Ambulatory oxygen for treatment of exertional hypoxaemia in pulmonary fibrosis (PFOX): a multicentre, randomised, sham-controlled trial

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Summary

Background Ambulatory oxygen therapy can be used to treat exertional hypoxaemia during daily life activities in people with fibrotic interstitial lung disease (ILD). However, evidence for its efficacy is scarce. This trial aimed to compare the effects of ambulatory oxygen with ambulatory air on physical activity in daily life over 6 months in people with fibrotic ILD and isolated exertional hypoxaemia.

Methods This multicentre, parallel-group, randomised, sham-controlled trial was done at seven hospital sites in Australia and Sweden. Eligible participants were aged ≥18 years with fibrotic ILD and isolated exertional hypoxaemia (ie, oxyhaemoglobin saturation [SpO_2] ≤88% on 6-min walk test). Participants were randomly assigned (1:1) to receive ambulatory oxygen during daily activities delivered using a portable oxygen concentrator (Inogen One G3HF), or air delivered using a device identical in appearance, display, weight, and operation (sham). The primary outcome was change in physical activity (mean steps per day) at 3 months, measured using the StepWatch activity monitor in the intention-to-treat population. The trial is registered with ClinicalTrials.gov (NCT03737409) and is completed.

Findings Between Aug 6, 2019, and Jan 10, 2024, 614 individuals were assessed for eligibility. 116 were randomly assigned to ambulatory oxygen (n=59) or ambulatory air (n=57). 79 (68%) of 116 participants were male and 37 (32%) were female. Mean age was 71 years (SD 10). There was no significant difference between ambulatory oxygen (–271 steps per day, 95% CI –702 to 161) and ambulatory air (64, –377 to 505) for change in mean steps per day at 3 months (–334, –803 to 134). There were no serious adverse events related to study treatments, and no difference between groups for the number or type of adverse events.

Interpretation In people with fibrotic ILD and exertional hypoxaemia, ambulatory oxygen delivered using a portable concentrator did not provide benefits over ambulatory air for physical activity in daily life. Routine prescription of ambulatory oxygen using a portable oxygen concentrator for people with fibrotic ILD with isolated exertional hypoxaemia might not be indicated. These results reinforce the pressing need for innovation in portable oxygen devices to ensure effective oxygen delivery and acceptability to patients.

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Introduction

Fibrotic interstitial lung disease (ILD) is characterised by distressing breathlessness on exertion, impaired physical function, and poor health-related quality of life (HRQOL). A hallmark of fibrotic ILD is exertional hypoxaemia, occurring in over 50% of patients.[1] Exertional hypoxaemia is associated with increased breathlessness and reduced physical activity in daily life.[2,3] The presence of exertional hypoxaemia confers a four-fold increase in risk of death, independent of lung function.[4] Exertional hypoxaemia is also an independent predictor of pulmonary hypertension,[5] which is itself a strong predictor of mortality.[6] The association between exertional hypoxaemia and poor outcomes provides a rationale for treatments to improve oxygen delivery during daily physical activity.

Ambulatory oxygen therapy is defined as oxygen delivered during exercise or activities of daily living when the individual is walking freely.[7] The American Thoracic Society guideline for home oxygen therapy makes a conditional recommendation in favour of ambulatory oxygen for people with ILD with exertional hypoxaemia.[8] This recommendation was largely underpinned by studies evaluating the effects of oxygen in the laboratory setting, with one crossover study evaluating oxygen use in the community over 2 weeks.[9] To date, there has not been a randomised, parallel-group trial powered to detect benefits of ambulatory oxygen therapy in daily life, the context for which it is clinically prescribed.[10] People with fibrotic ILD report substantial challenges with using ambulatory oxygen therapy, including cumbersome and complex equipment, high cost, poor access, and social

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Research in context

Evidence before this study

Exertional hypoxaemia is common in people with fibrotic ILD and is associated with increased breathlessness, reduced daily life activity, development of pulmonary hypertension, and increased mortality. Ambulatory oxygen therapy, defined as oxygen delivered during exercise or activities of daily living, can be used to treat isolated exertional hypoxaemia but evidence of efficacy is scarce. A systematic review underpinning international oxygen guidelines, with authors including members of our group, systematically reviewed Medline, EMBASE, CINAHL, and Cochrane Central Register of Controlled Trials to June, 2019, using search terms "Lung Diseases, Interstitial" and "Oxygen Inhalation Therapy" or "Oxygen Therapy", with no limit on start date or study design. Only one study evaluated the effects of ambulatory oxygen in daily life in people with fibrotic ILD and isolated exertional hypoxaemia. Effects on health-related quality of life favoured ambulatory oxygen, but the treatment period was only 2 weeks and a sham control was not used. We subsequently conducted a pilot parallel-group, randomised controlled trial using portable oxygen concentrators to test our methods, but this was not powered for clinical outcomes.

Added value of this study

To date, no studies have evaluated the effect of ambulatory oxygen on daily life activities. In this study, ambulatory oxygen delivered using a portable oxygen concentrator to people with fibrotic ILD and isolated exertional desaturation did not increase average daily steps at 3 months or 6 months compared with ambulatory air (sham). The minimal important difference for daily steps lies outside the 95% CI. Therefore, this study provides new evidence indicating that an effect of ambulatory oxygen on physical activity in daily life is unlikely. The PFOX trial provides new knowledge regarding the impact of ambulatory oxygen over 6 months, the longest study period to date.

