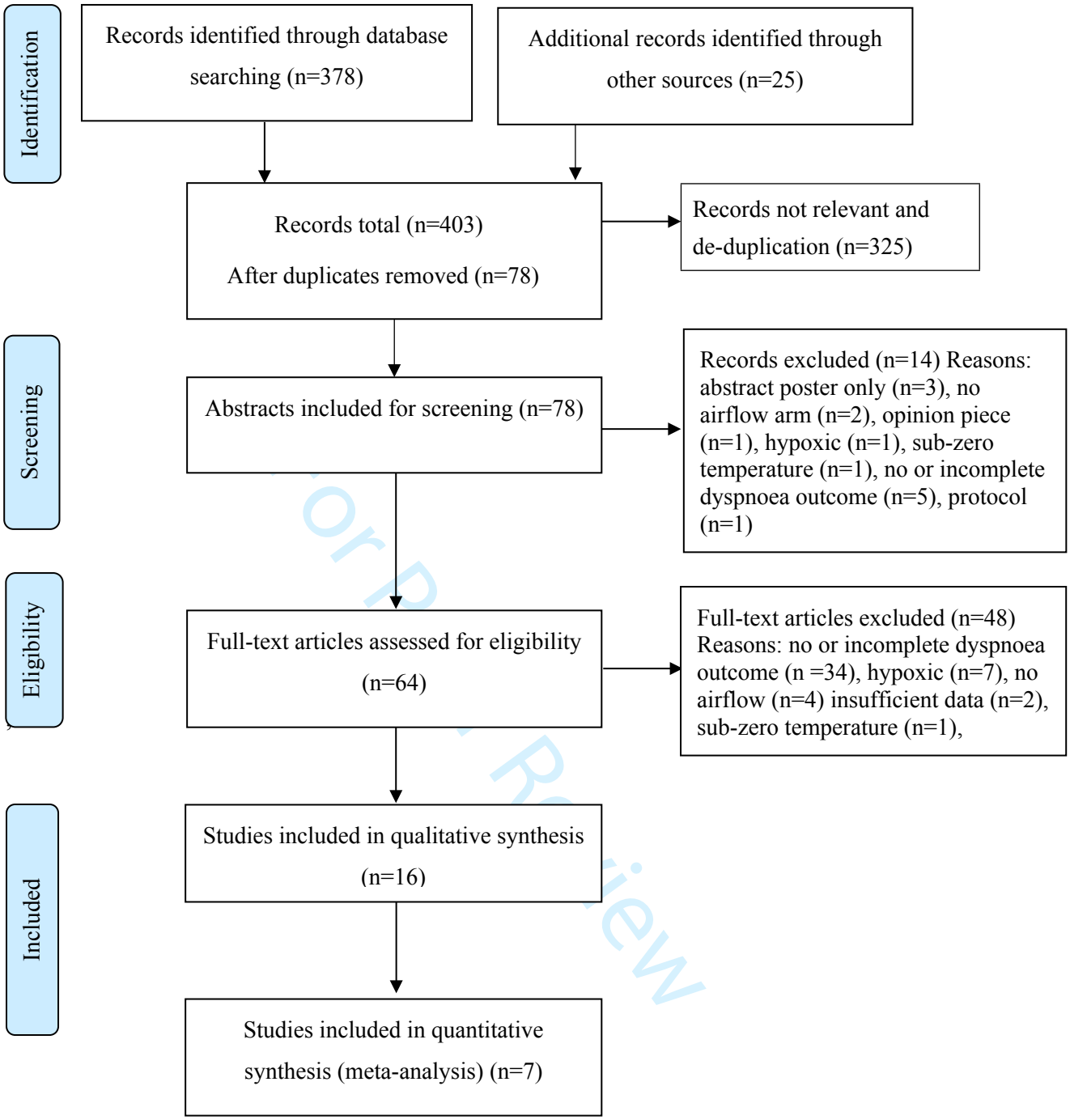

Figure 1 PRISMA 2009 Flow-diagram of study selection and retrieval (34)

Airflow was delivered by fan (13, 14, 16, 17, 44) or as medical air. (29, 32, 45-53) See Table 1 for study characteristics

Description of fan studies

Design: five studies (n=230) used the fan. Two feasibility RCTs; (n =49), (13) and (n=30), (44), a feasibility cohort study (n=31), (14), a feasibility longitudinal RCT (n=70), (16) and a phase III cross-over RCT (n=50), (17).

Patient characteristics: Four studies recruited a mixed population of people with breathlessness due to a variety of advanced conditions including COPD (n=101), cancer (n=55), heart failure (n=23) and other causes (n=21), (13, 14, 16, 17), and one study recruited advanced cancer only (n=30). (44)

Intervention and comparator characteristics: three studies used the fan to face at rest (14, 17, 44), two with comparator groups; fan to leg (17), or no fan use and carer support (44), and the other was a cohort design. (14) One study assessed acceptability of the fan when used with general activity over 6 months compared with an acupressure wristband (16), and the remaining study assessed the fan when used with exercise advice over 4 weeks. (13)

Breathlessness Outcome: Three studies focused on the sensory-perceptual domain of dyspnea measurement and used breathlessness intensity as the primary outcome (17) or main outcome (14, 44). These studies selected the VAS (17), the NRS (44), or both VAS and NRS (14). The other two studies assessed symptom impact as well as the sensory-perceptual domain. These studies selected the NRS breathlessness intensity (13) and the Modified Borg Scale of breathlessness severity. (16)

Other outcomes: All of the fan studies reported participant withdrawals (13, 14, 16, 17, 44). These ranged from 0 to 6 participants. (13, 14, 44) One study reported that there were no Adverse Events (AE) (13) and the other fan studies did not include any AE details. (14, 16, 17, 44) Airflow preferences were described in four fan studies (13, 16, 17, 44) and not in one study. (14) In addition, one study quantified the experience of fan use at 2 months. (16)

Description of medical air studies

Design: eleven RCT's (n=699) used oxygen, helium hyperoxia or both gases for the intervention compared with medical air. (29, 32, 45-53) Study size ranged from 16 to 239

participants. (29, 48) Four were cross-over (32, 48, 49, 51) and seven used a parallel group design. (29, 45-47, 50, 52, 53) Nine studies were double blind (29, 45-52), and two were single blind. (32, 53)

Patient characteristics: the eleven studies represent; COPD n=537, cancer n=109, other lung diseases n=21, cardiac disease n=14 and other causes n=18. Inclusion criteria required moderate to severe COPD (45-50, 52, 53), advanced cancer (51), or were a mixed population with no specific stipulation of severity. (29, 32)

