Interdisciplinary Weight Loss and Lifestyle Intervention for Obstructive Sleep Apnea: The INTERAPNEA Randomized Clinical Trial

International Doctoral Thesis / Tesis Doctoral Internacional

Interdisciplinary Weight Loss and Lifestyle Intervention for Obstructive Sleep Apnea: The INTERAPNEA Randomized Clinical Trial

Intervención Interdisciplinar para la Pérdida de Peso y Cambio de Hábitos de Vida en Apnea Obstructiva del Sueño: Ensayo Clínico Aleatorizado INTERAPNEA

PROGRAMA DE DOCTORADO EN PSICOLOGÍA
DEPARTAMENTO DE PERSONALIDAD, EVALUACIÓN Y TRATAMIENTO PSICOLÓGICO
FACULTAD DE PSICOLOGÍA
UNIVERSIDAD DE GRANADA
Almudena Carneiro Barrera
2021

Editor: Universidad de Granada. Tesis Doctorales
Autor: Almudena Carneiro Barrera
ISBN: 978-84-1117-193-9
URI: http://hdl.handle.net/10481/72069

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Que la Tesis Doctoral titulada "Interdisciplinary Weight Loss and Lifestyle Intervention for Obstructive Sleep Apnea: The INTERAPNEA Randomized Clinical Trial" que presenta **Dña. Almudena Carneiro Barrera** al superior juicio del Tribunal que designe la Universidad de Granada, ha sido realizado bajo mi dirección durante los años 2017-2021, siendo expresión de la capacidad técnica e interpretativa de su autor en condiciones tan aventajadas que le hacen merecedor del Título de Doctor, siempre y cuando así lo considere el citado Tribunal.

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La doctoranda Dña. Almudena Carneiro Barrera ha realizado la presente Tesis Doctoral como beneficiaria de un contrato con cargo al programa de Formación de Profesorado Universitario (FPU16/01093) del Ministerio de Ciencia, Innovación y Universidades y Ministerio de Educación y Formación Profesional, por resolución de 25 de septiembre de 2017, de la Secretaría de Estado de Educación, Formación Profesional y Universidades.

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Acknowledgements/Agradecimientos

RESEARCH PROJECT AND FUNDING

The present International Doctoral Thesis and, thus, the INTERAPNEA study was partially supported by the Spanish Ministry of Education and Vocational Training, through a grant provided to the author Almudena Carneiro Barrera (FPU16/01093); the University of Granada-LoMonaco S.L. Sleep Research Cathedra; the University of Granada Plan Propio de Investigación 2016 – Excellence actions: Unit of Excellence on Exercise and Health (UCEES); and the Regional Ministry of Economy, Knowledge, Enterprise and Universities (CECEU) of Andalusia (European Regional Development Funds; SOMM17/6107/UGR).

ABBREVIATIONS

AASM: American Academy of Sleep Medicine

AHI: apnea-hypopnea index

ALT: alanine transaminase

AST: aspartate aminotransferase

BDI-FS: Beck Depression Inventory-Fast Screen

BMI: body-mass index

BP: blood pressure

CI: confidence interval

CIMCYC: Mind, Brain, and Behavior Research Center

CPAP: continuous positive airway pressure

CRF: cardiorespiratory fitness

DXA: dual energy X-ray absorptiometry

EDS: excessive daytime sleepiness

ESS: Epworth Sleepiness Scale

FBC: Food Behavior Checklist

FOSQ: Functional Outcomes of Sleep Questionnaire

GHQ: General Health Questionnaire

HDL-C: high-density lipoprotein cholesterol

HOMA-IR: homeostasis model assessment of insulin resistance

IFIS: International Fitness Scale

iMUDS: Sport and Health University Research Institute

ISAK: International Society for the Advancement of Kinanthropometry

LDL-C: low-density lipoprotein cholesterol

MEDAS: Mediterranean Diet Adherence Screener

ODI: oxygen desaturation index

OSA: obstructive sleep apnea

PSG: polysomnography

PSQI: Pittsburgh Sleep Quality Index

RCT: randomized controlled trial

REM: rapid eye movement

SaO_2: oxygen saturation

SAQLI: Sleep Apnea Quality of Life

SD: standard deviation

SF-36: Medical Outcomes Study 36-Item Short-Form Health Survey

STAI: State-Trait Anxiety Inventory

STDI: State-Trait Depression Inventory

T2DM: type 2 diabetes mellitus

VO_{2max}: maximum oxygen uptake

WHO: World Health Organization

γ-GT: γ-glutamyl transferase

ABSTRACT

Obstructive sleep apnea (OSA), characterized by recurrent sleep-state dependent upper-airway collapse with obesity as the leading attributable cause, is a major public health problem owing not only to its high and increasing prevalence — up to one billion adults globally — but also to its wide spectrum of clinical and socioeconomic consequences. Although continuous positive airway pressure (CPAP) is the first-line treatment for this condition, CPAP is a chronic day-to-day treatment, adherence rates are suboptimal, and long-term benefits beyond reduction of upper-airway occlusions remain uncertain. Conversely, weight loss through alternative or combined behavioral interventions appears to substantially improve OSA and coexisting conditions in adults with moderate-to-severe OSA. However, weight loss and behavioral approaches, although suggested, are still not a standard recommendation in existing clinical practice guidelines owing to the modest quality of evidence and methodological weaknesses found in this field of research.

The main aim of this International Doctoral Thesis was to test the efficacy of an eight-week interdisciplinary weight loss and lifestyle intervention combined with usual-care (i.e., CPAP), as compared with usual-care alone, on OSA severity and OSA-related comorbidities among adults with moderate-to-severe OSA and overweight/obesity.

To this end, the Interdisciplinary Weight Loss and Lifestyle Intervention for Obstructive Sleep Apnea (INTERAPNEA) randomized, parallel-group, open-label trial was designed and conducted between April 2019 and October 2021. A total of 89 participants with CPAP-treated moderate-to-severe OSA and overweight/obesity were randomly assigned to a usual-care/control group (49 participants), or an eight-week weight loss and lifestyle intervention involving nutritional behavior change, aerobic exercise, sleep hygiene, and alcohol and tobacco cessation, combined with usual-care (40 participants). The primary outcome was the change in the number of apneas and hypopneas per hour of sleep (apnea-hypopnea index; AHI) at intervention endpoint and six months after intervention. Secondary outcomes comprised changes in other OSA sleep-related outcomes, body weight and composition, cardiometabolic risk, and health-related quality of life. Additional study outcomes included daily functioning and mood, physical fitness and dietary behavior.

According to results, the weight loss and lifestyle intervention group had a clinically meaningful reduction in AHI of 51% at intervention endpoint; 15% of participants attaining complete remission of OSA, and 45% no longer requiring CPAP therapy. After six months, the reduction in AHI was 57%; the complete remission of OSA being attained by 29% of participants; 62% no longer requiring CPAP therapy. Similarly, the intervention group notably exhibited 7%, 19% and 26% reductions in body weight, fat mass and visceral adipose tissue at 6 months after intervention, respectively. Furthermore, these results were strengthened by the evidence of significant improvements in key cardiometabolic outcomes involved in the pathogenesis of cardiovascular diseases. Clinically significant improvements in daily functioning and mood, physical fitness and dietary behavior outcomes were also found in the intervention group as compared with the control group.

In conclusion, this International Doctoral Thesis and thus, the INTERAPNEA trial, demonstrates that an interdisciplinary weight loss and lifestyle intervention involving adults with CPAP-treated moderate-to-severe OSA and overweight/obesity resulted in clinically meaningful and sustainable improvements not only in OSA severity and comorbidities but also in health-related quality of life, daily functioning and mood, physical fitness and dietary behavior. Given the high prevalence of OSA, its complex and reciprocal interaction with obesity, and the fact that both conditions are readily treatable through an integrated behavioral intervention, health-care providers and policy-makers should, at the very least, consider this approach as a central strategy to comprehensively address the staggering impact of OSA on the health and welfare of our society.

RESUMEN

La apnea obstructiva del sueño (AOS), caracterizada por un colapso recurrente de las vías aéreas superiores durante el sueño, siendo la obesidad la principal causa atribuible, es un importante problema de salud pública debido no sólo a su alta y creciente prevalencia — hasta mil millones de adultos en todo el mundo — sino también a su amplio espectro de consecuencias clínicas y socioeconómicas. Aunque la presión positiva continua en las vías respiratorias (CPAP) es el tratamiento estándar, CPAP es un tratamiento crónico diario, las tasas de adherencia son subóptimas y los beneficios a largo plazo más allá de la reducción de las oclusiones de las vías respiratorias superiores siguen siendo inciertos. Por el contrario, la pérdida de peso a través de intervenciones conductuales alternativas o combinadas parece mejorar sustancialmente la gravedad AOS y comorbilidades en adultos con AOS moderada-severa. Sin embargo, la pérdida de peso y los enfoques conductuales, aunque sugeridos, todavía no son una recomendación estándar en las directrices de práctica clínica existentes debido a la modesta calidad de la evidencia y a las debilidades metodológicas encontradas en este campo de investigación.

El objetivo principal de esta Tesis Doctoral Internacional fue evaluar la eficacia de una intervención interdisciplinar de ocho semanas para la pérdida de peso y el cambio del estilo de vida combinada con la atención habitual (es decir, CPAP), en comparación con la atención habitual sola, en la gravedad AOS (es decir, el número de apneas e hipopneas por hora de sueño; índice de apnea-hipopnea [IAH]) y comorbilidades relacionadas en adultos con AOS moderada- grave y sobrepeso/obesidad.

Con este fin, el ensayo controlado y aleatorizado de grupos paralelos *Interdisciplinary Weight Loss and Lifestyle Intervention for Obstructive Sleep Apnea* (INTERAPNEA) se diseñó y llevó a cabo entre abril de 2019 y octubre de 2021. Un total de 89 participantes con AOS moderada-grave tratados con CPAP y sobrepeso/obesidad se asignaron aleatoriamente a un grupo de atención habitual/control (49 participantes), o a una intervención de ocho semanas de pérdida de peso y estilo de vida que implicaba un cambio de comportamiento nutricional, ejercicio aeróbico, higiene del sueño y abandono del alcohol y el tabaco, combinado con la atención habitual (40 participantes). La variable principal fue el cambio en el número de apneas e hipopneas por hora de sueño (índice de apnea-hipopnea; IAH) tanto al finalizar la intervención como a los seis meses después de la intervención. Variables secundarias incluyeron cambios en otros variables relacionadas con el sueño, peso y composición corporal, riesgo cardiometabólico y calidad de vida relacionada con la salud. Otras variables adicionales del estudio incluyeron el funcionamiento diario y estado de ánimo, aptitud física y comportamiento dietético.

De acuerdo con los resultados, el grupo de intervención de pérdida de peso y cambio del estilo de vida tuvo una reducción clínicamente significativa del IAH del 51% tras la intervención; el 15% de los participantes alcanzando remisión completa de AOS y el 45% no requiriendo continuación con el tratamiento con CPAP. Después de seis meses, la reducción del IAH fue del 57%; el 29% de los participantes consiguieron remisión completa de AOS; y el 62% pudo prescindir de tratamiento con CPAP. Similarmente, a los seis meses después de la intervención, el grupo de intervención mostró reducciones significativas del 7%, 19% y 26% en peso corporal, masa grasa y tejido adiposo visceral, respectivamente. Además, estos resultados se vieron fortalecidos por la evidencia de mejoras significativas en variables cardiometabólicas implicadas en la patogénesis de enfermedades cardiovasculares. Así mismo, el grupo de intervención también mostró mejoras clínicamente significativas en el funcionamiento diario y estado de ánimo, aptitud física y comportamiento dietético.

En conclusión, esta Tesis Doctoral Internacional y, por tanto, el ensayo INTERAPNEA, demuestra que una intervención interdisciplinar para la pérdida de peso y el cambio del estilo de vida en adultos con AOS moderada-grave tratados con CPAP y sobrepeso/obesidad dio lugar a mejoras clínicamente significativas y sostenibles no sólo en la gravedad de AOS y comorbilidades, sino también en la calidad de vida relacionada con la salud, funcionamiento diario y estado de ánimo, aptitud física y comportamiento dietético. Dada la alta prevalencia de la AOS, su interacción compleja y recíproca con la obesidad, y el hecho de que ambas condiciones son fácilmente tratables a través de una intervención conductual integrada, los proveedores de atención médica y responsables de la formulación de políticas de salud deberían, al menos, considerar este enfoque como una estrategia central para abordar de manera integral el impacto asombroso de la AOS en la salud y el bienestar de nuestra sociedad.

INTRODUCTION

CHAPTER 1

Weight loss and lifestyle interventions for obstructive sleep apnea in adults: Systematic review and meta-analysis

(**Study 1**)

ABSTRACT

Lifestyle interventions addressing diet, exercise-training, sleep hygiene, and/or tobacco/alcohol cessation are recommended in the management of obstructive sleep apnea (OSA). Yet, their effectiveness on this condition still requires further research. This systematic review and meta-analysis was aimed at establishing 1) the effectiveness of lifestyle interventions on apnea-hypopnea index (AHI), oxygen desaturation index (ODI), excessive daytime sleepiness (EDS), and secondary OSA measures among adults, and 2) which intervention characteristics may drive the greatest improvements. A systematic search of studies was conducted using CINAHL, ProQuest, Psicodoc, Scopus, and Web of Science, from inception to April 2018. Standardized mean differences were calculated using the inverse variance method and random-effects models. The meta-analyses of 13 randomized controlled trials and 22 uncontrolled before-and-after studies (1,420 participants), revealed significant reductions on AHI (d = -0.61 and -0.46, respectively), ODI (d = -0.61 and -0.46) and EDS (d = -0.41 and -0.49). Secondary OSA outcomes were also improved after interventions. However, effectiveness of interventions differed depending on their components, OSA severity, and gender. Thus, until future research further supports the differential effectiveness among lifestyle interventions on OSA, those addressing weight loss through diet and exercise-training may be the most effective treatments for male patients with moderate-severe OSA.

Introduction

Obstructive sleep apnea (OSA), characterized by recurrent episodes of upper airway obstructions, has become a prime focus in medical and clinical research due to its wide range of adverse health consequences and increasing prevalence in recent years. Hypoxemia, hypercapnia, increased sympathetic activity and sleep fragmentation are the immediate consequences of airflow blockage events occurred while sleeping.[1] These physiological events, in turn, may lead to physical, cognitive and behavioral disturbances such as cardio-metabolic disorders,[2] memory and attention deficits,[3] and impaired daytime functioning[4] due to excessive daytime sleepiness (EDS). Therefore, OSA is a high-risk factor to morbidity and mortality from all-causes,[5] including workplace[6] and road accidents[7] with EDS as the core cause.

According to a recently published systematic review by Senaratna et al.,[8] the overall population prevalence of OSA in adults ranges from 9% to 38%, higher in the male gender. This prevalence is even greater in the elderly and in those who are overweight; a body-mass index (BMI) ≥ 25 kg/m^2 being the attributable cause of OSA in at least 41% of the patients.[9] Sleep restriction and fragmentation produced in OSA, in turn, are risk factors for weight gain and metabolic syndromes[10,11] so there is a reciprocal relationship between OSA and obesity. Thus, patients with high-risk of OSA may be middle-aged men with obesity and a sedentary lifestyle, who exhibit adverse health behaviors such as tobacco and/or alcohol consumption.[12]

The gold-standard treatment for OSA is continuous positive airway pressure (CPAP),[1] a mechanical device which prevents the episodes of airway blockage, such that it reduces the apnea-hypopnea index (AHI) and in turn, the symptoms and consequences of this condition.[13–16] However, not only has it been well-evidenced that CPAP compliance is worryingly low—up to 75% of patients with OSA tend to discontinue CPAP usage[17]—but it also does not address core high-risk OSA factors such as obesity and related adverse lifestyles. Therefore, the American Academy of Sleep Medicine (AASM) recommends non-surgical and non-pharmacological interventions focused on weight loss and lifestyle change, as either alternative or combined patient-care strategy.[1,18] Such interventions may include weight loss through hypocaloric diet and moderate exercise, smoking and alcohol avoidance, and sleep hygiene.[1,18]

Previous systematic reviews and meta-analyses about the effects of these interventions on OSA have been conducted,[15,19–24] concluding that weight loss is effective in reducing primary OSA outcomes (AHI; oxygen desaturation index, ODI; and EDS). However, there were a reduced number of studies included in these meta-analyses, so the standardization of results was not feasible. They have also only focussed on weight loss interventions; not considering the potential effects of other lifestyle components such as sleep hygiene and tobacco/alcohol cessation. Furthermore, the effects of lifestyle management on OSA have been analysed solely considering primary OSA outcomes; without consideration of other common OSA parameters such as arousal index, oxygen saturation (SaO_2) mean and nadir, sleep architecture and sleep

continuity. Lastly, specific intervention and participant characteristics which reach the greatest effectiveness on OSA have not yet been clarified.

Our systematic review and meta-analysis was aimed at establishing whether lifestyle interventions including diet, exercise-training, sleep hygiene, and/or smoking and alcohol cessations are effective in the enhancement of OSA in adults. Particularly, we hypothesised that lifestyle interventions would be effective in reducing OSA parameters such as AHI, ODI, EDS, and other common OSA outcomes (arousal index, SaO_2 mean, SaO_2 nadir, sleep efficiency, rapid eye movement [REM] sleep, light sleep and deep sleep). We also pursued to investigate, and so elucidate, those intervention components and characteristics which may drive the greatest improvements in OSA. In this respect, we expected that interventions addressing several components of lifestyle change, on male patients with severe OSA, would accomplish the greatest reductions of OSA symptomatology.

Methods

This systematic review and meta-analysis protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42018102740). To follow the quality of the design, implementation and reporting of this meta-analysis, we adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[25] (see Table S1) and relevant methodological references[26–29] throughout the entire process.

Search strategy

A systematic search of relevant studies was conducted using CINAHL, ProQuest (including Health & Medical Collection, MedLine, Nursing & Allied Health Database, ProQuest Dissertations & Theses Global, PsycARTICLES, PsycEXTRA, Psychology Database, PsycINFO and Social Science Database), Psicodoc, Scopus, and Web of Science, from inception to April 2018. The set of search terms used included apnea, treatment, lifestyle, diet, exercise, alcohol, tobacco, and sleep hygiene; with synonymous and truncation operators adapted to each database (see Table S2 for specific search strategies). We did not restrict the search by publication status or date, but by language (English or Spanish) and type of document (article, dissertation/thesis, and any other document with empirical data). We also manually searched the reference lists of previous meta-analyses and retrieved studies.

Study selection criteria

Randomized controlled trials (RCTs) and uncontrolled before-and-after studies (due to the reduced number of RCTs included in previous systematic reviews) were eligible to be included upon meeting the following criteria: a) all participants were adults (aged ≥ 18 years) diagnosed with OSA (AHI ≥ 5); b) the intervention program was based on lifestyle habits such as diet, exercise-training, sleep hygiene, cessation of alcohol and/or smoking (combined or non-combined with CPAP or mandibular advancement devices with the condition that these mechanical devices were not used

during the objective sleep assessments); c) the comparisons were between lifestyle change intervention and non-intervention or usual care; d) provided outcome measures of at least one of the most common OSA parameters; and e) the reported statistical data allowed the calculation of effect sizes. The exclusion criteria were: a) patients with other mental or physical conditions except comorbid OSA disorders (e.g., cardio-metabolic disorders or anxious-depressive symptoms); b) clinical case studies; c) previous or current surgical or pharmacological interventions for OSA; d) trials reported in other languages rather than English or Spanish.

Based on the selection criteria, screening by title and abstract was independently performed by two authors (A. C. and A. D.). Disagreements between authors were resolved by discussion and, if needed, a third author´s (A. G.) final decision was solicited. Full manuscripts of potential studies were obtained and screened for the final inclusion and data extraction following the same procedure.

Data extraction and study outcomes

Following a codebook and a coding protocol previously produced to this aim, the data extraction of the final selected studies was conducted in a standardized form by two independent coders (A. C. and A. D.). To ensure the reliability of this process, each coder performed the data extraction of all studies included in the meta-analyses. Discrepancies were resolved by consensus with a third author (A. G.). Inter-coder reliability was adequate with kappa coefficients ranging from 0.85 to 1 and intra-class correlations between 0.95 and 1. Apart from the study outcomes, the standardized form contained author´s names, country and year of publication (extrinsic variables); participants and treatment characteristics (substantive variables); and methodological variables. Authors of relevant studies were contacted in the case of unreported required data.

One of the primary outcomes of interest was AHI, defined by the AASM[30] as the number of apnea (airflow reduction ≥ 90%) and hypopnea (airflow reduction ≥ 30%) episodes per hour of sleep, each episode lasting more than 10 seconds and being accompanied by oxygen desaturation or arousal. The other two primary outcomes were EDS (measured by the Epworth sleepiness scale[31]) and ODI (defined as the number of oxygen desaturations ≥ 4%/hour). As secondary outcomes in this meta-analysis we included arousal index (defined as the number of arousal/hour), SaO_2 mean (average of oxygen saturation), SaO_2 nadir (minimum oxygen saturation), sleep efficiency (total sleep time/total time in bed), % REM sleep, % deep sleep (N3 stage) and % light sleep (N1 and N2 stages), all measured by polysomnography.

Risk of bias and quality assessment

All trials included in the meta-analysis were assessed for methodological quality using relevant items from the Cochrane´s risk-of-bias tool[32] and PEDro scale.[33] The assessment of RCTs included: specification of eligibility criteria, random allocation to groups, concealed allocation, inter-group similarity in main study outcomes at baseline, blinding (blinding of

outcome assessors and data analysts exclusively, as blinding of participants and therapists is not possible in these studies), sample drop-out rate (≤ 15%), intention to treat analysis, reported comparisons between groups, and report of effect size coefficients or other parameters which make calculation of them possible. Uncontrolled before-and-after studies were similarly assessed for methodological quality adapting the items from the scale or tool. Details of this quality assessment can be found in Table S3.

Statistical analysis

RCTs and uncontrolled before-and-after studies were analysed independently. However, all intervention groups from RCTs were also included in the uncontrolled before-and-after studies meta-analysis. Standardized effect size coefficients from RCTs were computed as the mean difference between the mean change in intervention and control groups, from baseline to post-intervention, divided by mean baseline standard deviation[34]: $d = c(df_{E,C}) \cdot [((\overline{X}_{pre,E} - \overline{X}_{pos,E}) - (\overline{X}_{pre,C} - \overline{X}_{pos,C})) / \overline{S}_{pre}]$. Regarding uncontrolled before-and-after studies, the mean change from baseline to post-intervention divided by baseline standard deviation was the calculated standardized effect size coefficient for each intervention group[35]: $d = c(df) \cdot [(\overline{X}_{pre,E} - \overline{X}_{pos,E}) / S_{pre}]$. Both coefficients included $c(df_{E,C})$ and $c(df)$, correction factors for small samples[36] (see all equations used in Table S4). The inverse variance method was used in both cases (RCTs and uncontrolled before-and-after studies) for the weighting of studies. Additionally, we calculated the raw (unstandardized) mean difference for before-and-after studies ($\overline{X}_{pre,E} - \overline{X}_{pos,E}$) and RCTs ($(\overline{X}_{pre,E} - \overline{X}_{pos,E}) - (\overline{X}_{pre,C} - \overline{X}_{pos,C})$), using the weights obtained in our standardized meta-analysis to estimate the pooled mean difference in each outcome.

Independent effect size coefficients from studies and outcomes were combined and analysed using the DerSimonian and Laird´s random-effects model.[37] Weighted standardized mean change from baseline to post-intervention was the pooled effect size of each outcome with confidence interval (CI) set at 95%.

In order to estimate potential statistical heterogeneity, Q test and I^2 index (moderate heterogeneity if $I^2 \geq 50\%$, $p < 0.05$) were calculated. Given the heterogeneity between studies, potential moderators of the effect sizes were analysed using meta-regression analyses for continuous variables and ANOVAs for the qualitative variables. Each moderator was analysed individually due to the reduced number of groups in some outcomes. Additional analysis of sensitivity was performed to assess the influence of each individual study on the pooled effect sizes. Potential publication bias was also analysed using Egger's test[38] and Rosenthal method.[39] Rosenthal method (*fail-safe N index*) calculates the number of studies with null results needed to be included so that the significance level drops to an alpha level of 0.05. Risk of bias/methodological quality of included primary studies was analysed as a potential qualitative (medium/high quality) or continuous (total quality score) moderator variable using ANOVA and meta-regression analyses in order to assess its

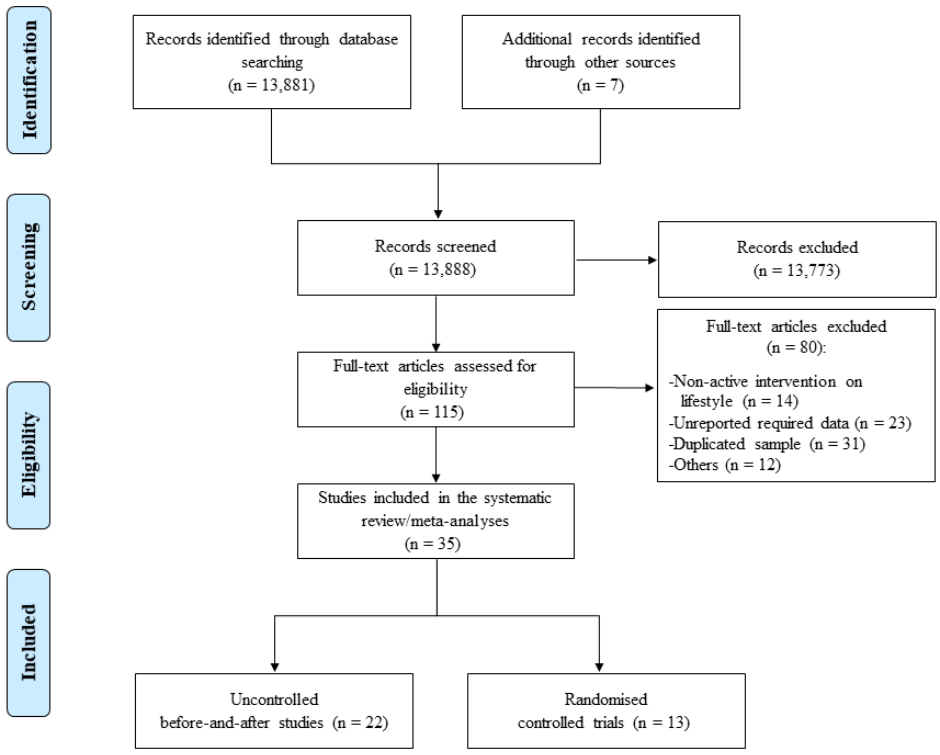
impact on effect sizes for primary OSA outcomes. All statistical analyses were performed using metaphor package[40] from R statistic program.[41]

Results

Search results

The systematic search yielded 13,889 studies. After removal of duplicates and screening by title and abstract, 115 eligible full-text documents were evaluated for the final inclusion in the meta-analysis. The flowchart of the search and selection of studies is shown in Fig. 1. A total of 13 RCTs[42–54] and 22 uncontrolled before-and-after studies[55–76] were selected for inclusion. One non-randomized study[49] was considered an RCT as there were not differences between groups at baseline. Additionally, one of the RCTs[47] was treated as an uncontrolled before-and-after study due to lack of reported control group results (even after attempting to contact authors); one RCT[53] was divided into two independent samples as there were two intervention groups (adjusting the control group such that each intervention group was compared to half of the original control group); and one uncontrolled before-and-after study[74] was also split into two as there were two different intervention groups. Original studies including comparisons between surgical/medical and lifestyle intervention were considered as uncontrolled before-and-after studies so that we only selected the lifestyle intervention arm. Thus, a total of 13 RCT groups and 37 single intervention groups (13 intervention groups from RCTs + 24 uncontrolled before-and-after groups) were included in the final meta-analyses.

Figure 1. Flow-Chart of the search and selection of studies



Study characteristics

General participant and treatment characteristics of all included studies are summarized in Table 1. The total sample comprised 1,420 participants (n = 399 control and 441 intervention from RCTs; and 580 from treated as before-and-after studies), being 26.70% women (standard deviation = 23.48) and the mean age 52.31 (standard deviation = 10.49). Most of the samples had moderate to severe OSA (n = 14), or from mild to severe OSA (n = 12). The majority of studies were originally from Brazil (n = 8), the United States of America (n = 5), and Finland (n = 4); the others being from Australia, Sweden, China, Japan, Norway, Canada, Spain, France, Greece, the United Kingdom, and Turkey. Components of lifestyle interventions included dietary weight loss (n = 7), moderate exercise-training (n = 9), sleep hygiene (n = 3), weight loss through a combination of hypocaloric diet and moderate exercise-training (n = 14), exercise-training and sleep hygiene (n = 1), or diet and sleep hygiene (n = 1). We did not find any study with an active intervention for alcohol or smoking cessation on patients with OSA. Interventions had an average duration of 20.40 weeks (ranging from 4 to 96) and were mostly performed in group modality.

Effects of lifestyle intervention on primary outcomes: AHI, ODI, and EDS

Effects of lifestyle intervention on AHI from 13 RCTs and 31 before-and-after intervention groups are shown in Fig. 2. The overall pooled effect size of RCTs on AHI was -0.61 (95% CI = -0.84 to -0.38), meaning that AHI was significantly reduced by lifestyle interventions (p < 0.0001). Differences between RCTs yielded substantial heterogeneity ($Q_{(12)}$ = 42.21, p < 0.0001; I^2 = 71.57%). Mean effect size of before-and-after intervention groups on AHI was -0.46 (-0.58 to -0.34); a significant reduction of apnea/hypopnea episodes (p < 0.0001). High heterogeneity was also found across these groups ($Q_{(30)}$ = 109.21, p < 0.0001; I^2 = 72.53%). Mean reductions on AHI, according to the pooled raw mean differences, were -9.11 (mean AHI at baseline = 30.24) for RCTs, and -8.36 (mean AHI at baseline = 31.36) for before-and-after studies.

Fig. 3 shows the effects of lifestyle intervention on ODI, from four RCTs and 13 before-and-after intervention groups. The mean effect size of RCTs on ODI was -0.61 (-0.99 to -0.22), ODI being significantly reduced by the interventions (p = 0.002). Heterogeneity between studies was high ($Q_{(3)}$ = 11, p = 0.012; I^2 = 72.73%). Similarly, the effects of lifestyle interventions from before-and-after intervention groups was highly significant (p < 0.0001), the mean effect size being -0.46 (-0.62 to -0.30). Heterogeneity between effect sizes was also found to be high ($Q_{(12)}$ = 38.34, p = 0.0001; I^2 = 68.7%). According to the pooled raw mean differences, mean reductions

Table 1. Characteristics of studies included

First author	Country	Design	Intervention	Duration (weeks)	*N*	% Females	Age (SD)	OSA severity[a]	% CPAP[b]
Ackel-d'elia et al., 2012[42]	Brazil	RCT	Exercise-training +Sleep hygiene	12	47 (n_C = 22, n_E = 25)	0	49.05 (8.22)	2+3	100
Barnes et al., 2009[55]	Australia	Uncontrolled	Diet+Exercise-training	16	12	75	42.3 (10.4)	1+2	NR
Cavagnolli et al., 2014[56]	Brazil	Uncontrolled	Exercise-training	8	17	0	40.5 (10.41)	1+2+3	0
Cayanan et al., 2017[57]	Australia	Uncontrolled	Diet	8	44	26	49.4 (9.4)	1+2+3	57.14
Chakravorty et al., 2002[58]	UK	Uncontrolled	Sleep hygiene	12	21	NR	52 (9.6)	2+3	0
Desplan et al., 2014[59]	France	Uncontrolled	Diet+Exercise-training	4	13	NR	35-70	2+3	0
Dixon et al., 2012[60]	Australia	Uncontrolled	Diet+Exercise-training	24	30	40	50 (8.2)	2+3	100
Dobrosielski et al., 2015[61]	USA	Uncontrolled	Diet+Exercise-training	12	25	60	67 (4)	1+2+3	0
Fernandes et al., 2015[43]	Brazil	RCT	Diet	16	29 (n_C = 15, n_E = 14)	47.62	41.48 (9.06)	1+2+3	NR
Foster et al., 2009[44]	USA	RCT	Diet+Exercise-training	48	264 (n_C = 139, n_E = 125)	59	61.3 (6.5)	1+2+3	NR
Fredheim et al., 2013[62]	Norway	Uncontrolled	Diet+Exercise-training	48	40	62	51.3 (8.9)	1+2+3	NR
Fujii et al., 2010[63]	Japan	Uncontrolled	Diet+Exercise-training	16	10	0	50.7 (7.8)	3	100
Guilleminault et al., 2008[64]	USA	Uncontrolled	Sleep hygiene	9	15	66.67	30.9 (5)	1	NR
Igelström et al., 2017[45]	Sweden	RCT	Diet+Exercise-training	24	86 (n_C = 44, n_E = 42)	17.4	54.9 (11.8)	2+3	100
Iguchi et al., 2013[65]	Japan	Uncontrolled	Diet+Exercise-training	12	60	60	47.81 (10.06)	1+2+3	NR
Johansson et al., 2009[46]	Sweden	RCT	Diet	9	63 (n_C = 33, n_E = 30)	0	49 (7.3)	2+3	100
Kajaste et al., 2004[66]	Finland	Uncontrolled	Diet	96	31	0	49.11 (7.89)	1+2+3	54.84
Kansanen et al., 1998[67]	Finland	Uncontrolled	Diet	12	15	6.67	52 (9)	1+2+3	0
Karlsen et al., 2017[47]	Norway	Uncontrolled	Exercise-training	12	15	25	51 (9)	2+3	78.57
Kline et al., 2011[48]	USA	RCT	Exercise-training	12	43 (n_C = 16, n_E = 27)	44	46.9 (1.2)	2+3	0
Lam et al., 2007[68]	China	Uncontrolled	Sleep hygiene	10	33	21	47 (11.49)	1+2	0
Lojander et al., 1998[69]	Finland	Uncontrolled	Diet	48	24	4.17	48 (7)	1+2+3	0
Maki-Nunes et al., 2015[49]	Brazil	RCT	Diet+Exercise-training	16	24 (n_C = 8, n_E = 16)	29.17	49.33 (8.64)	2+3	NR

(*continued*)

Table 1. Characteristics of studies included (continued)

McDoniel et al., 2010[70]	USA	Uncontrolled	Diet+Exercise-training	12	11	45.45	49.1 (8.2)	3	90.91
Mendelson et al., 2016[50]	Canada	RCT	Exercise-training	4	34 (n_C = 17, n_E = 17)	11.76	61.7 (10.15)	2+3	NR
Monasterio et al., 2001[71]	Spain	Uncontrolled	Diet+Sleep hygiene	12	65	9	54 (9)	1	0
Nerfeldt et al., 2008[72]	Sweden	Uncontrolled	Diet+Exercise-training	20	33	27.27	52 (31-68)	1+2+3	57.58
Ng et al., 2015[51]	China	RCT	Diet	48	104 (n_C = 43, n_E = 61)	25	51.63 (9.18)	2+3	41.3
Norman et al., 2000[73]	USA	Uncontrolled	Exercise-training	24	11	18.18	48 (9)	1+2	63.64
Papandreou et al., 2012 (1)[74]	Greece	Uncontrolled	Diet+Exercise-training	24	20	15	45.8 (14.2)	2+3	100
Papandreou et al., 2012 (2)[74]	Greece	Uncontrolled	Diet+Exercise-training	24	20	15	52.2 (10.5)	2+3	100
Schütz et al., 2013[75]	Brazil	Uncontrolled	Exercise-training	8	7	0	42.28 (8.28)	2+3	0
Sengul et al., 2011[52]	Turkey	RCT	Exercise-training	12	20 (n_C = 10, n_E = 10)	0	54.4 (6.57)	1+2	NR
Servantes et al., 2012 (1)[53]	Brazil	RCT	Exercise-training	12	23 (n_C = 6, n_E = 17)	53.32	51.39 (9.01)	1+2+3	NR
Servantes et al., 2012 (2)[53]	Brazil	RCT	Exercise-training	12	23 (n_C = 6, n_E = 17)	53.32	52.08 (9.26)	1+2+3	NR
Tuomilehto et al., 2009[54]	Finland	RCT	Diet+Exercise-training	48	81 (n_C = 41, n_E = 40)	26	50 (9)	1	0
Ueno et al., 2009[76]	Brazil	Uncontrolled	Exercise-training	16	8	12.5	58 (2)	2+3	NR

Abbreviations: CPAP, continuous positive airway pressure; n_C, *n* control group; n_E, *n* intervention group; NR, not reported; OSA, obstructive sleep apnea; RCT, randomised controlled trial; SD, standard deviation; Uncontrolled, uncontrolled before-and-after studies.

