



HAL
open science

Effects of an individualized exercise training program on severity markers of obstructive sleep apnea syndrome: a randomised controlled trial

François Bughin, M. Desplan, C. Mestéjanot, M.C. Picot, François Roubille, D. Jaffuel, Jacques Mercier, I. Jaussent, Y. Dauvilliers

► To cite this version:

François Bughin, M. Desplan, C. Mestéjanot, M.C. Picot, François Roubille, et al.. Effects of an individualized exercise training program on severity markers of obstructive sleep apnea syndrome: a randomised controlled trial. *Sleep Medicine*, 2020, 70, pp.33-42. 10.1016/j.sleep.2020.02.008 . hal-02513916

HAL Id: hal-02513916

<https://hal.science/hal-02513916>

Submitted on 30 Jun 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Effects of an individualized exercise training program on severity markers of obstructive sleep apnea syndrome: a randomised controlled trial

F. Bughin^a, M. Desplan^{b, c}, C. Mestejanot^d, M.C. Picot^e, F. Roubille^f, D. Jaffuel^g, J. Mercier^a, I. Jaussent^h, Y. Dauvilliers^{d, h, i, *}

^a PhyMedExp INSERM U1046 / CNRS UMR9214, Montpellier University, Montpellier, University Hospital, France

^b Specialized Medical Center Medimarien, Marcel Marien Street 21, 1030, Brussels, Belgium

^c LaboCenter for the Study of Sleep Disorders, Neuroscience Pole, DELTA Hospital, CHIREC, Boulevard of the Triumph 201, 1160, Brussels, Belgium

^d Unité du Sommeil, Centre National de Référence pour la Narcolepsie, CHU Montpellier, Hôpital Gui-de-Chauliac, Service de Neurologie, Montpellier, France

^e Clinical Research and Epidemiology Unit, CHU Montpellier, Montpellier, France

^f PhyMedExp, Université de Montpellier, INSERM, CNRS, Cardiology Department, CHU de Montpellier, France

^g Department of Pneumology, Arnaud de Villeneuve, Regional University Hospital of Montpellier, 371 Avenue du Doyen Giraud, 34295, Montpellier Cedex 5, France

^h INSERM, U1061, Neuropsychiatry, Montpellier, France

ⁱ University Montpellier, Montpellier, France

A B S T R A C T

Objective: Obstructive sleep apnea (OSA) is a high prevalent disorder with severe consequences including sleepiness, metabolic, and cardiovascular disorders. The aim of this study was to assess the effect of an individualized exercise-training (IET) program with educational sessions vs educational sessions alone on severity markers of OSA over an eight-week duration.

Methods: This was a randomised, controlled, parallel-design study. In sum, 64 patients with moderate-to-severe OSA (apnea-hypopnea index AHI 15–45/hour), low physical activity level (Voorrips < 9), body-mass index (BMI) < 40 kg/m² were included in intervention group (IG) or control group (CG), and 54 patients finished the study. All underwent polysomnography (PSG), multiple sleep latency test (MSLT), constant workload exercise test, blood samples and fulfilled questionnaires twice. The primary endpoint was the change in apnea-hypopnea (AHI) at eight weeks from baseline. Main secondary endpoints were daytime sleepiness assessed by questionnaire and objective tests.

Results: No significant between-group differences were found for changes in AHI. A reduction in AHI was found in IG only ($p = 0.005$). Compared to CG, exercise training leads to a greater decrease in AHI during REM sleep ($p = 0.0004$), with a significant increase in mean daytime sleep latency ($p = 0.02$). Between-group differences were significant for weight reduction, severity of fatigue, insomnia and depressive symptoms with trend for sleepiness symptoms.

Conclusions: In adult patients with moderate-to-severe OSA, IET did not decrease AHI compared to the control group but improved markers of severity of OSA, in particular AHI in rapid eye movement (REM) sleep and objective daytime sleepiness. Adding personalized exercise training to the management of patients with OSA should be considered.

ClinicalTrials.gov identifier: NCT01256307.

Keywords:

Obstructive sleep apnea

Sleepiness

Exercise

Controlled-trial

REM sleep

1. Introduction

Obstructive sleep apnea (OSA) is a common sleep breathing disorder characterized by recurrent episodes of upper airway obstruction leading to intermittent hypoxia, arousals, increasing of sympathetic activity, oxidative stress, systemic inflammation and changes in intrathoracic pressure [1]. Excessive daytime sleepiness

* Corresponding author. Narcolepsy national reference center, Sleep center, Department of Neurology, CHU Montpellier, France.

E-mail address: ydauvilliers@yahoo.fr (Y. Dauvilliers).

(EDS) is a cardinal symptom of OSA and is also associated with impaired quality of life, increased risk for accidents and metabolic and cardiovascular diseases [2–5].

Continuous positive airway pressure (CPAP) is the first-line treatment of OSA resulting in decrease of apnea-hypopnea index (AHI), EDS, and improvement of sleep quality. However, long-term CPAP effectiveness remains limited by low adherence [6] and no randomized controlled trial has demonstrated a key protective effect in prevention of cardiovascular diseases [7]. CPAP therapy showed no effect on weight loss, energy expenditure, and no clinical significant impact on metabolic disorders or biomarkers associated with OSA [8]. Other treatments such as oral appliances or upper airway surgery only partially correct OSA, may have side effects, and their efficacy on the metabolic and cardiovascular consequences of OSA are poorly studied [9].

OSA is closely related to being overweight/obese, with a bidirectional link. Obesity is the most important risk factor for OSA [10] and OSA by itself can contribute to weight gain [11]. Moreover, patients with OSA present a decreased level of physical activity [12]. Lifestyle modification including diet and exercise training may be effective in reducing weight and severity of OSA, and are therefore recommended for the management of OSA [13,14].

Currently, few studies addressed the impact of non-pharmacological strategies such as hypocaloric diets and exercise training on severity of OSA. Recent meta-analysis showed a significant decrease in AHI and subjective sleepiness after exercise training regardless of weight loss [15,16]. The mechanisms underlying such improvement remain unclear; however a reduction of adipose tissue and in fluid shift in the upper airway area, an increase in oropharyngeal muscle strength, a change in humoral mediators of inflammation and metabolism, and a modification of sleep architecture with increased slow wave sleep associated with an increased respiratory stability may attenuate the propensity towards airway collapse during sleep [15,16]. The benefits of exercise training may also reduce severity of comorbidities associated with OSA (eg, diabetes, hypertension or cardiovascular diseases) and increasing physical activity is recommended to prevent cardiovascular diseases [15]. We previously showed positive effects of exercise training on cardiometabolic parameters and subjective EDS assessed by the Epworth Sleepiness Scale (ESS) in OSA patients [17], but its impact on objective sleepiness had not been evaluated.

The aim of this randomized, parallel-design study was to evaluate the efficacy of an individualized exercise training (IET) program with educational sessions compared to educational sessions only in patients with low physical activity level and moderate-to-severe OSA over an eight-week duration on severity markers of OSA: (1) change in AHI at endpoint vs baseline, (2) changes in EDS assessed by questionnaire and objective tests, and (3) subgroups analyses of patients according to their age, gender, BMI, ESS and AHI levels.

2. Methods

2.1. Study design

The REEVASAS trial was a randomized, controlled, parallel-design study of the efficacy of an IET program with educational sessions vs educational sessions only over an eight-week duration in patients with moderate-to-severe OSA.

All participants were admitted to the Sleep Unit, Department of Neurology, University Hospital Center of Montpellier and gave their written informed consent. The study was conducted in accordance with the CONSORT ethical guidelines and was approved by the local ethics committee (CPP Sud-Méditerranée IV) ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01256307) identifier NCT01256307).