Intervention Characteristics: the source of airflow was an oxygen cylinder (32, 45-50), a sham concentrator (29), and a Douglas bag. (52) Two studies did not state the airflow source. (51, 53) Medical air or compressed air was delivered through nasal cannulae (29, 32, 45, 47, 49-51, 53), face-mask and nasal cannula (48), a non-rebreathing face-mask (46) and through a mouthpiece. (52) The flow rates varied widely in the studies; 2l/minute (29, 45), 3l/minute (47), 4l/minute (32, 49, 51), 5l/minute (53), 6l/minute (50) and 8l/minute *via* nasal cannula or 15l/minute with face mask. (48) Two studies did not report flow rate details. (46, 52) The timing of airflow delivery was; 15 minutes at rest (32, 51), with daily activity over 3 (50), or 6 months (45), 15 hours a day over one week (29), or in conjunction with exertion-induced breathlessness during pulmonary rehabilitation (PR), (46, 52, 53) or a walking test. (47-49) The PR programme parameters for airflow delivery were with treadmill exercise 3 times a week for 30 minutes over two months (53), a cycle ergometer used 3 times a week for 30 minutes over 6 weeks (46), or 3 times a week for 20 minutes over two months. (52) The 6MWT test parameters for airflow delivery were; i) three same day 6MWTs with 45 minutes washout, using room air for the basal walk and compressed air for the subsequent walks (47), ii) five 6MWTs performed over three visits, (timing not stated) using room air for the practice walk on visit one and cylinder air for the two 6MWTs with 60 minute washout on visits two and three (48), and iii) three same day 6MWTs using cylinder air with 20 minutes washout between tests at baseline, 6 and 12 weeks as well as short burst use at home with daily activity during the study period. (49)

Breathlessness outcome: two studies focused on the sensory-perceptual domain of dyspnea measurement and recorded breathlessness intensity as a primary outcome with the VAS and Borg scale (32) or the VAS only. (51) All of the other studies focused on symptom impact as well as the sensory-perceptual domain. (29, 45-50, 52, 53) Of these, three studies measured

breathlessness intensity as a primary outcome with the NRS (29) or the CRQ dyspnea domain. (45, 50) The remaining six studies identified the modified Borg scale as one of the main outcomes (47-49, 52, 53) or a secondary measure. (46) One study in addition selected the CRQ. (49)

Other outcomes: participant withdrawals were reported in all of the studies (29, 32, 45-51, 53), apart from one. (52) Five studies reported no withdrawals (32, 46-48, 51) and in the other five studies withdrawals ranged from 2 to 21 participants. (45, 53) AE were poorly reported with only two studies including details; "few" or "no AE". (29, 46) All of the other studies omitted reporting AE. (32, 45, 47-53) Airflow preferences were only reported in one study. (51) The remaining studies did not report airflow preferences (29, 32, 45-48, 50, 52, 53), although one study did quantify side-effects (29) and a second study examined preference for cylinder delivery of airflow. (50)

Table 1 Characteristics of included studies (fan)

Study author	Study Design	Population	Intervention	Comparator	Mode of gas delivery	Dyspnea Outcome measure(s)	Other Outcomes: withdrawals, Adverse Events (AE), airflow preferences	Timing of measurement	Results airflow arm only (before and after treatment)	Improvement with airflow Yes/No
Booth (2016) [14]	Feasibility observational cohort	n= 31 Males: 20 Age mean: 74.8 SD 11.49 Mixed population, non-malignant, cardiorespiratory disease: 8 (26%) Baseline dyspnoea score: Mean VAS 48mm SD 27.4	Hand-held fan to face	No comparator group	Airflow from hand-held fan to face for 5 minutes	VAS (mm), NRS	Withdrawals = 6 AE and airflow preferences not reported	After 5 minutes at rest	VAS = Mean 35mm SD 25.7 after 5min air Mean change = 12mm SD 21.2	Yes
Bausewein (2010) [16]	Feasibility longitudinal phase II RCT	n = 70 Males: 36 Age mean: 65.6yrs SD 8.80 COPD = 45, cancer = 25 Baseline dyspnoea score: 3.7 (1.83)	Hand-held fan to face	Wristband	Airflow from hand-held fan	Modified Borg score	Withdrawals at 2 months =16/33 (48%) AE not reported Airflow preferences: Positive = 13/38 Negative = 7/38	Monthly over 6 months	Mean Borg score change over 2 months = 0.6 (SD 2.1), p = 0.90	No, phase II not powered to test
Galbraith (2010) [17]	Cross-over RCT	n = 50 Males: 23 Age mean: 71.3, range 33-90yrs Mixed population; COPD = 26, lung cancer = 11, heart disease = 15 Baseline dyspnoea score: VAS Fan/face 1st group = 31mm (SD 12-61mm)	Hand-held fan to face	Hand-held fan to leg	Airflow from hand-held fan to face for 5 minutes	VAS (mm)	Withdrawals = 1 AE not reported Airflow preferences: positive patient comments, numbers not reported	After 5 minutes at rest and after 10 minute washout	VAS = -7.0mm Median change after 5 minutes Fan/face 1st group (IRQ 1.5 - 14.5) VAS = -10.0mm Median change incl 10 minute washout Fan/face 1st group (IRQ 3.5 – 17), P=0.003	Yes

Table 1 Characteristics of included studies (fan)

Study author	Study Design	Population	Intervention	Comparator	Mode of gas delivery	Dyspnea Outcome measure(s)	Other Outcomes: withdrawals, AE, airflow preferences	Timing of measurement	Results: airflow arm only (before and after treatment)	Improvement with airflow Yes/No
Johnson (2016) [13]	Feasibility phase II RCT	n =49 Males: 26 Age mean: 68 (range 46-88) Mixed population; COPD = 28, cancer =9, heart disease = 5, others = 7 Baseline dyspnoea score Mean NRS = 5.7 (SD 1.5)	Hand-held fan to face at high or low flow rate	Usual care: verbal and written exercise and breathlessness management advice	Airflow from hand-held fan	NRS	Withdrawals = 6 No AE Airflow preference: positive patient comments, numbers not reported	After 4 weeks	NRS = 6.0 (2.0) at 4 weeks Mean change 0.0 (3.0)	No, phase II not powered to test
Wong (2017) [44]	Feasibility phase II RCT	n=30 Males: 14 Age: NR Lung cancer = 13, other cancers = 17 Baseline dyspnoea score Control group: NRS mean 5.6 (SD 1.55) Intervention group: NRS mean 6.13 (SD 2.48)	Table fan with low flow rate	Placebo accompanied by carer	Airflow from table fan to face for 5 minutes	NRS	No withdrawals AE not reported Airflow preference: mixed patient comments, numbers not reported	After 5 minutes at rest	NRS = 4.60 after 5 minutes fan to face Mean change -1.53 (1.06) p< 0.001	Yes