Implications of all the available evidence

Routine prescription of ambulatory oxygen via a portable concentrator for people with fibrotic ILD and isolated exertional hypoxaemia might not be indicated. The evidence supports calls for shared decision making regarding prescription of ambulatory oxygen in fibrotic ILD due to uncertain benefits and potential for substantial burden. Currently, no technology can reliably and fully correct exertional desaturation in fibrotic ILD outside of the laboratory setting. There is a pressing need for innovation in ambulatory oxygen devices to ensure more effective oxygen delivery and acceptability to patients. Further clinical trials of ambulatory oxygen in fibrotic ILD might not be warranted until these important innovations occur.

stigma.[11] In this context, it is crucial that patients can adequately assess whether the benefits of ambulatory oxygen therapy on daily life activities and symptoms are sufficient to outweigh its burdens.

The aim of the Pulmonary Fibrosis ambulatory Oxygen (PFOX) trial was to evaluate the effects of ambulatory oxygen therapy compared with ambulatory air, delivered via a portable concentrator over 6 months, in people with fibrotic ILD. We hypothesised that ambulatory oxygen would result in increased physical activity, reduced symptoms, and increased HRQOL.

Methods

Study design

This multicentre, parallel-group, randomised, sham-controlled trial was conducted in five hospital sites in Australia and two hospital sites in Sweden. Eligible sites had existing clinical services providing specialist care for ILD and oxygen prescription. Ethics approval was granted in Australia by the Alfred Hospital Human Research Ethics Committee (HREC/18/Alfred/42), with governance approval at all Australian sites, and in Sweden (Lund Dnr 2019–02963). The published trial protocol[12] and statistical analysis plan are available in the appendix (pp 4–50). We used the CONSERVE reporting guidelines (appendix p 51) to document important modifications to the protocol due to the COVID-19 pandemic, including initiation of the intervention with remote training and supervision, and remote assessments. People with fibrotic ILD were involved in study design, including choice of portable concentrator. The trial was registered at ClinicalTrials.gov (NCT03737409) and is completed.

See Online for appendix

Participants

Eligible patients were aged 18 years and older with a physician-confirmed diagnosis of fibrotic ILD such as idiopathic pulmonary fibrosis (IPF), connective tissue disease-associated ILD, fibrotic hypersensitivity pneumonitis, idiopathic non-specific interstitial pneumonia, unclassifiable ILD, environmental or occupational lung disease, or sarcoidosis, and with features of diffuse fibrotic ILD with >10% extent on high-resolution CT chest scan.[13] All participants had stable pharmacotherapy during the past 3 months and showed exertional desaturation, defined as oxyhaemoglobin saturation (SpO_2) ≤88% for ≥10 consecutive seconds during a 6-min walk test performed on room air. Key exclusion criteria were current use of or eligible for long-term oxygen therapy (partial pressure of oxygen [PaO_2] ≤55 mm Hg at rest on room air or 56–59 mm Hg with evidence of right heart failure); current smoking; pregnancy; admission to an acute care hospital within the past 30 days; or anticipated death or transplant within the study period. Participants in pulmonary rehabilitation and those who were non-ambulant were

also excluded. Data on sex were self-reported; options provided were female or male. Data on race and/or ethnicity were not collected as it was not permitted in Sweden. All participants provided written informed consent.

Randomisation and masking

Randomisation was performed after completion of baseline assessment, including physical activity measures, using a secure, centralised online randomisation service. Participants who met inclusion criteria were randomly assigned (1:1) to receive ambulatory oxygen or ambulatory air using permuted blocks, with stratification for desaturation during the 6-min walk test (<80% *vs* ≥80%) and site of recruitment. Ambulatory oxygen (intervention) or ambulatory air (sham) was delivered via a portable concentrator with pulsed flow (Inogen One G3HF, Inogen; Beverly, MA, USA). Sham portable concentrators were modified by the manufacturer and were identical in appearance, display, weight, and operation, with the only difference being the gas delivered. Each portable concentrator was assigned a code before distribution to study sites to ensure that participants, researchers, and clinicians were masked to group allocation. The randomisation sequence was generated by an individual who was unrelated to the trial and had no further involvement with the study. Participants were enrolled by trial coordinators at each centre, with randomisation occurring after the baseline assessment was complete, at which point group assignment was made visible in the online system. Participants were advised against measuring oxygen saturation at home for the duration of the trial, and this was not usual clinical practice at the trial centres. Success of masking was evaluated using Bang's Blinding Index, with values ≤0·2 representing successful masking.[14]

Procedures

Participants were encouraged to use their allocated portable concentrator (weight 2·2 kg including battery) during physical activity for the 6-month study period, using the maximum flow setting of 5 for both groups. All participants were provided with a standard portable concentrator carry bag, worn over one shoulder, but could use a backpack if preferred. A spare battery, charger, and nasal cannulae were provided. All participants were informed that the aim of using a portable concentrator was to assist them to be more active, with fewer symptoms. They were encouraged to use the portable concentrator at all times when moving around, including walking at home or in the community, during exercise, or during other activities. The portable concentrator was not to be used when sitting still or sleeping. Written and verbal education were provided. Participants were contacted once a month by telephone by a member of the research team, to encourage portable concentrator use and allow the team to answer any questions.