2.2. Patients

Patients were adults aged between 30 and 65 years, with a diagnosis of moderate to severe OSA (AHI 15–45 events per hour), and low physical activity level (Physical activity score at the Voorrips questionnaire <9¹⁸). Key exclusion criteria as follows: were current treatment for OSA (CPAP or mandibular advancement devices), a body-mass index (BMI) ≥ 40 kg/m², contraindication for exercise training (like unstable cardiovascular disease), and taking drugs interfering with sleep architecture, continuity and daytime functioning.

A cardiopulmonary exercise test was performed at baseline using a cycle ergometer (Ergoline, GmbH) to determine the peak oxygen uptake (VO₂peak) and the ventilatory threshold to further individualize the exercise training intensity.

2.3. Intervention and control groups

Patients who fulfilled selection criteria were randomized between intervention group (IG) or control group (CG). The randomization sequence was computer-generated using random blocks in an order unknown by the investigators. The list was established by a statistician and only accessible by personnel in charge of randomization.

In the IG, patients received an eight-week IET program that includes sessions 3 times per week. Each 120-min session included the following exercises: warming up muscles (15 min), endurance training (45 min), resistance training (30 min), stretching (15 min), and postural and balance exercises (15 min). A gradual increase in exercise dose was performed over the eight-week program to limit the risk of injury. The endurance training consisted of lower limb exercises on a cycle ergometer at moderate intensity determined via the heart rate at 60% V' O₂ peak during the maximum exercise test. Heart rate was continuously measured with a heart rate monitor and load was adjusted every five minutes. Resistance training program included different exercises of upper and lower limbs with initial loads equivalent to 60% of the one repetition maximum. Resistance was increased when the patient could performed the current workload for 2 sets of 8 to 10 repetitions.

The sessions took place in the University Hospital of Montpellier and were supervised by a fitness trainer. The duration of IET was eight weeks and the composition of the sessions were based on the recommendations on respiratory rehabilitation [18–20].

Every week during 30–45 min, patients also benefited from group educational sessions aiming to better understand the role of sleep, OSA pathophysiology, disease management, diet balance, interest of physical activity practice and its impact on sleep. In the CG, patients received only educational sessions without exercise program. The health education program included similar educational activities and themes for both groups. No restrictive diet was prescribed in both groups but all patients were counseled on the nutritional balance.

2.4. Outcomes

The primary efficacy outcome was the change in AHI between baseline and eight-week follow-up in the IG group vs CG group.

Main secondary outcomes were changes from baseline in AHI in rapid eye movement (REM) and non-REM sleep, and in EDS using ESS and multiple sleep latency test (MSLT). Other outcomes were changes from baseline in others polysomnographic measures (total sleep time, sleep efficiency, micro arousal index, percentage of time spent at SpO₂ below 90%, and oxygen desaturation index), and in self-reported questionnaires to assess fatigue (Chalder Fatigue [21]), anxiety and depressive (Hospital Anxiety and Depression Scale-

HADS [22]) and insomnia (Insomnia Severity Scale, ISI [23]) symptoms, and in weight, glycemia, and cholesterol levels.

All patients underwent in an in-lab polysomnography (PSG) followed the next day by a MSLT at baseline and at endpoint. PSG included EEG leads, electrooculogram, electromyography of chin and tibialis anterior muscle, electrocardiogram, nasal cannula/pressure transducer, mouth thermistor, chest and abdominal bands, and pulse oximeter. Obstructive apnea was defined as an airflow cessation (>90%) for more than 10 s associated with thoracoabdominal movements, and hypopnea as airflow reduction of more than 30% associated with a drop in SpO₂ of more than 3% or a micro-arousal. Sleep stage, micro-arousals, periodic limb movements (PLM), and respiratory events were scored manually according to standard criteria [24]. Moderate OSA was defined by an AHI between 15 and 29.9 events per hour of sleep, and severe OSA by an AHI of more than 30 events per hour. Physicians who analysed the sleep data were blinded to the group allocation.

MSLT consisted of five naps scheduled at 2-h intervals between 9:00 AM and 5:00 PM. For each recording, the patients were allowed 20 min to fall asleep. If they did fall asleep, they were allowed to sleep an additional 15 min after which they were awakened. Sleep onset was determined by the first epoch of any stage of sleep. Mean sleep latency (MSL) from the five naps was computed for each subject. MSLT were scored by sleep experts blind to the experimental data and randomisation.

All patients were also administered standardised questionnaires and underwent clinical examinations, fasting blood intake to measure glycemia (mmol/L), and cholesterol total (g/L). Patients of both groups performed a constant-load exercise test on an electromagnetically braked cycle ergometer at a work rate equal to 80% of peak work capacity achieved during incremental cycle ergometry. Patients were asked to cycle for as long as possible and were told to stop when the pedalling rate of 60/min could not be kept up. All tests and evaluations of the study were assessed twice (at baseline and follow-up), at the same place for each group in the same conditions and with the same devices.

2.5. Power calculations

Statistical power was based on results comparing two groups of patients with moderate OSA with a change in AHI after intervention (four-months follow-up) equalled to -10.7 (SD = 7.7) in the trained group and -4.5 (SD = 6.9) in the control group [25]. Therefore, a total of 68 patients (34 per arm) provided a power of more than 90% for detecting a between-group difference for change in AHI of 6 at the endpoint using a 2-sided 2-sample t test with a significance level of 0.05.

2.6. Statistical analysis

Analyses of the primary outcome (AHI) were performed by intention-to-treat (ITT) principle. Missing data for the primary outcome were replaced using the Last Observation Carried Forward (LOCF) method. A sensitivity analysis was performed in a per-protocol population (PP) (excluding patients with major protocol violation with regard to inclusion or exclusion criteria ($n = 4$), with major protocol violation during the course of the treatment ($n = 9$) and premature discontinuation during the study ($n = 1$)). Secondary outcomes were analysed in PP population.

The characteristics of the study population were described using number and percentage for categorical variables and medians and interquartile ranges (IQR) for continuous variables because their distributions were mostly skewed according Shapiro–Wilk test. Nonparametric statistical tests were used due to the small sample size (less than 30 in each group in PP) and the distribution of

continuous variables. Chi-square or Fisher's exact tests were used to compare categorical variables between the two groups, and Mann–Whitney U test for continuous variables. Changes in each outcome between baseline and two-month follow-up were compared between the groups using a Mann–Whitney U test. For the between-group differences, 95% Confidence Intervals (CI) were constructed. To compare differences between baseline and two-month follow-up within group, Wilcoxon signed-rank tests were used. Spearman's rank order correlations were used to determine associations between continuous variables. Statistical significance was set at $p < 0.05$. Statistical analyses were performed with SAS version 9.4.

3. Results

3.1. Patients

Of the 68 patients who were randomized, 34 were in the IG and 34 in the CG (Fig. 1). Two patients randomized to IG and two patients randomized to CG were not eligible to continue the trial due to non-respect of selection criteria (due to a posteriori double blind rescoring of PSG to validate thresholds of baseline AHI). One death occurred in IG (unrelated to study). Of the 63 remaining patients, nine (four in IG and five in CG) discontinued the trial prior to endpoint without a post baseline assessment that include six patients due to withdrawal of consent and three with lost to follow-up. A total of 27 patients in IG and 27 in CG were included in per protocol analysis. Baseline characteristics were similar among the two groups (Table 1). Patients in IG who completed the eight-week intervention attended $77.9 \pm 24.9\%$ of their exercise sessions.

3.2. Main outcome

No significant between-group differences were found for changes in AHI from baseline to follow-up.

3.3. Secondary outcomes

In the IG, a significant decrease in AHI was found from baseline to endpoint ($p = 0.009$) with no effect in CG (Table 2). Compared to CG, IG resulted in greater decrease in AHI during REM sleep in PP analyses (Tables 2 and 3, Fig. 2). No effect of the IET was found on the postural AHI, with no between-group differences observed for supine and non-supine AHI at baseline and follow-up (Table 2). No other between-group differences were found on PSG measurements. A decrease in NREM 1–2 of sleep and an increase in NREM 3 were found in IG only.