Table 1 Characteristics of included studies (medical air)

Study author	Study Design	Population	Intervention	Comparator	Mode of gas delivery	Dyspnea Outcome measure(s)	Other Outcomes: withdrawals, AE, airflow preferences	Timing of measurement	Results airflow arm only (before and after treatment)	Improvement with airflow Yes/No
Abernethy (2010) [29]	Double-blind RCT	n = 239 Males: 63% Age mean: Air = 74yrs (SD 10) Mixed: COPD = 152, Primary lung cancer = 33 Baseline dyspnoea score: Am air = 4.6 (SD 2.4) Pm air = 4.7 (SD 2.3)	Oxygen	Room air via concentrator	2l/min via nasal cannula for at least 15hrs a day (LTOT)	NRS 1-10	Withdrawals = 15 Few AE, number not reported Side-effects reported Airflow preferences not reported, oxygen only	Am and pm each day, within 30 minutes of waking and bedtime for 7 days	Am = -0.7 NRS point change Pm = -0.5 NRS point change, (p = 0.5)	Yes
Booth (1996) [32]	Single-blind cross-over RCT	n = 38 Males: 22 Age Median: 71 Range: 54-90yrs Lung Cancer 20, COPD 13, Cardiac 4 Baseline dyspnoea score: VAS 59mm	Oxygen	Cylinder air	4l/minute for 15 minutes via nasal cannula	VAS (mm) Modified Borg Scale	No withdrawals AE and airflow preferences not reported	After 15 minutes of breathing oxygen or air at rest.	VAS = -11mm change after air 48mm, p<0.001	Yes
Eaton (2006) [45]	Double-blind parallel RCT	n = 78 Males: 36 Age mean: 77.3yrs (7.06) Moderate/severe COPD Baseline CRQ score: Air = 17.5 (SD 4.2)	Oxygen	Cylinder air	2l/minute via nasal cannula over 6 months (SBOT)	CRQ	Withdrawals = 21 AE and airflow preferences not reported	Monthly over 6 months	CRQ = Average change over 6 months: air group = -3.6	No

Table 1 Characteristics of included studies (medical air)

Study author	Study Design	Population	Intervention	Comparator	Mode of gas delivery	Dyspnea Outcome measure(s)	Other Outcomes: withdrawals, AE, airflow preferences	Timing of measurement	Results airflow comparator arm only (before and after treatment)	Improvement with airflow Yes/No
Eves (2009) [46]	Double-blind RCT	n = 38 Males: 23 Age mean: 65.5yrs (SD 8) Stable COPD Baseline dyspnoea score: constant load exercise Borg mean: Air = 6.0 (SD 2.2) incremental load exercise Borg mean: Air = 5.6 (SD2.0)	Helium-hyperoxia (60% HE: 40% O^2)	Cylinder air	Face mask (non-rebreathing)	Modified Borg score	No withdrawals No AE Airflow preferences not reported	During exercise test before and after 6 weeks pulmonary rehabilitation programme, 3 times a week for 30 minutes on cycle ergometer	constant load exercise Borg mean: Air = 4.2 (SD 2.1) mean change = -1.8 (95% CI -3.1 to -0.2), $p < 0.05$ incremental load exercise Borg mean: Air = 5.6 (SD 2.1) No change (95% CI -0.7 to 0.7)	Yes
Jolly (2001) [47]	Double-blind RCT	n = 20 Males: 19 Age mean: 68.5yrs (SEM 2.5) Stable COPD Baseline dyspnoea score: Borg mean score Desat group Baseline 6MWT = 5.82 (SEM 0.46) Non-desat group Baseline 6MWT = 4.22 (SEM 0.46)	Oxygen	Cylinder air	3l/minute via nasal cannula	Modified Borg score	No withdrawals AE and airflow preferences not reported	Before and after 3 x 6 MWTs with at least 45minutes washout between walks	Borg mean score: Desat group Air 6MWT = 5.82 (SEM 0.42) No change Non-desat group Air 6MWT = 4.44 (SEM 0.73) No change	No
Marciniuk (2007) [48]	Double-blind crossover RCT	n = 16 Males: 7 Age mean: 67 (SD 8) Moderate to severe COPD Baseline dyspnoea score: Borg mean score Baseline 6MWT = 5 (SD 2)	100% Oxygen or Helium-hyperoxia (70% HE: 30% O^2)	Cylinder air	15l/minute via face mask 8l/minute via nasal cannula	Modified Borg score	No withdrawals AE and airflow preferences not reported	Before and after each 6 MWTs on visit 1,2 and 3 with 60 minutes washout between walks	Borg mean score After 6MWT Air = 3.5 mean Borg score change = -1.5 decrease	Yes

Table 1 Characteristics of included studies (medical air)

Study author	Study Design	Population	Intervention	Comparator	Mode of gas delivery	Dyspnea Outcome measure(s)	Other outcomes: withdrawals, AE, airflow preferences	Timing of measurement	Results airflow comparator arm only (before and after treatment)	Improvement with airflow Yes/No
McDonald (1995) [49]	Double-blind crossover RCT	n = 26 Males: 24 Age mean: 73 (SD 6) Stable severe COPD Baseline dyspnoea score 6MWT: Air group = 3.8 (SD 1.4) CRQ = 14 (SD 5)	Oxygen	Cylinder air	4l/minute via nasal cannula	Modified Borg score CRQ	Withdrawals = 7 AE and airflow preferences not reported	After 6 and 12 weeks of home cylinder air using 6MWT exercise test with 20 minute washout between walks	Borg Mean score Home air: 6MWT with cylinder air = 3.8 (SD 1.5) No change CRQ score Home air = 17 (SD 6)3 point change	No with 6MWT Yes with CRQ
Moore (2011) [50]	Double-blind RCT	n = 143 Males: 99 Age mean: 71.8yrs (SD 9.8) Range: 43-78 Stable COPD Baseline dyspnoea score: Air = 17.5 (SD 4.9)	Oxygen	Cylinder air	6l/minute via nasal cannula at home for 12 weeks with activity (SBOT)	CRQ	Withdrawals = 4 AE not reported Airflow preferences 45% prefer no cylinder	At 4 weeks and 12 weeks	Air: 4 weeks = 18.4 (SD5.8) 12 weeks = 18.4 (SD 5.8) Air: CRQ = Mean change at 4 and 12 weeks = 0.9	Yes
Philip (2006) [51]	Double-blind cross-over RCT	n = 51 Males: 31 Age median: 65 Range: 33-82yrs NSCLC = 22, Small cell lung cancer = 6, Breast = 8, Colorectal = 4 Others = 11 Baseline dyspnoea score: VAS median Air 1st = 52mm (range 23-92) VAS median Air 2nd = 42mm (range 10-70)	Oxygen	Medical Air	4l/minute for 15 minutes via nasal cannula	VAS (mm)	No withdrawals AE not reported Airflow preferences: Positive: n=15 (29%)	Before and after 15 minutes of gas	VAS median After air 1st = -3mm change (range -19 to 7) VAS median After air 2nd = -11.5mm change (range -20 to 45) VAS mean change = -13.4mm	Yes