Assessments were conducted at study centres at baseline, 3 months, and 6 months. At each visit participants performed a 6-min walk test according to international standards,[15] with the longest of two tests used to assess exertional desaturation. All tests were performed breathing room air. To measure HRQOL, participants completed the St George's Respiratory Questionnaire[16] and the King's Brief Interstitial Lung Disease questionnaire.[17] Dyspnoea-12 was used to measure the physical and affective components of breathlessness.[18] Fatigue was measured using the Fatigue Severity Scale.[19] Anxiety and depression were evaluated using the Hospital Anxiety and Depression Scale.[20] To measure physical activity in daily life, participants were given the StepWatch (Modus Health, Washington DC, USA) and GENEActiv (GENEActiv, Cambridgeshire, UK) activity monitors to be worn for the following 7 days after the study visit.[21,22] The Nonin 3150 wrist oximeter (Nonin Medical; Plymouth, MN, USA) was also worn continuously for 2 consecutive weekdays during waking hours, with the display turned off to maintain masking.[23] The monitors were returned to the investigators by post.

Hours of portable concentrator usage recorded by the device were documented at 3 months and 6 months. If participants chose to cease using the portable concentrator during the study period, the reason for cessation of therapy was recorded. Participants who developed clinically significant resting hypoxaemia during the study period were offered long-term oxygen therapy as recommended by their treating physician. On commencement of long-term oxygen therapy, the participant ceased using the allocated trial portable concentrator. At the conclusion of their involvement in the trial and while still masked, participants were asked which treatment they believed they had been allocated to receive (oxygen, air, or do not know) and whether they had a pulse oximeter at home (yes or no).

Outcomes

The primary outcome was change from baseline in physical activity at 3 months, measured by the number of steps per day. Steps per day were measured using the StepWatch activity monitor, worn on the ankle continuously for 7 days (except for bathing) at baseline, 3 months, and 6 months. Days with <8 h recording or <200 steps were excluded. The mean number of steps per day was calculated using the mean for all included days. Secondary outcomes were change from baseline in HRQOL (measured with St George's Respiratory Questionnaire and King's Brief Interstitial Lung Disease questionnaire), dyspnoea (Dyspnoea-12), fatigue (Fatigue Severity Scale), anxiety and depression (Hospital Anxiety and Depression Scale), time spent in moderate to vigorous physical activity (GENEActiv), and sedentary time (GENEActiv). Tertiary (exploratory) outcomes were portable concentrator usage, reasons for cessation of portable concentrator use, and oxygen saturation in

daily life (Nonin 3150 wrist oximeter). Adverse events of specific interest are listed in the protocol (appendix pp 4–35). Adverse events were collected at each study visit (medical record review and participant report) and during monthly telephone calls (participant report) by trial coordinators at each site, using a proforma for adverse events of specific interest, with any additional reported harms documented as free text. Adverse events were not centrally adjudicated as participants, researchers, and clinicians were masked to assignment.

Statistical analysis

Analyses of the primary and secondary efficacy and safety outcomes were conducted in the intention-to-treat population, including all randomly assigned participants for whom data were available in the groups to which they were allocated, regardless of adherence. Continuous endpoints were analysed using linear mixed models, with site and participant within site as a random effect. None of the variables required transformation for analysis. We compared change from baseline in physical activity at 3 months and 6 months between groups, adjusted for the baseline measurement. Desaturation during 6-min walk test (nadir SpO_2 <80% *vs* ≥80%) was included in the model. Missing data were assumed to be missing-at-random and no imputation was undertaken. The treatment effect was presented as the mean difference between groups with the corresponding 95% CI. A prespecified exploratory analysis to investigate the impact of portable concentrator usage (mean h/day) on the primary outcome was undertaken with portable concentrator usage included as a covariate. Prespecified subgroup analyses for the primary outcome were type of fibrotic ILD (IPF *vs* other) and severity of ILD (forced vital capacity [FVC] <50% *vs* ≥50% predicted), assessed by adding an interaction term to the main model.

The study sample size was calculated based on improvement in physical activity measured by steps per day favouring ambulatory oxygen over ambulatory air. A total of 220 participants (110 per group) would provide 80% power to detect, at the two-sided 5% level, a clinically important difference between groups in the primary outcome of 599 steps per day,[24] assuming a SD of 1582 steps.

A detailed statistical analysis plan was written, finalised, and approved before the data lock (appendix pp 36–50). R version 2024.09.1 was used for statistical analysis. An independent data safety committee provided trial oversight.