A significant between-group increase in MSL on the MSLT ($p = 0.02$) was found (Table 3, Fig. 3). MSL was increased by 101.65 ± 206.05 s in IG ($p = 0.02$) with no change in CG. Among patients in IG, 12 patients had MSL below 900 s that corresponds to those with the greatest tendency to fall asleep during the day. These patients increased the MSL of 5 min or more after exercise training (median increase 300 s [288–480], $p = 0.001$) while no significant changes were found in patients from CG with baseline MSL below 900 s ($n = 7$; 24 s [-60–240], $p = 0.31$).

Between-group differences were significant for the weight ($p = 0.008$) that indicates a decrease in IG (Table 4) and no correlations were found between changes in AHI and weight ($r = -0.18$, $p = 0.38$). Moreover, no correlations were found between changes in weight and in AHI-REM or AHI-NREM in either IG or CG groups. Significant reduction were observed for fasting glycemia, with same tendency for cholesterolemia in IG group only, with no significant between-group differences.

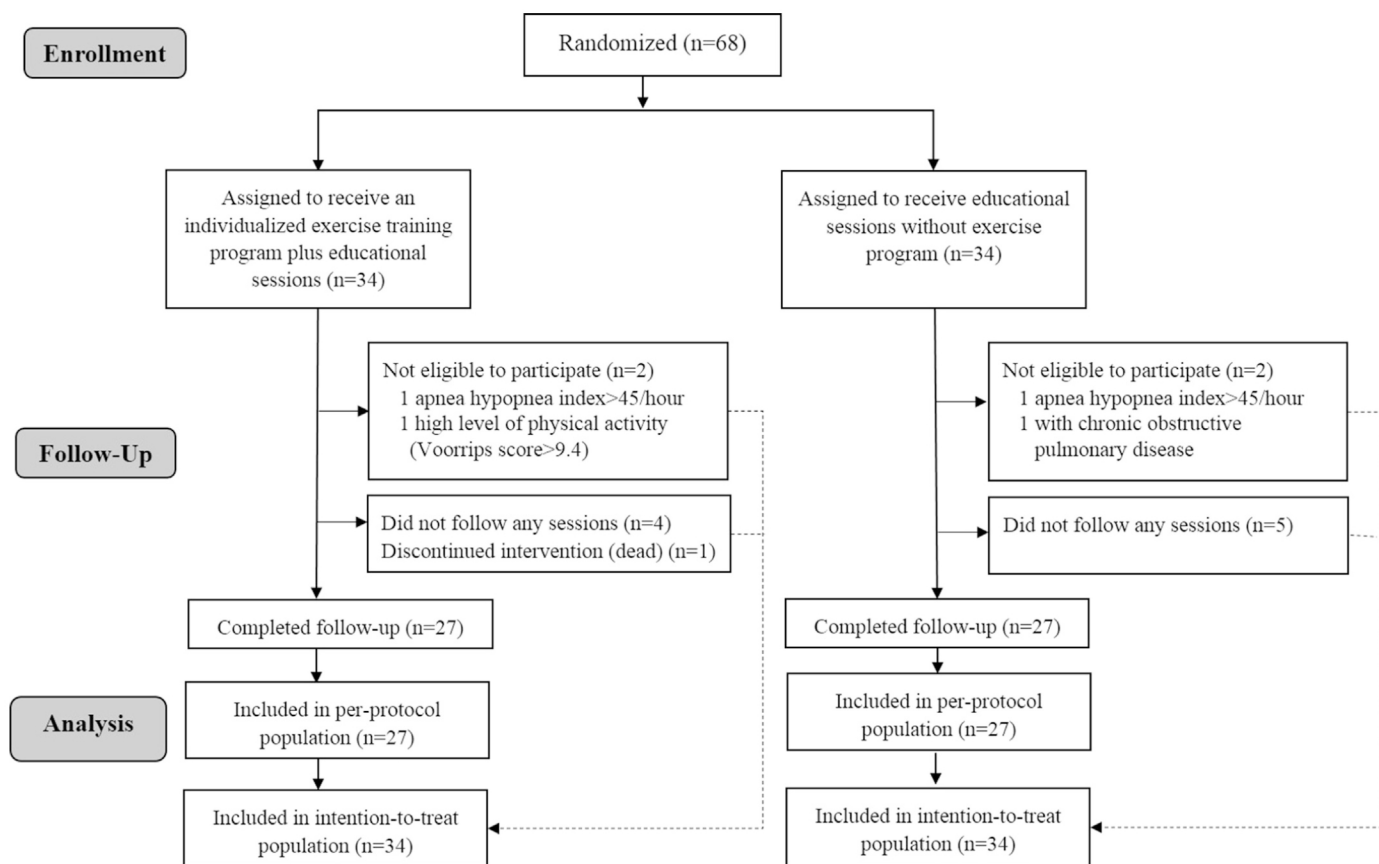


Fig. 1. Flow chart: REEVASAS study.

Significant between-group reductions were found for severity of fatigue, insomnia and depressive symptoms with similar trend for EDS using ESS ($p = 0.05$). Exercise training resulted in significant decrease of all these symptoms while no significant changes were found in CG. No correlations were found between changes in ESS and in MSL in the both groups ($r = -0.034$, $p = 0.86$ in CG; $r = 0.009$, $p = 0.97$ in IG) (Table 4).

Patients improved exercise tolerance and training adaptations at the end of the trial after IET with greater Voorrips scores and larger increased in cycle endurance time in the IG than in CG ($p < 0.02$, $p < 0.0001$ respectively) (Table 4).

3.4. Subgroup analyses

Additional analyses were performed by subgroups of patients according to their age, gender, BMI, ESS and AHI levels (Table 5). In intention-to-treat analyses, we found significant between-group differences for AHI only in female. In IG, AHI significantly decreased in male, patients obese and aged above 55 years and in those with initial AHI greater than 30 per hour. In contrast, between-group differences were found for AHI in REM sleep in patients obese, non-sleepy ($ESS \leq 10$), aged above 55 years and with moderate OSA in intention-to-treat analyses (Table 5).

4. Discussion

In adult patients with moderate-to-severe OSA, IET did not decrease AHI compared to the control group, but a significant reduction in AHI was found from baseline to end of the study in the group with IET. Compared to CG, IET resulted in greater decrease in

AHI during REM sleep and a significant increase in mean sleep latency on the MSLT. Besides, IET improve severity of fatigue, insomnia and depressive symptoms.

While the primary outcome was not reached, we found a reduction of 21.5% in AHI in IG in line with our previous study [17] and with a recent meta-analysis showing a mean reduction of 28% after exercise training interventions [15]. The lack of significant between-group difference may be partly explained by the improvement in CG patients with 33% decreasing their AHI by more than 20%. Such improvement in CG may be related to behavioral changes secondary to educational sessions on physical activity and diet balance, being finally not an optimal control group per se. We also found no effect of the IET on the postural AHI, with no between-group differences for changes in supine and non-supine AHI.

Our trial found a significant between-group improvement in weight. The loss of weight in our trial could be partly explained by changes in diet secondary to educational sessions, although no defined diet prescriptions were provided. We found no correlations between the changes in weight and in AHI, AHI in REM, and AHI in NREM that suggest an independent role of exercise in improving severity of OSA. The global effects of exercise training on OSA are really diverse, often moderate; thus the benefits reported of improving OSA severity were not directly related to weight reduction. Other mechanisms (eg, fat loss, fluid shifts, changes in mediators of inflammation and metabolism, changes in oropharyngeal muscle function, and increased slow-wave sleep) may be also involved and remain to be elucidated [14,15,26,27].

We reported that IET may improve objective measures of EDS. These results could be even better than those obtained with CPAP

Table 1
Characteristics of participants randomized to Intervention Group vs Control Group.