Table 1 Characteristics of included studies (medical air)

Study author	Study Design	Population	Intervention	Comparator	Mode of gas delivery	Dyspnea Outcome measure(s)	Other Outcomes: withdrawals, AE, airflow preferences	Timing of measurement	Results airflow comparator arm only (before and after treatment)	Improvement with airflow Yes/No
Scorsone (2010) [52]	Double-blind RCT	n = 30 Males: 23 Age mean: 67.3yrs (SD 8.3) Moderate to severe COPD Baseline dyspnoea score: Before training incremental load exercise Borg: Air = 7 (SD 3) Before training constant load exercise Borg: Air = 8 (SD 3)	40% Oxygen or Helium - hyperoxia (60% HE: 40% O^2)	Humidified room air	Mouthpiece from a Douglas bag	Modified Borg score	No withdrawals AE and airflow preferences not reported	During exercise before and after a 2 months pulmonary rehabilitation programme, 3 times a week for 20 minutes on cycle ergometer	After training incremental load exercise Borg: Air = 4 (SD 2) After training constant load exercise Borg = 5 (SD 3) Borg change = -3 point decrease both exercise tests	Yes
Wadell (2001) [53]	Single-blind crossover RCT	n = 20 Males: 10 Age mean: 67yrs Range: 52-73 Stable COPD Baseline dyspnoea median score: Test A (Air) At rest; Pre-training Borg: Air group = 1.5 (0-3) Test A (Air) After 6MWT, Pre-training Borg: Air group = 6.5 (4-9)	Oxygen	Air	5l/minute via nasal cannula	Modified Borg score	Withdrawals =2 AE and patient preferences not reported	During exercise using 2 x 6MWT (air/O^2 or O^2/air) with 1hour washout before and after a 2 months pulmonary rehabilitation programme, 3 times a week for 30 minutes on a treadmill	Test A (Air) At rest; Post-training Borg: Air group = 1 (0-3) Test A (Air) After 6MWT, Post-training Borg: Air group = 6 (1-7) Borg change = -0.5 point at rest and after exercise test	Yes

Risk of Bias

The quality appraisal is summarised in Online Supplementary Table 2 and described below.

Allocation: all of the studies, apart from one, a cohort design (14), were described as RCTs. It was possible to verify the randomisation process in eight studies. (13, 16, 17, 29, 32, 45, 46, 50). There was insufficient information to determine the risk of allocation bias in the other RCTs. (44, 47-49, 51-53)

Blinding: two of the fan studies attempted to blind the participants (16, 17); a placebo wristband was used as a comparator (16) and participants were not told if the fan to face or fan to leg was the active intervention. (17) There was no blinding in two studies, a cohort and phase II RCT (13, 14), and the fifth study stated single blinding that could not be verified from the methods described. (44) All five were judged high risk of bias due to incomplete blinding or limited description. Nine medical air RCTs were described as double blind. (29, 45-52) All were judged low risk of bias (29, 45, 46, 48-50, 52), apart from one study that was unclear due to the lack of detail reported. (51) Two RCTs were single blind (32, 53); one was judged low risk of bias (32) and the other was regarded as unclear risk due to the inadequate description. (53)

Incomplete outcome data: 13 studies adequately addressed withdrawals and incomplete outcome data; these were considered low risk of bias.(13, 14, 17, 29, 32, 46-53) Three studies were uncertain risk (16, 45); one due to the proportion of attrition (16) and the other two lacked description of how any missing data were statistically managed. (44, 45)

Selective Outcome reporting: all of the studies reported the pre-specified outcomes and were judged as low risk of bias. (13, 14, 16, 17, 29, 32, 44-53) Study protocols were available for eight studies. (13, 14, 16, 17, 29, 46, 50, 51)

Other issues of bias: twelve studies appeared free from other bias and were judged low risk. (13, 16, 17, 29, 44-46, 48, 50-53) Three studies reported insufficient information to adequately assess risk (32, 47, 49), and one study, a cohort design was judged high risk. (14)

Effect of interventions

The airflow was delivered, i) at rest (14, 17, 32, 44, 51) ii) over days or weeks (either intermittently or as periods of continuous flow) whilst the participant continued with usual general activities (13, 16, 29, 45, 50) or iii) during specific episodes of exertion induced breathlessness. (46-49, 52, 53)

i) At rest

Five studies demonstrated improvement with airflow delivery at rest.

Results from 5 minutes fan use to the face in three studies were VAS breathlessness intensity difference from baseline mean -7mm (CI -11.5 to -2.5) (17), and mean -12mm (CI -19.3 to -4.4) (14), and for the NRS mean change -1.53 (-9.6 to -6.5).(44)

Cylinder medical air delivery for 15 minutes demonstrated improvement VAS breathlessness intensity mean -11mm (CI -17.0 to -5.0) (32), and mean -13mm (CI -20.5 to-6.3). (51) Four studies were sub-divided into two groups and included in meta-analyses.

Fan

Airflow from the fan at rest improved breathlessness in a mixed population (n=111; 58% cancer) VAS (mm) mean difference (MD), -11.17 (CI -16.60 to -5.74), p=0.06. Significant heterogeneity was observed, Chi² p-value = 0.2, (I^2 = 64%) (See Figure 2).

<<insert Figure 2 Meta-analysis of fan at rest >>

Medical air

Airflow delivered as cylinder medical air at rest improved breathlessness in advanced cancer (n=89) VAS (mm) MD -12.0, (CI -16.6 to -7.4), P<0.0001. No evidence of heterogeneity was observed, Chi² P value = 0.6, (I^2 =0%).