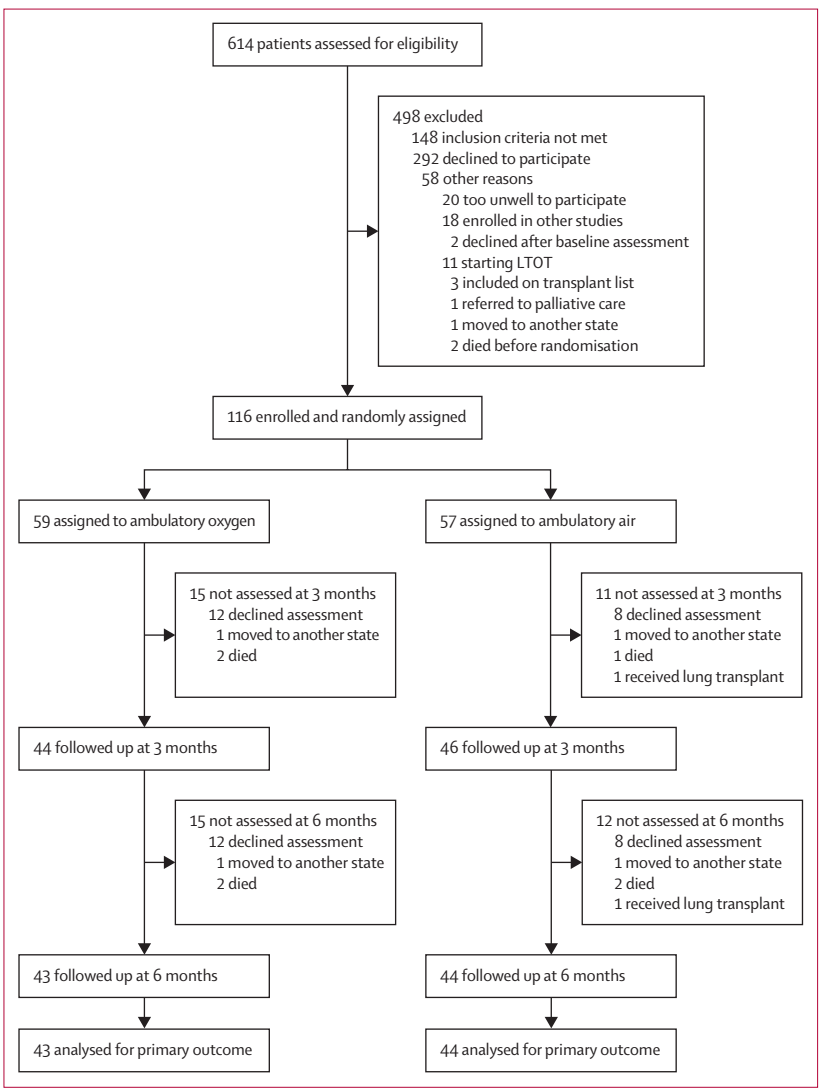

Figure 1: **Trial profile**
Number of participants at 3 months and 6 months represent the number of participants with follow-up data at that timepoint. LTOT=long-term oxygen therapy.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Aug 6, 2019, and Jan 10, 2024, 614 individuals with fibrotic ILD were assessed for eligibility (figure 1). Of 408 eligible individuals, 292 (72%) declined to participate, with 116 randomly assigned to ambulatory oxygen (n=59) or ambulatory air (n=57). 79 (68%) of 116 participants were male and 37 (32%) were female. Mean age was 71 years (SD 10). Demographic characteristics were similar across the groups (table 1). The most common fibrotic ILDs were IPF (56 [48%] of 116 patients), unclassifiable ILD (13 [11%]), fibrotic hypersensitivity pneumonitis (12 [10%]), and connective tissue disease-associated ILD (15 [13%]). On average, participants had moderate exertional desaturation (mean nadir SpO_2 on 6-min walk test was 83%) but with considerable variability (nadir SpO_2 range 70–88%).

During the COVID-19 pandemic, trial sites were closed to on-site assessment for a cumulative total of 1195 days.

A range of protocol modifications were undertaken to permit remote recruitment, consent, treatment initiation, and outcome assessment (appendix p 51). Despite these modifications, the planned sample size was not met. Primary outcome data were available for 43 (73%) of 59 participants in the oxygen group and 44 (77%) of 57 participants in the air group. Days excluded for the primary outcome (<8-h measuring time or <200 steps) were 2 days at 3 months (one participant in the oxygen group and one participant in the air group) and 3 days at 6 months (two and one).

For the primary outcome, there was no significant difference between the oxygen group (–271 steps per day, 95% CI –702 to 161) and air group (64, –377 to 505) for change in mean steps per day at 3 months (–334, –803 to 134; figure 2; table 2). Participants with missing data for the primary outcome at 3 months had a lower FVC% predicted than those who did not, but this finding was not significant (mean 65% [SD 20] *vs* 71% [SD 14]; p=0·092 for between-group comparison). There was no discernible relationship between age, type of ILD, or extent of exertional desaturation to missingness.

There were no significant differences between groups in secondary outcomes except for Dyspnoea-12 physical and total scores at 3 months and 6 months, which favoured air (table 2). There was a decline in FVC over the 6-month course of the trial in those in the oxygen group (–154 mL, 95% CI –270 to –39) and air group (–97 mL, –203 to 9), with no difference between groups (p=0·47).

Portable oxygen concentrator usage data were available for 53 participants at 3 months and 73 participants at 6 months (table 3). At 3 months, average daily portable concentrator usage was 0·78 h/day (range 0·19–2·66) in the oxygen group and 0·63 h/day (0·21–3·16; p=0·23 for between-group comparison) in the air group. At 6 months, average daily usage was 0·70 h/day (0·09–1·88) in the oxygen group and 0·50 h/day (0·11–1·57; p=0·11) in the air group. There were no significant differences between groups for portable concentrator usage, average SpO_2 in daily life, minimum SpO_2 in daily life, or the proportion of time in daily life spent with SpO_2 ≤88% (table 3). There was wide variation between groups in hours of portable concentrator use (appendix p 53) and proportion of time with SpO_2 ≤88% at 3 months (0·3–97% in the oxygen group *vs* 1–58% in the air group; appendix p 54). At 3 months, 13 participants had ceased portable concentrator usage (six in the oxygen group and seven in the air group), including three participants who commenced long-term oxygen therapy (two and one). At 6 months, 30 participants had ceased portable concentrator usage (13 and 17). Reasons for cessation of portable concentrator use were patient request (n=15), lack of perceived benefit (n=6), commencement of long-term oxygen therapy (n=3), being unwell (n=2), travel (n=2), safety around open flames (n=1), and device too heavy to carry (n=1). There were no differences between groups in reasons for cessation of portable concentrator usage.

There were few adverse events, with no difference between groups for either the number or type of events (table 4). The most common adverse event was worsening of lung function. There were no treatment-related adverse events.

