

Analysis plan 2026-03-03, [Before analysis]

Effect of sleep deprivation on breathlessness and exercise capacity in COPD: a randomized crossover trial

NCT number NCT04997200

Ethical approval Dnr 2021-02620, date 2021-07-08.

Statistical Analysis Plan

The **primary outcome** is the difference in breathlessness (Borg CR10) intensity ratings during exercise at isotime. Isotime is defined as the highest equivalent 2-minute interval breathlessness assessment completed by a given participant during both the intervention and control constant-workrate cycle cardiopulmonary exercise tests (CWR-CPETs). The **co-primary outcome** is the difference in exercise endurance time (EET), defined as the duration of loaded pedaling during CWR-CPET to symptom-limitation. **Secondary outcomes** include additional physiological and perceptual responses assessed at iso-time and at peak exercise (end of test).

Data Presentation:

- Normally distributed continuous variables will be expressed as mean \pm standard deviation (SD).
- Skewed continuous variables will be expressed as median with range or interquartile range (IQR).
- Categorical variables will be presented as frequencies and percentages.

Comparisons:

- Baseline characteristics and incremental-CPET values, seen in table 1, will be compared using independent t-tests (continuous normal), Wilcoxon rank-sum tests (continuous non-normal), and chi-square tests (categorical).
- Effect of sleep deprivation versus normal sleep on subjective breathlessness, sleepiness and motivation before performing a CWR-CPET constant-load will be compared using t-tests for continuous variables with normal distribution and rank sum tests for continuous non-normal variables (see table 2).
- For CWR-CPET outcomes, specified in table 3, within-subject comparisons between a sleepless night and a normal night's sleep will be performed using paired t-tests for continuous normally distributed variables and Wilcoxon signed-rank tests for non-normal variables. Categorical outcomes will be analyzed using McNemar's test.
- CWR-CPET variables will be compared between conditions at rest, isotime and peak exertion, specified in table 3.
- Two post hoc analyses will be performed: first, where participants sleeping less than 6h during the normal night's sleep will be excluded from the analysis of the primary outcome; and second, where participants reporting sleep disturbance (defined as a PSQI total score higher than five) at baseline will be excluded.

Modeling:

Changes throughout CWR-CPET may be further analyzed using mixed-effects regression models to account for repeated measures.

Reporting:

Estimates will be presented as mean differences (sleepless night and a normal night's sleep) with 95% confidence intervals (CIs). Statistical significance will be defined as two-sided $p < 0.05$.

Software:

Analyses will be conducted using Stata (StataCorp LP; College Station, TX).

Figures

Figures will be adapted from Abdallah et al¹ to illustrate perceptual and physiological responses during constant-load exercise testing. These will include:

- **Panels a and c:** Symptom ratings (breathlessness intensity and leg discomfort) plotted against time during exercise for sleepless night and a normal night's sleep conditions.
- **Panels d and f:** Post-dose differences (sleepless night and a normal night's sleep) at isotime and peak exercise for breathlessness intensity and exercise endurance time (EET), including individual participant data and group means with 95% CIs.
- **Panels g and h:** Distribution of individual responses and indication of clinically meaningful thresholds (e.g., minimally clinically important difference).

These figures will visualize symptom trajectories, treatment effects, and variability across participants, highlighting both statistical and clinical significance.

Table 1: Baseline participant characteristics (t-tests for continuous variables with normal distribution, rank sum tests for continuous non-normal variables and chi-square tests for categorical variables).

Parameter	No sleep first	Normal sleep first	All participants
N (%)			
Male:female (n)			
Age, mean years (SD)			
Height (cm)			
Weight (kg)			
BMI kg/m ² , mean (SD)			
Smoking history, pack-years (SD)			
Physical activity during normal week			
Average sleeping time (h)			
PSQI, mean (SD)			
Post-bronchodialator pulmonary function (spirometry)			
FEV ₁ , L (SD)			
FEV ₁ , % predicted (SD)			
FVC, L (SD)			
FVC, % predicted (SD)			
FEV ₁ /FVC, L (SD)			
FEV ₁ /FVC, % of predicted (SD)			
Breathlessness and health status			
mMRC 0-4			
CAT total score			
CAT breathlessness item			
CAT activity limitation item			
Underlying conditions			
Asthma			
Angina Pectoris			
Diabetes mellitus			
Hypertension			
Hyperlipidemia			
Ischaemic heart disease			
Obstructive sleep apnea			
Other lung disease			
Rheumatic disease			
Stroke			
Cancer			
None			
Other			