[a] 1 = mild; 2 = moderate; 3 = severe.

[b] CPAP was not used during the pre and post-intervention objective sleep assessments.

Figure 2. Forest plot of the standardized mean differences (d) for apnea/hypopnea index (AHI), grouped by uncontrolled before-and-after studies and randomized controlled trials (RCTs) A negative value means a reduction of the outcome after intervention. CI = confidence interval

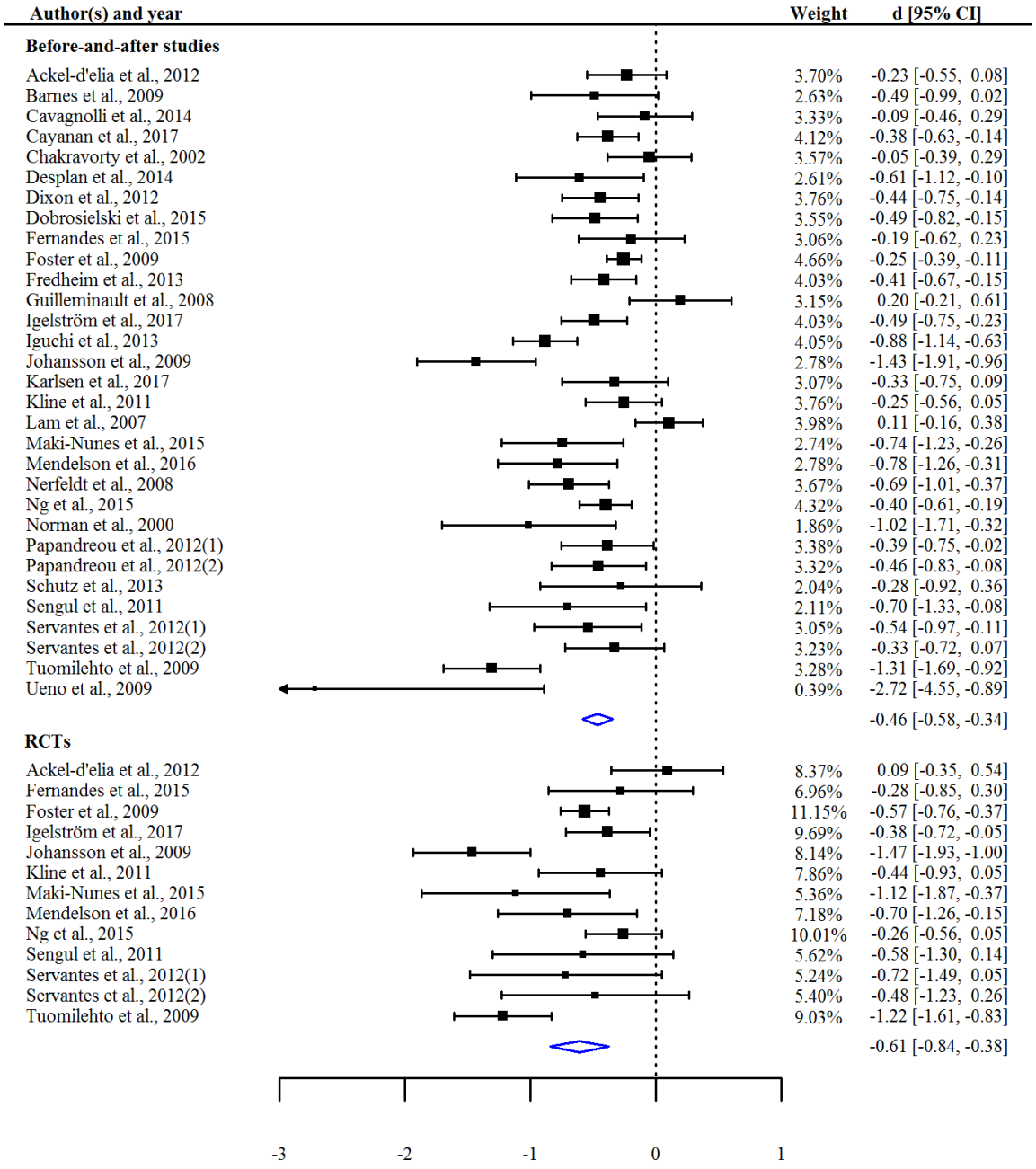
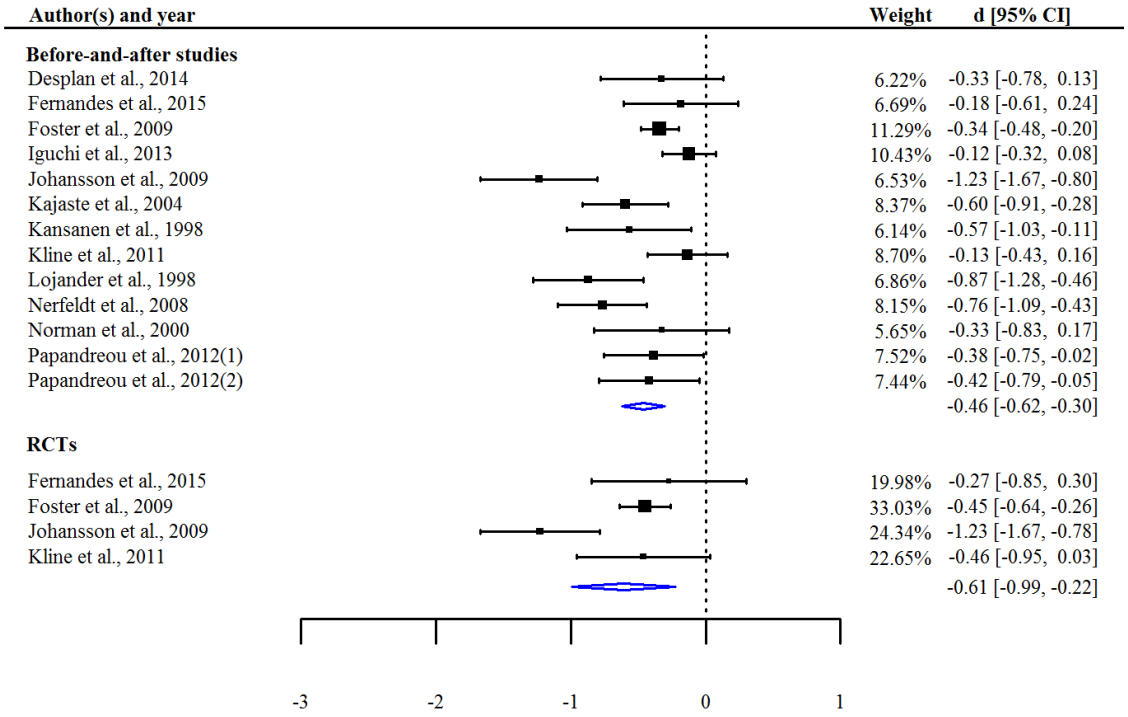


Figure 3. Forest plot of the standardized mean differences (d) for oxygen desaturation index (ODI), grouped by uncontrolled before-and-after studies and randomized controlled trials (RCTs). A negative value means a reduction of the outcome after intervention. CI = confidence interval



on ODI were -11.23 (mean ODI at baseline = 21.89) for RCTs, and -11.14 (mean ODI at baseline = 29.94) for before-and-after studies.

Effects of lifestyle interventions on EDS are shown in Fig. 4. The mean effect size of four RCTs on EDS was -0.41 (-0.68 to -0.14), moderately enhancing patients' daytime sleepiness (p = 0.003). Studies were moderately heterogeneous ($Q_{(3)}$ = 5.45, p = 0.141; I^2 = 44.97%). Similarly, mean effect size of 17 before-and-after intervention groups on EDS was -0.49 (-0.60 to -0.38), significantly reducing it (p < 0.0001). Heterogeneity was also found between these studies ($Q_{(16)}$ = 26.36, p = 0.049; I^2 = 39.31%). Mean reductions on EDS, according to the pooled raw mean differences, were -3.05 (mean EDS at baseline = 10.04) for RCTs, and -2.33 (mean EDS at baseline = 10.62) for before-and-after studies.

See raw data of each included study on primary OSA outcomes in Tables S5 and S6.

Effects of lifestyle intervention on secondary outcomes

Effects of lifestyle intervention on secondary outcomes are presented in Table 2. Arousal index and sleep efficiency were significantly enhanced by lifestyle interventions in the RCTs (d = -0.96 and 0.73, respectively). The rest of the secondary outcomes were also enhanced but in a non-significant manner. Regarding the before-and-after groups, the pooled effects of lifestyle interventions were significant on arousal index (d = -0.46), SaO_2 mean (d = 0.30), SaO_2 nadir (d = 0.30), sleep efficiency (d = 0.25), and REM sleep (d = 0.29); not being statistically significant in the case of deep and light sleep. Moderate to high heterogeneity across studies was found in all outcomes (Table 2).

See raw data of each included study on secondary OSA outcomes in Tables S7 and S8.

Figure 4. Forest plot of the standardized mean differences (d) for excessive daytime sleepiness (EDS), grouped by uncontrolled before-and-after studies and randomized controlled trials (RCTs). A negative value means a reduction of the outcome after intervention. CI = confidence interval

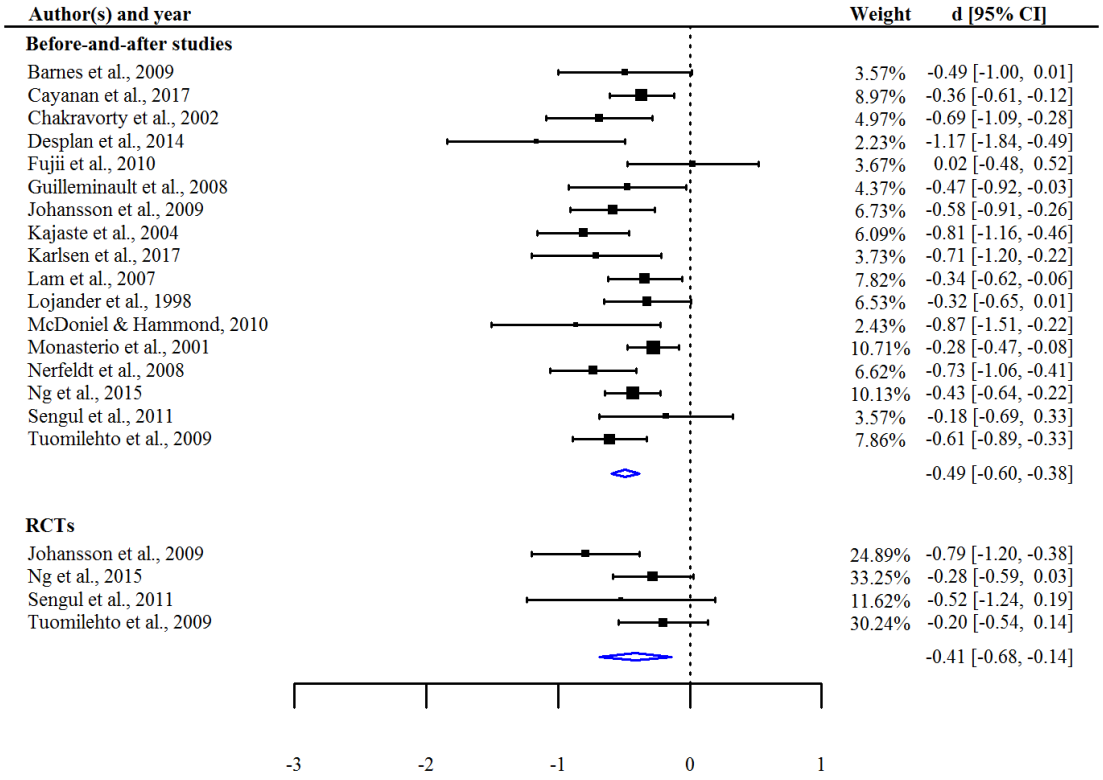


Table 2. Pooled standardized mean differences (*d*) and heterogeneity for secondary obstructive sleep apnea outcomes.

Outcome	*k*	*d* (95% CI)[a]	*Z*	*p*	*Q*	*p*	I^2
Randomized controlled trials							
Arousal index	6	-0.96 (-1.58 to -0.33)	-2.98	0.003	28.27	0.0001	82.32
SaO_2 nadir	6	0.33 (-0.12 to 0.78)	1.44	0.150	22.82	0.0004	78.09
SaO_2 mean	6	0.27 (-0.06 to 0.60)	1.60	0.111	10.27	0.068	51.32
Sleep efficiency	6	0.73 (0.23 to 1.24)	2.83	0.005	16.76	0.005	70.16
REM	3	0.19 (-0.12 to 0.51)	1.21	0.227	0.48	0.788	0
Light sleep	3	-0.14 (-0.46 to 0.17)	-0.89	0.372	1.53	0.466	0
Deep sleep	3	0.08 (-0.49 to 0.65)	0.28	0.782	6.19	0.045	67.72
Uncontrolled before-and-after studies							
Arousal index	31	-0.46 (-0.58 to -0.34)	-7.61	< 0.0001	109.22	< 0.0001	72.53
SaO_2 nadir	14	0.30 (0.12 to 0.49)	3.28	0.001	43.48	< 0.001	70.10
SaO_2 mean	11	0.30 (0.18 to 0.41)	5.06	< 0.0001	12.56	0.249	20.37
Sleep efficiency	14	0.25 (0.11 to 0.40)	3.40	0.0007	25.74	0.018	49.50
REM sleep	12	0.29 (0.13 to 0.44)	3.58	0.0003	22.07	0.024	50.16
Light sleep	8	-0.15 (-0.40 to 0.10)	-1.20	0.230	17.06	0.017	58.97
Deep sleep	13	0.14 (-0.07 to 0.36)	1.30	0.194	43.48	< 0.0001	72.40

Abbreviations: CI, confidence interval; *k*, number of studies; REM, rapid eye movement; SaO_2, oxygen saturation.
[a] A negative value means a reduction of the outcome after intervention.

Analyses of potential moderator variables

Due to the large heterogeneity found in the meta-analyses of lifestyle intervention effects on OSA outcomes, we considered evaluating treatment and participant characteristics of the studies which may explain the effect size variability. Particularly, we analysed the moderation from components and duration of lifestyle interventions as possible treatment characteristics affecting the effect size on primary outcomes. In addition, we also examined the impact of the inclusion of psychological/coaching support on effect sizes. In the case of participant characteristics, we considered OSA severity, percentage of participants using CPAP, gender, percentage of participants with a comorbid condition (type 2 diabetes mellitus; T2DM), and mean change in BMI as potential moderator variables.

The moderation from qualitative variables (severity of OSA and intervention components) did not reach statistical significance, possibly due to the low number of groups included in each categorical level. Yet, we observed differences across pooled effect sizes depending on the severity of OSA and intervention components, in both RCTs and before-and-after studies. Thus, lifestyle intervention effect on AHI, ODI and EDS was greater in those studies that included patients with moderate to severe OSA (d range from -0.49 to -0.86, p range from < 0.0001 to 0.042); being less effective in those which included less severe or mild OSA. Concerning intervention components, a combination of diet and exercise-training was the most effective at improving AHI, ODI and EDS (d range from -0.38 to -0.77, p range from < 0.0001 to 0.002); followed by diet intervention alone, and sleep hygiene in the case of EDS. With respect to the inclusion of psychological support, effect sizes on AHI, ODI, and EDS were greater in those studies which included this type of support (k = 16, d range from -0.48 to -0.86) than in those not including it (k = 19, d range from -0.36 to -0.46). However, these differences did not reach statistical significance (p range from 0.076 to 0.737).

With regard to continuous variables, the percentages of women included in the studies were solely moderating the effects of intervention on ODI; so a greater percentage of women yielded less intervention effectiveness, in both RCTs (β = 0.01, p = 0.002) and before-and-after studies (β = 0.01, p < 0.001). Yet, the moderation of this latter variable on AHI and EDS, although non-significant, had similar tendencies. Percentage of participants using CPAP and treatment duration, as other possible moderators, were non-significant in all primary outcomes in both RCTs and uncontrolled before-and-after studies. CPAP usage was only a minor moderator of effects on EDS in RCTs (β = -0.01, p = 0.031); so lifestyle interventions were more effective at reducing EDS in those studies which included a higher percentage of patients using CPAP. Duration of lifestyle interventions did not moderate any effect on OSA outcomes. Similarly, the percentage of participants with T2DM included in the samples of RCTs and before-and-after studies did not act as a moderator of lifestyle intervention effects on AHI, ODI and EDS. Weighted mean change in BMI of intervention groups was -2.81, only moderating the reductions in ODI (β = 0.14, p = 0.001) and EDS (β = 0.06, p = 0.04).

Sensitivity analysis and assessment of risk of bias

Sensitivity analyses of studies were only performed for those OSA outcomes which included more than 10 study groups.[32] Only two studies were influencing intervention effects on AHI[54] and ODI,[46] when they were treated as uncontrolled before-and-after studies. Yet, the reductions of pooled intervention effects after excluding them from analyses were not significant (Δd = 0.03 and 0.06 respectively), so we decided to include them in the total effect size calculation.

Potential publication bias was assessed using Egger's test and the Rosenthal method (*fail-safe N index*). None of these indicators were statistically significant in primary outcomes of RCTs and before-and-after studies when considering results from sensitivity analyses, such that there was no risk of publication bias (*fail-safe N* index range from 21 to 2,265; Egger's test: $p > 0.05$).

Risk of bias/methodological quality of primary studies ranged from medium to high quality (Table S3). The analyses of this variable as a potential moderator of effect sizes revealed non-significant results ($p \geq 0.2$ for both RCTs and before-and-after studies), so the methodological quality of studies did not affect effect sizes on primary OSA outcomes.

Discussion

This study aimed to systematically contrast, combine and synthesise the effectiveness of lifestyle intervention on OSA, not only on common parameters (AHI, ODI and EDS), but also on other previously unconsidered OSA variables such as arousal index, SaO_2 mean, SaO_2 nadir, sleep efficiency, REM, light and deep sleep. We also targeted to elucidate those intervention and participant characteristics with the greatest effectiveness.

Hence, we analysed 35 studies with lifestyle intervention which comprised 1,420 participants. They were mostly middle-aged men with obesity and moderate-severe OSA, who were treated with a combination of hypocaloric diet and exercise-training. Surprisingly, we did not find any study actively addressing the tobacco and/or alcohol consumption in these patients. This result may be concerning since smoking and alcohol intake are common in patients with OSA and both have been related to a higher risk and worsening of this condition.[77–79]

According to the meta-analyses performed on 12 RCTs and 23 uncontrolled before-and-after studies, lifestyle interventions exhibited statistically significant reductions of all primary OSA outcomes AHI, ODI, and EDS. The reductions of these parameters, although may not imply full remission of OSA, are still clinically relevant. These enhancements have also been found in previous meta-analyses where primary OSA outcomes were reduced through dietary weight loss and exercise-training.[19–24] These latter interventions may not only involve weight loss but also, in turn, a reduction of high levels of leptin; a hormone linked to inhibitory effects on respiratory center modulation as well as to energy homeostasis.[80] Thus, weight loss through diet and exercise-training may lead to enhancements of the upper airway structure and function, resting lung volume and, through reductions of leptin levels, respiratory modulation and balancing of energy intake and expenditure.[81]

Regarding secondary OSA outcomes, lifestyle interventions produced medium to high improvements in arousal index and sleep efficiency, from both RCTs and before-and-after intervention groups. This may be explained not only by the fact that a reduction of AHI implies less sleep fragmentation and, thus, higher sleep efficiency; but also by the beneficial effect that a balanced diet and exercise have on general sleep quality.[82] As sleep quality is related to daily functioning and mood, which have an impact on overall quality of life,[83,84] lifestyle interventions may entail not only reductions of cognitive impairments and depressive symptoms but also an increase of the patients' overall well-being.

The rest of the secondary outcomes were not significantly changed by interventions in RCTs, probably due to the reduced number of groups included in each outcome. Yet, when analysing before-and-after intervention groups, the outcomes of SaO_2 nadir, SaO_2 mean and REM sleep showed a significant increase. Effects on non-REM sleep still remain unclear as we included studies reporting great benefits of lifestyle intervention on light sleep and deep sleep[62,70,74] and others which indicate entirely the opposite.[54,71,73]

In terms of variability across studies, effects of lifestyle interventions on primary OSA outcomes were moderately heterogeneous. Although analyses of qualitative moderators provided inconclusive results—possibly due to the reduced number of groups included in each moderator level—differences in pooled effect sizes may be explained by OSA severity and components of intervention. Accurately, and in concordance with previous findings[18], the studies including a sample with greater OSA severity and a combination of diet and exercise-training as the intervention, obtained greater reductions on AHI, ODI and EDS. The effect on the latter outcome was also greater in those studies which included sleep hygiene as a component of the intervention. This finding may be essential considering that EDS entails impaired daytime functioning[85,86] and so is a major-risk factor for work-place[6] and road[87] accidents in patients with OSA. Concerning the inclusion of psychological/coaching support in the interventions, although not statistically significant, our results indicated a beneficial effect of this type of support for weight loss and lifestyle change in patients with OSA. This is consistent with reported data from previous research conducted on patients with other conditions.[88]

With regard to potential continuous moderators, the percentage of women included in the sample was also partly significant, such that a greater number of women in the sample was related to less effectiveness of the intervention on AHI, ODI and EDS. This noteworthy result may be in accordance with the well-evidenced gender differences in the clinical and polysomnographic characteristics of OSA. Generally, female patients with OSA are older with less severe OSA and worse sleep quality than men, presenting more comorbidity such as hypertension, diabetes mellitus, thyroid disease and asthma,[89] as well as higher symptoms of depression and insomnia.[90] Thus, women may present different OSA phenotype which may explain the lower beneficial effects of lifestyle intervention in female patients with OSA. Strategies to reduce weight effectively may also differ between men and women. Men are more unwilling to comply with nutrition strategies than women and benefit more from physical exercise, whereas women are less adherent to physical exercise and lose more weight from pharmacological and surgical approaches.[91]

Respecting the percentage of participants with T2DM included in the samples, the effects of lifestyle interventions on AHI, ODI and EDS were independent to the inclusion of participants with this comorbid condition. These results are consistent with the evidence provided by a recent systematic review of the benefits of lifestyle interventions on patients with T2DM and OSA.[92] Similarly, changes in participant's BMI did not moderate the effects of lifestyle interventions on AHI, although they partly explained the reductions in ODI and EDS. This result is in accordance with previous studies which reported that improvements on AHI after lifestyle interventions were independent to weight loss.[47,48,50]

Concerning the rest of the continuous moderators analysed, neither the duration of the intervention nor CPAP usage was related to the effect of lifestyle interventions on primary OSA outcomes. Lifestyle interventions were effective independently to their duration and whether or not participants were treated with CPAP. This further supports previous studies which found that the effectiveness of weight loss is not influenced by the duration of treatment.[19] However, these findings are based on assessment of benefits in the short-term, so the influence of treatment duration on benefits in the long-term still remains uncertain.

Overall, there are only a few follow-up studies reporting the beneficial effects of lifestyle intervention on OSA in the long-term. Kuna et al.[93] found that benefits of lifestyle management on OSA were maintained for four years after intervention, despite a 50% of weight regain. Tuomilehto et al.[94] also exposed that 57% of patients with OSA were still cured at two years after a weight loss intervention on mild OSA. Similarly, Johansson et al.[95] confirmed that improvements on OSA from weight loss were persistent after one year, being those patients with higher OSA severity who benefited the most in the long-term. These findings suggest that the beneficial effect of lifestyle intervention on OSA may remain for the long-term although further studies are needed to draw conclusions.

The current meta-analysis therefore has robust implications for clinical practice with patients with OSA. Firstly, interventions addressing lifestyle change have proved to be effective at reducing and so improving adverse OSA outcomes. Secondly, a greater effectiveness is obtained by those interventions including weight loss through diet and exercise-training on male patients with moderate to severe OSA. Thirdly, neither the duration of the intervention nor the CPAP usage displayed a statistical association with the effects of the intervention on OSA. Thus, dietary and exercise-training weight loss interventions should be indicated as a combined or alternative patient-care strategy for male patients with OSA with an AHI ≥ 15, independently to the duration of the intervention and/or the combined CPAP usage.

Nevertheless, our findings should be interpreted with caution since these are limited to the data obtained from the included studies. Our main limitation was the number of RCTs available; several OSA outcomes did not have a required number of studies for desirable statistical power. Consequently, we included uncontrolled before-and-after studies, although these could increase the effect sizes of interventions due to effects of uncontrolled variables. Another limitation was the high heterogeneity found across studies in respect to some participants' characteristics or when defining and

specifying the intervention components and techniques used. There is a lack of experimental studies including a combination of intervention components not only of weight loss but also of sleep hygiene and alcohol/tobacco cessation. The potential effects of these combined interventions therefore still remain unclear. Similarly, there are only few included studies[44,50,61] reporting effects of lifestyle intervention on older adults (> 60 years). Thus, although available research indicates beneficial effects of combined low-calorie diet and aerobic/resistance exercise in this age-population,[96,97] future studies should clarify the controversy between the potential benefits and adverse consequences of intentional weight loss in older patients with OSA.

Conclusion

In conclusion, although this meta-analysis indicates important beneficial effects of lifestyle intervention on OSA, future well-designed RCTs with longer follow-ups are needed to further support these evidences. Similarly, these experimental trials should provide more specific definitions of the intervention components and characteristics (e.g., timing of interventions), besides the inclusion of active components of tobacco and/or alcohol avoidance. There is a lack of studies assessing the potential benefits of including psychological/coaching support in the interventions so future research should address this matter. Apart from primary OSA outcomes, future studies should also include the assessment of other important OSA polysomnographic outcomes such as sleep architecture and continuity. Equally, they should not only include the reductions in AHI but also specify the reductions in REM apneas and non-REM apneas as the first may have more adverse consequences for patients with OSA.[98] Meanwhile, multidisciplinary lifestyle interventions addressing diet, exercise-training, sleep hygiene, and alcohol/tobacco cessation should be recommended; reducing OSA adverse consequences and thereby increasing these patients' quality of life.

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Supplementary Material

Table S1. PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3–4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5–6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Table S2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Figure 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6–7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7 and Table S3
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7–8 and Table S4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Table S3
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9–10 and Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10 and Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11 and Table S3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10–12, Table 2,

			Figures 2–4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10–12, Table 2, Figures 2–4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12–13
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15–18
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	19
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	19–20
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Title page

Table S2. Search strategy used in each database

Database	Search strategy
CINAHL	(AB (apnea OR apnea OR hypopnea OR "sleep disordered breathing" OR OSA OR OSAH OR OSAS OR OSAHS)) AND (AB (habit OR habits OR lifestyle OR health* OR diet* OR weight OR nutrition OR hygiene OR exercise OR "physical activity" OR training OR alcohol* OR drink* OR tobacco OR cigarette* OR smok*)) AND (AB (treatment OR intervention OR training)) NOT (AB (children OR teenager OR teens OR adolescen*))
ProQuest	(TI,AB,IF(apnea OR apnea OR hypopnea OR "sleep disordered breathing" OR OSA OR OSAH OR OSAS OR OSAHS) AND TI,AB,IF(habit OR habits OR lifestyle OR health* OR diet* OR weight OR nutrition OR hygiene OR exercise OR "physical activity" OR training OR alcohol* OR drink* OR tobacco OR cigarette* OR smok*) AND TI,AB,IF(treatment OR intervention OR training) NOT TI,AB,IF(children OR teenager OR teens OR adolescen*))
Psicodoc	(APNEA).TITO.|(APNEA).RESU.|(APNEA).DESC.
Scopus	(TITLE-ABS-KEY (apnea OR apnea OR hypopnea OR "sleep disordered breathing" OR osa OR osah OR osas OR osahs) AND TITLE-ABS-KEY (habit OR habits OR lifestyle OR health* OR diet* OR weight OR nutrition OR hygiene OR exercise OR "physical activity" OR training OR alcohol* OR drink* OR tobacco OR cigarette* OR smok*) AND TITLE-ABS-KEY (treatment OR intervention OR training) AND NOT TITLE-ABS-KEY (children OR teenager OR teens OR adolescen*))
Web of Science	(TS=(apnea OR apnea OR hypopnea OR "sleep disordered breathing" OR osa OR osah OR osas OR osahs) AND TS=(habit OR habits OR lifestyle OR health* OR diet* OR weight OR nutrition OR hygiene OR exercise OR "physical activity" OR training OR alcohol* OR drink* OR tobacco OR cigarette* OR smok*) AND TS=(treatment OR intervention OR training)) NOT TS=(children OR teenager OR teens OR adolescen*)

Table S3. Risk of bias and quality assessment

Author(s) and year	Specification of eligibility criteria	Random allocation to groups	Concealed allocation	Inter-group similarity at baseline	Blinding of assessors	Sample drop-out rate (≤ 15%)	Intention to treat analysis	Reported comparison between groups	Report of effect size or other parameters	Total quality score
Ackel-d'elia et al., 2012[42]	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	7/9
Barnes et al., 2009[55]	Yes	N/A	N/A	N/A	N/A	Yes	Yes	N/A	Yes	4/4
Cavagnolli et al., 2014[56]	Yes	N/A	N/A	N/A	N/A	No	Yes	N/A	Yes	3/4
Cayanan et al., 2017[57]	Yes	N/A	N/A	N/A	N/A	Yes	Yes	N/A	Yes	4/4
Chakravorty et al., 2002[58]	Yes	N/A	N/A	N/A	N/A	No	No	N/A	Yes	2/4
Desplan et al., 2014[59]	Yes	N/A	N/A	N/A	N/A	Yes	No	N/A	Yes	3/4
Dixon et al., 2012[60]	Yes	N/A	N/A	N/A	N/A	Yes	Yes	N/A	Yes	4/4
Dobrosielski et al., 2015[61]	Yes	N/A	N/A	N/A	N/A	No	Yes	N/A	Yes	3/4
Fernandes et al., 2015[43]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	7/9
Foster et al., 2009[44]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9/9
Fredheim et al., 2013[62]	No	N/A	N/A	N/A	N/A	No	Yes	N/A	Yes	2/4
Fujii et al., 2010[63]	Yes	N/A	N/A	N/A	N/A	Yes	Yes	N/A	Yes	4/4
Guilleminault et al., 2008[64]	Yes	N/A	N/A	N/A	N/A	Yes	Yes	N/A	Yes	4/4
Igelström et al., 2017[45]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9/9
Iguchi et al., 2013[65]	Yes	N/A	N/A	N/A	N/A	No	No	N/A	Yes	2/4
Johansson et al., 2009[46]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9/9
Kajaste et al., 2004[66]	Yes	N/A	N/A	N/A	N/A	Yes	No	N/A	Yes	3/4
Kansanen et al., 1998[67]	Yes	N/A	N/A	N/A	N/A	Yes	Yes	N/A	Yes	4/4
Karlsen et al., 2017[47]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Unclear	7/9
Kline et al., 2011[48]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9/9
Lam et al., 2007[68]	Yes	N/A	N/A	N/A	N/A	Yes	Yes	N/A	Yes	4/4
Lojander et al., 1998[69]	Yes	N/A	N/A	N/A	N/A	Yes	No	N/A	Yes	3/4
Maki-Nunes et al., 2015[49]	Yes	No	No	Yes	Yes	No	Yes	Yes	Yes	6/9
McDoniel et al., 2010[70]	Yes	N/A	N/A	N/A	N/A	Yes	Yes	N/A	Yes	4/4
Mendelson et al., 2016[50]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	7/9
Monasterio et al., 2001[71]	Yes	N/A	N/A	N/A	N/A	Yes	Yes	N/A	Yes	4/4

(continued)

Table S3. Risk of bias and quality assessment (continued)										
Nerfeldt et al., 2008[72]	Yes	N/A	N/A	N/A	N/A	Yes	Yes	N/A	Yes	4/4
Ng et al., 2015[51]	Yes	Yes	Unclear	Yes	Unclear	No	Yes	Yes	Yes	6/9
Norman et al., 2000[73]	Yes	N/A	N/A	N/A	N/A	No	Yes	N/A	Yes	3/4
Papandreou et al., 2012[74]	Yes	N/A	N/A	N/A	N/A	Yes	Yes	N/A	Yes	4/4
Schutz et al., 2013[75]	Yes	N/A	N/A	N/A	N/A	No	No	N/A	Yes	2/4
Sengul et al., 2011[52]	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	7/9
Servantes et al., 2012[53]	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	7/9
Tuomilehto et al., 2009[54]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9/9
Ueno et al., 2009[76]	Yes	N/A	N/A	N/A	N/A	Yes	Yes	N/A	Yes	4/4
N/A = not applicable.										