	Oxygen group (n=59)	Air group (n=57)
Sex		
Female	11 (19%)	26 (46%)
Male	48 (81%)	31 (54%)
Age, years	71 (10)	70 (10)
BMI, kg/m²	29·3 (5·4)	29·6 (5·9)
Diagnosis		
IPF	31 (53%)	25 (44%)
FHP	5 (8%)	7 (12%)
INSIP	4 (7%)	2 (4%)
CTD-ILD	7 (12%)	8 (14%)
Unclassifiable ILD	6 (10%)	7 (12%)
Other	6 (10%)	8 (14%)
FVC, L	2·6 (0·8)	2·4 (0·7)
FVC, % predicted	70% (15)	69 (17)
FEV_1, L	2·1 (0·6)	1·9 (0·6)
FEV_1, % predicted	74% (15)	73 (18)
TLCO, mL/min per mm Hg	10·8 (3·7)	10·5 (3·5)
TLCO, % predicted	45% (14)	46 (11)
6-min walk distance, m	430 (130)	399 (131)
Resting SpO_2	95% (2)	95% (2)
Nadir SpO_2 on 6-min walk test	84% (4)	83% (4)
Nadir SpO_2 <80% on 6-min walk test, cases	9 (15%)	10 (18%)
Waking hours with SpO_2 ≤88% in daily life	13% (4–20)	10% (5–22)
Steps per day, daily average	3055 (2032–4247)	2787 (1849–3442)
MVPA, daily average	46 (17–79)	40 (14 –71)
Sedentary time per day, min	519 (420–619)	497 (398–601)
KBILD		
Psychological symptoms	51·2 (16·4); 58	54·1 (18·2); 54
Breathlessness and activities	33·7 (16·5); 58	36·7 (15·0); 54
Chest symptoms	57·2 (22·0); 58	59·9 (20·8); 54
Total	50·6 (12·3); 58	52·8 (12·0); 54
Dyspnoea-12		
Physical	9·81 (6·01); 58	8·84 (5·34); 56
Affective	4·88 (4·54); 58	4·39 (4·31); 56
Total	14·69 (10·06); 58	13·23 (9·03); 56
HADS		
Anxiety, cases	9/58 (16%)	8/56 (14%)
Depression, cases	6/58 (10%)	7/56 (13%)

Data are n (%), median (IQR), mean (SD); n, or n/N (%). Percentage predicted values were calculated using NHANES reference equations. CTD-ILD=connective tissue disease-associated ILD. FHP=fibrotic hypersensitivity pneumonitis. FVC=forced vital capacity. HADS=Hospital Anxiety and Depression Scale. ILD=interstitial lung disease. INSIP=idiopathic non-specific interstitial pneumonia. IPF=idiopathic pulmonary fibrosis. KBILD=King's Brief Interstitial Lung Disease questionnaire. MVPA=moderate to vigorous physical activity. SpO_2=oxyhaemoglobin saturation. TLCO=transfer factor of the lung for carbon monoxide.

Table 1: **Demographic characteristics at baseline**

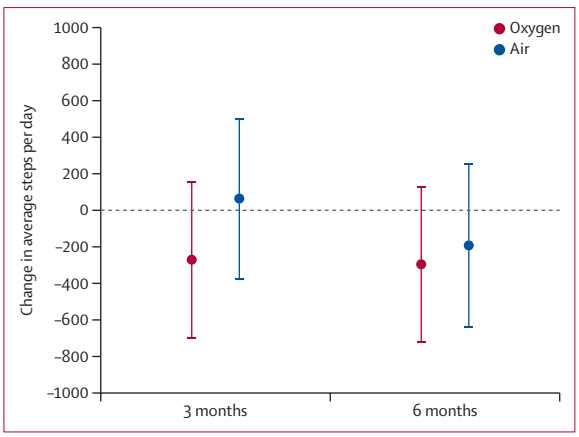

Figure 2: **Average steps per day**
Data are mean and 95% CI for change from baseline. There was no significant difference between groups at 3 months (primary outcome) or 6 months.

Prespecified subgroup analyses for the primary outcome showed no differences in effects for participants with IPF versus those without IPF, or participants with FVC <50% predicted versus those with ≥50% predicted (appendix p 52). A post-hoc analysis for transfer factor for carbon monoxide <40% predicted versus ≥40% predicted also showed no differences between groups (appendix p 52). A prespecified exploratory analysis to investigate the impact of portable concentrator usage on the primary outcome showed no difference in the adjusted means between groups at 3 months (–815 steps per day, 95% CI –1713 to 82) or 6 months (179, –386 to 744).

Success of masking was evaluated in 76 (66%) of 116 participants. Group allocation was correctly identified for 16 (43%) of 37 participants allocated to oxygen (Bang's Blinding Index –0·08) and for 22 (56%) of 39 participants allocated to air (Bang's Blinding Index 0·18), supporting effective blinding. Participants who had a pulse oximeter at home (28 [37%] of 76) were no more likely to correctly identify their group allocation than those who did not (p=0·33).

Discussion

In patients with fibrotic ILD and isolated exertional hypoxaemia, ambulatory oxygen delivered using a portable concentrator for 6 months did not improve daily physical activity compared with ambulatory air. There were no effects favouring ambulatory oxygen for the secondary outcomes of dyspnoea, fatigue, HRQOL, anxiety, or depression.