Variable	Control Group N = 34		Intervention Group N = 34		p
	n	%	n	%	
Demographic and clinical characteristics					
Sex, Female	4	11.76	9	26.47	0.12
Age, in years ^a	55.00 (10.27)		53.71 (9.86)		0.75
BMI, kg/m ^{2a}	30.60 (3.40)		30.65 (6.20)		0.92
Diabetes mellitus, Yes	5	14.71	3	9.09	0.71
Hypertension/antihypertensive intake, Yes	12	35.29	9	27.27	0.85
Dyslipidemia, Yes	14	41.18	9	27.27	0.32
Current smoker, Yes	8	23.53	4	12.12	0.30
Family history of cardiovascular diseases, Yes	13	39.39	11	33.33	0.67
Polysomnographic measurements					
TST, minutes ^a	440.00 (97.00)		436.00 (92.00)		0.73
Sleep efficiency, % ^a	83.57 (19.93)		78.74 (15.01)		0.32
N1–N2, % ^a	62.57 (9.77)		66.81 (12.76)		0.32
N3, % ^a	15.04 (11.81)		14.24 (9.00)		0.60
REM, % ^a	20.22 (10.73)		20.38 (6.93)		0.48
PLMS index,/hour ^a	1.45 (5.02)		3.93 (6.45)		0.08
AHI,/hour ^a	26.10 (15.78)		28.15 (12.89)		0.65
Time spent with SaO ₂ < 90%, min ^a	1.10 (3.25)		1.07 (2.10)		0.94
Mean SaO ₂ , % ^a	94.00 (2.00)		94.00 (2.00)		0.92
Arousal index events,/hour ^a	19.15 (10.81)		20.91 (11.22)		0.72
Oxygen desaturation Index,/hour ^a	18.23 (28.16)		22.29 (17.63)		0.22

BMI: body mass index; AHI: apnoea hypopnoea index; REM: rapid eye movement sleep.

^a Continuous variables were expressed as median (interquartile range).

or mandibular advancement device [28]. EDS is one of the most common symptom in OSA patients and is associated with lower quality of life, work or traffic accidents, obesity, and diabetes [29,30]. The severity of EDS is often quantified by ESS with either weak or no correlation with severity of AHI, and never with AHI in REM sleep [31]. Moreover, no or only weak correlations were found between ESS and objective measurement of EDS in patients with OSA or with other sleep conditions [32]. Here, we found a between-group difference for mean sleep latency with improvement of more than 2 min, with greater results in patients with the highest objective sleepiness at baseline. In contrast to narcolepsy [33,34], there is a lack of normative MSLT data in OSA with a wide range of baseline MSL results [35]. We found here no correlation between baseline MSL and ESS, AHI, AHI-REM and sleep stages, and between changes in MSL along the study with ESS, AHI or AHI-REM and sleep stage modifications. These results are consistent with the literature and confirmed that the determinants of EDS are multiple (ie, depressive symptoms, obesity, short sleep duration, age, race, low-grade inflammation) and complex, as well as to in OSA [32]. Other symptoms were frequently reported by patients with OSA such as fatigue, insomnia and depressive symptoms [36] and all improved after our exercise training program.

We found a significant between-group difference of AHI during REM sleep, with a larger reduction of 37.5% in IG. A reduction of AHI in REM sleep was already reported following exercise training in patients with AHI >15/hour [37], but not in a smaller four-week study including patients with coronary artery disease associated with OSA or central sleep apnea [26]. In contrast, the latter study found that exercise induced a reduction in the non-REM AHI. The decrease of AHI in REM sleep is of major interest given that OSA during REM sleep have worse cardiometabolic consequences than OSA in NREM sleep. Apnea and hypopnea in REM sleep are longer and associated with greater desaturation than in non REM sleep [38]. Recent studies found that OSA in REM sleep is independently associated with prevalent and incident hypertension, non-dipping nocturnal blood pressure, increased insulin resistance and cardiovascular diseases [39–41]. Therefore, decreasing AHI specifically in REM sleep after IET may be a target to prevent from metabolic and cardiovascular disorders. Our study emphasized that IET associated with health education program including diet balance improved anthropometric and metabolic parameters, in decreasing weight, fasting glycemia, with same tendency for cholesterolemia in IG. These results are of interest given the limited effects of CPAP on the glycemic and lipid balance, and on OSA in REM sleep [8]. The 4-h of

Table 2
Changes in apnea hypopnea indexes between baseline and 8-week follow-up in intention to treat population.

Variable	Control Group (N = 34)				Intervention Group (n = 34)				Between-Group Difference ^b	
	Baseline	Follow-up	Within-Group Difference ^a		Baseline	Follow-up	Within-Group Difference ^a			
	Median (IQR)	Median (IQR)	Median (IQR)	p	Median (IQR)	Median (IQR)	Median (IQR)	p	Median [95%CI]	p
Primary outcome										
AHI,/hour	26.10 (15.78)	25.47 (18.00)	0.00 (12.86)	0.83	28.15 (12.89)	21.80 (17.29)	-4.23 (12.35)	0.009	3.47 [-1.60; 9.67]	0.22
AHI-REM,/hour	20.84 (30.44)	23.38 (40.68)	0.06 (22.27)	0.33	40.28 (20.19)	28.39 (25.81)	-10.00 (20.89)	<0.001	13.70 [5.22; 24.70]	0.001
AHI-NREM,/hour	26.82 (14.66)	24.51 (21.97)	-1.41 (15.98)	0.50	24.75 (13.73)	19.83 (18.26)	-1.33 (9.65)	0.09	0.05 [-5.23; 6.72]	0.85
AHI-supine,/hour	30.95 (16.70)	31.16 (28.26)	0.00 (22.41)	0.67	30.60 (22.20)	22.90 (20.94)	0.00 (14.48)	0.41	2.47 [-4.73; 10.75]	0.54
AHI-non supine,/hour	10.35 (4.70)	11.35 (14.29)	0.00 (14.41)	0.74	11.90 (13.34)	8.34 (14.01)	-3.17 (11.93)	0.11	3.74 [-1.39; 9.31]	0.16

AHI: Apnea Hypopnea Index; REM: Rapid Eye Movement.

^a Indicates medians change between follow-up and baseline.

^b Indicates medians change difference between the control group and the intervention group.

Table 3
Changes in polysomnographic and daytime sleepiness measurements between baseline and 8-week follow-up in per-protocol population.