Table S4. Equations used for the calculation of effect sizes

	Randomised controlled trials	Uncontrolled before-and-after studies
Standardized mean change	$d = c(df_{E,C}) \cdot \left[\frac{(\bar{X}_{pre,E} - \bar{X}_{pos,E}) - (\bar{X}_{pre,C} - \bar{X}_{pos,C})}{\bar{S}_{pre}}\right]$	$d = c(df) \cdot \left[\frac{(\bar{X}_{pre,E} - \bar{X}_{pos,E})}{S_{pre}}\right]$
Mean baseline standard deviation	$\bar{S}_{pre} = \sqrt{\frac{(n_E - 1) \cdot S^2_{pre,E} + (n_C - 1) \cdot S^2_{pre,C}}{n_E + n_C - 2}}$	
Correction factor	$c(df_{E,C}) = 1 - \frac{3}{4(n_E + n_C - 2) - 1}$	$c(df) = 1 - \frac{3}{4(n - 1) - 1}$
Variance[a]	$S^2(d) = [c(df_{E,C})]^2 \cdot 2(1 - r) \cdot \left(\frac{n_E + n_C}{n_E n_C}\right) \cdot \left(\frac{n_E + n_C - 2}{n_E + n_C - 4}\right) \times \left[1 + \frac{n_E n_C d^2}{2(1 - r)(n_E + n_C)}\right] - d^2$	$S^2(d) = [c(df)]^2 \cdot \left[\frac{2 \cdot (1 - r)}{n}\right] \cdot \left(\frac{n - 1}{n - 3}\right) \cdot \left[1 + \frac{n \cdot d^2}{2 \cdot (1 - r)}\right] - d^2$

Abbreviations: C, control group; E, experimental group.

[a] r = 0.7, according to the standard r value recommended by Rosenthal [1].

1. Rosenthal R. Meta-analytic procedures for social research. Newbury Park, CA: Sage 1991.

Table S5. Raw data on primary obstructive sleep apnea outcomes from randomized controlled trials

Author(s) and year	AHI		ODI		EDS	
	Δ_E-Δ_C	$\bar{S}_{pre}$	Δ_E-Δ_C	$\bar{S}_{pre}$	Δ_E-Δ_C	$\bar{S}_{pre}$
Ackel-d'elia et al., 2012[42]	2.1	22.3				
Fernandes et al., 2015[43]	-7.35	25.62	-6.54	23.3		
Foster et al., 2009[44]	-9.4	16.49	-6.7	14.88		
Igelström et al., 2017[45]	-8	20.69				
Johansson et al., 2009[46]	-23	15.5	-18	14.48	-4	5
Kline et al., 2011[48]	-12.1	26.84	-9.4	20.01		
Maki-Nunes et al., 2015[49]	-27	23.31				
Mendelson et al., 2016[50]	-9.5	13.2				
Ng et al., 2015[51]	-5.2	20			-1.5	5.31
Sengul et al., 2011[52]	-3.62	5.97			-3.08	5.63
Servantes et al., 2012 (1)[53]	-13.1	17.55				
Servantes et al., 2012 (2)[53]	-11.6	23.17				
Tuomilehto et al., 2009[54]	-3.7	3			-1	4.9

Abbreviations: AHI, apnea/hypopnea index; EDS, excessive daytime sleepiness; ODI, oxygen desaturation index; Δ_E-Δ_C , difference between the mean change in intervention and control groups, from baseline to post-intervention; $\bar{S}_{pre,}$ mean baseline standard deviation.

Table S6. Raw data on primary obstructive sleep apnea outcomes from before-and-after studies

Author(s) and year	AHI		ODI		EDS	
	Δ_E	S_{pre}	Δ_E	S_{pre}	Δ_E	S_{pre}
Ackel-d'elia et al., 2012[42a]	-5.5	22.9				
Barnes et al., 2009[55]	-6.3	12			-2.7	5.1
Cavagnolli et al., 2014[56]	-2.03	22.06				
Cayanan et al., 2017[57]	-9.31	23.9			-1.5	4.04
Chakravorty et al., 2002[58]	-1	19.1			-3	4.2
Desplan et al., 2014[59]	-12.6	19.4	-5.5	15.8	-5.6	4.5
Dixon et al., 2012[60]	-13.8	30.3				
Dobrosielski et al., 2015[61]	-11.73	23.41				
Fernandes et al., 2015[43 a]	-7.22	35.21	-6.4	32.89		
Foster et al., 2009[44 a]	-4.6	18	-5.5	16.1		
Fredheim et al., 2013[62]	-8.8	20.9				
Fujii et al., 2010[63]					0.1	4
Guilleminault et al., 2008[64]	1	4.8			-0.6	1.2
Igelström et al., 2017[45 a]	-9.9	19.8				
Iguchi et al., 2013[65]	-2.52	2.82	-0.44	3.55		
Johansson et al., 2009[46 a]	-25	17	-19	15	-3	5
Kajaste et al., 2004[66]			-19	31	-3.4[b]	4.1[b]
Kansanen et al., 1998[67]			-12	20		
Karlsen et al., 2017[47]	-7.5	21.7			-2.7	3.6
Kline et al., 2011[48 a]	-7.6	29.1	-3	21.6		
Lam et al., 2007[68]	1.2	10.91			-2	5.74
Lojander et al., 1998[69]			-18	20	-10[b]	30[b]
Maki-Nunes et al., 2015[49 a]	-16	20.4				
McDoniel et al., 2010[70]					-3	3.2
Mendelson et al., 2016[50 a]	-10.6	12.9				
Monasterio et al., 2001[71]					-1.2	4.3
Nerfeldt et al., 2008[72]	-17	24	-18	23	-3	4
Ng et al., 2015[51 a]	-8.1	20			-2.5	5.7
Norman et al., 2000[73]	-9.9	9	-4.8	13.6		
Papandreou et al., 2012 (1)[74]	-14	34.9	-13.5	33.7		
Papandreou et al., 2012 (2)[74]	-15.6	32.8	-13.1	29.9		
Schütz et al., 2013[75]	-4.1	12.8				
Sengul et al., 2011[52 a]	-4.18	5.43			-1.2	6.14
Servantes et al., 2012 (1)[53 a]	-8.5	24.7				
Servantes et al., 2012 (2)[53 a]	-10	17.6				
Tuomilehto et al., 2009[54 a]	-4	3			-3.1	5
Ueno et al., 2009[76]	-12.24	4				

Abbreviatons: AHI, apnea/hypopnea index; EDS, excessive daytime sleepiness; ODI, oxygen desaturation index; Δ_E, mean change from baseline to post-intervention; S_{pre}, baseline standard deviation.

[a] These are the intervention groups from RCTs which were also included in the uncontrolled before-and-after studies meta-analysis.

[b] This data refers to daytime sleepiness measured by a scale different from Epworth sleepiness scale.

Table S7. Raw data on secondary obstructive sleep apnea outcomes from randomized controlled trials

Author(s) and year	Arousal index		SaO_2 nadir		SaO_2 mean		Sleep efficiency		% REM		% Light sleep		% Deep sleep	
	Δ_E-Δ_C	$\bar{S}_{pre}$	Δ_E-Δ_C	$\bar{S}_{pre}$	Δ_E-Δ_C	$\bar{S}_{pre}$	Δ_E-Δ_C	$\bar{S}_{pre}$	Δ_E-Δ_C	$\bar{S}_{pre}$	Δ_E-Δ_C	$\bar{S}_{pre}$	Δ_E-Δ_C	$\bar{S}_{pre}$
Ackel-d'elia et al., 2012[42]	-6.1	14.92	-3.3	10.25	0.3	2.94								
Fernandes et al., 2015[43]			5.2	8.52	0.5	2.98								
Johansson et al., 2009[46]			5	5.5										
Kline et al., 2011[48]	-2.6	19.43	2	7.43			3	6.92	1.9	5.76	-5.4	18.83	3.6	6.27
Maki-Nunes et al., 2015[49]	-26	9.95	7	7.48			13	6.43	1	7.38	2	8.62	0	7.46
Mendelson et al., 2016[50]	-5.3	18.42	-1.4	5.48			-0.8	10.98	0.5	5.84	-3.2	14.91	-2.9	8.02
Sengul et al., 2011[52]					-1.83	5.01	6.52	6.15						
Servantes et al., 2012 (1)[53]	-99.2[a]	51.06[a]			0.7	2.27	10.1	12.23						
Servantes et al., 2012 (2)[53]	-88.6[a]	69.09[a]			0.6	1.53	9.7	13.12						
Tuomilehto et al., 2009[54]					1.1	1.45								

Abbreviations: REM, rapid eye movement; SaO_2, oxygen saturation; Δ_E-Δ_C, difference between the mean change in intervention and control groups, from baseline to post-intervention; $\bar{S}_{pre}$, mean baseline standard deviation.

[a] This data refers to total number of arousals not arousal index.

Table S8. Raw data on secondary obstructive sleep apnea outcomes from before-and-after studies

Author(s) and year	Arousal index		SaO_2 nadir		SaO_2 mean		Sleep efficiency		% REM		% Light sleep		% Deep sleep	
	Δ_E	S_{pre}	Δ_E	S_{pre}	Δ_E	S_{pre}	Δ_E	S_{pre}	Δ_E	S_{pre}	Δ_E	S_{pre}	Δ_E	S_{pre}
Ackel-d'elia et al., 2012[42 a]	-3.7	14.2	-2.3	8.9	0.7	1.7								
Cavagnolli et al., 2014[56]	-0.94	17.07					0.43	6.68	1.54	5.11	0.82	16.37	-3.33	11.75
Chakravorty et al., 2002[58]	-15.3	28.5					2.80	12.8	5.40	40.5	-10.30[b]	73.3[b]	4.10	52.5
Desplan et al., 2014[59]	-9	17.5												
Dixon et al., 2012[60]	-4.8	26	3.75	19.2	0.7	2.7	-2.99	25.71	-1.60	7.77			2.60	21.42
Dobrosielski et al., 2015[61]			1.36	6.59	0.51	0.98								
Fernandes et al., 2015[43 a]			4.6	9.392	1	3.854								
Fredheim et al., 2013[62]			4	8.2	0.8	3.4								
Guilleminault et al., 2008[64]			0.3	1.6					0.60	1.6			1.00	1.2
Iguchi et al., 2013[65]														
Johansson et al., 2009[46 a]			5	6										
Kansanen et al., 1998[67]			7	17										
Kline et al., 2011[48 a]	-1.1	20.6	0.3	7.2			0.90	7.2	1.90	5.8	-2.20	13	0.40	6
Maki-Nunes et al., 2015[49 a]	-4	11.2	4	8			2.00	6.4	0.00	6.8	-2.00	4.4	3.00	6.4
Mendelson et al., 2016[50 a]	-8.3	23.8	-1.4	4.9			-2.00	12.8	2.90	6.5	-7.90	17.4	-0.70	9.3
Nerfeldt et al., 2008[72]	-9	15					5.00	10	2.00	7			8.00	11
Norman et al., 2000[73]	-11.1	11.5					10.70	9	3.90	5.9	4.30	21.6	-2.60	4
Papandreou et al., 2012 (1)[74]			3.1	8.4	1	2.9	1.40	15.01	1.80	3.4			1.10	4.5
Papandreou et al., 2012 (2)[74]			4.9	6.9	1.5	2.7	6.40	15.9	1.90	3.7			0.10	5.8
Schütz et al., 2013[75]	-4	11.3					3.80	9			6.40	10.8	-3.10	12.4
Sengul et al., 2011[52 a]					-0.3	4.53	5.77	6.34						
Servantes et al., 2012 (1)[53 a]	-39.2	78.2			0	1.6	5.20	12.9						
Servantes et al., 2012 (2)[53 a]	-49.8	57.2			0.1	2.5	5.60	11.7						
Tuomilehto et al., 2009[54 a]					0.8	1.5								
Ueno et al., 2009[76]	-19	8	4	2					3.00	2	-8.00	3	6.00	1

Abbreviations: REM, rapid eye movement; SaO_2, oxygen saturation; Δ_E, mean change from baseline to post-intervention; S_{pre}, baseline standard deviation.

[a] These are the intervention groups from RCTs which were also included in the uncontrolled before-and-after studies meta-analysis.

[b] This data refers to total minutes not percentage of light sleep.

AIMS & HYPOTHESIS

AIMS AND HYPOTHESES

The overall aim of this International Doctoral Thesis was to design, implement and study the effects of an interdisciplinary weight loss and lifestyle intervention combined with usual-care (i.e., continuous positive airway pressure; CPAP), as compared with usual-care alone, on obstructive sleep apnea (OSA) severity, other sleep-related outcomes, body weight and composition and cardiometabolic risk in adults with CPAP-treated moderate-to-severe OSA and overweight/obesity. In addition, the efficacy of this behavioral approach at improving daily functioning and psychiatric symptoms, physical fitness, and dietary behavior in this population (i.e., adults with CPAP-treated moderate-to-severe OSA and overweight/obesity) was also studied.

Correspondingly, the overall hypothesis of this International Doctoral Thesis was that a novel eight-week interdisciplinary weight loss and lifestyle intervention combined with usual-care (i.e., CPAP), as compared with usual-care alone, would result in clinically meaningful and sustainable improvements in OSA severity, other sleep-related outcomes, body weight and composition, and cardiometabolic comorbidities in adults with CPAP-treated moderate-to-severe OSA and overweight/obesity. Similarly, it was hyphotesized that this behavioral approach in this population would also result in clinically significant and sustainable improvements in daily functioning and psychiatric symptoms, physical fitness, and dietary behavior.

Interdisciplinary weight loss and lifestyle intervention for obstructive sleep apnea in adults: Rationale, design and methodology of the INTERAPNEA study (Study 2)

General objective 1: To describe the rationale, design and methodology of the Interdisciplinary Weight Loss and Lifestyle Intervention for Obstructive Sleep Apnea (INTERAPNEA) randomized clinical trial (Study 2)

Interdisciplinary weight loss and lifestyle intervention for obstructive sleep apnea: The INTERAPNEA randomized clinical trial (Study 3)

General objective 2: To determine the efficacy of a novel interdisciplinary weight loss and lifestyle intervention for the improvement of OSA and related comorbidities in adults with CPAP-treated moderate-to-severe OSA and overweight/obesity (**Study 3**).

> *Specific objective 2.1:* To establish the effects of an eight-week interdisciplinary weight loss and lifestyle intervention on OSA severity (i.e., apnea-hypopnea events per hour of sleep; apnea-hypopnea index [AHI]) and other sleep-related outcomes in adults with CPAP-treated moderate-to-severe OSA and overweight/obesity.
>
> > *Hypothesis 2.1:* An eight-week interdisciplinary weight loss and lifestyle intervention would result in clinically meaningfull and sustainable improvements in OSA severity (i.e., AHI) and other sleep-related outcomes in adults with CPAP-treated moderate-to-severe OSA and overweight/obesity.

Specific objective 2.2: To examine the effects of an eight-week interdisciplinary weight loss and lifestyle intervention on body weight and composition in adults with CPAP-treated moderate-to-severe OSA and overweight/obesity.

Hypothesis 2.2: An eight-week interdisciplinary weight loss and lifestyle intervention would result in clinically meaningfull and sustainable improvements in body weight and composition outcomes (i.e., body weight, neck, chest and waist circumferences, fat mass, visceral adipose tissue and lean mass) in adults with CPAP-treated moderate-to-severe OSA and overweight/obesity.

Specific objective 2.3: To analyse the effects of an eight-week interdisciplinary weight loss and lifestyle intervention on cardiometabolic risk in adults with CPAP-treated moderate-to-severe OSA and overweight/obesity.

Hypothesis 2.3: An eight-week interdisciplinary weight loss and lifestyle intervention would result in clinically meaningfull and sustainable improvements in cardiometabolic risk (i.e., blood pressure, glucose and lipid metabolism, and liver function) in adults with CPAP-treated moderate-to-severe OSA and overweight/obesity.

Effect of an interdisciplinary weight loss and lifestyle intervention on daily functioning and psychiatric symptoms in obstructive sleep apnea: The INTERAPNEA trial (Study 4)

General objective 3: To determine the efficacy of a novel interdisciplinary weight loss and lifestyle intervention for the improvement of daily functioning and psychiatric symptoms in adults with CPAP-treated moderate-to-severe OSA and overweight/obesity (**Study 4**).

Specific objective 3.1: To establish the effects of an eight-week interdisciplinary weight loss and lifestyle intervention on daily functioning in adults with CPAP-treated moderate-to-severe OSA and overweight/obesity.

Hypothesis 3.1: An eight-week interdisciplinary weight loss and lifestyle intervention would result in clinically meaningfull and sustainable improvements in daily functioning in adults with CPAP-treated moderate-to-severe OSA and overweight/obesity.

Specific objective 3.2: To examine the effects of an eight-week interdisciplinary weight loss and lifestyle intervention on psychological distress in adults with CPAP-treated moderate-to-severe OSA and overweight/obesity.

Hypothesis 3.2: An eight-week interdisciplinary weight loss and lifestyle intervention would result in clinically meaningfull and sustainable improvements in psychological distress in adults with CPAP-treated moderate-to-severe OSA and overweight/obesity.

Specific objective 3.3: To analyse the effects of an eight-week interdisciplinary weight loss and lifestyle intervention on anxiety in adults with CPAP-treated moderate-to-severe OSA and overweight/obesity.

Hypothesis 3.3: An eight-week interdisciplinary weight loss and lifestyle intervention would result in clinically meaningfull and sustainable improvements anxiety symptoms in adults with CPAP-treated moderate-to-severe OSA and overweight/obesity.

Specific objective 3.4: To analyse the effects of an eight-week interdisciplinary weight loss and lifestyle intervention on depression in adults with CPAP-treated moderate-to-severe OSA and overweight/obesity.

Hypothesis 3.4: An eight-week interdisciplinary weight loss and lifestyle intervention would result in clinically meaningfull and sustainable improvements in depression symptoms in adults with CPAP-treated moderate-to-severe OSA and overweight/obesity.

Effect of an interdisciplinary weight loss and lifestyle intervention on cardiorespiratory fitness in obstructive sleep apnea: The INTERAPNEA trial (Study 5)

General objective 4: To determine the effects of an eight-week interdisciplinary weight loss and lifestyle intervention combined with usual-care (i.e., CPAP), as compared with usual-care alone, on physical fitness in adults with CPAP-treated moderate-to-severe OSA and overweight/obesity (**Study 5**).

Specific objective 4.1: To establish the effects of an eight-week interdisciplinary weight loss and lifestyle intervention on cardiorespiratory fitness and self-reported physical fitness in adults with CPAP-treated moderate-to-severe OSA and overweight/obesity.

Hypothesis 4.1: An eight-week interdisciplinary weight loss and lifestyle intervention would result in clinically meaningfull and sustainable improvements in cardiorespiratory fitness and self-reported physical fitness in adults with CPAP-treated moderate-to-severe OSA and overweight/obesity.

Specific objective 4.2: To investigate the associations of changes in cardiorespiratory fitness and self-reported physical fitness with changes in OSA severity and body weight and composition outcomes after an eight-week interdisciplinary weight loss and lifestyle intervention in adults with CPAP-treated moderate-to-severe OSA and overweight/obesity.

Hypothesis 4.2: Changes in cardiorespiratory fitness and self-reported physical fitness after an eight-week interdisciplinary weight loss and lifestyle intervention would be related with changes in OSA severity and body weight and composition outcomes in adults with CPAP-treated moderate-to-severe OSA and overweight/obesity.

Effect of an interdisciplinary weight loss and lifestyle intervention on dietary behavior in obstructive sleep apnea: The INTERAPNEA trial (Study 6)

General objective 5: To determine the effects of an eight-week interdisciplinary weight loss and lifestyle intervention combined with usual-care (i.e, CPAP), as compared with usual-care alone, on dietary behavior in adults with moderate-to-severe OSA and overweight/obesity (**Study 6**).

Specific objective 5.1: To establish the effects of an eight-week interdisciplinary weight loss and lifestyle intervention on dietary behavior and adherence to the Mediterranean diet in adults with CPAP-treated moderate-to-severe OSA and overweight/obesity.

Hypothesis 5.1: An eight-week interdisciplinary weight loss and lifestyle intervention would result in clinically meaningfull and sustainable improvements in dietary behavior and adherence to the Mediterranean diet in adults with CPAP-treated moderate-to-severe OSA and overweight/obesity.

Specific objective 5.2: To investigate the associations of changes in dietary behavior and adherence to the Mediterranean diet with changes in OSA severity and body weight and composition outcomes after an eight-week interdisciplinary weight loss and lifestyle intervention in adults with CPAP-treated moderate-to-severe OSA and overweight/obesity.

Hypothesis 5.2: Changes in dietary behavior and adherence to the Mediterranean diet after an eight-week interdisciplinary weight loss and lifestyle intervention would be related with changes in OSA severity and body weight and composition outcomes in adults with CPAP-treated moderate-to-severe OSA and overweight/obesity.

MATERIAL & METHODS

CHAPTER 2

Interdisciplinary weight loss and lifestyle intervention for obstructive sleep apnea in adults: Rationale, design and methodology of the INTERAPNEA study (**Study 2**)

ABSTRACT

Obesity is a major risk factor for obstructive sleep apnoea (OSA), the most common sleep-disordered breathing related to neurocognitive and metabolic syndromes, type II diabetes, and cardiovascular diseases. Although strongly recommended for this condition, there are no studies on the effectiveness of an interdisciplinary weight loss and lifestyle intervention including nutrition, exercise, sleep hygiene, and smoking and alcohol cessation. INTERAPNEA is a randomized controlled trial with a two-arm parallel design aimed at determining the effects of an interdisciplinary tailored weight loss and lifestyle intervention on OSA outcomes. The study will include 84 males aged 18–65 with a body mass index of ≥25 kg/m^2 and severe to moderate OSA randomly assigned to usual care (i.e., continuous positive airway pressure), or interdisciplinary weight loss and lifestyle intervention combined with usual care. Outcomes will be measured at baseline, intervention end-point, and six-month post-intervention, including apnoea-hypopnoea index (primary outcome), other neurophysical and cardiorespiratory polysomnographic outcomes, sleep quality, daily functioning and mood, body weight and composition, physical fitness, blood biomarkers, health-related quality of life, and cost-effectiveness. INTERAPNEA may serve to establish a cost-effective treatment not only for the improvement of OSA and its vast and severe comorbidities, but also for a potential remission of this condition.

Introduction

Obstructive sleep apnoea (OSA), produced by repeated upper airway collapse during sleep, has increasingly become the focus of numerous current interdisciplinary research attributed not only to its high prevalence, but also to the wide range of adverse health consequences of this condition.[1] The repeated events of complete (apnoea) or partial (hypopnoea) pharyngeal obstruction that occur while sleeping lead to intermittent hypoxic episodes, hypercapnia, sleep fragmentation, and upsurges of sympathetic activity.[2] Driven by these short-term consequences, OSA is closely related to increased morbidity and mortality,[3] including cardio-metabolic disorders,[4] neurocognitive abnormalities,[5] impaired daily functioning and mood,[6] and greater risk of vehicle and occupational accidents.[7,8]

It has recently been estimated that up to 38% of adults suffer from OSA, being more prevalent in males, the elderly, and in those who are obese.[9] Therefore, OSA risk factors include obesity, sex, age, and adverse lifestyle habits such as sedentariness, poor nutrition, smoking, and alcohol intake.[10] According to epidemiological studies, nearly 60% of moderate to severe OSA is attributable to obesity,[11] which contributes to alterations of the airway anatomy and collapsibility, respiratory modulation, resting lung volume, and neurohormonal mediators on ventilation.[12] Given the exponential increase of obesity prevalence in the overall population, which has nearly tripled since 1975—in 2016 39% of adults aged 18 years and over were obese—OSA prevalence is not only worryingly high but also likely to rise in the upcoming years.[13]

The current treatment of choice is continuous positive airway pressure (CPAP),[14] a mechanical device used to maintain upper airway patency, thereby improving the main symptoms and consequences of OSA through the reduction of the number of apnoea-hypopnoea episodes per hour of sleep (i.e., apnoea-hypopnoea index, AHI).[15–17] However, CPAP is a chronic day-to-day treatment—it does not cure OSA in the long-term—and its use may be rejected or abandoned due to discomfort and/or other inconveniences.[18] Most importantly, CPAP does not address the major high-risk factors of OSA, i.e., obesity and adverse lifestyles.

Hence, alternative or combined behavioral interventions including weight loss through dietary approaches and exercise, sleep hygiene, and avoidance of alcohol and tobacco consumption are required and strongly recommended in the most recent practical guidelines from the American Academy of Sleep Medicine (AASM),[14,19] According to our recently published systematic review and meta-analysis on the effectiveness of these interventions,[1] the combination of diet and exercise may be an effective treatment in improving OSA outcomes in middle-aged males with moderate to severe OSA.

Yet, the number of reported randomized controlled trials addressing both diet and exercise components as a combination was significantly low and only included effects on specific OSA outcomes such as AHI, oxygen desaturation index, and excessive daytime sleepiness.[1] Furthermore, no original studies actively focusing on the cessation of tobacco and alcohol consumption were found,[1] factors which have been shown to be common in patients with OSA and associated with the worsening of this condition.[20,21] Thus, the actual effectiveness of potential interdisciplinary interventions for the improvement of the main symptoms and consequences of OSA still remains unclear. Considering the vast and severe OSA

consequences and comorbidities, with obesity being a major risk factor for this condition, there is a need for well-designed studies comprising all of these aspects and evaluating the potential clinical and economic relevance of these interventions for OSA and related diseases.

The INTERAPNEA randomized controlled trial (RCT) is aimed at implementing and testing the effectiveness of an eight-week interdisciplinary weight loss and lifestyle intervention on overweight-obese adults with CPAP-treated moderate to severe OSA. This intervention will include nutritional behavior change, supervised-exercise, sleep hygiene, and active alcohol and tobacco cessation components, comparing the impacts on primary and secondary OSA outcomes to the standard care, i.e., CPAP therapy. Furthermore, INTERAPNEA not only pursues to analyse the effect of this intervention on OSA outcomes but also on the overall physical and psychological health of patients with moderate to severe OSA.

Methods

Study Design

The INTERAPNEA study (ClinicalTrials.gov ID: NCT03851653) is an RCT with a two-arm parallel design where participants will be randomly allocated to a usual care/control group (i.e., CPAP therapy) or an 8-week interdisciplinary weight loss and lifestyle intervention combined with CPAP. The study conforms to the last revised Ethical Principles for Medical Research Involving Human Subjects comprised in the Declaration of Helsinki, and approval of the study protocol was obtained from the Clinical Research Ethics Committee of the "Junta de Andalucía" (0770-N-19). All participants will receive accurate information on the study assessments and intervention, and written informed consent from each participant will be obtained prior to any data collection.

Study Organisation and Coordination Center

Adults diagnosed with moderate to severe OSA potentially meeting the inclusion criteria will be recruited from the "Virgen de las Nieves" University Hospital (Granada, Spain). Data collection at baseline and follow-ups, as well as implementation of the intervention, will be performed in two different settings of the University of Granada (Granada, Spain): Sleep and Health Promotion Laboratory of the Mind, Brain, and Behavior Research Center (CIMCYC), and Sport and Health University Research Institute (iMUDS). The Sleep and Health Promotion Laboratory is the coordinating center for the study, responsible for the study design and organisation, patient recruitment process, data collection and management, randomisation and participant allocation, trial monitoring, and reporting of the study process and results.

Participants and Selection Criteria

Eligible participants will be adults previously diagnosed with moderate to severe OSA (AHI equal or greater than 15)[22] from the province of Granada (Spain). They must be between 18 and 65 years old, and have a body mass index (BMI) equal

to or greater than 25 kg/m². A full list of the study's inclusion and exclusion criteria are shown in Table 1. Due to the well-evidenced higher incidence and prevalence of OSA in males,[9] and the differences in OSA phenotypes between men and women,[23] we decided to include only male participants in the study. Furthermore, the effectiveness of non-pharmacological and non-surgical weight loss interventions have been shown to be less effective in women,[1,24] such that different approaches are needed in this population with OSA.

Potential participants will be medically examined and must complete a health history revision prior to their inclusion in the study in order to ensure no hindrance/harm related to the assessment and intervention protocols. Should any incident or medical problem arise during the intervention, participants will be physically and psychologically examined and, if necessary, excluded from the study. A clinical trial liability insurance will be contracted for the INTERAPNEA study, providing legal and financial protection to the sponsor-investigators, and compensation to participants in the case of an injury or any damage incurred in and as a result of the study.

Table 1. Eligibility criteria

Inclusion Criteria	Exclusion Criteria
• Men aged 18–65 years • CPAP-treated moderate to severe OSA (AHI equal to or greater than 15 events/h) • BMI equal to or greater than 25 kg/m² • Not participating in a weight loss program • Willing to provide informed consent and acceptance of random group assignment	• Presence of any other primary sleep disorder • Presence of any mental disorder (including depression, anxiety, and addiction to alcohol or other substances) • Presence of any other severe organic disease, except for those comorbid to OSA • Regular use of neuroleptic, sedative or hypnotic drugs, or any other medication that may cause sleep disturbances or increased daytime sleepiness

Abbreviations: AHI, apnoea-hypopnoea index; BMI, body mass index; CPAP, continuous positive airway pressure; OSA, obstructive sleep apnoea

Recruitment and Randomisation

Sample Size

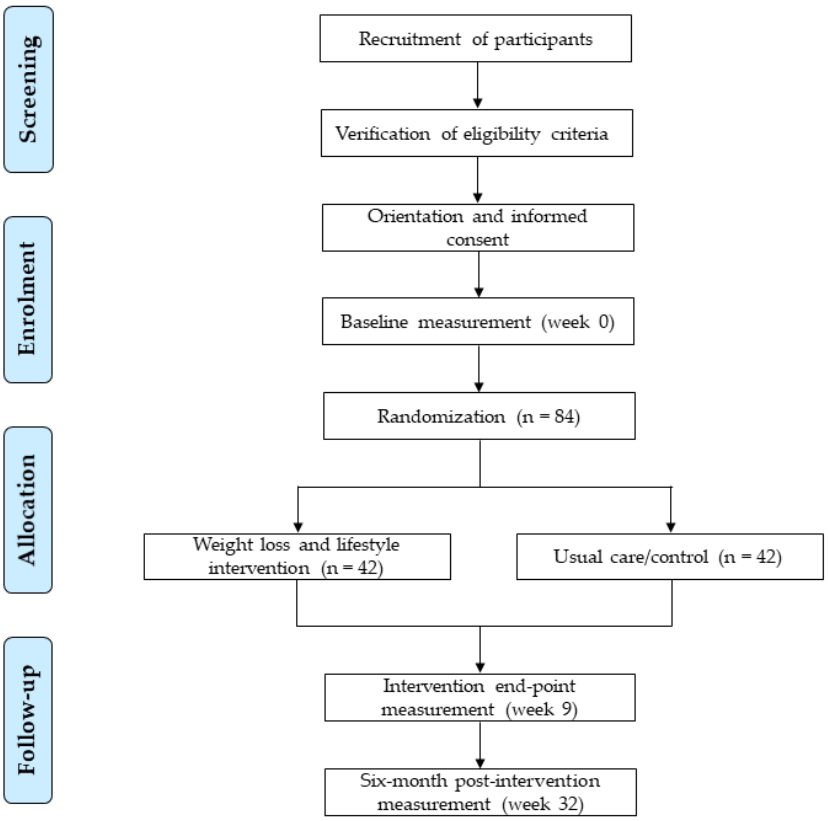
The sample size calculation and power of the study are based on the data of previously reported studies contrasted, combined, and synthesised in our recent systematic review and meta-analysis.[1] We considered following the formula $n = \frac{2(Z_\alpha + Z_{1-\beta})^2\sigma^2}{\Delta^2}$, where n is the required sample size, Z_a and $Z_{(1-\beta)}$ are the constants set by convention according to the accepted a error and power of the study, respectively, σ is the estimated standard deviation, and Δ is the expected effect size. Therefore, we expect to detect an effect size of −8.36 on AHI (pooled raw mean difference of previous trials),[1] considering a type 1 error/α error of 5% (Z_a = 1.64), and a statistical power of 90% ($Z_{(1-\beta)}$ = 1.28). Regarding the estimated AHI variability, we established an σ of 11.98, considering the AHI pooled standard deviation of all independent samples included in our previous research.[1] As a result, the expected sample size is ≈35 participants per arm of our controlled clinical trial. However, assuming a maximum of a 17.25% drop-out rate (based on the average drop-out rate of previous studies)[1] we decided to recruit a total sample size of ≈42 participants for each study group. Thus, a total of ≈84 patients

with moderate to severe OSA will be enrolled in the INTERAPNEA study. For practical and feasibility reasons, and based on our previous experience,[25,26] the study will be conducted in sets of a maximum of 30 persons.