<<insert Figure 3 Meta-analysis of cylinder air at rest >>

ii) General activity

Six studies used airflow at home with everyday general activity. A narrative description was used for these due to study diversity. Breathlessness points change from four cylinder air studies were mixed (29, 45, 49, 50), with CRQ -3.6 after 6 months (45), 3.0 after 12 weeks (49), or 0.9 at 12 weeks (50), or NRS -0.7 (am) and -0.5 NRS (pm) after 7 days. (29) In the two fan studies a modified Borg score of -0.6 (SD 2.1) was found after 2 months (16), but there was no NRS score change after 4 weeks of fan use with exercise advice. (13)

iii) Exertion-induced breathlessness

Six studies examined airflow delivery with exertion-induced breathlessness. Results for mean Borg breathlessness score during a walking test for three studies varied; no change during a 6MWT repeated on the same day (47), or at 12 weeks (49), and improvement -1.5 for a 6MWT repeated on 3 separate visits. (48) Airflow delivered during a constant load exercise test after PR in three studies also demonstrated variable improvement in mean Borg breathlessness scores; -1.8 points (46), and -3 point (52) using a cycle ergometer, and -0.5 point from a treadmill test. (53) Two studies were suitable to include in a meta-analysis (See Figure 4). (46, 52)

Medical air

Airflow delivered as cylinder medical air during a constant load exercise test after PR in COPD (n=29) significantly improved breathlessness Borg score MD -2.9, (CI -3.2 to -2.7), $p<0.0001$. No evidence of heterogeneity was observed, Chi^2 p-value = 0.7, (I^2 =0%), (Figure 4).

<< insert Figure 4 Meta-analysis of cylinder medical air for exertion-induced breathlessness>>

Discussion

These exploratory data support that facial and nasal airflow delivery at rest offers relief of breathlessness intensity consistent with a moderate clinically important difference, (54, 55) and during exertion. (46, 52) All participants in the cylinder medical air delivery at rest studies had advanced cancer, but nearly half of those in the fan "at rest" studies had other conditions indicating that airflow for breathlessness at rest is of benefit irrespective of cause.

In a recent pooled qualitative data study of facial airflow use from the fan in 133 people with chronic breathlessness (56), over 80% patients reported some or substantial benefit.(57) However, the data presented here varied with regard to relief of breathlessness intensity when facial or nasal airflow delivery was used with everyday general activity or with exertion induced breathlessness. This may reflect the use of outcome measures that do not reliably capture change in breathlessness intensity in the context of exertion. Studies that used a 6MWT (47-49) highlight the problem of a self-paced test that allows patients to control their walking speed and thus limit the maximal level of exertion–induced breathlessness experienced. In contrast, studies that used an externally paced test, such as the cycle ergometer, identified relief of breathlessness intensity. (46, 52) The relationship between exercise and breathlessness intensity is complex, and measuring one without taking the other into account may miss relevant improvement. Scores are likely to remain static after the introduction of an intervention as patients are able to exert themselves to the same level of breathlessness without noticing an increase in their exercise tolerance (58), or indeed the outcome may be of little value to the patient. (57)

A previous study of recovery time after an ISWT in people with thoracic cancer (n=57) reported a rapid reduction in breathlessness intensity with a return to baseline time of median 4 (IQR 2-5) minutes. (59) The analysis of 133 patient interviews found that a faster recovery time was a key patient-reported benefit of airflow delivered from the fan, irrespective of breathlessness intensity. (57) Even though recovery time may only be a matter of minutes, interventions which shorten this further are clearly welcomed and give the patient a sense of self-control that may help prevent a breathlessness-anxiety spiral. The ability to recover quickly and predictably from bouts of exertion is likely to encourage further activity and prevent the deconditioning cycle.

The fan therefore seems suitable as a patient-delivered intervention to target the recovery time from exertion-induced breathlessness. Preliminary magnetoencephalography (MEG) imaging data suggests airflow delivery during recovery from exercise may modulate central perception of breathlessness by modifying sensory attention. (60) Cooling of the facial skin innervated by the 2nd and 3rd branches of the trigeminal nerve and/or stimulation of nasal mucosa and upper airway 'flow' receptors are reported to improve breathlessness intensity and exercise tolerance (18, 19, 61, 62) and could "fool" the brain into thinking that the respiratory status is adequate. (22)

Unpleasant respiratory sensations associated with exercise are known to adversely influence adherence to an exercise regime. (63) Therefore, use of airflow as part of PR may help the problems of low patient attendance and poor maintenance of long term outcomes. (64-67) Facial airflow from fan use during a cycle ergometer test in COPD patients resulted in significant breathlessness reduction and a longer total exercise time. (68) Likewise, the meta-analysis result from this SR suggest significant relief of breathlessness when airflow is delivered during exercise. These data highlight the potential value of using airflow delivery with PR or home based exercise programmes. In addition, intervention preference and AE data support the role of the fan in this context as a portable device that is unlikely to harm and therefore appropriate for the majority of patients to try.

Finally, it is likely that any positive benefits of airflow delivery from fan use with everyday general activity and at rest were not captured in the review data. The lack of signal from the results may in part reflect the complexity and the nuances of when, where and how this intervention is used by patients. (57) Current breathlessness management is modelled on a complex intervention, of which the fan is identified as a valuable therapeutic component alongside other interventions and strategies that are tailored to the patient's breathlessness needs. (11, 69)

Limitation of methods

Data were analysed as cohort "before and after" design, and no adjustments were made to control for confounding bias. The pre-post comparison increases the potential risk of bias and it is possible that results may be influenced by the timing of "before and after" measures. For example, studies of longer duration (up to 6 months) may not be representative of the

immediate benefits of airflow, but rather reflect more complex use and mechanism of any observed benefit may be related to reconditioning, facilitated by airflow, over time. Risk of bias was assessed using a tool designed for RCTs therefore it is possible that this assessment may not capture potential sources of bias associated with the observational methods used in this SR.

Overall, the qualitative synthesis represents findings from 929 participants the largest to date, however the meta-analyses pertain to a small number of participants and only provide a preliminary indication of the pooled effect estimate of airflow. The meta-analyses involve few studies therefore heterogeneity is difficult to estimate and the accuracy of the I^2 value is less certain. (70) The number of studies that fulfilled the review criteria was restricted by the need for baseline breathlessness measures. Some of the included studies (32, 51) did not report repeated measurements in a format suitable for meta-analysis necessitating statistical assumptions. (42)

Implications for practice and further research

Airflow is safe and should be used as an adjunct to treatment for breathlessness at rest in those who do not require oxygen-enriched air. Clinicians should consider airflow an important intervention to use as part of a breathlessness management programme in breathlessness at rest irrespective of cause. The relief of breathlessness during exertion in those with COPD may provide a useful intervention during pulmonary rehabilitation where breathlessness is a reason for poor adherence.