Variable	Control Group (N = 27)				Intervention Group (n = 27)				Between-Group Difference ^b	
	Baseline	Follow-up	Within-Group Difference ^a	p	Baseline	Follow-up	Within-Group Difference ^a	p		
	Median (IQR)	Median (IQR)	Median (IQR)		Median (IQR)	Median (IQR)	Median (IQR)		Median [95%CI]	p
Primary outcome										
AHI,/hour	26.00 (12.70)	25.91 (22.03)	-1.60 (20.77)	0.94	26.50 (13.00)	16.80 (16.59)	-5.53 (12.63)	0.005	5.13 [-1.40; 13.64]	0.11
Secondary polysomnographic outcomes										
AHI-REM,/hour	20.95 (26.87)	31.54 (40.75)	2.68 (32.79)	0.18	40.26 (19.24)	26.47 (19.48)	-11.74 (22.58)	<0.001	20.43 [8.85; 33.48]	0.0007
AHI-NREM,/hour	25.83 (16.22)	26.81 (23.70)	-5.74 (22.04)	0.69	21.52 (14.67)	15.86 (19.75)	-3.08 (10.55)	0.07	0.52 [-6.12; 9.80]	0.88
Time spent with SaO ₂ < 90%, min	1.65 (4.24)	1.67 (4.21)	0.00 (2.12)	0.78	0.85 (1.50)	0.55 (1.30)	-0.11 (1.91)	0.38	0.25 [-0.61; 1.35]	0.47
Mean SaO ₂ , %	94.00 (2.00)	94.00 (2.00)	0.00 (2.00)	0.93	94.00 (1.00)	95.00 (2.00)	0.00 (2.00)	0.48	0 [-1; 1]	0.65
Arousal index events,/hour	19.31 (12.38)	22.50 (9.71)	3.73 (16.49)	0.13	20.96 (11.22)	20.58 (11.70)	-0.50 (14.46)	0.67	4.47 [-1.75; 10.73]	0.12
Oxygen desaturation Index,/hour	22.13 (22.83)	27.39 (15.57)	4.11 (23.69)	0.12	22.29 (17.63)	14.94 (14.52)	-1.38 (22.42)	0.29	8.86 [0.15; 17.50]	0.05
TST, minutes	433.00 (96.00)	437.00 (104.00)	2.00 (79.00)	0.50	438.00 (81.00)	447.00 (107.00)	14.00 (71.00)	0.47	1 [-32; 33]	0.99
Sleep efficiency, %	75.05 (21.62)	75.65 (15.39)	-0.90 (17.05)	0.61	79.40 (16.78)	77.28 (16.94)	1.01 (16.03)	0.80	-2.07 [-8.39; 5.81]	0.60
N1-N2, %	62.34 (10.79)	64.75 (14.09)	-1.28 (11.51)	0.54	66.90 (13.80)	62.49 (15.41)	-3.70 (13.04)	0.006	3.52 [-1.03; 8.18]	0.13
N3, %	15.40 (11.81)	16.15 (10.74)	0.80 (9.30)	0.33	13.98 (8.01)	16.60 (10.49)	2.23 (7.97)	0.02	-1.94 [-5.43; 1.00]	0.13
REM, %	19.30 (10.68)	20.00 (8.66)	-2.48 (7.21)	0.69	20.25 (5.69)	21.57 (9.70)	1.71 (8.86)	0.10	-2.50 [-5.69; 0.60]	0.11
PLMS index,/hour	1.45 (5.95)	3.72 (17.86)	0.21 (17.98)	0.06	3.93 (6.14)	4.50 (15.79)	0.56 (9.65)	0.11	0.28 [-2.81; 4.43]	0.82
Objective daytime sleepiness outcome										
MSLT, seconds	1032.00 (246.00)	915.00 (312.00)	-18.00 (202.50)	0.28	972.00 (444.00)	1050.00 (192.00)	54.00 (288.00)	0.02	-136.50 [-264.00; -24.00]	0.02

^a Indicates medians change between follow-up and baseline.

^b Indicates medians change difference between the control group and the intervention group. AHI: Apnea Hypopnea Index; MSLT: Multiple Sleep Latency Test; PLMS: Periodic Limb Movements of Sleep; REM: Rapid Eye Movement; SaO₂: Oxygen Saturation; TST: Total Sleep Time.

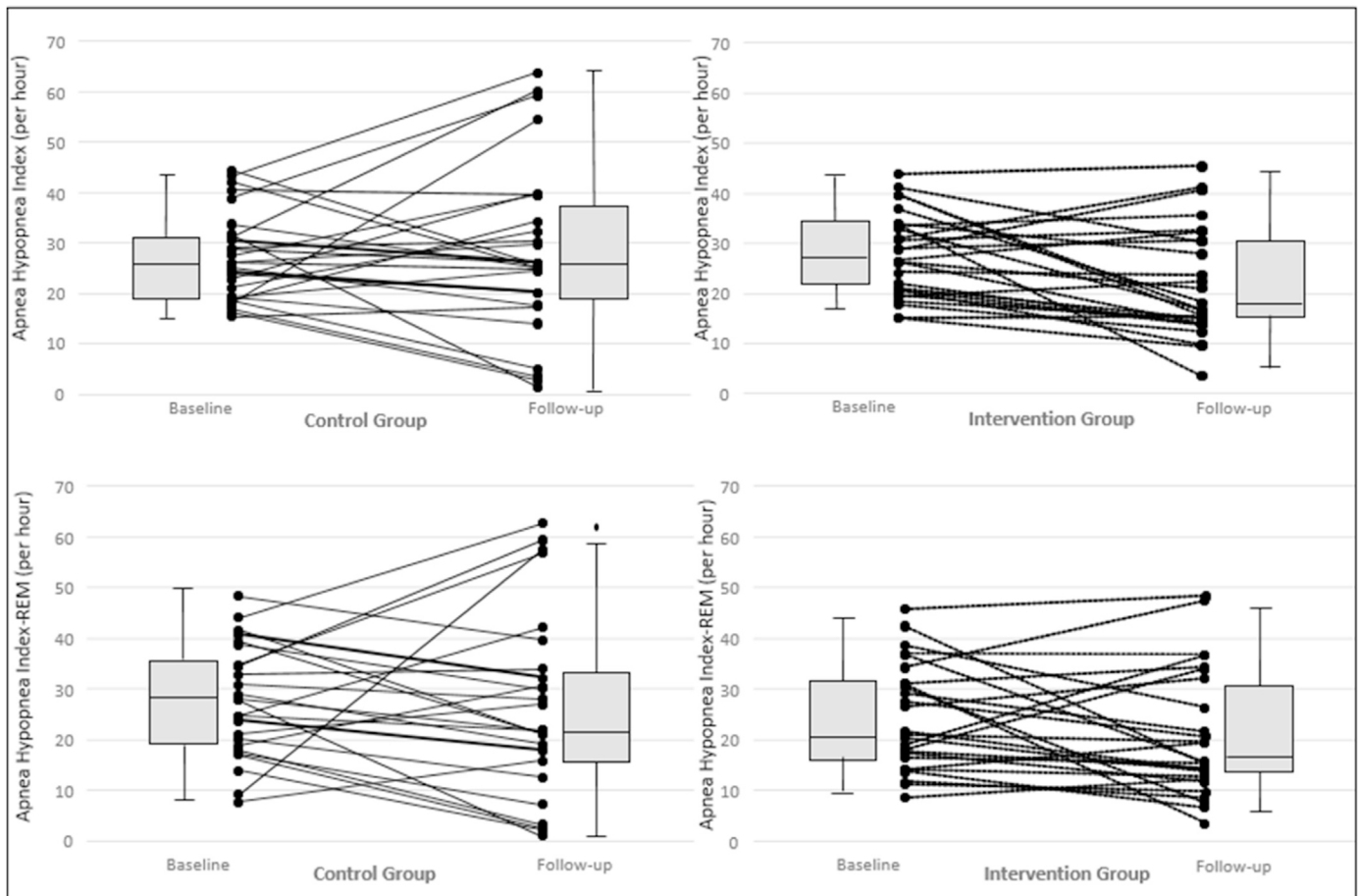


Fig. 2. Individual trajectories of apnea/hypopnea index (AHI) and AHI in REM sleep at baseline and after 8 weeks in patients in IG and CG groups. Results are shown as individual level and with a box-whisker plot, with median and 25th quartile of AHI.