The PFOX trial is the largest randomised, parallel-group trial of ambulatory oxygen for ILD reported to date. Due to prolonged closures of recruiting sites during the COVID-19 pandemic, the planned sample size was not achieved. However, the minimal important difference for the primary outcome of daily steps in IPF (+570 steps)[25] lies beyond the upper end of the 95% CI for the between-group difference at 3 months and 6 months (table 2), so a clinically important effect of ambulatory oxygen on daily steps seems unlikely. Participants in this study were well supported with portable concentrator use, including monthly telephone calls throughout the trial to encourage portable concentrator use during activity and to troubleshoot any difficulties. Despite this support, portable concentrator use was modest (mean 47 min/day for those using ambulatory oxygen at 3 months), although it was similar to the amount of time that participants spent in moderate to vigorous physical activity each day (mean 48 min/day; table 1). The average decline in steps over 6 months was similar to that previously reported in a cohort of individuals with IPF without intervention (mean –461 steps at 6 months),[25] which also supports the interpretation that changes in daily physical activity were not modified by ambulatory oxygen. Ambulatory oxygen did not change the average or minimum SpO_2 in daily life, or the proportion of time spent with SpO_2 ≤88%. Therefore, it is possible that despite being used on the maximum portable concentrator flow setting of 5, the dose of supplemental oxygen was insufficient to change patient outcomes such as daily activity or symptoms. It is also possible that our primary outcome of daily steps was not sensitive to changes with ambulatory oxygen, although as a direct measure of how a patient functions in daily life, it is well aligned with patient priorities and recommendations for meaningful endpoints in ILD clinical trials.[26]

Ambulatory oxygen is a widely used treatment for patients with fibrotic ILD and exertional hypoxaemia, with a conditional recommendation for its delivery in the American Thoracic Society guideline[8] and with expert consensus that it should be prescribed.[27] However, evidence to support its benefits in daily life is scarce. A systematic review underpinning the ATS guideline[8] reported improvements in HRQOL with ambulatory oxygen in ILD based on a single unblinded crossover study with a 2-week treatment period.[9] Other evidence of benefit, for exercise capacity and duration, was derived from studies evaluating single sessions of oxygen delivered during exercise in the laboratory setting.[8] In the PFOX trial, these short-term benefits for ILD were not found during longer-term daily use of ambulatory oxygen. This is similar to findings in chronic obstructive pulmonary disease (COPD), for which short-term physiological benefits of ambulatory oxygen have not been replicated in clinical trials with follow-up periods beyond 2 weeks.[28,29] Collectively these data support calls for shared decision making between patients and health professionals regarding prescription of ambulatory oxygen in fibrotic ILD, due to uncertain benefits and potential for burden.[8]

The PFOX trial tested the clinical efficacy of delivering ambulatory oxygen therapy using a portable concentrator, in contrast to a previous short-term study that used cylinder oxygen with continuous flow.[9] Our forerunner study to the PFOX trial[30] made a direct comparison of these approaches during exercise (6-min walk test), with