The fan, when taught by an appropriately trained clinician, offers patients an inexpensive and portable source of airflow likely to benefit exertion-induced breathlessness. Recovery time from exertion induced breathlessness is an important patient-reported outcome and further work is needed to explore the role of airflow in recovery, self-efficacy and increased daily activity as part of complex breathlessness intervention programmes including rehabilitation.

Conclusion

These data support facial or nasal airflow for clinically meaningful relief of breathlessness at rest. This SR pulls together the growing evidence to support airflow as an effective self-management option for people with chronic breathlessness and identifies airflow as an intervention for future study.

Declarations.

Authorship: Concept - FS; Design - FS, MJJ, CB, SB, JY; Data collection - FS, AN; Data analysis - FS, VA, MB; Data interpretation- All; Draft manuscript FS; critical revision of manuscript for intellectual content – All; approval final manuscript – All.

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Declaration of conflicts of interest: The Authors declare that there is no conflict of interest.

Data management and sharing: The full search strategy is found in the Online Supplementary materials and included and excluded papers are presented.

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Online Supplementary Table 1 Full Search strategy

1. *Exploded MeSH* lung diseases obstructive
2. *Exploded MeSH* pulmonary disease, chronic obstructive
3. COPD *key word*
4. *Exploded MeSH* neoplasms
5. *Exploded MeSH* lung diseases, interstitial
6. 1 OR 2 OR 3 OR 4 OR 5
7. *Exploded MeSH* heart failure, congestive
8. MotorADJ1neuroneADJ1disease *text word*
9. *Exploded* amyotrophic lateral sclerosis
10. Kyphoscoliosis *text word*
11. *Exploded MeSH* pulmonary fibrosis
12. 7 OR 8 OR 9 OR 10 OR 11 or / 1-5
13. Hand-held fan OR fan *text word*
14. Medical ADJ1 air *text word*
15. *Exploded MeSH* oxygen inhalation therapy
16. AirADJ1flow *text word*
17. Facial OR nasal AND cold OR cooling *text word*
18. 13 OR 14 OR 15 OR 16 OR 17
19. *Exploded MeSH* Dyspnea
20. dyspnoea *key word*
21. Difficulty OR short ADJ1 breath$ *text word*
22. *Exploded MeSH* Exercise
23. *Exploded MeSH* "Activities of Daily Living"
24. 19 OR 20 OR 21 OR 22 OR 23
25. 12 AND 18 AND 24

Online Supplementary Table 2 Risk of Bias. Methodological quality of included studies

Study reference	Study author	Study design	Sequence generation	Allocation concealment	Blinding	Withdrawals, incomplete data	Selective outcome reporting	Free of other issues or bias
14	Booth (2016)	cohort	n/a	n/a	high	low	low	high
16	Bausewein (2010)	RCT	low	low	high	unclear	low	low
17	Galbraith (2010)	RCT	low	low	high	low	low	low
13	Johnson (2016)	RCT	low	low	high	low	low	low
44	Wong (2017)	RCT	unclear	unclear	high	low	low	low
29	Abernethy (2010)	RCT	low	low	low	low	low	low
32	Booth (1996)	RCT	low	low	low	low	low	unclear
45	Eaton (2006)	RCT	low	low	low	unclear	low	low
46	Eves (2009)	RCT	low	low	low	low	low	low
47	Jolly (2001)	RCT	unclear	unclear	low	low	low	unclear
48	Marciniuk (2007)	RCT	unclear	unclear	low	low	low	low
49	McDonald (1995)	RCT	unclear	unclear	low	low	low	unclear
50	Moore (2011)	RCT	low	low	low	low	low	low
51	Philip (2006)	RCT	unclear	unclear	unclear	low	low	low

52	Scorsone (2010)	RCT	unclear	unclear	low	low	low	low
53	Wadell (2001)	RCT	unclear	unclear	unclear	low	low	low

Codes: low = low risk of bias unclear = unclear risk of bias high = high risk of bias n/a =not applicable

Online Supplementary Table 3 Characteristics of excluded studies (n=62)

Study	Reason	Study	Reason
Ahmedzai et al (2004)	No repeat measures	Light et al (1989)	No repeat measures
Alison et al (2016)	Protocol only	Liss et al (1988)	Hypoxic
Arizono (2015)	Abstract poster only	Maltais et al (2001)	No repeat measures
Baltzan et al (2000)	No baseline measures	Marchetti et al (2015)	No baseline or repeat measures
Bruera et al (1992)	Participants hypoxic	Marques-Magallanes (1988)	Hypoxic
Bruera et al (1993)	Insufficient data, hypoxaemia	McKeon et al (1988)	No repeat measures
Breura et al (2003)	No repeated measures	Meecham Jones et al (1995)	No repeat measures
Bruni et al (2012)	No baseline measures	Miki et al (2012)	No baseline measures
Chua et al (1996)	No baseline measures	Moore et al (1992)	No baseline or repeat measures
Currow et al (2009)	No airflow arm	Moore et al (2009)	Participants hypoxic
Davidson et al (1988)	No baseline measures	Nandi et al (2003)	No repeat measures
Dean et al (1992)	No repeat measures	Neunhauserer (2016)	No dyspnoea outcome
Derry et al (2006)	No breathlessness score	Nishiyama et al (2013)	No repeat measures
Dyer et al (2012)	No airflow	Nonoyama (2007)	No repeat measures
Eaton et al (2002)	No repeat measures	O'Driscoll et al (2011)	No repeat measures
Emtner et al (2003)	No repeat measures	Oliveira (2012)	No airflow arm
Evans et al (1986)	No follow up measures	Ozalevli et al (2007)	Room air, but not airflow
Garrod et al (1999)	No follow up measures	Quantrill et al (2007)	No repeat measures
Garrod et al (2000)	Participants hypoxic	Restrick et al (1992)	No repeat measures
Haidl et al (2003)	No airflow for control group	Ringbaek et al (2013)	No dyspnoea outcome
Killen & Corris (2000)	No repeat measures	Rooyackers et al (1997)	No airflow arm