COPD medications			
LABA+LAMA			
LABA+LAMA+ICS			
LABA			
LAMA			
Physiological responses at peak exercise of incremental CPET			
Cycle exercise time (min)			
Workload, W			
Workload, % of predicted			
Heart rate, beats/min			
Heart rate, % of predicted			
Breathing frequency (breaths/min)			
SpO ₂ (%)			
V _{O2} , mL/kg/min,			
V _{O2} (% of predicted),			
V'CO ₂ (mL/kg/min)			
RER			
V'E, L/min			
V _T , L			
V'E/V'CO ₂ (nadir value)			
Perceptual responses at peak exercise of incremental CPET			
Breathlessness intensity, Borg units			
Leg discomfort, Borg units			
Reasons for stopping exercise, n (%)			
Breathlessness			
Leg discomfort			
Breathlessness and Leg discomfort			
Other			

Table 2. Effect of sleep deprivation versus normal sleep on subjective breathlessness, sleepiness and motivation before performing a constant-load exercise test. (t-tests for continuous variables with normal distribution, rank sum tests for continuous non-normal variables)(Visit 2 and 3)

Parameter	No sleep	Normal sleep	Mean difference (95% CI)
mMRC			
Change in breathlessness(lickertscale 1-7)			
Hours of sleep the night before the test			
Subjective sleep quality (Lickertscale 1-5)			
Sleepiness before the test (0-10)			
Motivation to perform the test (0-10)			

Table 3: Effect of sleep deprivation versus normal sleep on physiological and perceptual responses at a standardized submaximal time during constant-load exercise testing (isotime) and at the symptom limited peak of constant-load exercise testing among individuals with Chronic obstructive pulmonary disease. (t-test for continuous variables with normal distribution, ranksum test for continuous non-normal variables and chi-square for categorical variables). (Visit 2 and 3)

Parameter, mean (SD)	Rest			Iso-time			Peak exercise		
	No sleep	Normal sleep	Mean difference (95% CI)	No sleep	Normal sleep	Mean difference (95% CI)	No sleep	Normal sleep	Mean difference (95% CI)
Perceptual responses									
Breathlessness intensity (Borg CR10)									
Leg discomfort (Borg CR10)									
Physiological responses									
Cycle exercise time, min									
Heart rate, beats/min									
Breathing frequency, breaths/min									
SpO ₂ , %									
V _{O₂} , ml/kg/min									
V _{O₂} , % of predicted									
V _{CO₂} (ml/kg/min)									
RER									
V _E , L/min									
V _T , L									
V _E /V _{CO₂} (Nadir value)									

Reasons for stopping test									
Breathlessness (n)									
Leg discomfort (n)									
Breathlessness and Leg discomfort (n)									
Other (n)									

Mean differences are for a sleepless night minus a normal nights sleep.

Table Abbreviations:

BMI, Body Mass Index

CAT, COPD Assessment Test

CI, Confidence Interval

Cm, Centimeter

COPD, Chronic Obstructive Pulmonary Disease

CO₂, Carbon Dioxide

CPET, Cardiopulmonary Exercise Test

FEV₁, Forced Expiratory Volume in the first second

FVC, Forced Vital Capacity

ICS, Inhaled Corticosteroids

Kg, Kilogram

L, Liter

LABA, Long-Acting Beta-Agonist

LAMA, Long-Acting Muscarinic Antagonist

Min, Minute

ml, Milliliter

mMRC, Modified Medical Research Council dyspnoea scale

O₂, Oxygen

PSQI, Pittsburgh Sleep Quality Index

RER, Respiratory Exchange Ratio

SD, Standard Deviation

SpO₂, Oxygen saturation

V, Ventilation

V_E, Expiratory Minute Ventilation

V_T, Tidal Volume

FIGURES

Figure 1: CONSORT diagram showing the flow of participants through each stage of the study