	Oxygen (difference [95% CI]; n)		Air (difference [95% CI]; n)		Oxygen *vs* air (difference or OR [95% CI])*		p value	$p_{interaction}$†
	3 months	6 months	3 months	6 months	3 months	6 months		
Primary outcome								
Steps per day	−271 (−702 to 161); 43	−296 (−726 to 134); 43	64 (−377 to 505); 44	−193 (−645 to 259); 44	−334 (−803 to 134)	−103 (−579 to 373)	0·16	0·28
Secondary outcomes								
Dyspnoea-12								
Physical	1·59 (−0·01 to 3·19); 44	2·74 (1·14 to 4·34); 44	−0·55 (−2·21 to 1·10); 42	0·84 (−0·84 to 2·52); 42	2·14 (0·46 to 3·83)	1·90 (0·22 to 3·58)	0·013	0·80
Affective	0·83 (−0·52 to 2·17); 44	1·99 (0·64 to 3·34); 44	−0·57 (−1·95 to 0·82); 42	0·81 (−0·60 to 2·21); 42	1·40 (−0·01 to 2·81)	1·18 (−0·22 to 2·59)	<0·0001	0·78
Total	2·43 (−0·43 to 5·29); 44	4·67 (1·80 to 7·54); 44	−1·26 (−4·21 to 1·68); 42	1·51 (−1·48 to 4·51); 42	3·69 (0·81 to 6·58)	3·16 (0·28 to 6·04)	0·012	0·73
King's Brief Interstitial Lung Disease questionnaire								
Psychological	−2·72 (−7·13 to 1·68); 43	−4·17 (−8·51 to 0·18); 43	—2·35 (−7·13 to 1·68); 42	−3·61 (−8·12 to 0·91); 42	−0·37 (−5·34 to 4·60)	−0·56 (−5·52 to 4·40)	0·88	0·94
Breathlessness and activities	−1·76 (−5·59 to 2·16); 43	−2·70 (−6·57 to 1·16); 43	−2·11 (−6·03 to 1·82); 42	−2·05 (−6·06 to 1·96); 42	0·34 (−4·07 to 4·76)	−0·65 (−5·05 to 3·75)	0·88	0·66
Chest symptoms	−0·85 (−7·88 to 6·18); 43	−4·93 (−11·88 to 2·02); 43	0·68 (−6·36 to 7·72); 42	−1·80 (−8·97 to 5·37); 42	−1·53 (−9·34 to 6·29)	−3·13 (−10·92 to 4·67)	0·70	0·67
Total	−1·29 (−4·19 to 1·62); 43	−2·83 (−5·70 to 0·04); 43	−1·40 (−4·30 to 1·51); 42	−2·04 (−4·99 to 0·91); 42	0·11 (−3·09 to 3·31)	−0·79 (−3·99 to 2·40)	0·95	0·54
St George's Respiratory Questionnaire								
Symptoms	4·23 (−2·31 to 10·77); 45	8·70 (2·20 to 15·21); 45	2·58 (−4·13 to 9·28); 41	1·22 (−5·73 to 8·17); 41	1·65 (−5·91 to 9·22)	7·48 (−0·17 to 15·13)	0·66	0·20
Activity	4·58 (−1·23 to 10·39); 45	7·50 (1·70 to 13·30); 45	3·68 (−2·31 to 9·67); 41	2·82 (−3·26 to 8·89); 41	0·90 (−5·31 to 6·93)	4·49 (−1·36 to 10·73)	0·77	0·17
Impact	0·66 (−4·16 to 5·49); 45	3·62 (−1·21 to 8·44); 45	−0·73 (−5·71 to 4·26); 41	−1·10 (−6·17to 3·95); 41	1·39 (−3·55 to 6·33)	4·73 (−0·24 to 9·69)	0·58	0·15
Total	1·91 (−2·23 to 6·06); 45	5·97 (1·85 to 10·09); 45	1·44 (−2·79 to 5·67); 41	0·91 (−3·42 to 5·42); 41	0·48 (−4·21 to 5·16)	5·06 (0·36 to 9·76)	0·84	0·067
Fatigue Severity Scale								
Total	4·19 (−0·55 to 8·93); 45	5·68 (0. 91 to 10·45); 45	2·07 (−2·80 to 6·93); 43	2·29 (−2·77 to 7·35); 43	2·12 (−2·95 to 7·20)	3·39 (−1·81 to 8·58)	0·41	0·72
Visual analogue scale	−1·64 (−2·66 to −0·62); 32	−0·99 (−1·99 to 0·02); 32	−0·62 (−1·61 to 0·38); 30	−0·72 (−1. 73 to 0·29); 30	−1·02 (−2·16 to 0·13)	−0·27 (−1·41 to 0·87)	0·080	0·24
Hospital Anxiety and Depression Scale								
Anxiety	0·42 (−0·65 to 1·50); 44	0·93 (−0·14 to 2·00); 44	−0·28 (−1·38 to 0·83); 41	−0·11 (−1·26 to 1·05); 41	0·70 (−0·52 to 1·92)	1·04 (−0·20 to 2·27)	0·26	0·61
Anxiety, change in number of cases	0	−1	−5	−4	OR 0·13 (0·02 to 0·87)	OR 0·50 (0·11 to 2·36)	0·044	0·32
Depression	0·09 (−0·97 to 1·15); 44	0·37 (−0·68 to 1·43); 44	−0·28 (−1·38 to 0·81); 41	−0·17 (−1·30 to 0·97); 41	0·38 (−0·73 to 1·49)	0·54 (−0·58 to 1·66)	0·50	0·78
Depression, change in number of cases	−2	−4	−6	−4	OR 0·23 (0·02 to 2·34)	OR 2·17 (0·23 to 20·63)	0·17	0·14
6-min walk distance	−23·8 (−54·1 to 6·6); 34	−45·4 (−72·6 to −18·2); 34	−19·7 (−48·7 to 9·2); 33	−35·4 (−63·0 to −7·7); 33	−4·0 (−39·5 to 31·5)	−10·0 (−41·2 to 21·1)	0·82	0·72
Physical activity								
MVPA, min/day	−9·13 (−20·50 to 2·20); 39	−8·90 (−19·80 to 1·97); 39	−3·84 (−15·9 to 8·26); 40	−5·26 (−17·40 to 6·92); 40	−5·30 (−18·30 to 7·67)	−3·64 (−16·60 to 9·32)	0·42	0·82
Sedentary time, min/day	16·07 (−54·0 to 86·1); 39	−2·46 (−68·8to 63·9); 39	−43·62 (−119·8to 32·5); 40	−41·94 (−116·8 to 33·0); 40	59·70 (−21·1 to 140·0)	39·50 (−39·8 to 119·0)	0·14	0·67

MVPA=moderate to vigorous physical activity. OR=odds ratio. *ORs represent odds of cases of depression and anxiety in the oxygen group versus air group, with positive OR favouring air. †Interaction between group and time in the mixed effect model.

Table 2: **Primary and secondary outcomes**

	Oxygen group		Air group		p value*	
	3 months	6 months	3 months	6 months	3 months	6 months
POC usage, h/day	0·78 (0·57); 30	0·70 (0·54); 34	0·63 (0·62); 23	0·50 (0·40); 39	0·23	0·11
SpO_2 in daily life	92% (3); 26	92% (3); 32	92% (1); 26	92% (1); 30	0·93	0·90
Minimum SpO_2 in daily life	73% (3); 26	73% (4); 32	72% (3); 26	72% (3); 30	0·44	0·23
Percentage time in SpO_2 ≤88%	16% (20); 26	18% (19); 32	14% (13); 26	18% (13); 30	0·72	0·45

Data are mean (SD); n, unless otherwise specified. POC=portable oxygen concentrator. SpO_2=oxyhaemoglobin saturation. *No significant differences between groups at any timepoint.

Table 3: **Portable oxygen concentrator usage and SpO_2 in daily life**

	Oxygen group (n=59)	Air group (n=57)
Total number of adverse events	16	18
Number of participants with adverse events	13 (22%)	15 (26%)
Worsening of lung function*	8 (14%)	13 (23%)
Development of resting hypoxaemia	2 (3%)	1 (2%)
Exacerbation of fibrotic ILD	1 (2%)	1 (2%)
Hospitalisation	2 (3%)	2 (4%)
Death	3 (5%)	1 (2%)
Bruising or infection at blood draw site	0	0
Fainting related to blood draw	0	0
Adverse events during 6-min walk test	0	0
Burns	0	0
Nosebleed or dry nose	0	0
Musculoskeletal injury	0	0

ILD=interstitial lung disease. *Absolute FVC decline >5% predicted over the 6-month trial.