Source of Participants

The recruitment of participants will be performed using different strategies including enrolment from the collaborating hospital sleep unit, and use of mass media (e.g., press, magazines, radio and television news, and websites). A brief in-person or phone screening will be conducted on potentially interested participants to provide general information about the study and determine suitability of inclusion. Patients willing to participate and appearing to meet the inclusion criteria will be required to attend an in-person briefing on the rationale and study aims, inclusion and exclusion criteria, assessments to be performed, and components and characteristics of the intervention. After clarification by the research staff of any participant's doubts or questions, signatures of informed consent will be obtained from participants that meet the eligibility criteria, and appointments for the baseline assessment will be given. Participant flow from recruitment to randomisation stages are shown in Figure 1.

Figure 1. Flow diagram of the INTERAPNEA study participants



Enrolment

Upon obtaining signed informed consents, participant demographics and medical history will be collected, and a medical/physical examination will be performed to ensure feasibility of participant inclusion in the study. Subsequently, a sleep study through a complete full-night polysomnography and other sleep measurements (daytime sleepiness, sleep

quality, circadian preference, functional outcomes of OSA) will be conducted on and taken from each participant. Furthermore, lifestyle habits such as diet, exercise, and tobacco and alcohol consumption will also be measured, as well as subjective health-related quality of life, and depressive and anxiety symptoms related to OSA. After completion of participant's medical and sleep studies, objective measurements of cardiorespiratory fitness and body composition will be taken from each participant. All test trials will be scheduled over three different days during a one to two-week period.

Randomisation and Blinding

After completing baseline measurements, eligible participants will be randomly assigned to either a control group or an interdisciplinary intervention group using computer generated simple (unrestricted) randomization.[27] Each participant will be specifically informed of which arm they have been assigned to and requested not to reveal their allocation to the research staff involved in further assessments. Bias related to unblinded participants, treatment counsellors and/or outcome assessors affecting data validity will be addressed by achieving different levels of blinding across the study personnel and participants, where feasible. Therefore, study personnel responsible for data collection and analysis will be blinded to allocation assignments at the follow-ups, and blinding of participants to details of study manuals and hypothesis will be attained. When blinding is not possible, rigorous procedures of standardisation of data collection and intervention, through study manuals and continuous assessment of fidelity, will be followed to avoid potential bias and ensure internal and external validity of the study.[28]

Assessment/Outcome Variables

The primary outcome of the INTERAPNEA study is the reduction in the number of apnoea and/or hypopnoea episodes per hour, i.e., AHI, assessed using a full-night ambulatory polysomnography. The main secondary outcomes include other neurophysical and cardiorespiratory polysomnographic outcomes, body weight and composition, physical fitness/cardiorespiratory fitness, and health blood biomarkers. Other variables of interest are subjective measurements of depressive and anxiety symptomatology related to OSA, impaired sleep (i.e., daytime sleepiness, sleep quality, and functional outcomes of OSA), health-related quality of life, and other lifestyle habit measurements (i.e., diet, physical activity, alcohol and tobacco consumption). All outcomes will be measured at baseline (week 0), intervention end-point (week 9), and 6 months post-intervention (week 32).

Assessment of primary and secondary outcomes will be organised and completed over three different days during a one to two-week period:

- Day 1: Potential participants will attend a medical examination and a fasting blood test at the Sleep Unit of "Virgen de las Nieves" University Hospital.
- Day 2: Eligible participants will complete a full-night in-laboratory polysomnography (PSG; the gold-standard objective testing recommended by the AASM),[29] at the Sleep and Health Promotion Laboratory (CIMCYC). In order

to avoid potential CPAP influence on PSG outcomes, participants will be required to withdraw from CPAP during the week prior to the PSG at baseline and follow-ups.[30] Prior to PSG, participants will also complete a set of questionnaires measuring subjective variables related to sleep, general physical and psychological health, and lifestyle habits including diet, physical exercise, and alcohol and tobacco consumption.

- Day 3: During the third and last assessment day, participants will be required to attend the iMUDS for the measurement of anthropometric parameters, body composition and cardiorespiratory fitness.

Baseline physical activity and sleep habits will also be obtained through a seven-day self-reported daily step log and sleep diary. See Table 2 for study outcomes and measurements.

Table 2. INTERAPNEA study outcomes and measurements

Variable	Measurement	Assessment
General health history and sociodemographic information	General medical examination (i.e., anamnesis, physical exploration, vital measurements, etc.)	Week 0
	Clinical and socio-demographic interview	Week 0
	Fasting blood test	Week 0, 9, 32
Sleep quality and health-related quality of life		
Sleep habits	Sleep diary	Week 0, 9, 32
Circadian preference/chronotype	Morningness-Eveningness Questionnaire	Week 0, 9, 32
Sleep quality	The Pittsburgh Sleep Quality Index	Week 0, 9, 32
Daytime sleepiness	Epworth Sleepiness Scale	Week 0, 9, 32
	Psychomotor Vigilance Test	Week 0, 9, 32
Perceived health-related quality of life	Sleep Apnea Quality of Life	Week 0, 9, 32
	Short-Form 36 Health Survey	Week 0, 9, 32
	General Health Questionnaire	Week 0, 9, 32
Objective sleep		
Neurophysiological outcomes	Polysomnography equipment	Week 0, 9, 32
Cardiorespiratory outcomes	Polysomnography equipment	Week 0, 9, 32
Body weight and composition		
BMI and anthropometric measurements	Weight and height measurement, and neck, chest and waist circumferences	Week 0, 9, 32
Body composition	Dual Energy X-ray Absorptiometry	Week 0, 9, 32
Lifestyle habits		
Physical exercise habits	Spring-levered pedometer and daily step logs	Week 0, 9, 32
Dietary habits	Food Behavior Checklist	Week 0, 9, 32
	Mediterranean Diet Adherence Screener	Week 0, 9, 32
Tobacco dependence and consumption	Self-reported tobacco consumption logs	Week 0, 9, 32
	The Fagerstrom Test for Nicotine Dependence	Week 0, 9, 32
Alcohol consumption	Self-reported alcohol consumption logs	Week 0, 9, 32
Physical fitness		
Cardiorespiratory fitness	2 km walk test	Week 0, 9, 32
Subjective physical fitness	International Fitness Scale	Week 0, 9, 32
Daily functioning and mood		
Functional outcomes related to sleepiness	Functional Outcomes of Sleep Questionnaire	Week 0, 9, 32
Subthreshold anxiety symptoms	State-Trait Anxiety Inventory	Week 0, 9, 32
Subthreshold depression symptoms	Beck Depression Inventory-Fast Screen	Week 0, 9, 32
	Inventario de Depresión Estado-Rasgo	Week 0, 9, 32

Primary Outcome: Apnoea-Hypopnoea Index

The primary outcome of the INTERAPNEA study is AHI, defined as the number of apnoea (90% or greater drop in airflow for 10 s or longer) and hypopnoeas (30% or greater drop in airflow for 10 s or longer associated with ≥3% oxygen desaturation or an arousal) episodes per hour of sleep.[31]

We will measure this outcome and other neurophysical and cardiorespiratory secondary outcomes through an in-laboratory PSG using SOMNOScreen™ PSG-Tele (SOMNOmedics, GmbH, Randersacker, Germany), or Somté PSG v2 system (Compumedics Limited, Abbotsford, Australia). The recordings will include all recommended physiologic signals such as electroencephalogram (three channels: F4-M1, C4-M1, O2-M1), electrooculogram (two channels: E1 and E2), electromyogram (two channels: submental and anterior tibialis muscles), and electrocardiogram (two channels). Cardiorespiratory measurements will include oral and nasal airflow (triple thermistor), oxyhaemoglobin saturation (SpO_2) and pulse-rate (pulse oximeter), respiratory effort (chest and abdomen bands), and body position (sensor). All electrodes will be placed in accordance with the international 10–20 system,[32] and recordings will be automatically and manually scored in 30 s epochs[33] by trained physicians using DOMINO (v2.7, SOMNOmedics, GmbH, Randersacker, Germany), or ProFusion PSG 3 (v3.3, Compumedics Limited, Abbotsford, Australia) associated computer software. All parameters, settings, filters, technical specifications, sleep stage scoring and event scoring will be performed in accordance with the AASM Manual for the Scoring of Sleep and Associated Events.[31]

We will also specifically analyse AHI in rapid eye movement (REM) and non-REM sleep stages (N1, N2, and N3). Although it has been shown that REM apnoea episodes may yield more adverse cardiovascular consequences than non-REM obstructions,[34] previous similar RCTs have rarely included the reduction in AHI differentiated by these sleep stages.[1]

Secondary Outcomes

Neurophysical and Cardiorespiratory Polysomnographic Outcomes

Secondary polysomnographic outcomes related to OSA measured by PSG, as mentioned above, are oxygen desaturation index (number of oxygen desaturation ≥3% per hour), SpO2 mean (average of oxygen saturation), SpO2 nadir (minimum oxygen saturation), arousal index (number of arousal per hour), total sleep time, sleep efficiency (total sleep time/total time in bed), sleep latency, wake after sleep onset (number of awakenings), REM sleep stage, REM latency, and nonREM sleep stages (N1, N2, and N3).

Physical Fitness

Cardiorespiratory fitness will be measured through a 2 km walking test, which has been widely used and validated for accurate estimation of maximum oxygen uptake (VO_{2max}).[35] Participants will be required to walk over a marked 2 km track on a firm surface wearing a heart rate monitor (Polar RS800cx, Polar Electro, Kempele, Finland). Walking time and heart

rate (HR) will be recorded at the end of the test. The maximal aerobic power will then be calculated considering age, BMI, performance time, and HR with the following formula $VO_{2max}((ml/min)/kg) = 116.2 - 2.98 * walking\ time$ (sec) $- 0.11 * HR - 0.14 * age - 0.39 * BMI$.[36] Participant's scores will be obtained and placed within a fitness category. Subjective physical fitness will also be measured using the International Fitness Scale (IFIS).[37]

Body Weight and Composition

Body weight and height will be measured using a calibrated scale and stadiometer (model 799, Electronic Column Scale, Hamburg, Germany) with participants wearing undergarments. Neck, chest and waist circumferences will also be measured following standard procedures recommended by the International Society for the Advancement of Kinanthropometry (ISAK).[38] Body composition measurements including fat mass (kg), fat free mass, lean mass (kg), visceral adipose tissue (kg), and bone mineral density (g/cm^2) will be obtained through a full-body dual energy X-ray absorptiometry (DXA) scanner (Discovery Wi, Hologic, Inc., Bedford, MA, USA). Quality controls, positioning of participants and analyses of results will be performed following the manufacturer's recommendations. Automatic delineation of anatomic regions will be performed using APEX 4.0.2. software.

Blood Biomarkers

Blood samples will be obtained from participants' antecubital vein in a supine position during the morning in a fasting state. Blood parameters will include insulin, glucose, triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), alanine transaminase (ALT), and γ-glutamyl transferase (γ-GT). Glucose levels will be measured by spectrophotometric techniques (AU5800, Beckman Coulter, Brea, California, USA). Insulin will be assessed by chemiluminescence immunoassay with paramagnetic particles (UniCel DxI 800, Beckman Coulter, Brea, California, USA). Triglycerides, total cholesterol, and HDL-C will be automatically evaluated by spectrophotometric techniques (AU5800, Beckman Coulter, Brea, California, USA). LDL-C will be considered as $(Total\ cholesterol) - (HDL - C) - 0.45 * (Triglycerides)$. ALT and γ-GT will be calculated by absorption spectrophotometric techniques (Beckman Coulter, Brea, California, USA). Insulin glucose ratio (insulin/glucose), LDL-C/HDL-C ratio (LDL-C/HDL-C), and triglycerides/HDL-C ratio (triglycerides/HDL-C) will also be determined.

Lifestyle Habits: Dietary Habits, Physical Activity, Smoking, and Alcohol Intake

Participants' dietary habits will be evaluated using the validated 14-item Mediterranean diet screener (MEDAS), which evaluates food consumption frequency (12 items) and characteristic dietary habits of the Mediterranean diet (2 items).[39] MEDAS items are scored with 0 or 1, the total score ranging from 0 to 14 points. The 22-item Food Behavior Checklist (FBC) will also be used to assess participants' food intake and habits.[40] FBC comprises seven subscales including consumption of fruit and vegetables (9 items), diet quality (4 items), fast food (3 items), dairy/calcium (2 items), sweetened

beverages (2 items), meat (1 item) and food security (1 item). This instrument has been shown to be effective at evaluating dietary behavior changes after nutrition education interventions promoting healthy diets.[40]

Physical activity will be measured using daily step logs recorded by participants with a spring-levered pedometer (OcioDual, Alicante, Spain). Participants will be required to wear the pedometer all day and register the number of steps achieved per day in a seven-day step log. The average steps per day will then be calculated at baseline and follow-ups.

Regarding the remaining lifestyle habits, smoking and alcohol intake will be measured at baseline and follow-ups using seven-day self-reported tobacco and alcohol consumption logs. Recordings will include number of cigarettes/alcoholic units consumed per day, cigarette brand/type of alcoholic drink, time, situation, and perceived pleasure (from 0 to 10). The validated form of the Fagerström Test for Nicotine Dependence[41] will also be used to assess participants' nicotine dependence in all assessments.

Daily Functioning and Mood

OSA impact on daily functioning and mood will be measured through validated versions of the Functional Outcomes of Sleep Questionnaire (FOSQ),[42] Beck Depression Inventory-Fast Screen (BDI-FS),[43] State-Trait Anxiety Inventory (STAI)[44] and *Inventario de Depresión Estado-Rasgo* (IDER).[45] It has been shown that impaired daytime functioning and depressive and anxiety symptoms are very common in patients with OSA, being higher in patients with more severe OSA and a greater BMI.[46] Hence, participants will complete a set of questionnaires on these symptoms not only to measure inclusion/exclusion criteria but also to analyse potential changes in daily functioning and mood driven by the INTERAPNEA study intervention.

Daytime Sleepiness, Sleep Quality and Health-Related Quality of Life

The Epworth Sleepiness Scale (ESS),[47] an 8-item Likert-based scale, will be used to obtain subjective measurements of participant's daytime sleepiness. Excessive daytime sleepiness is the most common consequence of OSA due to sleep fragmentation and deprivation, and one of the mediating factors for other OSA outcomes such as daily functioning, social and occupational disturbances.[6–8] We will also include the Psychomotor Vigilance Test (PVT),[48] regarded as a potential and reliable objective measure of sleepiness, using PC-PVT v 2.0 software (Biotechnology HPC Software Applications Institute [BHSAI], https://pcpvt.bhsai.org/pcpvt/register.xhtml, Frederick, Maryland, USA) on a personal computer.[49,50] This 10 min sustained attention task consists of responding to visual stimulus randomly presented in a black screen each 2 to 10 s, to which participants have to respond by clicking the mouse, with the reaction time being registered and analysed in terms of response speed and number of lapses (reaction time >500 ms).

As sleep quality is also closely related to daily functioning, mood and, thus, participant's general quality of life and well-being,[51,52] we will measure potential benefits of the INTERAPNEA study intervention on these variables through the

validated versions of the Pittsburgh Sleep Quality Index (PSQI),[53] Sleep Apnea Quality of Life (SAQLI),[54] Short-Form 36 Health Survey (SF-36),[55] and General Health Questionnaire (GHQ-28).[56]

In addition, we will subjectively measure circadian preference or individual's chronotype using the validated reduced 5-item version of the Morningness-Eveningness Questionnaire (MEQ),[57] an outcome which has been closely related to age, BMI and, in turn, OSA.[58] Evidence suggests that evening-type chronotype may be highly associated with greater unhealthy eating behaviors, sleep disruption, poor sleep quality and mood disturbances, all playing a part in the development and severity of OSA.[58,59]

Cost-Effectiveness Analysis Outcome

Cost-effectiveness analysis (CEA) is an essential outcome measurement to be included in RCTs in order to evaluate not only whether a new/alternative intervention produces higher beneficial effects than standard care, but also if those benefits are sufficiently significant to justify the additional costs.[60–62] INTERAPNEA will include CEA as an important variable considering the incremental cost-effectiveness ratio (ICER) of the interdisciplinary weight loss and lifestyle intervention related to the usual care (i.e., CPAP). Thus, following standard measures used in medical cost-effectiveness studies and international recommendations,[60,61] we will calculate the ratio of the incremental costs and the incremental clinical benefits as the additional expenditure required to generate an additional unit of benefit, expressed as cost per quality-adjusted life-year (QALY) added, and calculated as $CE = \frac{Cost_2 - Cost_1}{QALY_2 - QALY_1}$.[62] With regard to the cost measurements, we will follow the WHO recommendations for estimating costs contemplated in its CEA guidelines such as the cost of providing the intervention (e.g., labour, capital, and consumables), and costs of accessing the intervention (e.g., resources used and time costs related to seeking or obtaining the intervention).[60] Furthermore, we will conduct additional sensitivity analyses considering age-weighting as well as weighting of other potential variables such as OSA severity and other secondary outcomes. Apart from calculating the cost-effectiveness ratio of the intervention related to usual care, we will consider the acceptable Spanish cost-effectiveness ratio threshold of 25.000 €–30.000 € per QALY added.[63,64] Subject to the interdisciplinary weight loss and lifestyle intervention resulting in significantly better clinical outcomes and considerably lower costs, the INTERAPNEA intervention could potentially be labelled as a 'dominant strategy'.[62]

The Intervention Rationale

The design, implementation and evaluation of the INTERAPNEA study intervention components and characteristics are based on results of previous epidemiological and clinical research[1,10] as well as on international evidenced-based clinical practice guidelines for the management of OSA.[14,19] Considering our previous research[1] and with the final aim of the intervention being adaptable to actual primary health-care settings, the intervention will last eight weeks, and will be composed of five different modules: (i) Nutritional behavior change, (ii) moderate aerobic exercise, (iii) smoking reduction and cessation, (iv) alcohol intake avoidance, and (v) sleep hygiene (see Table 3). Each component will include group-based

weekly sessions of 60–90 min lead and supervised by a trained professional in the field (i.e., human nutrition and dietetics, physical activity and sport sciences, and psychology).

The key-factor of this interdisciplinary intervention will be the use of the Transtheoretical Model of Health Behavior Change (TM) by Prochaska and Diclemente.[65] This well-evidenced model of behavior change is based on integrating different intervention theories into an interventional approach that considers different stages, processes and principles of change with the premise of establishing sustainable health-related behaviors or habits.[65] Consciousness raising, self-reevaluation, counterconditioning, stimulus control, contingency management, goal-setting, self-monitoring, self-efficacy, and decisional balance are some of the processes and principles of change addressed by this theory and, therefore, included in the five different INTERAPNEA intervention components. Physical and dietary interventions for weight loss using strategies of TM and, thus, psychological support, have been shown to be more effective than other approaches in overweight and obese patients[66] and, specifically, in those with OSA.[1]

Table 3. Description and timing of the INTERAPNEA intervention modules and components

Module	Objectives/Description	Number of Sessions	Frequency of Sessions	General Behavioral Change Techniques
Nutritional behavior change	Nutrition education and dietary patterns change	8	Once a week	• Motivation and preparation for action • Goal-setting and action-planning • Self-monitoring and functional behavioral analysis • Review of behavioral goals, action plans, and adherence • Problem solving and social skills • Self-efficacy, maintenance, and relapse prevention
Physical exercise	Supervised moderate aerobic exercise and increase daily steps by 15% each week	8	Once a week	
Sleep hygiene	Change of inappropriate sleep habits: Insufficient sleep, consumption of coffee, alcohol and tobacco, and inappropriate sleep schedule and environment	4	Once every two weeks	
Tobacco cessation	Nicotine and cigarette fading: Reduction of nicotine and number of cigarettes by 30% each week	8	Once a week	
Alcohol avoidance	Alcohol consumption fading: Reduction of alcohol consumption by 30% each week	4	Once every two weeks	

2.6.1. Nutritional Behavior Change

Diet quality and dietary patterns have been shown to be closely related to biologic pathways involved in chronic disease etiology[67] and, specifically, to sleep disruption, fragmentation and poor sleep quality found in OSA.[68] Recent studies have shown that high-fat intake is associated with lower sleep efficiency and REM sleep and higher arousal index, whereas high-carbohydrate intake may improve sleep duration and architecture by producing reductions in sleep-onset latency and higher proportions of REM sleep.[68] Regarding intake of micronutrients, vitamin D—which has been associated with insulin resistance in OSA[69]—and magnesium deficiencies have also been related to shorter sleep duration, poorer sleep quality and higher daytime sleepiness.[70,71] Therefore, dietary components including milk, fish, fruit and vegetables may yield beneficial effects on sleep and, in turn, OSA.[68]

Furthermore, evidence suggests that sleep disturbances occurring in OSA, in turn, have adverse consequences on calorie intake and expenditure, therefore, exposing a two-way relationship between dietary habits and sleep.[72] Empirical studies

have revealed that sleep fragmentation and deprivation are related to higher energy intake of unhealthy foods due to increased hunger, food craving, food reward and portion size selection.[73–75] Neurocognitive impairments found in patients with OSA such as attention and episodic memory deficits[76] have also been associated with higher intake of saturated fats, loss of control over food intake, and thus uncontrolled eating.[77]

Hence, the INTERAPNEA intervention includes a nutrition module comprising eight 60–90 min sessions (once a week) in a group format addressing dietary patterns using integrated techniques of nutrition education and behavioral change such as specific goal-setting, cognitive restructuring, stimulus control, progressive muscle relaxation, social skills and assertiveness, and problem-solving skills. The nutrition education is based on the World Health Organisation's (WHO) latest recommendations on food intake and healthy diet (see Table 4 for detailed topics) and each session will follow a three-part format: (i) Brief review of previous session and participant's adherence to recommendations; (ii) development of the main nutrition education components of each session using an interactive group discussion layout; (iii) resolution of participant's questions and/or concerns, and setting of specific goals. No specific or individualised diet will be indicated to participants.

Table 4. Description of nutrition education per session

Session	Nutrition Education Topics
Session 1	Adverse consequences of obesity, importance of healthy nutrition and body composition on health, and positive effects of changes in nutrition.
Session 2	Maintenance of a healthy nutrition based on the Harvard Plate model: increasing consumption of healthy food (vegetables, fruits, legumes, nuts, extra virgin olive oil, fish and shellfish, white meat, eggs and herbs) and decreasing consumption of unhealthy food (ultra-processed foods, excessive salt consumption, processed meats, red meat, alcohol, and high-calorie foods and beverages).
Session 3	Food myths and health risks of miracle diets.
Session 4	Strategies to improve satiety and decrease appetite: Decreasing dishes dietary energy density, choosing food with low dietary energy density, managing dietary fat intake, including enough fibre and protein, limiting sugar and ultra-processed foods, choosing water and low-calorie beverages, and managing portion sizes.
Session 5	Healthy breakfast and snacks: Avoiding unhealthy breakfasts and snacks and making them healthier.
Session 6	Healthy cooking, food purchase and choices when eating out.
Session 7	How to read nutritional labels of food and distinguish between healthy and unhealthy food.
Session 8	Nutritional strategies to improve sleep quality.

Physical Exercise

Physical exercise has been shown to be effective in enhancing OSA outcomes and health-related consequences.[1,78,79] Due to the close association between OSA and obesity, a significant and sustainable increase of physical activity could lead to a reduced body weight and, in turn, improvement of the upper airway structure, function, and resting lung volume.[12] Furthermore, physical exercise could also assist the balance of energy intake and expenditure,[80] and improve respiratory center modulation through a reduction of the high leptin and ghrelin hormone levels, which are abnormalities linked to excessive energy intake found in OSA patients.[81] Yet, some research found that exercise benefits on OSA were independent to weight loss,[79] suggesting that there are other related mechanisms potentially leading to OSA enhancement such as the

increase of sleep efficiency and slow wave sleep,[82] and a decrease of fluid accumulation implicated in the upper airway collapse,[83] both due to the direct association between physical exercise and sleep.

Therefore, the INTERAPNEA study will include an eight-week physical exercise programme consisting of weekly 60 min sessions of supervised moderated aerobic exercise (i.e., 55–65% of the heart rate reserve) and individualised goal-setting to increase daily steps per week. Previous studies have emphasised that walking may be the exercise modality to achieve higher levels of weight loss and increased cardiorespiratory fitness in adults with obesity and CPAP-treated OSA.[84] Thus, in the weekly supervised training sessions, participants will be required to walk at a moderate intensity for 60 min wearing a heart rate monitor in order to train themselves to walk at that intensity during the week. With respect to goal-setting, they will be advised to increase their daily steps by 15% per week, based on their daily steps logs.

Sleep Hygiene

Sleep hygiene refers to the practice of certain behaviors that facilitate sleep onset and maintenance (e.g., regular sleep schedule, appropriate sleep environment, exercise-training, and healthy nutrition), and avoidance of habits interfering with sleep (e.g., daytime napping, smoking, alcohol intake, and use of hypnotics).[85] Patients with OSA frequently exhibit poor sleep hygiene including voluntary sleep restriction, irregular sleep schedule, inappropriate sleep environment, and excessive consumption of alcohol, nicotine and/or caffeine.[86] Accordingly, previous studies have supported the inclusion of this component in the treatment of OSA as effective in improving sleep quantity and efficiency, and therefore daytime sleepiness.[1,87,88]

The INTERAPNEA study intervention will include a sleep hygiene module comprising 60 min sessions supervised by a psychologist, specialised in the evaluation and treatment of sleep disorders. As most sleep hygiene topics will be covered in simultaneous modules, there will be four sessions distributed over the eight weeks of the intervention, consisting of sleep hygiene education on causes of sleep disturbances and mistaken sleep related knowledge (see Table 5). Sessions will also be based on treating those frequent inadequate sleep habits found in patients with OSA, i.e., sleep restriction, irregular schedule and inappropriate sleep environment.

Table 5. Summary of components of the sleep hygiene module per session

Session	Intervention Objectives/Components
Session 1	• Goal-setting and action-planning: Objective specification and commitment • Self-monitoring: Sleep diary • Psychoeducation: What is sleep hygiene? • Cognitive restructuring: Irrational, false or inaccurate beliefs about sleep • Breathing and relaxation techniques: Diaphragmatic breathing and progressive muscle relaxation
Session 2	• Review of behavioral goals, action plans, and compliance (participant's homework) • Self-monitoring: Sleep diary • Psychoeducation: Voluntary sleep restriction; coffee, alcohol and tobacco consumption before sleep; and irregular sleep schedule and environment • Cognitive restructuring: Irrational, false or inaccurate beliefs about sleep • Review of diaphragmatic breathing and progressive muscle relaxation
Session 3	• Review of behavioral goals, action plans, and compliance (participant's homework) • Self-monitoring: Sleep diary • Vicarious and self-reinforcement: Changes in sleep habits achieved and benefits • Stimulus control and bedtime restriction • Review of diaphragmatic breathing and progressive muscle relaxation
Session 4	• Review of behavioral goals, action plans, and compliance (participant's homework) • Self-monitoring: Sleep diary • Vicarious and self-reinforcement: Changes in sleep habits achieved and benefits • Review of all intervention components: Main factors of sleep hygiene, diaphragmatic breathing and progressive muscle relaxation, stimulus control and bedtime restriction • Maintenance and relapse prevention: Analysis of high-risk situations for unhygienic sleep.

Reduction and Avoidance of Tobacco Consumption

Smoking has been related to the worsening of OSA via different mechanisms such as changes in sleep architecture and increase of arousal threshold from sleep, reduction of the upper airway muscle tones and neural reflexes, and increased inflammation of the upper airway, all due to nicotine and smoke inhalation.[21] In turn, OSA could also be a predisposing factor for smoking addiction, with nicotine acting as a reward or self-medication for the depressive and anxiety symptoms commonly found in OSA.[89] Although this association has been well elucidated, there is no empirical evidence of the potential beneficial effects of smoking cessation on OSA as, surpringsily, there are no studies focusing on active smoking cessation interventions in patients with this condition.[1]

Therefore, we will include a smoking reduction and avoidance module in the INTERAPNEA study intervention. Participants with smoking addiction who are willing to quit will be required to attend a weekly 60–90 min session over eight weeks lead by two clinical psychologists. The specific intervention is based on the group behavior therapy for smoking cessation by Becoña et al.[90] This therapy seeks the progressive reduction of tobacco consumption through the use of nicotine and cigarette fading,[91] as well as behavior-change techniques such as information on smoking, self-monitoring, stimulus control, avoidance of withdrawal symptoms, and relapse prevention (see Table 6). Nicotine and cigarette fading

has been shown to be the most effective method to reduce and stop smoking with abstinence rates of 86% at the end of treatment and nearly 60% at a 12-month follow-up.[92]

Thus, participants will be mainly required to keep a daily record of the number of cigarettes smoked, and triggers for smoking (self-monitoring), change the type of cigarette smoked to a lesser nicotine content brand each week (30%, 60% and 90% nicotine reductions from baseline), reduce the number of cigarettes smoked by 30% weekly, and avoid smoking in three different situations per week (stimulus control). Through the sessions, other behavior change techniques will be implemented such as discussions on the health consequences of smoking and quitting (motivation), muscle and cognitive relaxation techniques to address withdrawal symptoms, and identification of high-risk situations for smoking and problem-solving skills (relapse prevention).

Table 6. Summary of components of the smoking cessation module per session

Session	Intervention Objectives/Components
Session 1	• Goal-setting and action-planning: Objective specification and commitment • Self-monitoring: Cigarette consumption logs • Psychoeducation: Cigarette components and smoking consequences • Cognitive restructuring: Irrational, false or inaccurate beliefs about smoking cessation • Stimulus control: Reduction strategies • Nicotine and cigarette fading: Reduction of nicotine/number of cigarettes by 30% from baseline • Breathing and relaxation techniques: Diaphragmatic breathing and progressive muscle relaxation
Session 2	• Review of behavioral goals, action plans, and compliance (participant's homework) • Self-monitoring: Cigarette consumption logs • Cognitive restructuring: Irrational, false or inaccurate beliefs about smoking cessation • Stimulus control: Smoking avoidance in three different situations and other reduction strategies • Nicotine and cigarette fading: Reduction of nicotine/number of cigarettes by 30% from week 1 • Maintenance and relapse prevention: Avoidance of withdrawal symptoms • Review of diaphragmatic breathing and progressive muscle relaxation
Session 3	• Review of behavioral goals, action plans, and compliance (participant's homework) • Self-monitoring: Cigarette consumption logs • Vicarious and self-reinforcement: Changes in smoking achieved and benefits • Stimulus control: Smoking avoidance in six different situations and other reduction strategies • Nicotine and cigarette fading: Reduction of nicotine/number of cigarettes by 30% from week 2 • Maintenance and relapse prevention: Avoidance of withdrawal symptoms • Review of diaphragmatic breathing and progressive muscle relaxation
Session 4	• Review of behavioral goals, action plans, and compliance (participant's homework) • Self-monitoring: Cigarette consumption logs • Vicarious and self-reinforcement: Changes in smoking achieved and benefits • Stimulus control: Smoking avoidance in nine different situations and other reduction strategies • Nicotine and cigarette fading: Reduction of nicotine/number of cigarettes by 30% from week 3 • Maintenance and relapse prevention: Avoidance of withdrawal symptoms • Review of diaphragmatic breathing and progressive muscle relaxation

(continued)

Table 6. Summary of components of the smoking cessation module per session (continued)

Session 5	• Review of behavioral goals, action plans, and compliance (participant's homework) • Self-monitoring: Cigarette consumption logs • Vicarious and self-reinforcement: Changes in smoking achieved and benefits • Abstinence planning: Setting the day when abstinence starts • Problem solving and social skills: High risk situations for smoking and alternative behaviors • Maintenance and relapse prevention: Avoidance of withdrawal symptoms • Review of diaphragmatic breathing and progressive muscle relaxation
Sessions 6, 7, 8	• Review of behavioral goals, action plans, and compliance (participant's homework) • Self-monitoring: Cigarette consumption logs/review of abstinence • Abstinence planning: Setting the day when abstinence starts • Vicarious and self-reinforcement: Changes in smoking achieved and benefits • Problem solving and social skills: High risk situations for smoking and alternative behaviors • Review of diaphragmatic breathing and progressive muscle relaxation • Maintenance and relapse prevention: Difference between lapse and relapse

Reduction and Avoidance of Alcohol Intake

Alcohol intake has also been related to the development and worsening of OSA not only for its direct and indirect effects on weight gain but also due to its negative impact on breathing parameters during sleep.[20] Recent meta-analyses on alcohol and risk of sleep apnoea emphasised that alcohol intake increases the risk of breathing cessation episodes by 25%, thus increasing AHI and reducing mean SaO_2 during sleep.[93] Potential explanations for these adverse consequences may be the alcohol-related hypotonia of oropharyngeal muscles during sleep, and depression of the arousal response to asphyxia, both caused by the alcohol depressant effects on the central nervous system.[94]

Therefore, the INTERAPNEA study intervention will include an alcohol intake reduction and avoidance module supervised by two clinical psychologists. As we will be treating excessive alcohol intake as opposed to alcohol dependence, this module will last eight weeks comprising fortnightly sessions of 60 min. Similar to the smoking cessation module, the main content of this specific component is the progressive reduction of alcohol intake in those participants with no alcohol addiction but excessive consumption (see Table 7). Thus, participants will be indicated to reduce the number of units of alcohol consumed per day/week by 30% each week, keeping a log of alcohol-consumption per day including units of alcohol consumed and triggers of consumption. During the sessions, participants will receive detailed information of alcohol general and specific to OSA health-related consequences. Furthermore, behavior change techniques such as stimulus control, muscle and cognitive relaxation and problem-solving skills related to alcohol consumption will be used.