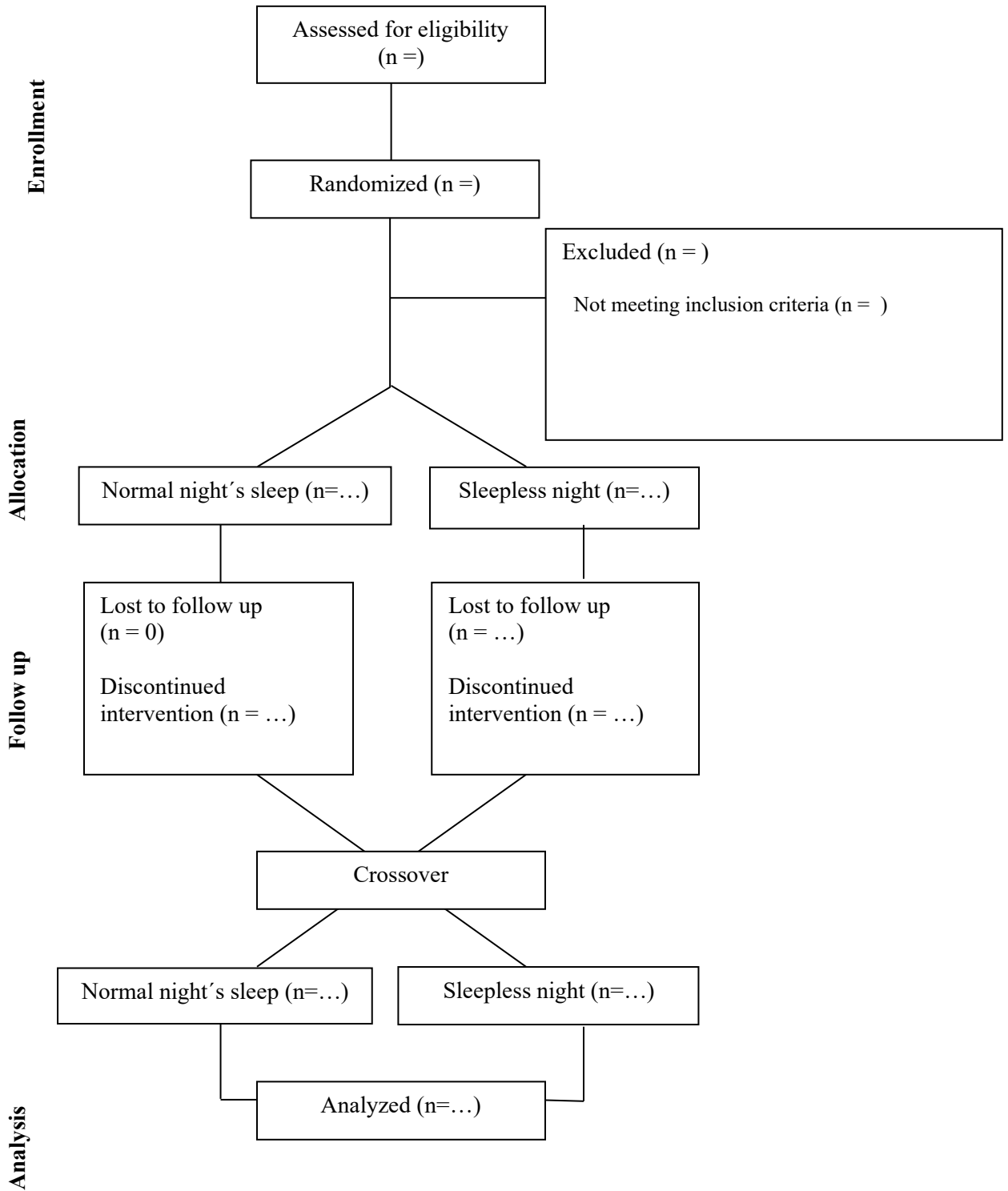


Figure 2.