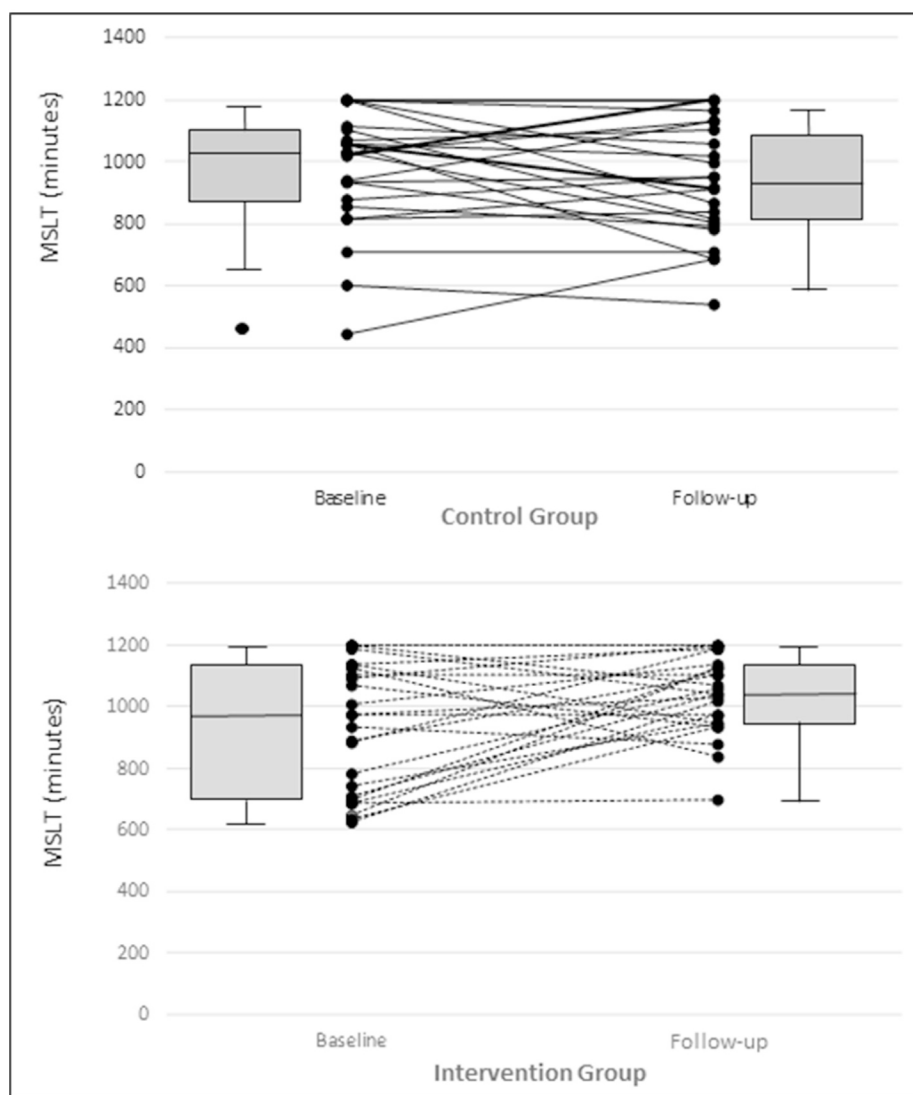


Fig. 3. Individual trajectories of mean sleep latency on the multiple sleep latency test (MSLT) at baseline and after 8 weeks in patients in IG and CG groups. Results are shown as individual level and with a box–whisker plot, with median and 25th quartile of MSL.

nightly CPAP use is often considered an adequate adherence to therapy, however it does not cover the early morning hours associated with REM OSA at risk for cardiovascular and metabolic risks.

We reported a clinically meaningful increase in cycle endurance time after IET, reflecting an improvement of exercise tolerance and training adaptations at follow-up. This result is consistent with those obtained after respiratory rehabilitation in patients with chronic obstructive pulmonary disease [42]. This is a noteworthy result as OSA patients have reduced maximal aerobic capacity and intensity of physical activity below recommendations [40]. The low levels of physical activity in patients with OSA may relate to fatigue, EDS, obesity, exercise intolerance and neurocognitive problems that may all contribute to cardiovascular disorders. Although CPAP reduces EDS and improves quality of life, a recent meta-analysis showed that CPAP did not increase physical activity [15].

Our study also aimed to identify OSA subgroups likely to greater improvement after IET and found that females were associated with the highest decrease in AHI although a limited number of females participated in this study. In contrast, obese, non-sleepy ($ESS \leq 10$), moderate OSA and patients aged above 55 years were associated with the largest decrease of AHI in REM sleep.

Accordingly, obese middle-aged and elderly patients with moderate OSA, often associated with cardiometabolic comorbidities, may be the target population that would benefit the most from IET.

There are limitations in our study. First, the low sample size, the possible underestimated effect size, the high number of drop-outs in the two groups could have affected the magnitude of the results; however this study is the largest randomised study evaluating the efficacy of an IET program in patients with moderate to severe OSA with assessment of EDS by questionnaire and MSLT. The sample size calculation is based on an old study [25] with different duration and design than our study that may have underestimated the effect size; however it was one of the only study available when the current study was planned. The duration of exercise training is also questionable, it may have been too short (eight-week duration) to obtain maximal effects, and to assess on long-term maintenance on both increased physical activity levels and OSA severity; although recent analyses reported that the length of the intervention was not associated with changes in AHI [14,42,43]. Second, physical activity level was assessed at baseline by the Voorrips questionnaire and not by objective measure because the trial was designed long time ago. However, a significant increase in cycle

Table 4
Changes in on weight, metabolic, sleep, psychological and endurance parameters between baseline and 8-week follow-up in per-protocol population.

Variable	Control Group (N = 27)				Intervention Group (n = 27)					
	Baseline		Follow-up		Within-Group Difference ^a		Between-Group Difference ^b			
	Median (IQR)	Median (IQR)	Median (IQR)	p	Median (IQR)	Median (IQR)	Median (IQR)	p	Median [95%CI]	p
Anthropometric and metabolic parameters										
Weight, kg	87.40 (11.90)	88.20 (9.60)	0.50 (2.80)	0.45	89.60 (13.40)	89.40 (11.50)	-1.45 (2.60)	0.006	-1.7 [-2.8;-0.4]	0.0009
Glycemia, mmol/L	5.50 (0.60)	5.10 (0.90)	-0.20 (0.60)	0.09	5.10 (1.20)	5.25 (1.10)	-0.25 (0.55)	0.03	-0.2 [-0.5; 0.2]	0.39
Cholesterol total, g/L	2.14 (0.61)	2.10 (0.49)	0.02 (0.37)	0.65	2.15 (0.45)	2.00 (0.47)	-0.08 (0.30)	0.05	0.05 [-0.06; 0.16]	0.31
Fatigue, depression, anxiety and sleep measurements										
Fatigue Mental score	9.00 (3.00)	8.00 (2.00)	0.00 (2.00)	0.69	8.00 (2.00)	7.00 (2.00)	-2.00 (4.00)	0.001	2 [1; 3]	0.002
Fatigue Physical score	16.00 (4.00)	15.50 (4.00)	0.00 (4.00)	0.79	16.00 (6.00)	10.50 (6.00)	-6.00 (9.00)	<0.0001	6 [3; 9]	0.0003
HAD-Depression	6.00 (6.00)	5.00 (6.00)	-0.50 (2.00)	0.54	5.00 (5.00)	3.00 (4.00)	-3.00 (3.00)	0.0002	2 [1; 4]	0.007
HAD-Anxiety	8.00 (5.00)	8.00 (5.00)	0.00 (4.00)	0.99	8.00 (6.00)	6.00 (6.00)	-1.00 (5.00)	0.06	1 [-1; 3]	0.17
ISI Score	13.00 (9.00)	12.50 (8.00)	-1.50 (4.00)	0.50	13.00 (6.00)	7.50 (8.00)	-4.00 (9.00)	0.0008	4 [1; 7]	0.03
ESS score	9.00 (7.00)	10.00 (8.00)	0.00 (3.00)	0.99	10.00 (7.00)	8.00 (6.00)	-2.00 (6.00)	0.004	2 [0; 4]	0.05
Endurance test and Vooorrips score										
Endurance Test, sec	261.00 (275.00)	480.00 (583.00)	138.00 (225.00)	<0.001	423.00 (462.00)	1590.00 (1455.00)	1120.00 (1296.00)	<0.001	-695 [-1200;-344]	<0.0001
Vooorrips score	4.90 (4.60)	3.50 (4.40)	0.40 (2.56)	0.30	4.06 (4.89)	5.44 (5.46)	1.92 (4.16)	<0.001	-1.59 [-3.69;-0.36]	0.02

ESS: Epworth Sleepiness Scale; ISI: Insomnia Severity Index; HAD-Depression: Hospital Anxiety Depression- Depression sub-scale; HAD-Anxiety: Hospital Anxiety Depression- Anxiety sub-scale.

^a Indicates medians change between follow-up and baseline.

^b Indicates medians change difference between the control group and the intervention group.

Table 5
Changes in Apnea hypopnea index and Apnea hypopnea index in REM sleep in response to the individualized exercise training program by participant characteristics in intention to treat population.