Table 7. Summary of components of the alcohol avoidance module per session	
Session	Intervention Objectives/components
Session 1	• Goal-setting and action-planning: Objective specification and commitment • Self-monitoring: Alcohol-consumption logs • Psychoeducation: Alcohol consumption and adverse consequences for obstructive sleep apnoea • Cognitive restructuring: Irrational, false or inaccurate beliefs about alcohol consumption • Alcohol fading: Reduction of alcohol consumption/number of alcoholic drinks by 30% from baseline • Breathing and relaxation techniques: Diaphragmatic breathing and progressive muscle relaxation
Session 2	• Review of behavioral goals, action plans, and compliance (participant's homework) • Self-monitoring: Alcohol-consumption logs • Cognitive restructuring: Irrational, false or inaccurate beliefs about smoking cessation • Alcohol fading: Reduction of alcohol consumption/number of alcoholic drinks by 30% from week 1 • Stimulus control: Reduction/abstinence strategies • Review of diaphragmatic breathing and progressive muscle relaxation
Session 3	• Review of behavioral goals, action plans, and compliance (participant's homework) • Self-monitoring: Alcohol-consumption logs • Vicarious and self-reinforcement: Changes in alcohol consumption achieved and benefits • Abstinence planning: Setting the day when abstinence starts • Stimulus control: Reduction/abstinence strategies • Review of diaphragmatic breathing and progressive muscle relaxation
Session 4	• Review of behavioral goals, action plans, and compliance (participant's homework) • Self-monitoring: Alcohol-consumption logs • Vicarious and self-reinforcement: Changes in alcohol consumption achieved and benefits • Problem solving and social skills: High risk situations for drinking alcohol and alternative behaviors • Review of all intervention components: Diaphragmatic breathing and progressive muscle relaxation, stimulus control • Maintenance and relapse prevention: Difference between lapse and relapse

Standard Care/Control Group

Participants with moderate-severe OSA randomly assigned to the usual care group (control) will receive, apart from CPAP treatment, general advice on weight loss and lifestyle changes from a sleep disordered-breathing specialist. Informative leaflets describing the positive effects of healthy nutrition, physical activity, sleep hygiene and tobacco and alcohol avoidance for OSA will also be provided to these participants. Additionally, the opportunity to receive the INTERAPNEA study intervention will be offered to this control group after the six-month follow-up.

Assessment of Compliance and Integrity of Intervention

Integrity of the intervention and treatment fidelity will be evaluated and ensured including the design and implementation of different strategies of process assessment, monitoring and enhancement in order to guarantee internal and external validity of the trial.[95]

Firstly, regarding the study design and provider of intervention training, we developed a comprehensive hand-book for the qualified INTERAPNEA study intervention providers/professionals/training personnel of each module (nutrition, physical exercise, sleep hygiene, and tobacco and alcohol consumption). Each intervention manual identifies the theoretical model of the intervention and provides detailed descriptions of session objectives, treatment guidelines in accordance with each objective (i.e., contents, tasks and activities, recommendations, and timing), participant's homework, and material needed for each session. We will also provide each participant with an adapted patient-handbook for each intervention component including descriptions of sessions, and work and logging sheets.

Secondly, we will ensure fidelity in the treatment delivery, receipt, and enactment through the use of these intervention protocols/manuals and monitoring of the implementation. Regarding the treatment delivery, the standardisation of the intervention will support the protocol adherence of providers and the treatment differentiation (i.e., the delivery of the target treatment and no other). Furthermore, we will include a check-list for provider's self-report concerning the achievement of session objectives. With respect to the treatment receipt and enactment, fidelity will be assessed and confirmed through different strategies such as the structuring of the intervention around achievement-based objectives, collecting and reviewing of participants self-monitored data (daily steps log, sleep diaries, alcohol and tobacco consumption records), and information delivery in different formats (e.g., written in the handbooks, and verbal and visual in the sessions).

Finally, apart from the above mention strategies, we will consider complementary approaches in order to reduce participant drop-out rates and increase adherence such as prevention of commitments or vacation periods, use of well-equipped and conditioned facilities, and supervision by a qualified and certified pair of providers in each session, motivating and supporting participants. Participants' attendance to each intervention session will be recorded by providers, and phone-calls will be made to assess causes of absence and determine further participation in the intervention.

Analytical Approach and Statistical Power/Data Management

We will perform descriptive and exploratory preliminary analyses of all the study variables to reveal violations of statistical assumptions, distributions, imbalances between the study groups, associations between study variables, covariates/confounders, amount of missing data, and drop-out patterns. Covariates or confounders will be secondarily included in the main statistical analysis, evaluating therefore, their impact on the results. To ensure that conclusions are robust, attrition bias will be overcome through intention-to-treat-analysis, including all participants as originally allocated after randomisation using multiple imputation methods for predicting end-points missing values. Per-protocol

comparison of groups, including only those participants who fully completed the originally allocated treatment, will also be computed and compared with intention-to-treat analysis results.

The intervention effects on primary and secondary study outcomes will be assessed through multi-level mixed analyses using the package *nlme*[96] from the R statistical program. This method will allow us to analyse differences including time and group allocation as within and between subject factors, respectively, adjusting for potential covariates and levels such as group or set of participants. Therefore, group/condition will be considered as a fixed variable (intervention group compared to control group), and sets/waves of participants as a random factor. With these specifications, we will be able to control the intra-class correlation (per set of participants nested within conditions) between scores at baseline and post-test or follow-up. We will adjust the model including the baseline values of outcomes that are to be analysed in the specific analysis as covariates, as well as other potential covariates such as age, OSA severity, BMI, motivation to change, and attrition propensity. The latter will be calculated using a model predicting the actual attrition with baseline value.[97] Baseline measurements included in these attrition propensity prediction models will include set of participants, participant's allocation, age, OSA severity, BMI, and motivation to change. The primary and secondary study outcomes that are to be analysed will be those previously mentioned in the outcomes section.

Lastly, we will also estimate standardised effect sizes using Cohen's d coefficients as the mean difference between the mean change in intervention and control groups from baseline to post-intervention divided by the mean baseline standard deviation:[98] $d = [((\overline{X}_{pre,E} - \overline{X}_{pos,E}) - (\overline{X}_{pre,C} - \overline{X}_{pos,C})) / \overline{X}_{pre}]$

Potential impact of INTERAPNEA

OSA is a global health issue with a concerning and increasing prevalence associated with the rising epidemic of obesity.[9,13] Both these related conditions are predisposing factors for the development and worsening of metabolic dysfunctions, type II diabetes, and, in turn, life-threating cardiovascular diseases such as heart failure, atrial fibrillation, coronary artery disease and stroke.[99] Due to these vast and severe health consequences, besides the direct cost of OSA diagnosis, treatment, and workplace and motor vehicle accidents produced by daytime sleepiness, OSA has become a substantial clinical and economic burden on the health system.[100]

An epidemiological study by Hillman et al.,[101] concluded that the overall cost of sleep disorders in Australia—with OSA as the most prevalent condition—was $7494 million in 2004 (population: 20.1 million), including direct health costs (i.e., sleep disorders and associated conditions), indirect financial costs (i.e., work-related injuries, motor vehicle accidents, and other production losses), and nonfinancial costs (net cost of suffering). Taking into account that the prevalence of OSA has dramatically increased in recent years (9% to 38% in the overall population),[9] the cost should respectively now be ominously higher. Other retrospective and longitudinal studies have also emphasised the major clinical and financial costs of OSA by reporting significantly greater healthcare utilisation by patients with this condition compared to those without

OSA.[102–105] Furthermore, a recent study by Derose et al.[106] concluded that even after the provision of positive airway pressure, the rates of acute care and medication use of patients with OSA did not reduce over several years of follow-up.

The INTERAPNEA study is aimed at demonstrating the potential and beneficial effects of a non-pharmacological and non-surgical tailored weight loss and lifestyle intervention for the management, improvement, and even complete remission of OSA. Although a number of studies have separately shown that physical exercise and diet may improve OSA primary outcomes, there is a lack of studies including a combination of both weight loss components.[1] Furthermore, there are no studies including active intervention components addressing tobacco and/or alcohol avoidance in patients with this condition[1] despite the well-evidenced severe consequences that smoking and alcohol intake have on OSA and comorbid diseases.[20,21,89,93,94]

To our knowledge, this is the first study to describe the effects of a well-established interdisciplinary weight loss and lifestyle intervention on the primary and secondary outcomes of OSA, and other important physical and psychological health-related outcomes such as blood biomarkers, body composition, cardiovascular risk, daytime functioning and mood, and general quality of life. The inclusion of all these secondary outcomes, in turn, will potentially allow us to determine which may be the key variables mediating and/or predicting the main changes in OSA. The use of objective measurements ensuring validity of results such as full-night PSG, blood test, body composition, and cardiorespiratory fitness, besides the addition of psychological/coaching support on the design and implementation of the intervention components, provides the INTERAPNEA study with unique and strong characteristics in this field of research.

In conclusion, the INTERAPNEA study will overcome all the shortcomings found in previous OSA research and, therefore, our findings will have a potential impact not only on the knowledge and management of this condition but also on high-risk comorbidities such as obesity, type II diabetes, cardiovascular disease, and neurocognitive dysfunctions. Considering the feasibility of the intervention in real life settings, it may contribute to the standardisation of a cost-effective treatment for preventing, improving and/or curing the severe health-consequences of this increasingly common sleep-disordered breathing.

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RESULTS

CHAPTER 3

Interdisciplinary weight loss and lifestyle intervention for obstructive sleep apnea: The INTERAPNEA randomized clinical trial (**Study 3**)

ABSTRACT

Obesity is the leading attributable cause of obstructive sleep apnea (OSA); however, the effects of weight loss and lifestyle interventions on OSA and comorbidities still remain uncertain. This study was aimed at evaluating the efficacy of an interdisciplinary weight loss and lifestyle intervention on OSA and comorbidities among overweight/obese adults with moderate-to-severe OSA. The INTERAPNEA study was a randomized, parallel-group, open-label trial conducted from April 2019 to October 2020. Adults aged 18-65 years with CPAP-treated moderate-to-severe OSA and a body mass index equal or greater than 25 kg/m2 from a hospital-based referral center were randomly assigned to usual-care (continuous positive airway pressure; CPAP), or an eight-week weight loss and lifestyle intervention involving nutritional behavior change, aerobic exercise, sleep hygiene, and alcohol and tobacco cessation, combined with usual-care. The primary endpoint was the change in the apnea-hypopnea index (AHI). Secondary endpoints comprised changes in other OSA sleep-related outcomes; body weight and composition; cardiometabolic risk; and health-related quality of life. Out of the 89 participants who underwent randomization (mean [±SD] age, 54±8 years; mean AHI, 41±22 events/hr), 49 were randomly assigned to the control group and 40 to the intervention group. The intervention group had a greater reduction in AHI (51% reduction; change in AHI, -21.2; 95% confidence interval, -25.4 to -16.9) than the control group (2.5; -2.0 to 6.9) at intervention endpoint, with a mean between-group difference of -23.6 events/hr (-28.7 to -18.5). At 6 months after intervention, the reduction in AHI in the intervention group was of 57%, with a mean between-group difference of -23.0 events/hr (-28.4 to -17.4). In the intervention group, 45% of participants no longer required CPAP at intervention endpoint; 15% attaining complete OSA remission. At 6 months after intervention, complete remission of OSA was attained by 29% of participants; 62% no longer requiring CPAP therapy. Greater improvements in body weight and composition, cardiometabolic risk, and health-related quality of life were also found in the intervention group as compared with the control group. An interdisciplinary weight loss and lifestyle intervention involving adults with CPAP-treated moderate-to-severe OSA resulted in clinically meaningful and sustainable improvements not only in OSA severity and comorbidities but also in health-related quality of life. This approach may therefore be considered as a central strategy to comprehensively address the staggering impact of this increasingly common sleep-disordered breathing.

Introduction

Obstructive sleep apnea (OSA), characterized by recurrent sleep-state dependent upper-airway collapse, is a globally recognized major public health problem affecting up to 38% of adults in the general population, with obesity as the leading attributable cause.[1,2] OSA has indeed recently emerged as a prime target of medical research and practice owing not only to its increasing prevalence — associated with the rising obesity epidemic —[3] but also to its wide spectrum of clinical and socioeconomic consequences.[4-6] The intermittent pharyngeal obstructions sustained during sleep result in long-term exposure to hypoxia, hypercapnia, increased sympathetic activity, oxidative stress, and systemic inflammation.[7] Given these pathophysiological responses, OSA is strongly and independently associated with a substantial increased likelihood of hypertension, dyslipidemia, diabetes, life-threatening cardiovascular diseases, and all-cause mortality.[8-12]

The first-line treatment for OSA is continuous positive airway pressure (CPAP); a device serving to maintain upper-airway patency through positive pressure applied with a nasal or oronasal interface.[13] Although effective at reducing upper-airway occlusions when used as prescribed, CPAP adherence rates are suboptimal, and long-term benefits remain uncertain.[13-15] Large observational and experimental studies revealed no significant reductions in metabolic risk or cardiovascular events after long-term CPAP therapy,[15-18] which may evidence the complex and reciprocal interaction between OSA and obesity.[19]

Conversely, weight loss through alternative or combined behavioral interventions appears to substantially improve OSA and coexisting conditions in adults.[20-27] However, previous trials in this regard, although enlightening, comprised limitations inherent to the study design or methodology including, but not limited to, stringent eligibility criteria, limited reported outcomes, and/or non-randomized allocation; which restrict generalizability of results.[22,28] Furthermore, weight loss has only been addressed through restricted diets or exercise, without either a combination of both components or behavioral approaches pursuing maintenance of benefits.[22] Most remarkably, there is no study focusing on alcohol avoidance and smoking cessation;[22] well-evidenced behavioral risk factors associated with the occurrence and worsening of OSA.[29,30]

The interdisciplinary weight loss and lifestyle intervention for OSA (INTERAPNEA) trial sought to determine the efficacy of a novel interdisciplinary weight loss and lifestyle intervention for the improvement of OSA and comorbidities in overweight/obese adults with CPAP-treated moderate-to-severe OSA.[31]

Methods

Study Design and Oversight

The INTERAPNEA study was an investigator-initiated, randomized, parallel-group, open-label trial designed to evaluate the effects of an eight-week interdisciplinary weight loss and lifestyle intervention combined with usual-care (i.e. CPAP),

as compared with usual-care alone, on OSA severity (i.e. apnea-hypopnea index [AHI]; number of apneas and hypopneas per hour of sleep), and OSA-related comorbidities among adults with moderate-to-severe OSA.

This research was design by the two first and last authors, and conducted with the collaboration of all authors (see Methods in Supplementary Material for study organization). The trial rationale, design, and methodology has previously been published[31] and the full protocol is available in Annexes. The study was registered and approved by all regulatory authorities and ethics committees of each collaborating center, with all participants providing written informed consent.

Study Population

Eligible participants were men aged 18-65 years with CPAP-treated moderate-to-severe OSA (AHI equal or greater than 15 events per hour of sleep), and a body mass index (BMI) equal or greater than 25 kg/m^2. Exclusion criteria was current participation in a weight loss program, presence of any psychological/psychiatric disorder, and coexistence of any other primary sleep disorder. The eligibility criteria was based on a thorough consideration of the potential generalizability of results and, thus, no criteria regarding potential responsiveness, comorbidities, compliance rates, or use of non-hypnotic medications was established; our sample therefore reflecting the heterogeneity of the OSA population. Further details of eligibility criteria are provided in the Methods in Supplementary Material.

Study Recruitment, Enrollment and Randomization

Recruitment, enrollment, randomization and allocation of participants were performed in three consecutive sets of 30-35 participants. They were recruited from the sleep-disordered breathing unit of the collaborating hospital. Prior to their enrollment, potential participants were clinically/physically examined and completed baseline measurements to ensure inclusion feasibility. Successively, enrolled participants were randomly assigned to either usual-care (control group) or weight loss and lifestyle intervention combined with usual-care (intervention group). Randomization was performed by means of a computer-generated simple (unrestricted) randomization.[32]

Given the nature of the intervention, participants and clinicians were aware of trial-group assignments after randomization. However, the research personnel responsible for data collection and analysis was blinded to allocation assignments at the follow-up. Additionally, rigorous procedures of standardization of data collection and intervention were followed to ensure internal and external validity of the trial.[33]

Study Assessments and Endpoints

Assessments at baseline, intervention endpoint (i.e., after 8 weeks) and 6 months after intervention included a full-night in-laboratory polysomnography, a set of questionnaires, a full-body dual energy X-ray absorptiometry (DXA) scanner, and a fasting blood test. The primary endpoint of the INTERAPNEA trial was the change in AHI objectively measured by polysomnography. Secondary endpoints included changes in other sleep-related variables; body weight and composition; and cardiometabolic risk endpoints including blood pressure, glucose and lipid metabolism, and liver function. Health-related quality of life and lifestyle habits were also included as additional endpoints. Primary and secondary sleep-related endpoints, as well as self-reported endpoints related to general physical and psychological health were measured at each

study assessment after a week without CPAP use. Full descriptions of study assessments and endpoints are provided in the Methods in Supplementary Material.

Study Intervention and Control Groups

The interdisciplinary weight loss and lifestyle intervention was precisely designed and implemented based on previous research[22] and existing evidenced-based clinical practice guidelines for the management of obesity[34,35] and OSA.[4,5,20,21] Accordingly, and with an additional consideration of feasible implementation in real-world clinical practice, the intervention lasted eight weeks and was composed of five components/modules: nutritional behavior change; moderate aerobic exercise; smoking cessation; alcohol intake avoidance; and sleep hygiene. Each component included group-based weekly sessions of 60–90 min lead and supervised by trained professionals in each field. A detailed intervention description, including the assessment of intervention compliance and integrity, has previously been published[31] and is also provided in the Methods in Supplementary Material.

Participants randomly assigned to usual-care received, apart from CPAP, general advice on weight loss and lifestyle change from a sleep-disordered breathing specialist in a single 30 min session. Additionally, the opportunity to receive the INTERAPNEA trial intervention was offered to all participants at the end of the trial.

Statistical Analysis

The sample size and power of the INTERAPNEA trial were estimated based on previous studies synthesized in our recent systematic review and meta-analysis.[22] Assuming a standard deviation of 11.98 in our primary endpoint (AHI pooled standard deviation of previous research),[22] we estimated that the enrollment of 35 participants per arm of our trial would provide a statistical power of 90% at an alpha level of 0.05 to detect a minimum effect size of -8.36 in AHI (pooled mean difference of previous trials).[22] However, considering a maximum dropout rate of 17.25% (average dropout rate of previous studies),[22] we decided to recruit 42 participants for each trial group. Owing to practical and feasibility reasons, the trial was conducted in three consecutive sets of 30-35 participants.[31]

Intervention effects on primary and secondary endpoints were assessed based on linear mixed-effects models, with individual measures of growth being modeled as the function of randomly assigned group, assessment time (baseline, 8 weeks and 6 months after intervention), and the interaction between group and time.[36] Estimations were performed using the restricted maximum-likelihood method, including an unstructured covariance matrix to adjust for within-participant clustering resulting from the repeated-measures design. The model assumed that missing values were missing-at-random, all values presented in the tables being therefore model-based estimates. Nevertheless, attrition propensity was calculated using a logistic model predicting attrition with baseline values of set of participants, allocation group, OSA severity, age and BMI. Among these variables, only set of participants significantly predicted attrition, which was attributable to the emergence of the Covid-19 pandemic at the trial endpoint (endpoint assessment of the third set of participants). Thus, model assumptions of missing values being missing-at-random were further supported, which is advocated in recent recommendations for handling missing data in randomized trials affected by a pandemic specific to our case.[37]

All estimations and analyses were performed with an intention-to-treat approach (including all participants as originally allocated after randomization) and an additional per-protocol approach restricted to participants with a CPAP usage equal or greater than 4 hours per night on 70% of nights and, regarding the intervention group, at least an 80% attendance rate at intervention sessions. All analyses were performed using R version 4.0.3 (R Project for Statistical Computing).

It should be noted that intervention effect assessments were not only based on statistical and practical significance, but also on a practical benefit approach emphasizing and reporting unadjusted values that are intuitive to human judgment and readily replicable considering the design and methodology of this study.[38,39]

Results

Study Participants

Out of 156 participants who were initially screened for participation, 89 were enrolled and randomly assigned to either the usual-care/control group (49 participants) or the intervention (40 participants) from April 2019 to January 2020; the study completion date being October 2020 (Figure 1). The loss to follow-up rate was 15.7% (14 participants from the control group) at intervention endpoint; owing mainly to the Covid-19 pandemic (10 participants). A total of 89 participants were thus included in the intention-to-treat analyses and, according to prespecified adherence criteria, 75 in the additional per-protocol approach (see Methods in Supplementary Material for intervention adherence). Baseline sociodemographic and clinical characteristics were fairly well-balanced between groups (Table 1). The mean age was 54 years (range, 30 to 65); the mean AHI, 41 events/hr (range, 15 to 107); and the mean BMI, 34 kg/m^2 (range, 26 to 56). Participants had a mean walking distance of 6 km/day; 24 (27%) were current smokers; and 65 (73%) reported light-to-moderate alcohol intake. Baseline characteristics were equivalent when adopting a per-protocol approach (Supplementary Table S1).

Primary and Secondary Sleep-Related Endpoints

Participants in the intervention group outstandingly reduced AHI from the baseline value of 41.6 events/hr to 20.4 events/hr at intervention endpoint (51% reduction; change in AHI, -21.2; 95% confidence interval [CI], -25.4 to -16.9); and to 17.8 events/hr at 6 months after intervention (57% reduction; change in AHI, -23.8; 95% CI, -28.3 to -19.3). No discernible differences in AHI were observed in the control group at intervention endpoint (2.5; 95% CI, -2.0 to 6.9), nor at 6 months after intervention (-0.8; 95% CI, -5.8 to 4.1); the mean difference between groups in AHI change being -23.6 events/hr (95% CI, -28.7 to -18.5) at intervention endpoint, and -23.0 events/hr (95% CI, -28.4 to 17.4) at 6 months after intervention, (both $P<0.001$) (Table 2). According to AHI thresholds for OSA severity categorization, 23 of 40 (57.5%) participants in the intervention group improved by one category; three of 25 (12%) improved from severe to mild OSA; and six of 40 (15%) showed complete remission of OSA at intervention endpoint (Figure 2 and Supplementary Figure S1). At 6 months after

Figure 1. Flow-chart diagram of the study participants

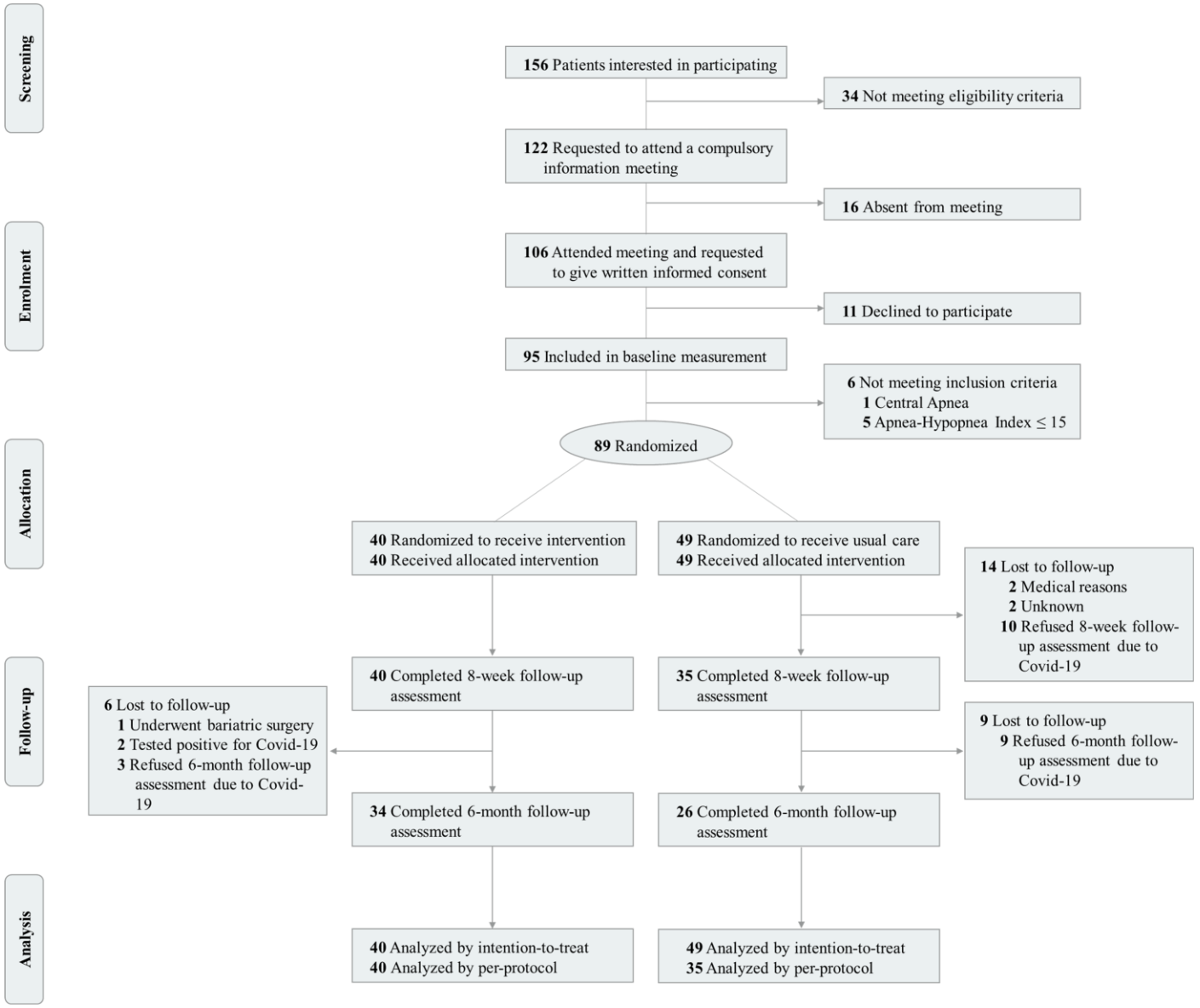


Table 1. Baseline characteristics of the study participants

Characteristic[b]	No. (%)[a]	
	Control (n = 49)	Intervention (n = 40)
Age, mean (SD), y	55.3 (8.5)	52.6 (7.1)
Educational level		
Primary Education	13 (26.5)	10 (25.0)
Secondary Education	10 (20.4)	6 (15.0)
Vocational Education	13 (26.5)	17 (42.5)
Higher Education	13 (26.5)	7 (17.5)
Marital status		
Single	7 (14.3)	2 (5.0)
Married	34 (69.4)	34 (85.0)
Divorced	8 (16.3)	4 (10.0)
Occupational status		
Employed	27 (55.1)	21 (52.5)
Self-employed	8 (16.3)	12 (30.0)
Unemployed	4 (8.2)	5 (12.5)
Retired	10 (20.4)	2 (5.0)
Medical Conditions[c]		
Hypertension	33 (67.4)	27 (67.5)
Diabetes Mellitus II	12 (24.5)	10 (25.0)
Cardiovascular disease	9 (18.4)	7 (17.5)
Other medical conditions	29 (59.2)	26 (65.0)
Medication[c]		
Antihypertensive	31 (63.3)	24 (60.0)
Statins	15 (30.6)	7 (17.5)
Oral antidiabetic	5 (10.2)	2 (5.0)
Insulin	3 (6.1)	1 (2.5)
Beta-blockers	7 (14.3)	5 (12.5)
Polymedication[d]	14 (28.6)	6 (15.0)
Body height, mean (SD), cm	171 (7.9)	172 (6.3)
Body weight status		
Overweight	10 (20.4)	5 (12.5)
Class I obesity	21 (42.9)	19 (47.5)
Class II obesity	16 (32.7)	11 (27.5)
Class III obesity	2 (4.1)	5 (12.5)
Obstructive sleep apnea severity		
Moderate	20 (40.8)	15 (37.5)
Severe	29 (59.2)	25 (62.5)
Time since obstructive sleep apnea diagnosis, mean (SD), y	7.4 (5.7)	6.5 (6.5)
Physical activity, mean (SD), km/day	5.2 (3.9)	6.1 (3.8)
Dietary habits, mean (SD), Food Behavior Checklist score[e]	59.1 (9.3)	59.5 (8.5)
Alcohol consumption		
Never	11 (22.5)	13 (32.5)
Occasionally	12 (24.5)	8 (20.0)
Frequently	15 (30.6)	12 (30.0)
Daily	11 (22.5)	7 (17.5)
Tobacco consumption		
Non-smoker	17 (34.7)	15 (37.5)
Ex-smoker	18 (36.7)	15 (37.5)
Smoker	14 (28.6)	10 (25.0)

[a] No. (%) reported unless otherwise specified.
[b] No significant between-group differences were observed in any of the baseline characteristics.
[c] Participants could have more than one condition or medication.
[d] Defined as the use of five or more medications.
[e] Scores on the Food Behavior Checklist range from 23 to 85, with higher scores indicating healthier dietary pattern.

intervention, 14 of 34 (41%) improved by one category; five of 21 (24%) improved from severe to mild OSA; and 10 of 34 (29%) showed complete remission of OSA. Remarkably, 18 of 40 (45%) and 21 of 34 (62%) participants in the intervention group no longer required CPAP at intervention endpoint and at 6 months after intervention, respectively, and cessation of this therapy was counseled based on an OSA severity reduction to a mild category and the non-presence of concomitant symptoms of sleepiness, impaired cognition, mood disturbance, insomnia or other conditions such as hypertension, ischemic heart disease, or a history of stroke. Similar results were observed for changes in oxyhemoglobin saturation endpoints, sleep efficiency and maintenance, sleep architecture, and subjective sleep quality and sleepiness. These results were almost identical with those obtained with a per-protocol approach (Supplementary Table S2). According to changes from intervention endpoint to 6 months after intervention, participants in the intervention group not only maintained improvements in all sleep-related endpoints, but also significantly continued improving oxyhemoglobin desaturation index and sleepiness (Supplementary Figure S2 and Supplementary Table S3). Individual values at baseline, intervention endpoint and 6 months after intervention, as well as changes by group in AHI (primary endpoint), are shown in Figure 2.

Secondary Body Composition and Cardiometabolic Risk Endpoints

Participants in the intervention group had greater reductions in body weight at intervention endpoint (change in body weight, -7.1; 95% CI, -8.6 to -5.5) than participants in the control group (-0.3; 95% CI, -1.9 to 1.4), with a mean difference of -6.8 kg (95% CI, -8.7 to -4.9) between groups (P<0.001) (Table 3). Similar results were found at 6 months after intervention, the mean difference being -5.7 kg (95% CI, -7.7 to -3.6) between groups (P<0.001). Concomitantly, participants in the intervention group had greater reductions in BMI, neck, chest and waist circumferences, fat mass and visceral adipose tissue than did those in the control group at both intervention endpoint and 6 months after intervention.

Greater improvements in cardiometabolic risk endpoints including blood pressure, glucose and lipid metabolism, and liver function endpoints were also found in the intervention group as compared with the control group at both intervention endpoint and 6 months after intervention. These results were almost identical with those obtained with a per-protocol approach (Supplementary Table S4). Notably, according to changes from intervention endpoint to 6 months after intervention, benefits in body composition and cardiometabolic risk endpoints in the intervention group were not only sustained but also significantly increased as revealed by significant reductions in neck and waist circumferences, fat mass and systolic blood pressure, among others (Supplementary Table S5).