Table 4: **Adverse events**

results showing no difference in nadir SpO_2 between devices (cylinder: mean continuous flow at 5 L/min 80% [SD 2·2] *vs* Inogen One G2: 82% [3·5]; p=0·14). No difference was found despite a higher delivered fraction of inspired oxygen (FiO_2) using cylinder oxygen with continuous flow. Data from lung models indicate that at a respiratory rate of 30 breaths per min (consistent with exercise) the delivered FiO_2 is approximately 0·30 for cylinder oxygen at 5 L/min continuous flow versus 0·24 for Inogen One.[31] However, modelled differences in alveolar oxygen volume during exercise are much smaller[32] because a larger proportion of the oxygen delivered using continuous flow remains in the anatomical deadspace at the end of inspiration and does not reach the gas exchange regions.[32,33] This mechanism likely contributes to the similar effect on exertional desaturation during exercise despite greater delivered FiO_2.[30] However, neither of these commonly used approaches to deliver ambulatory oxygen could completely correct exertional hypoxaemia in patients with ILD. The degree to which current ambulatory oxygen systems correct exertional hypoxaemia in ILD is variable across published studies. In a recent systematic review of six studies delivering ambulatory oxygen,[34] the average minimum SpO_2 during exertion ranged from 84% to 93%. Three of the six studies did not achieve an average minimum SpO_2 of 90% using ambulatory oxygen, and these studies also had the lowest minimum SpO_2 during exertion on room air.[34] New approaches to ambulatory oxygen technology are urgently needed to ensure that oxygen delivery can meet oxygen demand during exertion for people with ILD across the range of exertional desaturation that is commonly seen in clinical practice.

The acceptability of and adherence to oxygen therapy in people with chronic lung disease is often low due to its considerable burden and perceived stigma.[11] Poor acceptability of this treatment might contribute to the challenges of evaluating this therapy in clinical trials. Of 408 eligible individuals in the PFOX trial, 292 (72%) declined to participate, with most citing a reluctance to use ambulatory oxygen. Clinical trials of ambulatory oxygen in COPD have reported similarly high refusal rates.[28] Other recent trials of long-term oxygen therapy[35] and oxygen therapy for moderate hypoxaemia[29] made post-commencement changes to trial inclusion criteria and outcomes due to poor recruitment rates, and a trial of nocturnal oxygen therapy was ceased early due to recruitment and retention difficulties.[36] Of 59 participants who commenced ambulatory oxygen in our trial, 13 (22%) had ceased using it by 6 months, citing reasons that have been well documented in previous qualitative studies (eg, preference, lack of perceived benefit, and problems with equipment).[11] Although patients report a preference for portable concentrators over cylinders due to lighter weight and greater portability,[30] these devices are associated with other limitations including lower oxygen flow rates and battery life issues.[11] Our results reinforce the pressing need for innovation in portable oxygen devices to ensure effective oxygen delivery and acceptability to patients.

The strengths of this trial include recruitment from seven centres across two countries, use of a sham control, successful masking, and 6-month follow-up, representing the longest trial of ambulatory oxygen conducted to date in fibrotic ILD. The impact of the COVID-19 pandemic on this trial was considerable, with the planned sample size not achieved. The precision of our results is therefore reduced, and findings should be interpreted with caution.

It is possible that follow-up data were not missing at random, with a tendency for participants who had missing data at 3 months to have a lower FVC% predicted than those who did not. Our trial was not sufficiently powered to exclude any subgroup differences related to ILD diagnosis or severity of lung disease. We did not prespecify a subgroup analysis for sex, but this would likely be confounded by diagnosis, with IPF being more common in men. We could not collect data on participants' race and ethnicity, so it is not possible to assess the representativeness of our sample. We only included people with fibrotic ILD who had isolated exertional hypoxaemia, and thus our results do not apply to those with resting hypoxaemia who also desaturate on exertion. We used a portable concentrator delivering pulsed flow and findings might differ for devices delivering continuous flow, although this could be offset by increased device weight and reduced portability. We did not evaluate the degree to which the portable concentrator improved oxygen saturation during exertion, and as a result we were not able to show whether outcome improvements were associated with the extent to which oxygen desaturation was alleviated.

In conclusion, the results of the PFOX trial do not support beneficial effects of ambulatory oxygen delivered using a portable concentrator on physical activity in daily life, symptoms, or HRQOL in people with fibrotic ILD and isolated exertional hypoxaemia. Routine prescription of ambulatory oxygen using a portable oxygen concentrator for people with fibrotic ILD with isolated exertional hypoxaemia might not be indicated.

Contributors

AEH led the study design and funding application and, as chief investigator, had oversight for the trial. AEH and CFM conceived the original idea for the study. AEH, CFM, TJC, DCC, AJP, MPE, IC, IG, NSG, and GH contributed to funding acquisition. MH, TJC, DCC, IG, KS, LD, NSG, YHK, JE, JAM, JDP, MS, NS, and CFM recruited participants. MH, CB, JB, LF, MT, SS, and PN undertook the study assessments. GH and AEH planned the statistical analyses. GH conducted the statistical analysis. AEH wrote the first draft of the manuscript. All authors had access to the raw data, and AEH and MH have verified the underlying data. All authors accept responsibility for the decision to submit for publication.

Declaration of interests

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Data sharing

De-identified individual participant data may be made available on approval of a written request to the corresponding author. The request will be evaluated by a committee formed by a subset of co-authors to determine the research value. A data sharing agreement will be required and approved before any data transfer.

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