Variable	Control Group N = 32			Intervention Group N = 32			Between-Group Difference ^b	
	Within-Group Difference ^a			Within-Group Difference ^a				
	n	Median (IQR)	p	n	Median (IQR)	p	Median [95%CI]	p
Apnea hypopnea index								
Sex								
Male	30	-1.19 (9.97)	0.29	25	-5.53 (12.52)	0.02	2.23 [-2.96; 9.67]	0.50
Female	4	10.65 (21.57)	0.13	9	0.00 (5.50)	0.44	14.98 [3.78; 36.60]	0.03
Age, in years								
<55	17	0.00 (13.49)	0.38	19	0.00 (15.40)	0.19	0.00 [-7.60; 10.99]	0.99
≥55	17	0.00 (16.62)	0.71	15	-5.50 (8.27)	0.006	5.84 [-0.78; 16.07]	0.09
BMI, kg/m ²								
<30.0	14	-1.21 (19.77)	0.91	14	0.00 (7.39)	0.58	0.00 [-7.68; 10.99]	0.98
≥30.0	19	0.00 (12.86)	0.86	20	-5.75 (13.65)	0.008	5.53 [-1.53; 15.82]	0.14
ESS								
≤10	18	-1.61 (17.68)	0.78	18	-5.35 (17.71)	0.06	5.89 [-2.66; 18.09]	0.19
>10	16	0.00 (13.33)	0.68	15	-3.29 (11.23)	0.08	1.64 [-6.30; 9.39]	0.60
AHI, /h								
[15-30]	21	0.00 (9.78)	0.77	20	-1.99 (6.79)	0.23	2.25 [-2.43; 7.59]	0.33
≥30	13	-0.78 (17.29)	0.56	14	-8.36 (23.93)	0.03	5.45 [-7.69; 20.53]	0.61
Apnea hypopnea index in REM sleep								
Sex								
Male	30	0.00 (22.04)	0.80	25	-8.90 (21.27)	0.002	11.09 [0.64; 23.93]	0.02
Female	4	23.69 (25.66)	0.13	9	-11.38 (15.90)	0.03	33.18 [14.50; 53.77]	0.02
Age, in years								
<55	17	0.00 (14.16)	0.97	19	-8.90 (25.56)	0.005	10.73 [0; 27.35]	0.07
≥55	17	6.65 (22.96)	0.13	15	-11.09 (20.89)	0.01	17.61 [5.85; 30.93]	0.01
BMI, kg/m ²								
<30.0	14	0.00 (22.96)	0.91	14	-3.07 (13.79)	0.18	4.11 [-8.65; 20.83]	0.43
≥30.0	19	1.81 (30.59)	0.21	20	-12.06 (22.55)	<0.001	21.27 [8.85; 36.98]	0.002
ESS								
≤10	18	0.06 (26.78)	0.27	18	-11.56 (15.89)	0.001	14.97 [3.09; 31.27]	0.01
>10	16	0.91 (26.78)	0.85	15	-8.90 (21.27)	0.02	11.67 [-3.22; 27.54]	0.12
AHI, /h								
[15-30]	21	1.81 (17.10)	0.20	20	-11.88 (23.41)	<0.001	16.45 [5.98; 30.40]	0.002
≥30	13	0.00 (22.27)	0.99	14	-6.28 (12.50)	0.05	7.59 [-5.95; 28.82]	0.21

^a Indicates medians change between follow-up and baseline.

^b Indicates medians change difference between the control group and the intervention group.

endurance time was found after IET. The use of actimeters would have been of interest to control for any spontaneous physical activity that participants did outside the structured sessions. Third, CG is not a real control group as patients benefited to educational sessions including diet balance that may be a confounding factor limiting the observed changes in the group with IET. Fourth, we included only adults with moderate-to-severe OSA, low physical activity level, without psychotropic drugs intake that may limit the generalizations of our findings. Finally, the subgroup analyses could be limited by the low number of subjects in each subgroup (such as the gender effect).

In conclusion, while the primary outcome was not reached, this is the first randomised controlled trial demonstrating that individualized exercise training improved objective measure of sleepiness and AHI in REM sleep in patients with moderate-to-severe OSA. Personalized exercise training also improved weight, severity of fatigue, insomnia and depressive symptoms. However, the mechanisms underlying the relationships between physical activity, OSA in REM sleep, and sleep remain unclear. Further studies are required to optimize treatment strategies and personalize therapy to achieve long-term benefits as function of OSA phenotypes.

Study funding

This was not an industry-supported study. This work was supported by a national grant (PHRC interregional).

Y Dauvilliers received funds for seminars, board engagements and travel to conferences by UCB Pharma, Jazz, TheraNexus, Idorsia, Flamel and Bioprojet.

F Bughin, M Desplan, C Mestejanot, MC Picot, F Roubille, D Jaffuel, J Mercier, I Jaussent report no disclosures.

CRedit authorship contribution statement

F. Bughin: Investigation, Data curation, Writing - original draft. **M. Desplan:** Investigation, Data curation, Funding acquisition, Writing - review & editing. **C. Mestejanot:** Investigation, Data curation, Writing - review & editing. **M.C. Picot:** Methodology, Validation, Resources, Writing - review & editing. **F. Roubille:** Investigation, Data curation, Writing - review & editing. **D. Jaffuel:** Investigation, Data curation, Writing - review & editing. **J. Mercier:** Methodology, Validation, Writing - review & editing. **I. Jaussent:** Methodology, Formal analysis, Writing - review & editing. **Y. Dauvilliers:** Funding acquisition, Writing - original draft, Conceptualization, Supervision.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: <https://doi.org/10.1016/j.sleep.2020.02.008>.