Additional Health-Related Quality of Life and Lifestyle Habits Endpoints

Health-related quality of life was significantly improved at intervention endpoint and 6 months after intervention as shown by changes in the Sleep Apnea Quality of Life Index and Short-Form 36 Health Survey scores (Supplementary Table S6). No significant changes from intervention endpoint to 6 months after intervention in these health-related quality of life endpoints were found (Supplementary Table S7). Those participants in the intervention group who reported light-to-moderate alcohol consumption at baseline — 27 of 40 (67.5%) participants — drastically reduced alcohol intake to complete abstinence from the first week of the intervention to intervention endpoint. At 6 months after intervention, six

Table 2. Primary and Secondary Sleep-Related Endpoints

	Control (n=49)	Intervention (n=40)	Mean difference between groups (95% CI)[a]
Primary endpoint			
Apnea-hypopnea index, events/hr (95% CI)			
At baseline	41.1 (35.3 to 46.9)	41.6 (35.1 to 48.0)	
Change at 8 wk	2.5 (-2.0 to 6.9)	-21.2 (-25.4 to -16.9)	-23.6 (-28.7 to -18.5)[d]
Change at 6 mo	-0.8 (-5.8 to 4.1)	-23.8 (-28.3 to -19.3)	-23.0 (-28.4 to -17.4)[d]
Secondary endpoints			
Oxygen desaturation index ≥3%, events/hr (95% CI)			
At baseline	45.4 (39.0 to 51.7)	45.4 (38.4 to 52.5)	
Change at 8 wk	3.0 (-2.7 to 8.6)	-16.0 (-21.4 to -10.7)	-19.0 (-25.4 to -12.6)[d]
Change at 6 mo	-0.8 (-7.0 to 5.5)	-23.5 (-29.2 to -17.8)	-22.7 (-29.6 to -15.7)[d]
Mean SpO_2, % (95% CI)			
At baseline	90.3 (89.3 to 91.2)	91.3 (90.3 to 92.3)	
Change at 8 wk	-0.6 (-1.8 to 0.5)	1.5 (0.4 to 2.6)	2.1 (0.8 to 3.4)[c]
Change at 6 mo	-0.8 (-2.1 to 0.5)	2.6 (1.4 to 3.8)	3.4 (1.9 to 4.8)[d]
SpO_2 Nadir, % (95% CI)			
At baseline	76.8 (74.2 to 79.3)	78.1 (75.2 to 80.9)	
Change at 8 wk	0.3 (-1.6 to 2.2)	2.8 (1.0 to 4.6)	2.5 (0.3 to 4.7)[b]
Change at 6 mo	-1.6 (-3.7 to 0.6)	4.4 (2.5 to 6.4)	6.0 (3.6 to 8.4)[d]
Sleep time with SpO2 <90%, % (95% CI)			
At baseline	11.3 (8.2 to 14.3)	9.1 (5.7 to 12.5)	
Change at 8 wk	1.7 (-1.8 to 5.2)	-4.4 (-7.8 to -1.1)	-6.1 (-10.1 to 2.1)[c]
Change at 6 mo	1.1 (-2.7 to 5.0)	-5.5 (-9.0 to -1.9)	-6.6 (-10.9 to -2.3)[c]
Sleep efficiency, % (95% CI)			
At baseline	85.6 (83.6 to 87.7)	86.0 (83.8 to 88.3)	
Change at 8 wk	-1.7 (-4.9 to 1.5)	5.7 (2.5 to 8.8)	7.4 (3.7 to 11.1)[d]
Change at 6 mo	-1.6 (-5.2 to 1.9)	7.6 (4.3 to 10.9)	9.2 (5.2 to 13.2) [d]
Sleep latency, min (95% CI)			
At baseline	21.5 (17.5 to 25.6)	23.0 (18.5 to 27.5)	
Change at 8 wk	2.9 (-4.3 to 10.1)	-7.1 (-14.3 to 0.1)	-10.0 (-18.3 to -1.6)[b]
Change at 6 mo	4.5 (-3.3 to 12.3)	-11.2 (-18.8 to -3.7)	-15.7 (-24.6 to -6.8)[d]
Wake after sleep onset, min (95% CI)			
At baseline	54.4 (44.4 to 64.4)	47.6 (36.5 to 58.7)	
Change at 8 wk	11.7 (-3.8 to 27.3)	-17.18 (-32.5 to -1.9)	-28.9 (-46.8 to -11.0)[c]
Change at 6 mo	9.4 (-7.7 to 26.5)	-25.8 (-41.9 to -9.7)	-35.2 (-54.4 to -15.8)[d]
N1+N2 sleep, % (95% CI)			
At baseline	64.9 (62.5 to 67.3)	63.4 (60.8 to 66.0)	
Change at 8 wk	3.4 (-0.4 to 7.1)	-6.2 (-9.8 to -2.5)	-9.5 (-13.9 to -5.2)[d]
Change at 6 mo	4.9 (0.7 to 9.0)	-8.9 (-12.8 to -5.00)	-13.8 (-18.4 to -9.1)[d]
N3 sleep, % (95% CI)			
At baseline	20.6 (18.6 to 22.5))	20.4 (22.6 to 18.2)	
Change at 8 wk	-4.2 (-7.4 to -1.0)	3.7 (0.5 to 6.9)	7.9 (4.1 to 11.6)[d]
Change at 6 mo	-7.4 (-10.9 to -3.8)	4.5 (1.1 to 7.8)	11.8 (7.8 to 15.9)[d]
REM sleep, % (95% CI)			
At baseline	14.5 (13.2 to 15.8)	16.2 (17.7 to 14.8)	
Change at 8 wk	0.9 (-1.3 to 3.1)	2.5 (0.3 to 4.7)	1.6 (-1.0 to 4.1)
Change at 6 mo	2.7 (0.3 to 5.1)	4.5 (2.2 to 6.8)	1.8 (-0.9 to 4.5)
AHI in REM sleep, events/hr (95% CI)			
At baseline	41.6 (36.0 to 47.2)	45.1 (39.0 to 51.3)	
Change at 8 wk	5.2 (-2.6 to 13.0)	-22.6 (-30.2 to -15.1)	-27.8 (-36.7 to -18.9)[d]
Change at 6 mo	-3.6 (-12.2 to 4.9)	-26.6 (-34.6 to -18.6)	-23.0 (-32.6 to -13.3)[d]
AHI in NREM sleep, events/hr (95% CI)			
At baseline	40.6 (34.5 to 46.7)	41.0 (34.2 to 47.8)	
Change at 8 wk	2.2 (-2.8 to 7.1)	-21.0 (-25.7 to -16.3)	-23.2 (-28.7 to -17.6)[d]
Change at 6 mo	-1.2 (-6.6 to 4.3)	-23.5 (-28.5 to -18.6)	-22.4 (-28.5 to -16.3)[d]

(continued)

Table 2. Primary and Secondary Sleep-Related Endpoints (continued)			
Pittsburgh Sleep Quality Index score (95% CI)[e]			
At baseline	8.8 (7.7 to 9.9)	7.2 (6.0 to 8.4)	
Change at 8 wk	-0.4 (-1.5 to 0.6)	-2.8 (-3.8 to -1.8)	-2.3 (-3.5 to -1.1)[d]
Change at 6 mo	0.2 (-1.0 to 1.3)	-3.6 (-4.7 to -2.5)	-3.7 (-5.0 to -2.4)[d]
Epworth Sleepiness Scale score (95% CI)[f]			
At baseline	9.0 (7.7 to 10.3)	10.3 (8.8 to 11.7)	
Change at 8 wk	-0.2 (-2.0 to 1.5)	-4.6 (-6.3 to -2.9)	-4.3 (-6.3 to -2.3)[d]
Change at 6 mo	-1.0 (-2.9 to 1.0)	-6.8 (-8.6 to -5.0)	-5.8 (-8.0 to -3.7)[d]

Abbreviations: CI, confidence interval; SpO_2, oxygen saturation; AHI, apnea-hypopnea index; REM, rapid eye movement; NREM, non-rapid eye movement.

[a] Using the group × visit interaction term from a linear mixed-effects model including study group, time (baseline, 8 weeks and 6 months), and study group × time as fixed effects and participant as random effects.

[b] $P < 0.05$ from the time × study group interactions.

[c] $P < 0.01$ from the time × study group interactions.

[d] $P < 0.001$ from the time × study group interactions.

[e] Pittsburgh Sleep Quality Index scores range from 0 to 21, with higher scores indicating worse sleep quality.

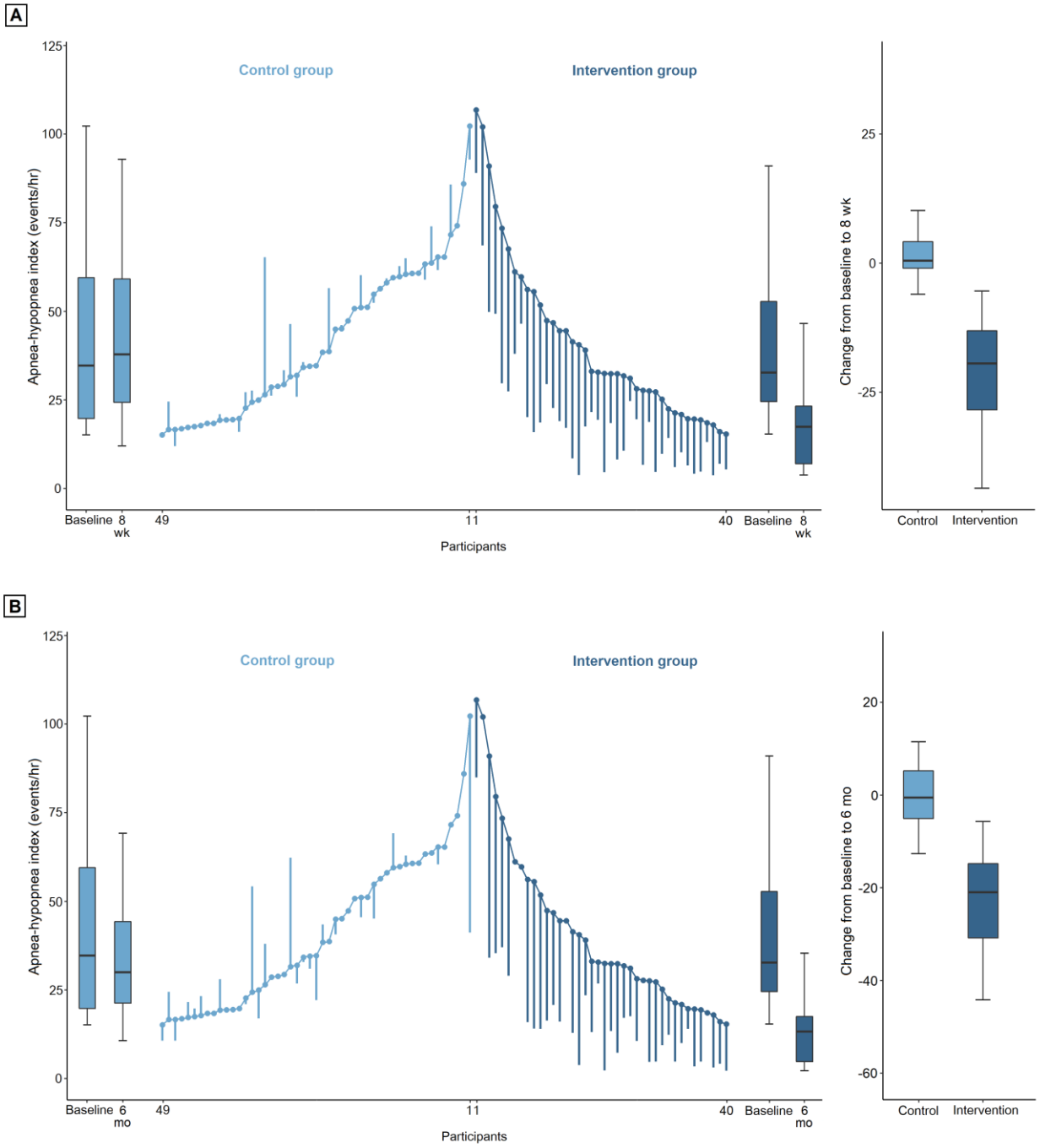
[f] Epworth Sleepiness Scale scores range from 0 to 24, with higher scores indicating more daytime sleepiness.

of 34 (17.5%) reported occasional alcohol intake (<1 drink per week), and 28 (87.5%) maintained complete abstinence. Seven of 10 (70%) participants in the intervention group who were current smokers at baseline attained complete smoking cessation at intervention endpoint, and three (30%) reduced tobacco consumption by 45-75%. At 6 months after intervention, 9 of 10 (90%) maintained/achieved complete smoking cessation. Participants in the intervention group also had substantial improvements regarding physical activity and dietary behaviors at both intervention endpoint and 6 months after intervention (Supplementary Table S8), although slight reductions from the intervention endpoint to 6 months after intervention in both endpoints were found (Supplementary Table S9). No discernible differences in lifestyle habits were found in participants in the control group from baseline to intervention endpoint nor 6 months after intervention.

Adverse Events

No serious adverse events that led to death, life-threatening illness, permanent impairment, or hospitalization with serious health conditions, related or unrelated to the study intervention or participation, occurred from baseline to intervention endpoint nor 6 months after intervention.

Figure 2. Apnea-Hypopnea Index Endpoint



The ends of the boxes in the boxplots are located at the first and third quartiles, with the black line in the middle illustrating the median. Whiskers extend to the upper and lower adjacent values, the location of the furthest point within a distance of 1.5 interquartile ranges from the first and third quartiles. The parallel line plot contains 1 vertical line for each patient which extends from their baseline value to their 8-week (A) or 6-month (B) value. Descending lines indicate an improvement in the outcome. Baseline values are placed in ascending order for the control group and descending order for the intervention group. The apnea-hypopnea index indicates the number of apnea and hypopnea events per hour of sleep (0-5 is classified as normal; 5-14, mild OSA; 15-30, moderate OSA; >30, severe OSA; a change of at least 15 is considered clinically meaningful and would move a patient 2 levels from severe to mild with established benefit for health).

Table 3. Secondary body composition and cardiometabolic risk endpoints

	Control (n=49)	Intervention (n=40)	Mean difference between groups (95% CI)[a]
Body composition			
Body weight, kg (95% CI)			
At baseline	99.6 (94.5 to 104.6)	103.3 (97.6 to 108.9)	
Change at 8 wk	-0.3 (-1.9 to 1.4)	-7.1 (-8.6 to -5.5)	-6.8 (-8.7 to -4.9)[d]
Change at 6 mo	-1.2 (-3.0 to 0.6)	-6.9 (-8.5 to -5.2)	-5.7 (-7.7 to -3.6)[d]
Body mass index, kg/m^2 (95% CI)			
At baseline	33.9 (35.5 to 32.4)	35.0 (33.4 to 36.7)	
Change at 8 wk	-0.2 (-0.8 to 0.4)	-2.5 (-3.0 to -1.9)	-2.3 (-2.9 to -1.6)[d]
Change at 6 mo	-0.6 (-1.2 to 0.02)	-2.4 (-3.0 to -1.8)	-1.8 (-2.5 to -1.1)[d]
Neck circumference, cm (95% CI)			
At baseline	45.5 (44.4 to 46.5)	45.0 (43.9 to 46.2)	
Change at 8 wk	-0.3 (-0.9 to 0.2)	-2.3 (-2.8 to -1.7)	-1.9 (-2.6 to -1.3)[d]
Change at 6 mo	0.2 (-0.5 to 0.8)	-2.9 (-3.5 to -2.3)	-3.1 (-3.8 to -2.4)[d]
Chest circumference, cm (95% CI)			
At baseline	117.4 (114.5 to 120.2)	118.0 (114.9 to 121.2)	
Change at 8 wk	0.5 (-0.8 to 1.8)	-3.4 (-4.6 to -2.1)	-3.8 (-5.3 to -2.4)[d]
Change at 6 mo	0.7 (-0.8 to 2.1)	-4.1 (-5.4 to -2.8)	-4.8 (-6.4 to -3.2)[d]
Waist circumference, cm (95% CI)			
At baseline	117.9 (114.3 to 121.5)	119.0 (115.0 to 122.9)	
Change at 8 wk	-0.2 (-1.7 to 1.3)	-6.9 (-8.3 to -5.5)	-6.8 (-8.5 to -5.0)[d]
Change at 6 mo	0.3 (-1.4 to 2.0)	-8.8 (-10.3 to -7.2)	-9.0 (-10.9 to -7.2)[d]
Fat mass, kg (95% CI)			
At baseline	33.8 (31.0 to 36.7)	34.9 (31.8 to 38.0)	
Change at 8 wk	1.4 (-0.3 to 3.1)	-2.9 (-4.5 to -1.3)	-4.3 (-6.2 to -2.4)[d]
Change at 6 mo	0.2 (-1.7 to 2.1)	-6.5 (-8.2 to -4.8)	-6.6 (-8.7 to -4.6)[d]
Visceral adipose tissue, g (95% CI)			
At baseline	1049.2 (969.8 to 1128.5)	1017.3 (929.5 to 1105.2)	
Change at 8 wk	32.6 (-52.0 to 117.1)	-106.2 (-187.2 to -25.3)	-138.8 (-234.7 to -42.6)[c]
Change at 6 mo	-26.3 (-119.7 to 67.1)	-268.4 (-354.3 to -182.6)	-242.2 (-346.1 to -137.8)[d]
Lean mass, kg (95% CI)			
At baseline	60.8 (63.4 to 58.3)	63.0 (60.2 to 65.8)	
Change at 8 wk	-2.2 (-3.5 to -0.9)	-2.7 (-4.0 to -1.5)	-0.5 (-2.0 to 0.9)
Change at 6 mo	-1.3 (-2.7 to -0.2)	0.3 (-1.0 to 1.6)	1.6 (-0.05 to 3.2)
Blood pressure			
Systolic BP, mm Hg (95% CI)			
At baseline	142.3 (138.3 to 146.3)	143.7 (139.2 to 148.1)	
Change at 8 wk	-0.7 (-5.1 to 3.6)	-7.9 (-12.1 to -3.7)	-7.2 (-12.2 to -2.2)[c]
Change at 6 mo	2.6 (-2.2 to 7.4)	-13.9 (-18.3 to -9.5)	-16.5 (-21.9 to -11.1)[d]
Diastolic BP, mm Hg (95% CI)			
At baseline	82.1 (79.0 to 85.2)	84.0 (80.6 to 87.4)	
Change at 8 wk	0.2 (-4.4 to 4.8)	-5.7 (-10.3 to -1.2)	-6.0 (-11.3 to -0.6)[b]
Change at 6 mo	2.0 (-3.1 to 7.1)	-7.4 (-12.1 to -2.6)	-9.3 (-15.1 to -3.6)[c]
Mean BP, mm Hg (95% CI)			
At baseline	102.2 (99.2 to 105.2)	103.9 (100.6 to 107.2)	
Change at 8 wk	2.2 (-2.1 to 6.6)	-6.5 (-10.3 to -2.6)	-6.4 (-10.9 to -1.9)[c]
Change at 6 mo	2.3 (-2.2 to 6.8)	-9.6 (-13.6 to -5.5)	-11.8 (-16.6 to -6.9)[d]
Glucose metabolism			
Glucose, mg/dl (95% CI)			
At baseline	102.0 (96.0 to 107.9)	95.5 (102.0 to 89.1)	
Change at 8 wk	0.1 (-4.9 to 5.1)	-6.7 (-11.4 to -2.0)	-6.8 (-12.4 to -1.2)[b]
Change at 6 mo	3.6 (-1.9 to 9.0)	-6.6 (-11.6 to -1.6)	-10.2 (-16.2 to -4.1)[c]
Insulin, IU/ml (95% CI)			
At baseline	14.1 (11.9 to 16.2)	13.0 (10.7 to 15.3)	
Change at 8 wk	1.6 (-0.5 to 3.7)	-4.9 (-6.9 to -2.9)	-6.5 (-8.9 to -4.2)[d]
Change at 6 mo	0.3 (-2.0 to 2.5)	-5.2 (-7.3 to -3.1)	-5.4 (-8.0 to -2.9)[d]
HOMA-IR index (95% CI)			
At baseline	3.5 (2.7 to 4.2)	3.2 (2.3 to 4.0)	
Change at 8 wk	0.5 (-0.6 to 1.6)	-1.3 (-2.4 to -0.3)	-1.9 (-3.1 to -0.6)[c]
Change at 6 mo	0.4 (-0.8 to 1.6)	-1.4 (-2.5 to -0.3)	-1.8 (-3.1 to -0.5)[c]

(continued)

Table 3. Secondary body composition and cardiometabolic risk endpoints (continued)

	Control (n=49)	Intervention (n=40)	Mean difference between groups (95% CI)[a]
Lipid metabolism			
Total cholesterol, mg/dl (95% CI)			
At baseline	176.4 (165.8 to 187.1)	189.6 (178.1 to 201.0)	
Change at 8 wk	6.4 (-4.4 to 17.2)	-19.4 (-29.5 to -9.3)	-25.8 (-37.9 to -13.7)[d]
Change at 6 mo	5.7 (-6.0 to 17.4)	-16.6 (-27.3 to -5.9)	-22.3 (-35.3 to -9.3)[c]
HDL-C, mg/dl (95% CI)			
At baseline	44.7 (41.5 to 47.8)	47.1 (43.9 to 50.3)	
Change at 8 wk	1.9 (-0.9 to 4.8)	0.2 (-2.2 to 2.6)	-1.7 (-4.7 to 1.3)
Change at 6 mo	0.7 (-2.5 to 3.8)	3.0 (0.5 to 5.4)	2.3 (-1.0 to 5.6)
LDL-C, mg/dl (95% CI)			
At baseline	113.0 (103.7 to 122.3)	119.5 (110.1 to 128.9)	
Change at 8 wk	0.5 (-8.9 to 10.0)	-15.0 (-22.9 to -7.1)	-15.5 (-25.5 to -5.5)[c]
Change at 6 mo	8.2 (-2.3 to 18.7)	-14.2 (-22.4 to -6.0)	-22.4 (-33.3 to -11.6)[d]
Triglycerides, mg/dl (95% CI)			
At baseline	156.5 (136.3 to 176.7)	129.5 (107.7 to 151.2)	
Change at 8 wk	1.5 (-19.1 to 22.2)	-24.5 (-43.7 to -5.2)	-26.0 (-49.2 to -2.9)[b]
Change at 6 mo	8.3 (-14.0 to 30.6)	-23.7 (-44.1 to -3.3)	-32.0 (-56.9 to -7.3)[b]
Apolipoprotein A1, mg/dl (95% CI)			
At baseline	128.1 (122.4 to 133.7)	131.0 (124.9 to 137.1)	
Change at 8 wk	5.7 (-0.5 to 12.0)	-0.6 (-6.5 to 5.4)	-6.3 (-13.4 to 0.7)
Change at 6 mo	0.9 (-5.5 to 7.4)	9.5 (3.6 to 15.5)	8.6 (1.4 to 15.8)[b]
Apolipoprotein B, mg/dl (95% CI)			
At baseline	96.2 (89.9 to 102.6)	102.5 (95.6 to 109.3)	
Change at 8 wk	2.2 (-4.3 to 8.8)	-11.9 (-18.2 to -5.6)	-14.1 (-21.6 to -6.7)[d]
Change at 6 mo	-1.1 (-7.8 to 5.7)	-15.2 (-21.5 to -8.9)	-14.1 (-21.7 to -6.6)[d]
Liver function			
AST, IU/l (95% CI)			
At baseline	25.3 (22.3 to 28.3)	25.3 (22.2 to 28.4)	
Change at 8 wk	0.7 (-3.6 to 5.0)	-2.4 (-6.3 to 1.5)	-3.1 (-7.8 to 1.6)
Change at 6 mo	-0.7 (-5.1 to 3.6)	-4.8 (-8.7 to -0.9)	-4.0 (-8.8 to 0.7)
ALT, IU/l (95% CI)			
At baseline	28.9 (24.9 to 32.9)	29.6 (25.3 to 34.0)	
Change at 8 wk	0.5 (-4.6 to 5.6)	-4.0 (-8.9 to 0.8)	-4.6 (-10.4 to 1.2)
Change at 6 mo	-0.2 (-5.8 to 5.3)	-7.1 (-12.3 to -2.0)	-6.9 (-13.1 to -0.6)[d]
γ-GT, IU/l (95% CI)			
At baseline	44.1 (34.6 to 53.6)	38.2 (48.5 to 27.9)	
Change at 8 wk	3.7 (-4.7 to 12.0)	-11.2 (-18.9 to -3.5)	-14.9 (-24.2 to -5.6)[c]
Change at 6 mo	0.5 (-8.4 to 9.5)	-14.0 (-22.2 to -5.9)	-14.6 (-24.5 to -4.6)[c]
Fatty liver index (95% CI)			
At baseline	85.7 (80.5 to 90.8)	86.2 (80.6 to 91.7)	
Change at 8 wk	-1.5 (-6.3 to 3.3)	-13.7 (-18.0 to -9.4)	-12.2 (-17.5 to -6.9)[d]
Change at 6 mo	-0.1 (-5.1 to 5.0)	-17.5 (-22.1 to -12.9)	-17.4 (-23.0 to -11.8)[d]

Abbreviations: CI, confidence interval; BP, blood pressure; HOMA-IR, homeostasis model assessment of insulin resistance; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase;γ-GT, γ-glutamyltransferase.

SI conversion factors: To convert glucose to millimoles per liter, multiply by 0.05551. To convert insulin to picomoles per liter, multiply by 6.945. To convert total, high-density lipoprotein, and low-density lipoprotein cholesterol to millimoles per liter, multiply by 0.02586. To convert triglycerides to millimoles per liter, multiply by 0.01129. To convert apolipoprotein A1 and B to gram per liter, multiply by 0.01. To convert aspartate aminotransferase to micro-katal per liter, multiply by 0.017. To convert aspartate aminotransferase and γ-glutamyltransferase to micro-katal per liter, multiply by 0.017.

[a] Using the group × visit interaction term from a linear mixed-effects model including study group, time (baseline, 8 weeks and 6 months), and study group × time as fixed effects and participant as random effects.

[b] $P < 0.05$ from the time × study group interactions.

[c] $P < 0.01$ from the time × study group interactions.

[d] $P < 0.001$ from the time × study group interactions.

Discussion

Weight loss and lifestyle interventions for OSA treatment, although recommended, are rarely implemented in the care of patients with this condition owing to the modest quality of evidence and the methodological weaknesses found in this field of research.[20,21] The current trial evidences the efficacy of a novel eight-week interdisciplinary weight loss and lifestyle intervention, meticulously designed in conformity with existing evidenced-based clinical practice guidelines,[20,21,34,35] for the improvement or even remission of OSA and coexisting conditions in overweight-obese adults with CPAP-treated moderate-to-severe OSA.

The weight loss and lifestyle intervention group had a clinically meaningful reduction in AHI of 51% at intervention endpoint; 15% of participants attaining complete remission of OSA, and 45% no longer requiring CPAP therapy. After 6 months, the reduction in AHI was 57%; the complete remission of OSA being attained by 29% of participants; 62% no longer requiring CPAP therapy. Similarly, the intervention group notably exhibited 7%, 19% and 26% reductions in body weight, fat mass and visceral adipose tissue at 6 months after intervention, respectively. Furthermore, these results were strengthened by the evidence of significant improvements in key cardiometabolic endpoints involved in the pathogenesis of cardiovascular diseases. Simply considering reductions in systolic and diastolic blood pressure at intervention endpoint — which were not only sustained but also significantly enlarged at 6 months after intervention — our intervention group may have lowered risk of stroke death by 40% and risk of death from ischemic heart disease or other vascular causes by 30%.[40]

These results are representative of the best that has been achieved with current behavioral approaches.[22] The mechanisms by which weight loss and lifestyle changes intensely ameliorate OSA and coexisting conditions are probably multifactorial. Gathered evidence suggests that nearly 60% of moderate-to-severe OSA is attributable to obesity,[41] which contributes to alterations of the airway anatomy and collapsibility, and respiratory modulation.[19] Simultaneously, adverse lifestyles such as poor diet, low physical activity, smoking and alcohol intake, have also been shown to be closely related to OSA independent of body habitus.[29-31,42] Thus, a combination of both weight loss and lifestyle change may even resolve OSA in overweight/obese populations.[5,21] Additionally, there is a well-recognized dose-dependent relationship between weight loss and improvement of cardiometabolic endpoints; even a 5% weight loss resulting in enhanced metabolic function.[43] Given that OSA and obesity act synergistically and have independent causal relations to cardiovascular risk,[19] beneficial effects of weight loss on cardiometabolic risk-factor profiles are likely to be exacerbated in patients with both obesity and OSA.

Strengths and Limitations

The current trial has certain strengths and limitations. A major strength is the balance in the efficacy-effectiveness continuum achieved by our trial, with a satisfactory internal validity being accompanied by a high degree of generalizability.[28] Given the study design and outstanding results obtained, this trial may be a clear and compelling

rationale for an alternative approach readily adaptable to real-world practice settings. Another noteworthy strength is the pioneering inclusion of smoking and alcohol avoidance; previously disregarded factors despite their recognized contribution to the occurrence and worsening of OSA.[29,30]

A main limitation is the sole inclusion of men in our sample; the generalization of our findings being therefore limited to this population. However, this was not only based on the higher incidence and prevalence of OSA in this population,[2] but also on the well-evidenced differences between men and women in OSA phenotypes[44] and the effectiveness of weight loss interventions.[22, 45-47] Similarly, our sample only included Spanish participants, our results being thus also restricted to this population/ethnicity. We did not include any group in which no therapy was implemented due to ethical considerations; CPAP is the standard care for moderate-to-severe OSA and the inclusion of a group without CPAP may not be feasible.[20]

Conclusion

In this trial involving overweight/obese participants with CPAP-treated moderate-to-severe OSA, we demonstrated that an eight-week interdisciplinary weight loss and lifestyle intervention not only resulted in clinically meaningful and sustainable improvements in specific OSA-related outcomes and cardiometabolic comorbidities but also pragmatically increased health-related quality of life. Given the high prevalence of OSA, its complex and reciprocal interaction with obesity, and the fact that both conditions are readily treatable through an integrated behavioral intervention, health-care providers and policy-makers should, at the very least, consider this approach as a central strategy to comprehensively address the staggering impact of OSA on the health and welfare of our society.

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Supplementary Material

Methods

Study Organization

The Sleep and Health Promotion Laboratory of the Mind, Brain and Behavior Research Center (CIMCYC) from the University of Granada (Granada, Spain) was responsible for the study design and organization, participant recruitment process, data collection and management, randomization and participant allocation, trial monitoring, and reporting of the study process and results. Participants previously diagnosed with moderate-to-severe OSA and potentially meeting the inclusion criteria were recruited from the collaborating sleep-disordered breathing unit of the Virgen de las Nieves University Hospital (Granada, Spain). Data collection at baseline and intervention endpoint, as well as implementation of the weight loss and lifestyle intervention, was performed in two different settings of the University of Granada (Granada, Spain): the Sleep and Health Promotion Laboratory (CIMCYC) and the Sport and Health University Research Institute (iMUDS). General and specific OSA standard care (i.e., continuous positive airway pressure [CPAP]) of all participants enrolled in the trial continued being provided by their primary care team from the Virgen de las Nieves University Hospital.

Eligibility Criteria

The INTERAPNEA eligibility criteria was based on a thorough consideration of the potential generalizability of results and its external validity. A common and substantial limitation of randomized controlled trials (RCTs; mostly efficacy/explanatory trials) is the use of stringent eligibility criteria to minimize adverse events and potential nonresponders; which results in a highly selected sample unrepresentative of the overall population.[1] To ensure external validity, trials should include a sample with those comorbidities and use of medication, as well as variable compliance rates, that are commonly found in the general population affected by the condition under consideration.[1-3]

Therefore, eligible participants of the INTERAPNEA trial were men aged between 18 and 65 years with CPAP-treated moderate-to-severe OSA (apnea-hypopnea index [AHI] equal or greater than 15 events/hour), and a body mass index (BMI) equal or greater than 25 kg/m^2. A CPAP use for at least 4 hours a day for 5 or more days per week reported by the participant was considered CPAP compliance. The sole inclusion of men in our sample was not only based on the higher incidence and prevalence of OSA in this population,[4] but also on the well-evidenced differences between men and women in OSA phenotypes[5] and the effectiveness of weight loss interventions.[6-9]

Regarding exclusion criteria, this only included current participation in a weight loss program, presence of any psychological/psychiatric disorder including alcohol or other substance dependence or abuse, and coexistence of any other primary sleep disorder which was not secondary to OSA. To ensure no hindrance/harm related to the assessment and intervention protocols, all participants were also medically examined and completed a health history revision prior to their final enrollment in the trial. Nonetheless, clinical trial liability insurance was also contracted for the provision of legal and financial protection of the sponsors-investigators and participants of the trial.

Study Assessments and Endpoints

Assessments of primary and secondary endpoints of the trial were organized and completed at baseline, 8 weeks (intervention endpoint) and 6 months after intervention over three different days during a one to two-week period:[10]

• Day 1: Potential participants attended a medical examination and blood test after a 12-hour overnight fast at the Sleep Unit of the Virgen de las Nieves University Hospital.