Koshy (2016)	No baseline measures	Russell et al (1999)	No repeat measures
Jarosch et al (2017)	No repeat measures	Sandland et al (2008)	Participants hypoxic
Knebel et al (2000)	No repeat measures	Sharma et al (2011)	Opinion piece
Koskela et al (1988)	Sub-zero temperature -20°C	Somfay et al (2001)	No repeat measures
Lacasse et al (2005)	Participants hypoxic	Spence et al, (1993)	Sub-zero temperature
Laude et al (2006)	No repeat measures	Spielmanns (2015)	No dyspnoea outcome
Leach et al (1992)	No repeat measures	Stevenson et al (2004)	No repeat measures
Lellouche (2016)	No dyspnoea outcome	Swinburn et al (1991)	Participants hypoxic
Lewis et al (2003)	No repeat measures	Troy et al (2014)	Abstract poster only
Lewis et al (2003)	No repeat measures	Woodcock et al (1981)	No repeat measures

eAppendix 1 References to excluded studies

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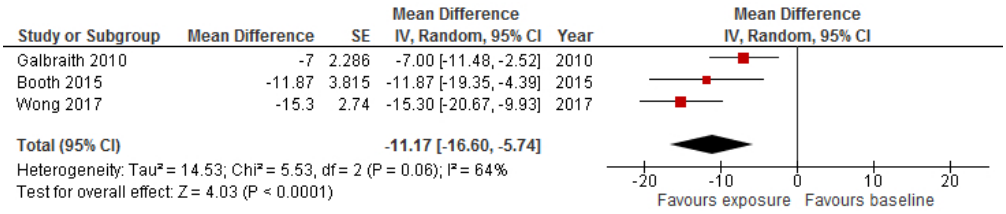

Figure 2 Meta-analysis of fan at rest

193x42mm (96 x 96 DPI)

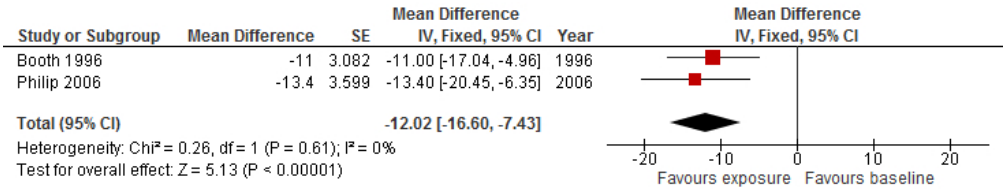

Figure 3 Meta-analysis of cylinder air at rest

193x38mm (96 x 96 DPI)

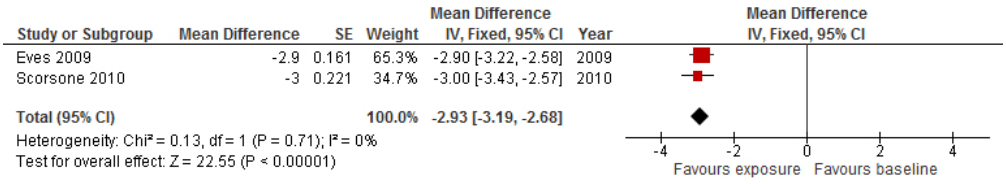

Figure 4 Meta-analysis of cylinder medical air for exertion-induced breathlessness

203x38mm (96 x 96 DPI)

PALLIATIVE MEDICINE AUTHOR SUBMISSION CHECKLIST

Please complete this checklist for all papers submitted. Please indicate, very briefly, how this has been addressed. This checklist is a mandatory upload on submission.

Item	Explanation	How this has been addressed (briefly, a sentence will suffice)
Article title	***WHY: Because we want readers to find your work.*** Have you followed our guidelines on writing a good title that will be found by search engines? (E.g. with methods in the title, use of common words for the issue addressed, no country names, and possibly indicating findings). If your study has an acronym is it included in the title?	We have indicated that we have found benefit from airflow and included the methodology in the title
Abstract	***WHY: Because structured abstracts have more detail for readers and search engines.*** Have you followed our guidelines on writing your structured abstract? Please remember we have separate abstract structures for original research, reviews and case reports. There should be **no** abbreviations in the abstract, EXCEPT a study acronym which should be included if you have one. If a trial (or other design formally registered with a database) have you included your registration details?	We have written a structured abstract. The protocol was not registered with PROSPERO
Key statements	***WHY: Because readers want to understand your paper quickly.*** Have you included our key statements within the body of your paper (after abstract and before the main text is a good place!) and followed our guidelines for how these are to be written? There are three main headings required, and each may have 1-3 separate **bullet** points. Please use clear, succinct, single sentence separate bullet points rather than complex or multiple sentences.	These have been included
Keywords	***WHY: Because MeSH headings mean it is properly indexed.*** Have you given keywords for your study? We ask that these are current **MeSH** headings unless there is no suitable heading for use (please give explanation in cover letter). https://meshb.nlm.nih.gov/search	We have used MeSH headings with the addition of freetext for airflow as this is the topic of the paper and in the title
International relevance	***WHY: We have readers from around the world who are interested in your work.*** Have you contextualised your work for an international audience and explained how your work contributes to an international knowledge base? Avoid drawing from policy from one context only, think how your work could be relevant more widely. Do define terms clearly e.g. hospice has a different	This systematic review draws on papers from around the world

	meaning in many countries.	
Publishing guidelines	***WHY: Because clear and robust reporting helps people interpret your work accurately*** Have you submitted a completed checklist for a relevant publishing guideline as a supplementary file? http://www.equator-network.org/ These include CONSORT, PRISMA, COREQ checklists, but others may be more relevant for your type of manuscript. If no published checklist exists please create one as a table from the list of requirements in your chosen guideline. If your study design does not have a relevant publishing guideline please review closest matches and use the most appropriate with an explanation.	Yes (PRISMA)
Word count	***WHY: Because readers want to find the core information quickly.*** Does your paper adhere to our word count for your article type? Please insert number of words in the box to the right. Remember that tables, figures, qualitative data extracts and references are not included in the word count.	4,422
Figures and tables and/or quotations	***WHY: Because readers want to find the core information quickly.*** Have you adhered to our guidelines on the number of tables and figures for your article type? Data (e.g. quotations) for qualitative studies are not included in the word count, and we prefer that they are integrated into the text (e.g. not in a separate table).	Yes
Study registration	***WHY: Because this means readers understand how you planned your study*** Where appropriate have you included details (including reference number, date of registration and URL) of study registration on a database e.g. trials or review database. If your study has a published protocol, is this referenced within the paper?	Not applicable
Other study publications?	***WHY: So readers can understand the full context of your study*** If there are other publications from this study are these referenced within the body of the paper? Please do not reference papers in preparation or submitted, but in-press publications are acceptable.	No
Scales, measures or questionnaires	***WHY: So readers can understand your paper in the context of this information*** If your study primarily reports the development or testing of scales/measures or questionnaires have you included a copy of the instrument as a supplementary file?	Not applicable