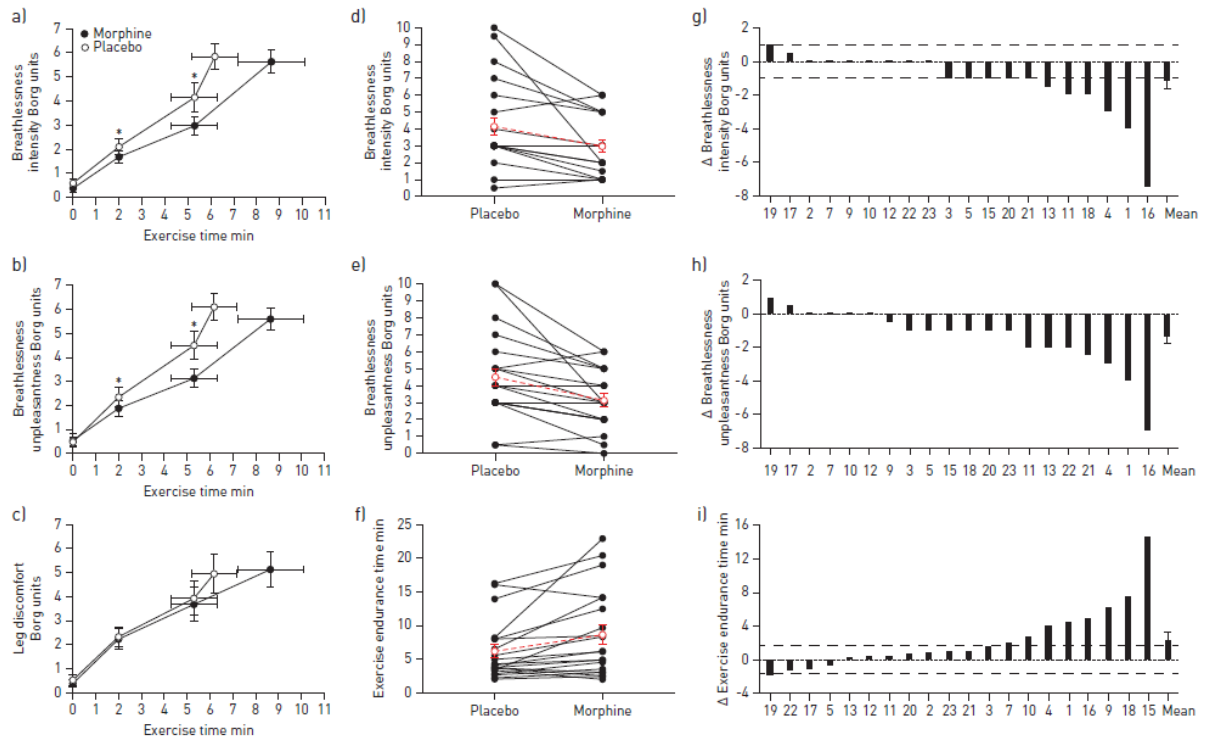


FIGURE 2 Effect of immediate-release oral morphine *versus* placebo on exertional breathlessness and exercise endurance in adults with advanced chronic obstructive pulmonary disease (COPD) and chronic breathlessness syndrome. Mean \pm SEM a) breathlessness intensity ratings, b) breathlessness unpleasantness ratings and c) leg discomfort ratings at rest and during constant-load cycle exercise testing at 75% of peak incremental power output. Individual participant post-dose values and post-dose differences in d and g) breathlessness intensity ratings during exercise at isotime, e and h) breathlessness unpleasantness ratings during exercise at isotime and f and i) exercise endurance time, where red symbols with dashed horizontal lines in panels d, e and f denote mean \pm SEM. Dashed horizontal lines in panels g and i denote minimally clinically important difference for breathlessness intensity [36] and exercise endurance time [37]. Δ : post-dose difference (i.e., morphine *minus* placebo). *: $p < 0.05$ versus placebo.

Example from Abdallah 2017¹ - panels (a,b och c) to be reported for both of “intensity and leg discomfort”.

1. Abdallah SJ, Wilkinson-Maitland C, Saad N, Li PZ, Smith BM, Bourbeau J, Jensen D. Effect of morphine on breathlessness and exercise endurance in advanced COPD: a randomised crossover trial. *Eur Respir J.* 2017;50(4). Epub 2017/10/21. doi: 10.1183/13993003.01235-2017. PubMed PMID: 29051274.