• Day 2: Eligible participants completed a full-night in-laboratory polysomnography (PSG; the gold-standard objective sleep testing recommended by the American Academy of Sleep Medicine (AASM),[11] at the Sleep and Health Promotion Laboratory (CIMCYC). In order to avoid potential CPAP influence on PSG endpoints, participants were required to withdraw from CPAP during the week prior to the PSG at baseline and follow-ups.[12] Prior to the PSG, participants also completed a set of questionnaires assessing subjective endpoints related to sleep, general physical and psychological health, and lifestyle habits including diet, physical exercise, and alcohol and tobacco consumption.

• Day 3: Participants were required to attend the Sport and Health University Research Institute (iMUDS) for the measurement of anthropometric parameters and body composition through a full-body dual energy X-ray absorptiometry (DXA) scanner.

Baseline physical activity and sleep habits were also be obtained through a seven-day self-reported daily step/km log and sleep diary.

Primary Endpoint

The primary endpoint of the INTERAPNEA trial was the change in OSA severity as measured by AHI, defined as the number of apnea (90% or greater drop in airflow for 10 s or longer) and hypopneas (30% or greater drop in airflow for 10 s or longer associated with ≥3% oxygen desaturation or an arousal) episodes per hour of sleep.[13] This primary endpoint and other neurophysical and cardiorespiratory secondary endpoints were measured through an in-laboratory PSG using SOMNOScreen™ PSG-Tele (SOMNOmedics, GmbH, Randersacker, Germany), or Somté PSG v2 system (Compumedics Limited, Abbotsford, Australia). The recordings included all recommended physiologic signals, namely electroencephalogram (three channels: F4-M1, C4-M1, O2-M1), electrooculogram (two channels: E1 and E2), electromyogram (two channels: submental and anterior tibialis muscles), and electrocardiogram (two channels). Cardiorespiratory measurements included oral and nasal airflow (triple thermistor), oxyhaemoglobin saturation (SpO_2) and pulse-rate (pulse oximeter), respiratory effort (chest and abdomen bands), and body position (sensor). All electrodes were placed in accordance with the international 10–20 system,[14] and recordings were automatically and manually scored in 30 s epochs[15] by trained physicians using DOMINO (v2.7, SOMNOmedics, GmbH, Randersacker, Germany), or ProFusion PSG 3 (v3.3, Compumedics Limited, Abbotsford, Australia) associated computer software. All parameters, settings, filters, technical specifications, sleep stage scoring and event scoring were performed in accordance with the AASM Manual for the Scoring of Sleep and Associated Events.[13] Owing to the more severe cardiovascular consequences of apnea episodes in rapid eye movement (REM) sleep as compared with non-REM obstructions,[16-18] we also specifically

analyzed AHI in REM sleep and non-REM sleep stages (N1, N2, and N3); which has generally been disregarded in previous similar RCTs.[6]

Secondary Sleep-Related Endpoints

Secondary polysomnographic endpoints related to OSA and measured by PSG were changes in oxygen desaturation index (number of oxygen desaturation ≥3% per hour of sleep), SpO_2 mean (%; average of oxygen saturation during sleep), SpO_2 nadir (%; minimum oxygen saturation during sleep), percentage of time with SpO_2 <90% during sleep, sleep efficiency (%; total sleep time/total time in bed), sleep latency (min; time from lights out to first epoch of any sleep stage), wake after sleep onset (min; time awake in bed minus sleep latency), N1+N2 sleep stages (%; N1+N2 sleep stages/total sleep time), N3 sleep stage (%; N3 sleep stage/total sleep time), and REM sleep stage (%; REM sleep stage/total sleep time). Other secondary sleep-related endpoints included changes in subjective sleep quality and daytime sleepiness as measured by the Pittsburgh Sleep Quality Index (PSQI)[19] and the Epworth Sleepiness Scale (ESS),[20] respectively. The PSQI includes a total of 19 self-rated items combined to form seven component scores (i.e., subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction), each of which has a range of 0–3 points. The sum of these seven PSQI component scores is considered to obtain a global PSQI score (ranging from 0–21), with higher scores indicating poorer sleep quality.[19] The ESS is a widely used 8 item Likert-based scale that measures propensity for dozing during several daily activities, its total score ranging from 0 to 24 (the sum of the 8 item scores, 0–3). Hypersomnolence is considered when a total score greater than 10 is attained.[20]

Secondary Body Composition Endpoints

Body anthropometric endpoints included changes in weight, BMI, and neck, chest and waist circumferences. Body weight and height were measured using a calibrated scale and stadiometer (model 799, Electronic Column Scale, Hamburg, Germany) with participants wearing undergarments. Neck, chest and waist circumferences were measured following standard procedures recommended by the International Society for the Advancement of Kinanthropometry (ISAK).[21] Body composition endpoints including changes in fat mass (kg), visceral adipose tissue (g), and lean mass (kg) were obtained through a full-body DXA scanner (Discovery Wi, Hologic, Inc., Bedford, MA, USA). Quality controls, positioning of participants and analyses of results were performed following the manufacturer's recommendations. Automatic delineation of anatomic regions was conducted using APEX 4.0.2. software.

Secondary Cardiometabolic Risk Endpoints

Cardiometabolic risk endpoints included changes in glucose metabolism (glucose [mg/dl], insulin [IU/ml] and insulin resistance as indicated by the homeostasis model assessment of insulin resistance [HOMA-IR] index), lipid metabolism (total cholesterol [mg/dl], high-density lipoprotein cholesterol [HDL-C; mg/dl], low-density lipoprotein cholesterol [LDL-C; mg/dl], triglycerides [mg/dl], and apolipoproteins A1 and B [mg/dl]), and liver function (aspartate aminotransferase [AST; IU/l], alanine aminotransferase [ALT; IU/l], γ-glutamyltransferase [γ-GT], and fatty liver index [FLI]). These endpoints were measured through blood samples obtained from participants' antecubital vein in a supine position during

the morning in a fasting state. Samples were collected into prechilled ethylene diamine tetra-acetic acid-containing tubes (Vacutainer SST, Becton Dickinson, Plymouth, UK) and immediately centrifuged (i.e. 15 min at 3,000 rpm), aliquoted and stored at −80°C for further plasma analysis. Glucose levels were measured by spectrophotometric techniques (AU5800, Beckman Coulter, Brea, California, USA). Insulin was assessed by chemiluminescence immunoassay with paramagnetic particles (UniCel DxI 800, Beckman Coulter, Brea, California, USA). HOMA-IR was calculated as fasting glucose (mmol/l) times the level of fasting insulin (UU/ml) divided by 22.5.[22] Total cholesterol, HDL-C, triglycerides, and apolipoproteins A1 and B were automatically evaluated by spectrophotometric techniques (AU5800, Beckman Coulter, Brea, California, USA). LDL-C was calculated as the level of total cholesterol minus the level of HDL-C minus 0.45 times the level of triglycerides. AST, ALT and γ-GT were calculated by absorption spectrophotometric techniques (Beckman Coulter, Brea, California, USA). FLI was calculated with the formula FLI = ((e 0.953·loge (Triglycerides) + 0.139·BMI + 0.718·loge (γ-GT) + 0.053·Waist Circumference - 15.745)) / ((1 + e 0.953·loge (Triglycerides) + 0.139·BMI + 0.718·loge (γ-GT) + 0.053·Waist Circumference - 15.745)) ·100.[23]

Changes in systolic blood pressure (mm Hg), diastolic blood pressure (mm Hg) and mean blood pressure (mm Hg) were also considered as cardiometabolic risk endpoints. Blood pressure was measured with an ambulatory blood pressure monitor (Omron M3 Blood Pressure Monitor, OMRON Healthcare, Hoofddorp, Netherlands) in a sitting position after at least five min of rest. The mean of two measurements was recorded. Mean blood pressure was calculated at each reading as one third of systolic pressure plus two thirds of diastolic pressure.

Additional Health-Related Quality of Life and Lifestyle Habits Endpoints

Additional endpoints included health-related quality of life and lifestyle habits. Health-related quality of life scores were obtained through the Sleep Apnea Quality of Life (SAQLI)[24] and the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36).[25,26] SAQLI is a 35 item self-report instrument assessing OSA specific quality of life through four core domains: daily functioning, social interactions, emotional functioning, and symptoms. The total score (average of the four components, 1 to 7) ranges from 1 to 7, with higher scores indicating better health-related quality of life.[24] SF-36 is also a widely used self-report measure of quality of life composed by eight scaled scores (vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health). Final physical and mental component summaries scores range from 0 to 100, with higher scores indicating better health-related quality of life with respect to either the physical or mental component.[25,26]

The Food Behavior Checklist (FBC)[27] was used to assess participants' food intake and habits. FBC comprises seven subscales including consumption of fruit and vegetables (9 items), diet quality (4 items), fast food (3 items), dairy/calcium (2 items), sweetened beverages (2 items), meat (1 item) and food security (1 item). A total FBC score was calculated as the sum of these subscales ranging from 22 to 81, with higher scores indicating healthier dietary pattern.[27] Physical activity was measured using daily step/km logs recorded by participants with a spring-levered pedometer. Participants were required to wear the pedometer all day and register the number of step/km achieved per day in a seven-day step log. The

average step/km per day was then calculated at baseline and follow-ups. Regarding the remaining lifestyle habits, smoking and alcohol intake were measured at baseline and follow-ups using seven-day self-reported tobacco and alcohol consumption logs. Recordings included number of cigarettes/alcoholic units consumed per day, cigarette brand/type of alcoholic drink, time, situation, and perceived pleasure (from 0 to 10).

Weight Loss and Lifestyle Intervention

The design and implementation of the INTERAPNEA weight loss and lifestyle intervention was based on results of previous research[6,28] and the most recent international evidenced-based clinical practice guidelines for the management of obesity and OSA.[29-31] The intervention lasted eight weeks and was composed of five different modules: nutritional behavior change, moderate aerobic exercise, smoking reduction and cessation, alcohol intake avoidance, and sleep hygiene. Each component included group-based weekly sessions of 60-90 min lead and supervised by a trained professional in the field (i.e. human nutrition and dietetics, physical activity and sport sciences, clinical psychology, and sleep medicine).

The cornerstone of this intervention was the use of the Transtheoretical Model of Health Behavior Change,[32] a well-recognized biopsychosocial model based on integrating key strategies, processes and principles of behavior change theories into a comprehensive interventional approach for the achievement of sustainable health-related behaviors.[32] The general behavioral change techniques used in each component of the intervention included motivation and preparation for action; goal-setting and action-planning; self-monitoring and functional behavioral analysis; review of behavioral goals, action plans, and adherence; problem solving and social skills; and self-efficacy, maintenance, and relapse prevention (a detailed description and timing of the INTERAPNEA intervention modules and components, as well as the rationale and specific session topics of each module, has previously been published).[10]

Nutritional Behavior Change[10]

The nutrition module consisted of eight 60-90-min sessions in a group format addressing dietary patterns using integrated techniques of nutrition education and behavioral change such as goal-setting, cognitive restructuring, stimulus control, progressive muscle relaxation, social skills and assertiveness, and problem-solving skills. The nutrition education was based on the World Health Organization (WHO) latest recommendations on food intake and healthy diet, and each session followed a three-part format: i) Brief review of previous session and participant's adherence to recommendations; ii) Development of the main nutrition education component of each session using an interactive group discussion layout; iii) Resolution of participant's questions and/or concerns, and setting of specific goals. No specific or individualized diet was indicated to participants.

Physical Exercise[10]

The eight-week physical exercise program consisted of weekly 60-min sessions of supervised moderate intensity aerobic exercise (i.e. 55-65% of the heart rate reserve) and individualized goal-setting consisting of increasing daily step/km per

week. In the weekly supervised training sessions, participants were required to walk at a moderate intensity for 60 min wearing a heart rate monitor in order to train themselves to walk at that intensity during the week. With respect to goal-setting, they were advised to increase their daily steps/km by 15% per week, based on their daily steps/km logs.

Sleep Hygiene[10]

The sleep hygiene module comprised four 60-min sessions supervised by a psychologist specialized in the evaluation and treatment of sleep disorders. Owing to most sleep hygiene topics being covered in simultaneous modules, there were four sessions distributed over the eight weeks of the intervention. Generally, this module consisted of sleep hygiene education on causes of sleep disturbances and mistaken sleep related knowledge. Sessions were also based on treating those frequent inadequate sleep habits found in patients with OSA, i.e. sleep restriction, irregular schedule and inappropriate sleep environment.

Smoking Reduction and Cessation[10]

Participants who were current smokers and willing to quit were required to attend a weekly 60-90-min session over eight weeks lead by two clinical psychologists. The intervention was based on the group behavior therapy for smoking cessation by Becoña et al.,[33] which seeks the progressive reduction of tobacco consumption through the use of nicotine and cigarette fading,[34] and behavior change techniques such as information on smoking, self-monitoring, stimulus control, avoidance of withdrawal symptoms, and relapse prevention. Nicotine and cigarette fading has been shown to be the most effective method to reduce and stop smoking with abstinence rates of 86% at the end of treatment and nearly 60% at a 12 month follow-up.[35]

Participants were mainly required to keep a daily record of number of cigarettes smoked and triggers for smoking (self-monitoring), change the type of cigarette smoked to a lesser nicotine content brand each week (30%, 60% and 90% nicotine reductions from baseline), reduce the number of cigarettes smoked by 30% weekly, and avoid smoking in three different situations per week (stimulus control). Through the sessions, other behavior change techniques such as discussion of health consequences of smoking and quitting (motivation), muscle and cognitive relaxation techniques to address withdrawal symptoms, and identification of high-risk situations for smoking and problem-solving skills (relapse prevention) were used.

Alcohol Intake Avoidance[10]

The INTERAPNEA alcohol intake reduction and avoidance module lasted eight weeks comprising fortnightly sessions of 60 min supervised by two clinical psychologists. Similar to the smoking reduction and cessation module, progressive reduction of alcohol intake in those participants with no alcohol addiction but excessive consumption was pursued. Participants were indicated to reduce the number of units of alcohol consumed per day/week by 30% each week, keeping a log of alcohol-consumption per day including units of alcohol consumed and triggers of consumption. During the

sessions, participants received detailed information of alcohol general and specific to OSA health-related consequences. Furthermore, behavior change techniques such as stimulus control, muscle and cognitive relaxation and problem-solving skills related to alcohol consumption were used.

Assessment of Compliance and Integrity of Intervention[10]

Integrity of the intervention and treatment fidelity was evaluated and ensured through the design and implementation of different strategies of process assessment, monitoring and enhancement in order to guarantee internal and external validity of the trial.[36] Regarding the study design and provider of intervention training, we developed a comprehensive hand-book for the qualified INTERAPNEA study intervention providers/professionals/training personnel of each module. Each intervention manual identified the theoretical model of the intervention and provided detailed descriptions of session objectives, treatment guidelines in accordance with each objective (i.e., contents, tasks and activities, recommendations, and timing), participant's homework, and material needed for each session. We also provided each participant with an adapted patient-handbook for each intervention component including descriptions of sessions, and work and logging sheets.

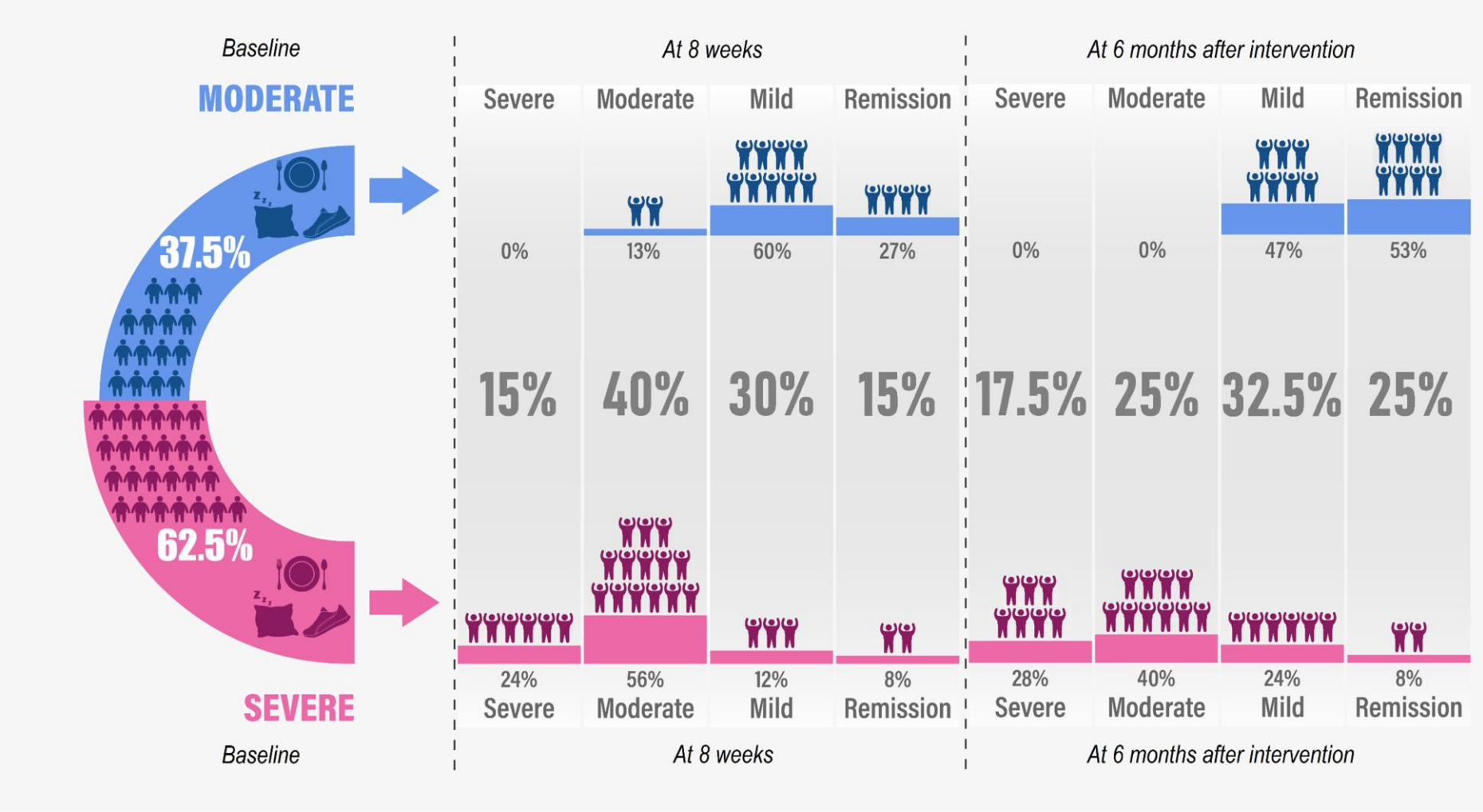
Furthermore, we ensured fidelity in the treatment delivery, receipt, and enactment through the use of these intervention protocols/manuals and monitoring of the implementation. Regarding the treatment delivery, the standardization of the intervention supported the protocol adherence of providers and the treatment differentiation (i.e., the delivery of the target treatment and no other). Similarly, we included a check-list for provider's self-report concerning the achievement of session objectives. With respect to the treatment receipt and enactment, fidelity was assessed and confirmed through different strategies such as the structuring of the intervention around achievement-based objectives, collecting and reviewing of participants self-monitored data (daily step/km log, sleep diaries, alcohol and tobacco consumption records), and information delivery in different formats (e.g., written in the handbooks, and verbal and visual in the sessions).

Apart from the above mention strategies, we also considered complementary approaches in order to reduce participant drop-out rates and increase adherence, such as prevention of commitments or vacation periods, use of well-equipped and conditioned facilities, and supervision by a qualified and certified pair of providers in each session, motivating and supporting participants. Participants' attendance to each intervention session was recorded by providers and causes of absence were recorded through phone-calls.

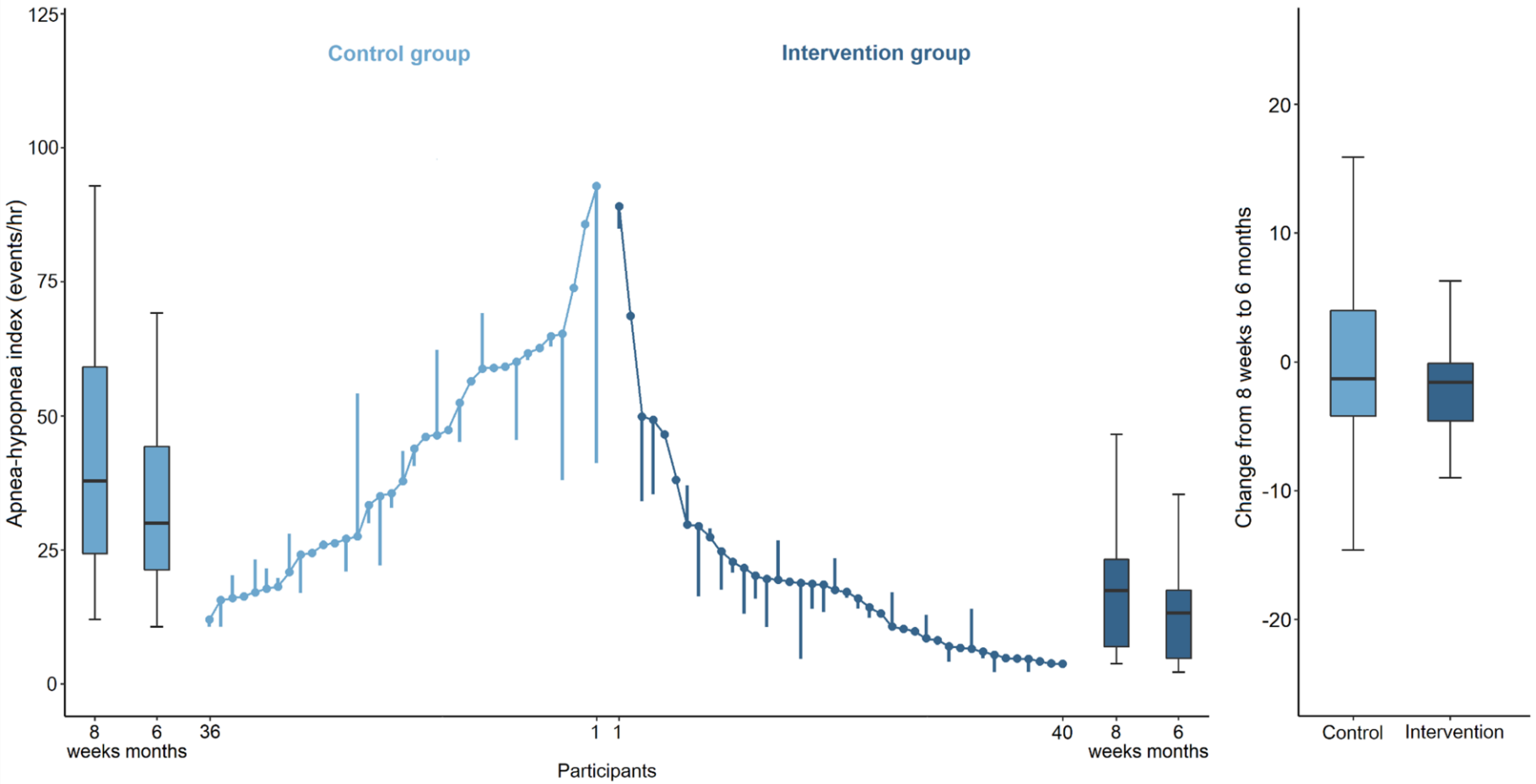
Intervention Adherence

Most participants in the intervention group attended all sessions of each intervention component (i.e. nutritional behavior change, physical exercise, sleep hygiene, smoking cessation and alcohol avoidance). Of 40 participants and 32 sessions (eight sessions of nutrition; eight of physical exercise; four of sleep hygiene; eight of smoking cessation, and four of alcohol avoidance), 24 participants (60%) attended all sessions (100%); 4 (10%) attended 30 sessions (93.8%); 10 (25%) attended 29 sessions (90.6%); and 2 (5%) attended 28 sessions (87.5%). Therefore, 30.8 sessions (96.4%) were attended on average.

Supplementary Figure S1. OSA severity at baseline, after 8 weeks and at 6 months after intervention in the intervention group



Supplementary Figure S2. Apnea-Hypopnea Index Endpoint (Change from 8 weeks to 6 months)



The ends of the boxes in the boxplots are located at the first and third quartiles, with the black line in the middle illustrating the median. Whiskers extend to the upper and lower adjacent values, the location of the furthest point within a distance of 1.5 interquartile ranges from the first and third quartiles. The parallel line plot contains 1 vertical line for each patient which extends from their 8-week value to their 6-month value. Descending lines indicate an improvement in the outcome. Eight-week values are placed in ascending order for the control group and descending order for the intervention group. The apnea-hypopnea index indicates the number of apnea and hypopnea events per hour of sleep (0-5 is classified as normal; 5-14, mild OSA; 15-30, moderate OSA; >30, severe OSA; a change of at least 15 is considered clinically meaningful and would move a patient 2 levels from severe to mild with established benefit for health).

Supplementary Table S1. Baseline characteristics of the study participants (per-protocol approach)

Characteristic[b]	No. (%)[a]	
	Control (n = 35)	Intervention (n = 40)
Age, mean (SD), y	55.4 (8.9)	52.6 (7.2)
Educational level		
Primary Education	8 (22.9)	10 (25.0)
Secondary Education	6 (17.1)	6 (15.0)
Vocational Education	11 (31.4)	17 (42.5)
Higher Education	10 (28.6)	7 (17.5)
Marital status		
Single	4 (11.4)	2 (5.0)
Married	25 (71.4)	34 (85.0)
Divorced	6 (17.1)	4 (10.0)
Occupational status		
Employed	19 (54.3)	21 (52.5)
Self-employed	6 (17.1)	12 (30.0)
Unemployed	3 (8.6)	5 (12.5)
Retired	7 (20.0)	2 (5.0)
Medical Conditions[c]		
Hypertension	22 (62.9)	27 (67.5)
Diabetes Mellitus II	12 (34.3)	10 (25.0)
Cardiovascular disease	8 (22.9)	7 (17.5)
Other medical conditions	18 (51.4)	26 (65.0)
Medication[c]		
Antihypertensive	21 (60.0)	24 (60.0)
Statins	9 (25.7)	7 (17.5)
Oral antidiabetic	4 (11.4)	2 (5.0)
Insulin	3 (8.6)	1 (2.5)
Beta-blockers	5 (14.3)	5 (12.5)
Polymedication[d]	9 (25.7)	6 (15.0)
Body height, mean (SD), cm	171 (8.6)	172 (6.3)
Body weight status		
Overweight	7 (20.0)	5 (12.5)
Class I obesity	17 (48.6)	19 (47.5)
Class II obesity	10 (28.6)	11 (27.5)
Class III obesity	1 (2.9)	5 (12.5)
Obstructive sleep apnea severity		
Moderate	15 (42.9)	15 (37.5)
Severe	20 (57.1)	25 (62.5)
Time since obstructive sleep apnea diagnosis, mean (SD), y	8.6 (6.0)	6.5 (6.5)
Physical activity, mean (SD), km/day	5.6 (4.2)	6.1 (3.8)
Dietary habits, mean (SD), Food Behavior Checklist score[e]	59.6 (9.4)	59.5 (8.5)
Alcohol consumption		
Never	8 (22.9)	13 (32.5)
Occasionally	11 (31.4)	8 (20.0)
Frequently	9 (25.7)	12 (30.0)
Daily	7 (20.0)	7 (17.5)
Tobacco consumption		
Non-smoker	13 (37.1)	15 (37.5)
Ex-smoker	14 (40.0)	15 (37.5)
Smoker	8 (22.9)	10 (25.0)

[a] No. (%) reported unless otherwise specified.
[b] No significant between-group differences were observed in any of the baseline characteristics.
[c] Participants could have more than one condition or medication.
[d] Defined as the use of five or more medications.
[e] Scores on the Food Behavior Checklist range from 23 to 85, with higher scores indicating healthier dietary pattern.

Supplementary Table S2. Primary and secondary sleep-related endpoints (per-protocol approach)

	Control (n=35)	Intervention (n=40)	Mean difference between groups (95% CI)[a]
Primary endpoint			
Apnea-hypopnea index, events/hr (95% CI)			
At baseline	39.2 (32.4 to 45.9)	41.6 (35.2 to 47.9)	
Change at 8 wk	2.8 (-1.7 to 7.4)	-21.2 (-25.4 to -16.9)	-24.0 (-29.1 to -18.8)[d]
Change at 6 mo	-0.4 (-5.5 to 4.7)	-23.8 (-28.3 to -19.3)	-23.4 (-29.0 to -17.8)[d]
Secondary endpoints			
Oxygen desaturation index ≥3%, events/hr (95% CI)			
At baseline	43.0 (35.5 to 50.5)	45.4 (38.4 to 52.5)	
Change at 8 wk	3.4 (-2.3 to 9.2)	-16.0 (-21.4 to -10.6)	-19.5 (-26.0 to -13.0)[d]
Change at 6 mo	-0.4 (-6.8 to 6.1)	-23.5 (-29.2 to 17.7)	-23.1 (-30.2 to -16.0)[d]
Mean SpO_2, % (95% CI)			
At baseline	91.0 (90.0 to 92.0)	91.3 (90.3 to 92.3)	
Change at 8 wk	-0.9 (-2.1 to 0.3)	1.5 (0.4 to 2.6)	2.4 (1.1 to 3.7)[d]
Change at 6 mo	-1.0 (-2.4 to 0.3)	2.6 (1.4 to 3.8)	3.6 (2.2 to 5.1)[d]
SpO_2 Nadir, % (95% CI)			
At baseline	78.4 (75.8 to 81.0)	78.1 (75.6 to 80.5)	
Change at 8 wk	0.1 (-1.9 to 2.1)	2.8 (1.0 to 4.6)	2.7 (0.5 to 4.9)[b]
Change at 6 mo	-1.6 (-3.8 to 0.6)	4.4 (2.5 to 6.4)	6.0 (3.6 to 8.4)[d]
Sleep time with SpO2 <90%, % (95% CI)			
At baseline	11.3 (7.6 to 15.0)	9.1 (5.6 to 12.6)	
Change at 8 wk	1.6 (-2.0 to 5.2)	-4.4 (-7.8 to -1.0)	-6.0 (-10.1 to -1.9)[c]
Change at 6 mo	1.0 (-3.0 to 5.0)	-5.5 (-9.1 to -1.9)	-6.5 (-10.9 to -2.0)[c]
Sleep efficiency, % (95% CI)			
At baseline	86.0 (83.5 to 88.4)	86.0 (83.7 to 88.4)	
Change at 8 wk	-2.0 (-5.4 to 1.4)	5.7 (2.5 to 8.8)	7.7 (3.8 to 11.5)[d]
Change at 6 mo	-2.1 (-5.8 to 1.7)	7.6 (4.2 to 10.9)	9.7 (5.5 to 13.8) [d]
Sleep latency, min (95% CI)			
At baseline	21.2 (16.5 to 25.9)	23.0 (18.6 to 27.4)	
Change at 8 wk	3.2 (-4.4 to 10.8)	-7.1 (-14.2 to 0.04)	-10.2 (-18.8 to -1.7)[b]
Change at 6 mo	5.1 (-3.2 to 13.3)	-11.2 (-18.7 to -3.8)	-16.3 (-25.4 to -7.1)[d]
Wake after sleep onset, min (95% CI)			
At baseline	53.2 (41.2 to 65.2)	47.6 (36.4 to 58.9)	
Change at 8 wk	12.6 (-3.9 to 29.1)	-17.2 (-32.6 to -1.8)	-29.8 (-48.3 to -11.3)[c]
Change at 6 mo	10.7 (-7.5 to 28.9)	-25.8 (-42.0 to -9.5)	-36.5 (-56.4 to -16.3)[d]
N1+N2 sleep, % (95% CI)			
At baseline	64.3 (61.6 to 67.0)	63.4 (60.8 to 65.9)	
Change at 8 wk	3.8 (-0.1 to 7.7)	-6.2 (-9.8 to -2.5)	-10.0 (-14.3 to -5.6)[d]
Change at 6 mo	5.3 (1.0 to 9.6)	-8.9 (-12.8 to -5.1)	-14.2 (-18.9 to -9.5)[d]
N3 sleep, % (95% CI)			
At baseline	20.3 (18.0 to 22.6)	20.4 (18.2 to 22.5)	
Change at 8 wk	-4.0 (-7.4 to -0.7)	3.7 (0.5 to 6.8)	7.7 (3.9 to 11.5)[d]
Change at 6 mo	-7.3 (-11.0 to -3.6)	4.5 (1.2 to 7.8)	11.8 (7.7 to 15.9)[d]
REM sleep, % (95% CI)			
At baseline	15.4 (13.9 to 17.0)	16.2 (14.8 to 17.7)	
Change at 8 wk	0.2 (-2.1 to 2.6)	2.5 (0.3 to 4.7)	2.3 (-0.4 to 4.9)
Change at 6 mo	2.1 (-0.5 to 4.7)	4.5 (2.2 to 6.8)	2.4 (-0.5 to 5.2)
AHI in REM sleep, events/hr (95% CI)			
At baseline	39.8 (33.1 to 46.4)	45.1 (39.0 to 51.3)	
Change at 8 wk	6.1 (-2.0 to 14.2)	-22.6 (-30.2 to -15.1)	-28.7 (-37.9 to -19.6)[d]
Change at 6 mo	-2.8 (-11.8 to 6.2)	-26.6 (-34.6 to -18.6)	-23.8 (-33.6 to -13.9)[d]
AHI in NREM sleep, events/hr (95% CI)			
At baseline	38.5 (31.3 to 45.6)	41.0 (34.3 to 47.7)	
Change at 8 wk	2.6 (-2.4 to 7.6)	-21.0 (-25.7 to -16.3)	-23.6 (-29.2 to -17.9)[d]
Change at 6 mo	-0.7 (-6.3 to 5.0)	-23.6 (-28.5 to -18.6)	-22.9 (-29.1 to -16.7)[d]
Pittsburgh Sleep Quality Index score (95% CI)[e]			
At baseline	8.2 (7.0 to 9.4)	7.2 (6.1 to 8.4)	
Change at 8 wk	-0.3 (-1.4 to 0.8)	-2.8 (-3.8 to -1.8)	-2.5 (-3.7 to -1.2)[d]
Change at 6 mo	0.2 (-1.0 to 1.4)	-3.6 (-4.7 to -2.5)	-3.8 (-5.1 to -2.5)[d]
Epworth Sleepiness Scale score (95% CI)[f]			
At baseline	9.1 (7.6 to 10.7)	10.3 (8.8 to 11.7)	
Change at 8 wk	-0.3 (-2.1 to 1.5)	-4.6 (-6.3 to -2.9)	-4.3 (-6.3 to -2.2)[d]
Change at 6 mo	-1.0 (-3.0 to 1.0)	-6.8 (-8.6 to -5.0)	-5.8 (-8.0 to -3.6)[d]

Abbreviations: CI, confidence interval; SpO_2, oxygen saturation; AHI, apnea-hypopnea index; REM, rapid eye movement; NREM, non-rapid eye movement.