Abbreviations	***WHY: Because abbreviations make a paper hard to read, and are easily misunderstood*** Have you removed **all** abbreviations from the text except for extremely well known, standard abbreviations (e.g. SI units), which should be spelt out in full first? We do not allow abbreviations for core concepts such as palliative or end of life care.	We have kept the well-known abbreviations for ease of reading
Research ethics and governance approvals for research involving human subjects	***WHY: We will only publish ethically conducted research, approved by relevant bodies*** Have you given full details of ethics/governance/data protection approvals with reference numbers, full name of the committee(s) giving approval and the date of approval? If such approvals are not required have you made it explicit within the paper why they were not required. Are details of consent procedures clear in the paper?	Not applicable
Date(s) of data collection	***WHY: So readers understand the context within which data were collected*** Have you given the dates of data collection for your study within the body of your text? If your data are over 5 years old you will need to articulate clearly why they are still relevant and important to current practice.	yes
Structured discussion	***WHY: So readers can find key information quickly*** Papers should have a structured discussion, with sub headings, summarising the main findings, addressing strengths and limitations, articulating what this study adds with reference to existing international literature, and presenting the implications for practice.	yes
Case reports	***WHY: So that participants are protected, and its importance made clear*** If your study is a case report have you followed our clear structure for a case report, including highlighting what research is needed to address the issue raised? Have you made clear what consent was required or given for the publication of the case report? Have you provided evidence of such consent as a supplementary file to the editor?	Not applicable
Acknowledgements and declarations	***WHY: So readers understand the context of the research*** Have you included a funding declaration according to the SAGE format? Are there acknowledgements to be made? Have you stated where data from the study are deposited and how they may be available to others? Have you conflicts of interest to declare?	Yes
Supplementary	***WHY: So the context is clear, but the main paper succinct for the reader***	We have provided supplementary

data and materials	Is there any content which could be provided as supplementary data which would appear only in the online version of accepted papers? This could include large tables, full search strategies for reviews, additional data etc.	details to ensure the reader has access to these
References	***WHY: So people can easily find work you have referenced*** Are your references provided in SAGE Vancouver style? You can download this style within Endnote and other referencing software.	yes
Ownership of work.	Can you assert that you are submitting your original work, that you have the rights in the work, that you are submitting the work for first publication in the Journal and that it is not being considered for publication elsewhere and has not already been published elsewhere, and that you have obtained and can supply all necessary permissions for the reproduction of any copyright works not owned by you.	Yes

PRISMA-DTA Checklist

Section/topic	#	PRISMA-DTA Checklist Item	Reported on page #
TITLE / ABSTRACT			
Title	1	Identify the report as a systematic review (+/- meta-analysis) of diagnostic test accuracy (DTA) studies.	1
Abstract	2	Abstract: See PRISMA-DTA for abstracts.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Clinical role of index test	D1	State the scientific and clinical background, including the intended use and clinical role of the index test, and if applicable, the rationale for minimally acceptable test accuracy (or minimum difference in accuracy for comparative design).	
Objectives	4	Provide an explicit statement of question(s) being addressed in terms of participants, index test(s), and target condition(s).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (participants, setting, index test(s), reference standard(s), target condition(s), and study design) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8
Search	8	Present full search strategies for all electronic databases and other sources searched, including any limits used, such that they could be repeated.	8 and online Table 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Definitions for data extraction	11	Provide definitions used in data extraction and classifications of target condition(s), index test(s), reference standard(s) and other characteristics (e.g. study design, clinical setting).	8
Risk of bias and applicability	12	Describe methods used for assessing risk of bias in individual studies and concerns regarding the applicability to the review question.	8
Diagnostic accuracy measures	13	State the principal diagnostic accuracy measure(s) reported (e.g. sensitivity, specificity) and state the unit of assessment (e.g. per-patient, per-lesion).	
Synthesis of results	14	Describe methods of handling data, combining results of studies and describing variability between studies. This could include, but is not limited to: a) handling of multiple definitions of target condition. b) handling of multiple thresholds of test positivity, c) handling multiple index test readers, d) handling of indeterminate test results, e) grouping and comparing tests,	9

PRISMA-DTA Checklist

		f) handling of different reference standards	

Section/topic	#	PRISMA-DTA Checklist Item	Reported on page #
Meta-analysis	D2	Report the statistical methods used for meta-analyses, if performed.	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
RESULTS			
Study selection	17	Provide numbers of studies screened, assessed for eligibility, included in the review (and included in meta-analysis, if applicable) with reasons for exclusions at each stage, ideally with a flow diagram.	9-10
Study characteristics	18	For each included study provide citations and present key characteristics including: a) participant characteristics (presentation, prior testing), b) clinical setting, c) study design, d) target condition definition, e) index test, f) reference standard, g) sample size, h) funding sources	Table 1
Risk of bias and applicability	19	Present evaluation of risk of bias and concerns regarding applicability for each study.	Online Table 2 and page 20
Results of individual studies	20	For each analysis in each study (e.g. unique combination of index test, reference standard, and positivity threshold) report 2x2 data (TP, FP, FN, TN) with estimates of diagnostic accuracy and confidence intervals, ideally with a forest or receiver operator characteristic (ROC) plot.	
Synthesis of results	21	Describe test accuracy, including variability; if meta-analysis was done, include results and confidence intervals.	21-22
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression; analysis of index test: failure rates, proportion of inconclusive results, adverse events).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence.	Beginning of discussion page 23, and conclusion page 25
Limitations	25	Discuss limitations from included studies (e.g. risk of bias and concerns regarding applicability) and from the review process (e.g. incomplete retrieval of identified research).	Page 24-25

PRISMA-DTA Checklist

Conclusions	26	Provide a general interpretation of the results in the context of other evidence. Discuss implications for future research and clinical practice (e.g. the intended use and clinical role of the index test).	Discussion 23 - 25
FUNDING			
Funding	27	For the systematic review, describe the sources of funding and other support and the role of the funders.	Page 26

Adapted From: McInnes MDF, Moher D, Thombs BD, McGrath TA, Bossuyt PM, The PRISMA-DTA Group (2018). Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies: The PRISMA-DTA Statement. JAMA. 2018 Jan 23;319(4):388-396. doi: 10.1001/jama.2017.19163.

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