References

- [1] Bradley TD, Floras JS. Obstructive sleep apnoea and its cardiovascular consequences. *The Lancet* 2009;373(9657):82–93.
- [2] Pichel F, Zamarrón C, Magán F, et al. Health-related quality of life in patients with obstructive sleep apnea: effects of long-term positive airway pressure treatment. *Respir Med* 2004;98(10):968–76.
- [3] Marin JM, Carrizo SJ, Vicente E, et al. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet* 2005;365(9464):1046–53. [https://doi.org/10.1016/S0140-6736\(05\)71141-7](https://doi.org/10.1016/S0140-6736(05)71141-7).
- [4] Lévy P, Kohler M, McNicholas WT, et al. Obstructive sleep apnoea syndrome. *Nat Rev Dis Primer* 2015;1:15015. <https://doi.org/10.1038/nrdp.2015.15>.
- [5] Newman AB, Spiekerman CF, Enright P, et al. Daytime sleepiness predicts mortality and cardiovascular disease in older adults. The cardiovascular health study research group. *J Am Geriatr Soc* 2000;48(2):115–23.
- [6] Sawyer AM, Gooneratne NS, Marcus CL, et al. A systematic review of CPAP adherence across age groups: clinical and empiric insights for developing CPAP adherence interventions. *Sleep Med Rev* 2011;15(6):343–56. <https://doi.org/10.1016/j.smrv.2011.01.003>.
- [7] McEvoy RD, Antic NA, Heeley E, et al. CPAP for prevention of cardiovascular events in obstructive sleep apnea. *N Engl J Med* 2016;375(10):919–31. <https://doi.org/10.1056/NEJMoa1606599>.
- [8] Jullian-Desayes I, Joyeux-Faure M, Tamisier R, et al. Impact of obstructive sleep apnea treatment by continuous positive airway pressure on cardiometabolic biomarkers: a systematic review from sham CPAP randomized controlled trials. *Sleep Med Rev* 2015;21:23–38. <https://doi.org/10.1016/j.smrv.2014.07.004>.
- [9] Recoquillon S, Pépin J-L, Vielle B, et al. Effect of mandibular advancement therapy on inflammatory and metabolic biomarkers in patients with severe obstructive sleep apnoea: a randomised controlled trial. *Thorax* October 2018. <https://doi.org/10.1136/thoraxjnl-2018-212609>.
- [10] Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. *Am J Respir Crit Care Med* 2002;165(9):1217–39.
- [11] Ong CW, O'Driscoll DM, Truby H, et al. The reciprocal interaction between obesity and obstructive sleep apnoea. *Sleep Med Rev* 2013;17(2):123–31. <https://doi.org/10.1016/j.smrv.2012.05.002>.
- [12] Chasens ER, Sereika SM, Houze MP, et al. Subjective and objective appraisal of activity in adults with obstructive sleep apnea. *J Aging Res* 2011;2011. <https://doi.org/10.4061/2011/751819>.
- [13] Edwards BA, Bristow C, O'Driscoll DM, et al. Assessing the impact of diet, exercise and the combination of the two as a treatment for OSA: a systematic review and meta-analysis. *Respirol Carlton Vic* 2019;24(8):740–51. <https://doi.org/10.1111/resp.13580>.
- [14] Epstein LJ, Kristo D, Strollo PJ, et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *J Clin Sleep Med* 2009;5:263–76 (03).
- [15] Mendelson M, Bailly S, Marillier M, et al. Obstructive sleep apnea syndrome, objectively measured physical activity and exercise training interventions: a systematic review and meta-analysis. *Front Neurol* 2018;9. <https://doi.org/10.3389/fneur.2018.00073>.
- [16] Bollens B, Reyckler G. Efficacy of exercise as a treatment for obstructive sleep apnea syndrome: a systematic review. *Compl Ther Med* 2018;41:208–14. <https://doi.org/10.1016/j.ctim.2018.10.002>.
- [17] Desplan M, Mercier J, Sabaté M, et al. A comprehensive rehabilitation program improves disease severity in patients with obstructive sleep apnea syndrome: a pilot randomized controlled study. *Sleep Med* 2014;15(8):906–12. <https://doi.org/10.1016/j.sleep.2013.09.023>.
- [18] Voorrips LE, Ravelli AC, Dongelmans PC, et al. A physical activity questionnaire for the elderly. *Med Sci Sports Exerc* 1991;23(8):974–9.
- [19] Nici L, Donner C, Wouters E, et al. American thoracic society/European respiratory society statement on pulmonary rehabilitation. *Am J Respir Crit Care Med* 2006;173(12):1390–413. <https://doi.org/10.1164/rccm.200508-1211ST>.
- [20] Spruit MA, Singh SJ, Garvey C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med* 2013;188(8):e13–64.
- [21] Cella M, Chalder T. Measuring fatigue in clinical and community settings. *J Psychosom Res* 2010;69(1):17–22. <https://doi.org/10.1016/j.jpsychores.2009.10.007>.
- [22] Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67(6):361–70. <https://doi.org/10.1111/j.1600-0447.1983.tb09716.x>.
- [23] Bastien CH, Vallières A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med* 2001;2(4):297–307.
- [24] Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM manual for the scoring of sleep and associated events. *J Clin Sleep Med* October 2012. <https://doi.org/10.5664/jcsm.2172>.
- [25] Puhon MA, Suarez A, Lo Cascio C, et al. Didgeridoo playing as alternative treatment for obstructive sleep apnoea syndrome: randomised controlled trial. *BMJ* 2006;332(7536):266–70. <https://doi.org/10.1136/bmj.38705.470590.55>.
- [26] Mendelson M, Lyons OD, Yadollahi A, et al. Effects of exercise training on sleep apnoea in patients with coronary artery disease: a randomised trial. *Eur Respir J* 2016;48(1):142–50. <https://doi.org/10.1183/13993003.01897-2015>.
- [27] Dolezal BA, Neufeld EV, Boland DM, et al. Interrelationship between sleep and exercise: a systematic review. *Adv Prev Med* 2017;2017. <https://doi.org/10.1155/2017/1364387>.
- [28] He K, Kapur VK. Sleep-Disordered breathing and excessive daytime sleepiness. *Sleep Med Clin* 2017;12(3):369–82. <https://doi.org/10.1016/j.jsmc.2017.03.010>.
- [29] Garbarino S, Guglielmi O, Sanna A, et al. Risk of occupational accidents in workers with obstructive sleep apnea: systematic review and meta-analysis. *Sleep*. 39(6):1211. doi:10.5665/sleep.5834
- [30] Ronksley PE, Hemmelgarn BR, Heitman SJ, et al. Obstructive sleep apnoea is associated with diabetes in sleepy subjects. *Thorax* 2009;64(10):834–9. <https://doi.org/10.1136/thx.2009.115105>.

- [31] Pamidi S, Knutson KL, Ghods F, et al. Depressive symptoms and obesity as predictors of sleepiness and quality of life in patients with REM-related obstructive sleep apnea: cross-sectional analysis of a large clinical population. *Sleep Med* 2011;12(9):827–31. <https://doi.org/10.1016/j.sleep.2011.08.003>.
- [32] Prasad B, Steffen AD, Van Dongen HPA, et al. Determinants of sleepiness in obstructive sleep apnea. *Sleep* February 2018. <https://doi.org/10.1093/sleep/zsx199>.
- [33] Dauvilliers Y, Arnulf I, Mignot E. Narcolepsy with cataplexy. *Lancet Lond Engl* 2007;369(9560):499–511. [https://doi.org/10.1016/S0140-6736\(07\)60237-2](https://doi.org/10.1016/S0140-6736(07)60237-2).
- [34] Baumann CR, Mignot E, Lammers GJ, et al. Challenges in diagnosing narcolepsy without cataplexy: a consensus statement. *Sleep* 2014;37(6):1035–42. <https://doi.org/10.5665/sleep.3756>.
- [35] Arand D, Bonnet M, Hurwitz T, et al. The clinical use of the MSLT and MWT. *Sleep* 2005;28(1):123–44. <https://doi.org/10.1093/sleep/28.1.123>.
- [36] Bardwell WA, Moore P, Ancoli-Israel S, et al. Fatigue in obstructive sleep apnea: driven by depressive symptoms instead of apnea severity? *Am J Psychiatr* February 2003. <https://doi.org/10.1176/appi.ajp.160.2.350>.
- [37] Kline CE, Crowley EP, Ewing GB, et al. The effect of exercise training on obstructive sleep apnea and sleep quality: a randomized controlled trial. *Sleep* 2011;34(12):1631–40. <https://doi.org/10.5665/sleep.1422>.
- [38] Findley LJ, Wilhoit SC, Suratt PM. Apnea duration and hypoxemia during REM sleep in patients with obstructive sleep apnea. *Chest* 1985;87(4):432–6.
- [39] Mokhlesi B, Finn LA, Hagen EW, et al. Obstructive sleep apnea during REM sleep and hypertension. results of the Wisconsin Sleep Cohort. *Am J Respir Crit Care Med* 2014;190(10):1158–67. <https://doi.org/10.1164/rccm.201406-1136OC>.
- [40] Chami HA, Gottlieb DJ, Redline S, et al. Association between glucose metabolism and sleep-disordered breathing during REM sleep. *Am J Respir Crit Care Med* 2015;192(9):1118–26. <https://doi.org/10.1164/rccm.201501-0046OC>.
- [41] Aurora RN, Crainiceanu C, Gottlieb DJ, et al. Obstructive sleep apnea during REM sleep and cardiovascular disease. *Am J Respir Crit Care Med* 2018;197(5):653–60. <https://doi.org/10.1164/rccm.201706-1112OC>.
- [42] Borel B, Provencher S, Saey D, et al. Responsiveness of various exercise-testing protocols to therapeutic interventions in COPD. *Pulm Med* 2013;2013:1–11. <https://doi.org/10.1155/2013/410748>.
- [43] Vivodtzev I, Mendelson M, Croteau M, et al. Physiological correlates to spontaneous physical activity variability in obese patients with already treated sleep apnea syndrome. *Sleep Breath* 2017;21(1):61–8. <https://doi.org/10.1007/s11325-016-1368-2>.