[a] Using the group × visit interaction term from a linear mixed-effects model including study group, time (baseline, 8 weeks and 6 months), and study group × time as fixed effects and participant as random effects.

[b] $P < 0.05$ from the time × study group interactions.

[c] $P < 0.01$ from the time × study group interactions.

[d] $P < 0.001$ from the time × study group interactions.

[e] Pittsburgh Sleep Quality Index scores range from 0 to 21, with higher scores indicating worse sleep quality.

[f] Epworth Sleepiness Scale scores range from 0 to 24, with higher scores indicating more daytime sleepiness.

Supplementary Table S3. Primary and secondary sleep-related endpoints (change from 8 weeks to 6 months)

	Control (n=49)			Intervention (n=40)		
	8 wk Mean (95% CI)	6 mo Mean (95% CI)	Mean change (95% CI)[a]	8 wk Mean (95% CI)	6 mo Mean (95% CI)	Mean change (95% CI)[a]
Primary endpoint						
Apnea-hypopnea index, events/hr	43.6 (37.5 to 49.7)	40.3 (34.0 to 46.7)	-3.3 (-8.3 to 1.8)	20.4 (14.0 to 26.9)	17.8 (11.3 to 24.4)	-2.6 (-7.1 to 1.9)
Secondary endpoints						
Oxygen desaturation index ≥3%, events/hr	48.3 (41.6 to 55.1)	44.6 (7.5 to 51.7)	-3.7 (-10.1 to 2.6)	29.4 (22.4 to 36.4)	22.0 (14.8 to 29.2)	-7.4 (-13.1 to -1.7)[c]
Mean SpO_2, %	89.6 (88.6 to 90.7)	89.5 (88.4 to 90.6)	-0.2 (-1.5 to 1.1)	92.8 (91.7 to 93.8)	93.9 (92.8 to 94.9)	1.1 (-0.1 to 2.3)
SpO_2 Nadir, %	77.1 (74.3 to 79.8)	75.2 (72.4 to 78.0)	-1.8 (-4.1 to 0.3)	80.9 (78.0 to 83.7)	82.5 (79.5 to 85.4)	1.6 (-0.3 to 3.6)
Sleep time with SpO2 <90%, %	12.9 (9.5 to 16.3)	12.4 (8.8 to 16.0)	-0.5 (-4.5 to 3.4)	4.7 (1.3 to 8.1)	3.6 (0.1 to 7.1)	-1.1 (-4.6 to 2.5)
Sleep efficiency, %	83.9 (81.5 to 86.3)	84.0 (81.3 to 86.6)	0.1 (-3.6 to 3.8)	91.7 (89.4 to 94.0)	93.6 (91.2 to 96.1)	1.9 (-1.4 to 5.3)
Sleep latency, min	24.4 (19.6 to 29.2)	26.0 (20.6 to 31.5)	1.6 (-6.7 to 9.9)	15.9 (11.4 to 20.4)	11.8 (6.9 to 16.6)	-4.1 (-11.7 to 3.4)
Wake after sleep onset, min	66.1 (54.5 to 77.8)	63.8 (50.7 to 76.8)	-2.4 (-20.2 to 15.5)	30.4 (19.3 to 41.5)	21.8 (9.9 to 33.7)	-8.6 (-24.7 to 7.5)
N1+N2 sleep, %	68.3 (65.5 to 71.0)	69.8 (66.7 to 72.9)	1.5 (-2.8 to 5.8)	57.2 (54.6 to 59.8)	54.5 (51.7 to 57.3)	-2.7 (-6.6 to 1.1)
N3 sleep, %	16.3 (14.0 to 18.7)	13.2 (10.5 to 15.8)	-3.2 (-6.9 to 0.6)	24.1 (21.8 to 26.3)	24.8 (22.5 to 27.2)	0.8 (-2.6 to 4.2)
REM sleep, %	15.5 (13.9 to 17.0)	17.2 (15.5 to 19.0)	1.8 (-0.8 to 4.3)	18.7 (17.3 to 20.2)	20.7 (19.2 to 22.3)	2.0 (-0.3 to 4.3)
AHI in REM sleep, events/hr	46.8 (40.4 to 53.2)	38.0 (45.0 to 30.9)	-8.8 (-17.7 to 0.1)	22.5 (16.3 to 28.7)	18.6 (12.0 to 25.1)	-4.0 (-11.9 to 4.0)
AHI in NREM sleep, events/hr	42.8 (49.2 to 36.3)	39.5 (32.7 to 46.2)	-3.3 (-8.9 to 2.2)	20.0 (13.2 to 26.8)	17.4 (10.5 to 24.4)	-2.6 (-7.5 to 2.4)
Pittsburgh Sleep Quality Index score[d]	8.4 (7.2 to 9.5)	9.0 (7.7 to 10.2)	0.6 (-0.6 to 1.8)	4.5 (3.2 to 5.7)	3.7 (2.4 to 4.9)	-0.8 (-1.9 to -0.3)
Epworth Sleepiness Scale score[e]	8.8 (7.3 to 10.3)	8.1 (6.4 to 9.7)	-0.7 (-2.7 to 1.3)	5.7 (4.2 to 7.2)	3.5 (1.9 to 5.0)	-2.2 (-4.0 to -0.4)[b]

Abbreviations: CI, confidence interval; SpO_2, oxygen saturation; AHI, apnea-hypopnea index; REM, rapid eye movement; NREM, non rapid eye movement.

[a] Using post-hoc test (pairwise comparison) in a linear mixed-effects model including study group, time (baseline, 8 weeks and 6 months), and study group × time as fixed effects and participant as random effects.

[b] $P < 0.05$.

[c] $P < 0.01$.

[d] Pittsburgh Sleep Quality Index scores range from 0 to 21, with higher scores indicating worse sleep quality.

[e] Epworth Sleepiness Scale scores range from 0 to 24, with higher scores indicating more daytime sleepiness.

Supplementary Table S4. Secondary body composition and cardiometabolic risk endpoints (per-protocol approach)

	Control (n=35)	Intervention (n=40)	Mean difference between groups (95% CI)[a]
Body composition			
Body weight, kg (95% CI)			
At baseline	94.0 (87.8 to 100.1)	102.2 (96.8 to 107.6)	
Change at 8 wk	-0.2 (-1.9 to 1.5)	-7.1 (-8.6 to -5.5)	-6.9 (-8.7 to -5.0)[d]
Change at 6 mo	-1.1 (-3.0 to 0.8)	-6.9 (-8.5 to -5.2)	-5.8 (-7.8 to -3.7)[d]
Body mass index, kg/m² (95% CI)			
At baseline	33.7 (35.5 to 31.9)	35.0 (36.7 to 33.4)	
Change at 8 wk	-0.2 (-0.8 to 0.4)	-2.5 (-3.0 to -1.9)	-2.3 (-2.9 to -1.6)[d]
Change at 6 mo	-0.6 (-1.2 to 0.1)	-2.4 (-3.0 to -1.8)	-1.8 (-2.5 to -1.1)[d]
Neck circumference, cm (95% CI)			
At baseline	45.1 (43.9 to 46.2)	45.0 (43.9 to 46.2)	
Change at 8 wk	-0.3 (-0.9 to 0.3)	-2.3 (-2.8 to -1.7)	-2.0 (-2.6 to -1.3)[d]
Change at 6 mo	0.2 (-0.5 to 0.9)	-2.9 (-3.5 to -2.3)	-3.1 (-3.9 to -2.4)[d]
Chest circumference, cm (95% CI)			
At baseline	116.1 (112.9 to 119.4)	118.0 (115.0 to 121.1)	
Change at 8 wk	0.5 (-0.8 to 1.9)	-3.4 (-4.6 to -2.1)	-3.9 (-5.4 to -2.4)[d]
Change at 6 mo	0.7 (-0.8 to 2.2)	-4.1 (-5.5 to -2.8)	-4.8 (-6.4 to -3.1)[d]
Waist circumference, cm (95% CI)			
At baseline	116.6 (112.5 to 120.8)	119.0 (115.1 to 122.9)	
Change at 8 wk	-0.1 (-1.6 to 1.4)	-6.9 (-8.4 to -5.5)	-6.8 (-8.5 to -5.1)[d]
Change at 6 mo	0.3 (-1.4 to 2.2)	-8.8 (-10.3 to -7.2)	-9.1 (-11.0 to -7.2)[d]
Fat mass, kg (95% CI)			
At baseline	33.0 (29.8 to 36.3)	34.9 (31.8 to 37.9)	
Change at 8 wk	1.5 (-0.2 to 3.2)	-2.9 (-4.5 to -1.3)	-4.4 (-6.3 to -2.4)[d]
Change at 6 mo	0.2 (-1.7 to 2.2)	-6.5 (-8.2 to -4.8)	-6.7 (-8.8 to -4.6)[d]
Visceral adipose tissue, g (95% CI)			
At baseline	1021.8 (929.2 to 1114.4)	1017.3 (930.7 to 1104.0)	
Change at 8 wk	42.1 (-44.6 to 128.8)	-106.2 (-187.3 to -25.2)	-148.3 (-245.7 to -51.0)[c]
Change at 6 mo	-13.9 (-110.6 to 82.8)	-268.5 (-354.5 to -182.5)	-254.5 (-360.6 to -148.4)[d]
Lean mass, kg (95% CI)			
At baseline	60.5 (57.6 to 63.5)	63.0 (60.2 to 65.8)	
Change at 8 wk	-2.1 (-3.5 to -0.8)	-2.7 (-4.0 to -1.5)	-0.6 (-2.1 to 0.9)
Change at 6 mo	-1.2 (-2.7 to 0.3)	0.3 (-1.0 to 1.7)	1.5 (-0.2 to 3.1)
Blood pressure			
Systolic BP, mm Hg (95% CI)			
At baseline	142.6 (137.8 to 147.4)	143.7 (139.2 to 148.2)	
Change at 8 wk	-0.9 (-5.4 to 3.6)	-7.9 (-12.1 to -3.7)	-7.0 (-12.1 to -2.0)[c]
Change at 6 mo	2.2 (-2.8 to 7.3)	-13.9 (-18.4 to -9.4)	-16.1 (-21.6 to -10.6)[d]
Diastolic BP, mm Hg (95% CI)			
At baseline	81.7 (78.0 to 85.4)	84.0 (80.5 to 87.5)	
Change at 8 wk	0.5 (-4.4 to 5.4)	-5.7 (-10.3 to -1.2)	-6.2 (-11.7 to -0.7)[b]
Change at 6 mo	2.4 (-3.0 to 7.8)	-7.4 (-12.2 to -2.5)	-9.7 (-15.7 to -3.8)[c]
Mean BP, mm Hg (95% CI)			
At baseline	102.0 (98.4 to 105.6)	103.9 (100.5 to 107.3)	
Change at 8 wk	0.03 (-4.1 to 4.2)	-6.5 (-10.3 to -2.6)	-6.5 (-11.1 to -1.9)c
Change at 6 mo	2.3 (-2.3 to 6.9)	-9.6 (-13.6 to -5.5)	-11.8 (-16.9 to -6.8)[d]
Glucose metabolism			
Glucose, mg/dl (95% CI)			
At baseline	100.1 (93.3 to 106.9)	95.5 (89.1 to 101.9)	
Change at 8 wk	0.6 (-4.4 to 5.7)	-6.7 (-11.4 to -2.1)	-7.3 (-13.0 to -1.7)[b]
Change at 6 mo	4.5 (-1.1 to 10.0)	-6.6 (-11.6 to -1.7)	-11.1 (-17.2 to -4.9)[d]
Insulin, IU/ml (95% CI)			
At baseline	14.7 (12.2 to 17.3)	13.0 (10.6 to 15.4)	
Change at 8 wk	1.5 (-0.7 to 3.6)	-4.9 (-6.9 to -2.9)	-6.4 (-8.8 to -4.0)[d]
Change at 6 mo	0.2 (-2.2 to 2.5)	-5.2 (-7.3 to -3.1)	-5.3 (-7.9 to -2.7)[d]
HOMA-IR index (95% CI)			
At baseline	3.5 (2.6 to 4.4)	3.2 (2.3 to 4.0)	
Change at 8 wk	0.5 (-0.7 to 1.6)	-1.3 (-2.4 to -0.3)	-1.8 (-3.1 to -0.5)[c]
Change at 6 mo	0.4 (-0.9 to 1.7)	-1.4 (-2.5 to -0.3)	-1.8 (-3.2 to -0.4)[b]

(continued)

Supplementary Table S4. Secondary body composition and cardiometabolic risk endpoints (per-protocol approach) (continued)

	Control (n=35)	Intervention (n=40)	Mean difference between groups (95% CI)[a]
Lipid metabolism			
Total cholesterol, mg/dl (95% CI)			
At baseline	174.1 (162.5 to 185.6)	189.6 (178.9 to 200.2)	
Change at 8 wk	6.3 (-4.7 to 17.2)	-19.4 (-29.4 to -9.4)	-25.7 (-37.8 to -13.5)[d]
Change at 6 mo	3.9 (-8.1 to 15.8)	-16.6 (-27.2 to -6.0)	-20.5 (-33.6 to -7.4)[c]
HDL-C, mg/dl (95% CI)			
At baseline	42.4 (39.0 to 45.9)	47.1 (44.0 to 50.2)	
Change at 8 wk	2.4 (-0.5 to 5.3)	0.2 (-2.1 to 2.5)	-2.2 (-5.2 to 0.8)
Change at 6 mo	0.9 (-2.4 to 4.1)	3.0 (0.5 to 5.4)	2.1 (-1.2 to 5.4)
LDL-C, mg/dl (95% CI)			
At baseline	113.8 (103.1 to 124.4)	119.4 (110.1 to 128.8)	
Change at 8 wk	-1.6 (-10.3 to 7.1)	-15.0 (-21.9 to -8.0)	-13.3 (-22.4 to -4.3)[c]
Change at 6 mo	2.9 (-6.8 to 12.7)	-14.3 (-21.5 to -7.0)	-17.2 (-27.1 to -7.3)[c]
Triglycerides, mg/dl (95% CI)			
At baseline	153.6 (131.7 to 175.5)	129.5 (109.1 to 149.8)	
Change at 8 wk	4.4 (-14.1 to 22.9)	-24.5 (-41.3 to -7.6)	-28.9 (-49.4 to -8.4)[c]
Change at 6 mo	16.0 (-4.3 to 36.2)	-23.8 (-41.7 to -5.8)	-39.7 (-61.8 to -17.5)[d]
Apolipoprotein A1, mg/dl (95% CI)			
At baseline	125.9 (119.4 to 132.4)	131.0 (125.0 to 137.1)	
Change at 8 wk	6.2 (-0.2 to 12.5)	-0.6 (-6.5 to 5.3)	-6.8 (-13.9 to 0.3)
Change at 6 mo	0.9 (-5.8 to 7.5)	9.5 (3.4 to 15.4)	8.6 (1.4 to 15.9)[b]
Apolipoprotein B, mg/dl (95% CI)			
At baseline	94.4 (87.4 to 101.3)	102.5 (95.9 to 109.0)	
Change at 8 wk	2.5 (-4.2 to 9.2)	-11.9 (-18.2 to -5.6)	-14.4 (-22.0 to -6.9)[d]
Change at 6 mo	-1.3 (-8.3 to 5.7)	-15.1 (-21.5 to -8.8)	-13.9 (-21.6 to -6.1)[d]
Liver function			
AST, IU/l (95% CI)			
At baseline	25.3 (21.9 to 28.7)	25.3 (22.4 to 28.3)	
Change at 8 wk	0.8 (-3.7 to 5.3)	-2.4 (-6.2 to 1.4)	-3.2 (-8.0 to 1.6)
Change at 6 mo	-0.6 (-5.2 to 4.0)	-4.8 (-8.6 to -0.9)	-4.1 (-9.0 to 0.8)
ALT, IU/l (95% CI)			
At baseline	28.6 (24.0 to 33.2)	29.6 (25.3 to 33.9)	
Change at 8 wk	0.8 (-4.5 to 6.0)	-4.0 (-8.9 to 0.8)	-4.8 (-10.7 to 1.1)
Change at 6 mo	0.3 (-5.5 to 6.1)	-7.1 (-12.3 to -2.0)	-7.4 (-13.8 to -1.0)[b]
γ-GT, IU/l (95% CI)			
At baseline	40.9 (30.1 to 51.6)	38.2 (28.2 to 48.2)	
Change at 8 wk	4.5 (-3.9 to 12.9)	-11.2 (-18.9 to -3.5)	-15.7 (-25.0 to -6.3)[c]
Change at 6 mo	1.6 (-7.6 to 10.8)	-14.0 (-22.2 to -5.9)	-15.6 (-25.6 to -5.5)[c]
Fatty liver index (95% CI)			
At baseline	84.4 (78.4 to 90.5)	86.2 (80.5 to 91.8)	
Change at 8 wk	-1.2 (-6.1 to 3.6)	-13.7 (-9.3 to -18.0)	-12.4 (-17.8 to -7.1)[d]
Change at 6 mo	0.2 (-5.1 to 5.4)	-17.5 (-12.9 to -22.1)	-17.7 (-23.4 to -12.0)[d]

Abbreviations: CI, confidence interval; BP, blood pressure; HOMA-IR, homeostasis model assessment of insulin resistance; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase;γ-GT, γ-glutamyltransferase.

SI conversion factors: To convert glucose to millimoles per liter, multiply by 0.05551. To convert insulin to picomoles per liter, multiply by 6.945. To convert total, high-density lipoprotein, and low-density lipoprotein cholesterol to millimoles per liter, multiply by 0.02586. To convert triglycerides to millimoles per liter, multiply by 0.01129. To convert apolipoprotein A1 and B to gram per liter, multiply by 0.01. To convert aspartate aminotransferase to micro-katal per liter, multiply by 0.017. To convert aspartate aminotransferase and γ-glutamyltransferase to micro-katal per liter, multiply by 0.017.

[a] Using the group × visit interaction term from a linear mixed-effects model including study group, time (baseline, 8 weeks and 6 months), and study group × time as fixed effects and participant as random effects.

[b] $P < 0.05$ from the time × study group interactions.

[c] $P < 0.01$ from the time × study group interactions.

[d] $P < 0.001$ from the time × study group interactions.

Supplementary Table S5. Secondary body composition and cardiometabolic risk endpoints (change from 8 weeks to 6 months)

	Control (n=49)			Intervention (n=40)		
	8 wk Mean (95% CI)	6 mo Mean (95% CI)	Mean change (95% CI)[a]	8 wk Mean (95% CI)	6 mo Mean (95% CI)	Mean change (95% CI)[a]
Body composition						
Body weight, kg	99.3 (94.1 to 104.4)	98.4 (93.2 to 103.5)	-0.9 (-2.8 to 0.9)	96.2 (90.5 to 101.8)	96.4 (90.7 to 102.1)	0.2 (-1.4 to 1.9)
Body mass index, kg/m^2	33.7 (32.2 to 35.3)	33.3 (31.8 to 34.9)	-0.4 (-1.0 to 0.2)	32.6 (30.9 to 34.3)	32.6 (30.9 to 34.3)	0.1 (-0.5 to 0.6)
Neck circumference, cm	45.1 (44.0 to 46.2)	45.6 (44.5 to 46.8)	0.5 (-0.1 to 1.2)	42.8 (41.6 to 43.9)	42.1 (40.9 to 43.3)	-0.7 (-1.2 to -0.1)[b]
Chest circumference, cm	117.8 (115.0 to 120.7)	118.0 (115.1 to 121.0)	0.2 (-1.3 to 1.7)	114.7 (111.5 to 117.8)	113.9 (110.8 to 117.1)	-0.8 (-2.1 to 0.6)
Waist circumference, cm	117.7 (114.1 to 121.3)	118.2 (114.5 to 121.9)	0.5 (-1.2 to 2.2)	117.7 (114.1 to 121.3)	118.2 (114.5 to 121.9)	-1.8 (-3.3 to -0.3)[b]
Fat mass, kg	35.2 (32.3 to 38.2)	34.0 (31.0 to 37.0)	-1.3 (-3.2 to 0.7)	32.0 (28.9 to 35.1)	28.4 (25.2 to 31.6)	-3.6 (-5.3 to -1.9)[d]
Visceral adipose tissue, g	1081.7 (995.0 to 1168.5)	1022.9 (930.1 to 1115.6)	-58.9 (-154.7 to 37.0)	911.1 (823.3 to 998 to9)	748.9 (658.0 to 839.8)	-162.2 (-248.1 to -76.3)[d]
Lean mass, kg	58.7 (56.0 to 61.3)	59.6 (62.2 to 56.9)	0.9 (-0.5 to 2.4)	60.3 (57.5 to 63.1)	63.3 (60.5 to 66.2)	3.0 (1.7 to 4.4)[d]
Blood pressure						
Systolic BP, mm Hg	141.6 (137.2 to 146.0)	144.9 (140.2 to 149.6)	3.3 (-1.6 to 8.3)	135.7 (131.3 to 140.2)	129.8 (125.2 to 134.4)	-6.0 (-10.4 to -1.5)[c]
Diastolic BP, mm Hg	82.3 (78.7 to 85.9)	84. 1 (80.1 to 88.1)	1.8 (-3.5 to 7.1)	78.3 (74.9 to 81.7)	76.7 (73.0 to 80.3)	-1.6 (-6.4 to 3.2)
Mean BP, mm Hg	102.1 (98.8 to 105.5)	104.4 (100.8 to 108.1)	2.3 (-2.2 to 6.8)	97.4 (94.1 to 100.7)	94.3 (90.9 to 97.8)	-3.1 (-7.1 to 1.0)
Glucose metabolism						
Glucose, mg/dl	102.1 (95.7 to 108.4)	105.6 (99.0 to 112.1)	3.5 (-2.1 to 9.1)	88.8 (82.3 to 95.3)	88.9 (82.3 to 95.5)	-0.1 (-4.8 to 5.1)
Insulin, IU/ml	15.7 (13.4 to 18.0)	14.3 (11.9 to 16.8)	-1.4 (-3.7 to 1.0)	8.1 (5.8 to 10.4)	7.8 (5.4 to 10.2)	-0.3 (-2.4 to 1.8)
HOMA-IR index	4.0 (3.1 to 4.8)	3.8 (2.9 to 4.8)	-0.1 (-1.4 to 1.1)	1.8 (1.0 to 2.6)	1.8 (0.9 to 2.6)	-0.1 (-1.2 to 1.0)
Lipid metabolism						
Total cholesterol, mg/dl	182.8 (171.4 to 194.2)	182.1 (170.0 to 194.2)	-0.7 (-12.8 to 11.4)	170.2 (158.7 to 181.6)	172.9 (161.1 to 184.8)	2.8 (-7.9 to 13.5)
HDL-C, mg/dl	46.6 (43.4 to 49.8)	45.3 (41.9 to 48.8)	-1.3 (-4.2 to 1.7)	47.3 (44.1 to 50.5)	50.1 (46.8 to 53.3)	2.8 (0.3 to 5.2)[b]
LDL-C, mg/dl	113.5 (104.0 to 123.0)	121.2 (110.8 to 131.5)	7.7 (-2.3 to 17.6)	104.5 (95.2 to 113.9)	105.3 (95.7 to 114.9)	0.7 (-7.3 to 8.8)
Triglycerides, mg/dl	158.1 (136.3 to 179.8)	164.8 (141.8 to 187.8)	6.8 (-16.3 to 29.8)	105.0 (83.2 to 126.8)	105.7 (83.2 to 128.2)	0.7 (-19.7 to 21.1)
Apolipoprotein A1, mg/dl	133.8 (127.5 to 140.1)	129.0 (122.5 to 135.5)	-4.8 (-11.7 to 2.1)	130.4 (124.1 to 136.7)	140.5 (134.2 to 146.9)	10.1 (4.0 to 16.3)[d]
Apolipoprotein B, mg/dl	98.5 (91.5 to 105.5)	95.2 (88.0 to 102.3)	-3.3 (-10.6 to 4.0)	90.6 (97.6 to 83.6)	87.3 (80.3 to 94.3)	-3.3 (-9.8 to 3.2)
Liver function						
AST, IU/l	26.0 (22.8 to 29.3)	24.5 (21.2 to 27.8)	-1.5 (-5.8 to 2.8)	22.9 (20.0 to 25.9)	20.6 (17.5 to 23.6)	-2.4 (-6.2 to 1.4)
ALT, IU/l	29.5 (25.0 to 33.9)	28.7 (23.8 to 33.5)	-0.8 (-6.5 to 5.0)	25.6 (21.3 to 29.9)	22.5 (17.9 to 27.0)	-3.1 (-8.3 to 2.0)
γ-GT, IU/l	47.8 (37.6 to 57.9)	44.7 (34.1 to 55.2)	-3.1 (-12.4 to 6.2)	27.0 (16.7 to 37.3)	24.2 (13.6 to 34.7)	-2.8 (-11.0 to 5.3)
Fatty liver index	84.2 (78.7 to 89.7)	85.6 (79.9 to 91.2)	1.4 (-3.9 to 6.7)	72.5 (66.9 to 78.0)	68.6 (63.0 to 74.3)	-3.8 (-8.4 to 0.8)

Abbreviations: CI, confidence interval; BP, blood pressure; HOMA-IR, homeostasis model assessment of insulin resistance; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase;γ-GT, γ-glutamyltransferase.

SI conversion factors: To convert glucose to millimoles per liter, multiply by 0.05551. To convert insulin to picomoles per liter, multiply by 6.945. To convert total, high-density lipoprotein, and low-density lipoprotein cholesterol to millimoles per liter, multiply by 0.02586. To convert triglycerides to millimoles per liter, multiply by 0.01129. To convert apolipoprotein A1 and B to gram per liter, multiply by 0.01. To convert aspartate aminotransferase to micro-katal per liter, multiply by 0.017. To convert aspartate aminotransferase and γ-glutamyltransferase to micro-katal per liter, multiply by 0.017.

[a] Using post-hoc test (pairwise comparison) in a linear mixed-effects model including study group, time (baseline, 8 weeks and 6 months), and study group × time as fixed effects and participant as random effects.

[b] $P < 0.05$.

[c] $P < 0.01$.

[d] $P < 0.001$.

Supplementary Table S6. Health-related quality of life endpoints

	Control		Intervention		Mean difference between groups (95% CI)[a]
	N	Mean (95% CI)	N	Mean (95% CI)	
Intention-to-treat approach					
Sleep Apnea Quality of Life Index score[e]					
At baseline	49	4.7 (4.4 to 5.0)	40	4.8 (4.5 to 5.1)	
Change at 8 wk	49	0.1 (-0.3 to 0.4)	40	0.8 (0.5 to 1.1)	0.8 (0.4 to 1.2)[d]
Change at 6 mo	49	0.1 (-0.3 to 0.5)	40	1.1 (0.7 to 1.5)	1.0 (0.6 to 1.5)[d]
SF-36 Physical-component summary score[f]					
At baseline	49	45.3 (42.4 to 48.1)	40	46.5 (43.3 to 49.6)	
Change at 8 wk	49	2.5 (-1.3 to 6.2)	40	6.0 (2.4 to 9.7)	3.5 (-0.8 to 7.8)
Change at 6 mo	49	-0.02 (-4.2 to 4.1)	40	6.5 (2.6 to 10.3)	6.5 (1.9 to 11.1)[c]
SF-36 Mental-component summary score[f]					
At baseline	49	46.7 (43.5 to 49.9)	40	48.3 (44.8 to 51.9)	
Change at 8 wk	49	1.6 (-3.0 to 6.1)	40	3.6 (-0.8 to 8.1)	2.1 (-3.2 to 7.3)
Change at 6 mo	49	-0.1 (-5.2 to 4.9)	40	6.1 (1.4 to 10.8)	6.2 (0.6 to 11.9)[b]
Per-protocol approach					
Sleep Apnea Quality of Life Index score[e]					
At baseline	35	4.7 (4.4 to 5.1)	40	4.8 (4.5 to 5.1)	
Change at 8 wk	35	0.04 (-0.3 to 0.4)	40	0.8 (0.5 to 1.1)	0.8 (0.4 to 1.2)[d]
Change at 6 mo	35	0.1 (-0.4 to 0.5)	40	1.1 (0.7 to 1.5)	1.0 (0.6 to 1.5)[d]
SF-36 Physical-component summary score[f]					
At baseline	35	45.9 (42.7 to 49.0)	40	46.5 (43.5 to 49.4)	
Change at 8 wk	35	2.2 (-1.6 to 6.0)	40	6.0 (2.5 to 9.6)	3.9 (-0.4 to 8.1)
Change at 6 mo	35	-0.4 (-4.6 to 3.9)	40	6.5 (2.7 to 10.3)	6.9 (2.2 to 11.5)[c]
SF-36 Mental-component summary score[f]					
At baseline	35	47.9 (44.2 to 51.7)	40	48.3 (44.8 to 51.9)	
Change at 8 wk	35	0.9 (-3.9 to 5.6)	40	3.6 (-0.8 to 8.1)	2.8 (-2.6 to 8.1)
Change at 6 mo	35	-0.9 (-6.2 to 4.3)	40	6.1 (1.4 to 10.8)	7.0 (1.2 to 12.8)[b]

Abbreviations: CI, confidence interval.

[a] Using the group × visit interaction term from a linear mixed-effects model including study group, time (baseline, 8 weeks and 6 months), and study group × time as fixed effects and participant as random effects.

[b] $P < 0.05$ from the time × study group interactions.

[c] $P < 0.01$ from the time × study group interactions.

[d] $P < 0.001$ from the time × study group interactions.

[e] Sleep Apnea Quality of Life Index scores range from 1 to 7, with higher scores indicating better health-related quality of life.

[f] Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) scores range from 0 to 100, with higher scores indicating better health-related quality of life with respect to either the physical or mental component.

Supplementary Table S7. Health-related quality of life endpoints (change from 8 weeks to 6 months)

	Control (n=49)			Intervention (n=40)		
	8 wk Mean (95% CI)	6 mo Mean (95% CI)	Mean change (95% CI)[a]	8 wk Mean (95% CI)	6 mo Mean (95% CI)	Mean change (95% CI)[a]
Sleep Apnea Quality of Life Index score[b]	4.8 (4.5 to 5.1)	4.8 (4.4 to 5.1)	0.02 (-0.4 to 0.4)	5.6 (5.3 to 5.9)	5.9 (5.6 to 6.2)	0.3 (-0.1 to 0.6)
SF-36 Physical-component summary score[c]	47.7 (44.5 to 50.9)	45.2 (41.7 to 48.7)	-2.5 (-6.8 to 1.8)	52.5 (49.4 to 55.6)	52.9 (49.6 to 56.2)	0.4 (-3.4 to 4.3)
SF-36 Mental-component summary score[c]	48.3 (44.6 to 52.0)	46.6 (42.5 to 50.7)	-1.7 (-6.9 to 3.5)	51.9 (48.4 to 55.5)	54.4 (50.6 to 58.2)	2.4 (-2.2 to 7.1)

Abbreviations: CI, confidence interval.

[a] Using post-hoc test (pairwise comparison) in a linear mixed-effects model including study group, time (baseline, 8 weeks and 6 months), and study group × time as fixed effects and participant as random effects.

[b] Sleep Apnea Quality of Life Index scores range from 1 to 7, with higher scores indicating better health-related quality of life.

[c] Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) scores range from 0 to 100, with higher scores indicating better health-related quality of life with respect to either the physical or mental component.

Supplementary Table S8. Physical activity and dietary behavior endpoints

	Control		Intervention		Mean difference between groups (95% CI)[a]
	N	Mean (95% CI)	N	Mean (95% CI)	
Intention-to-treat approach					
Physical activity, km/day					
At baseline	49	5.2 (3.9 to 6.4)	40	6.1 (4.8 to 7.5)	
Change at 8 wk	49	0.4 (-1.2 to 2.0)	40	8.8 (7.3 to 10.4)	8.4 (6.5 to 10.2)[b]
Change at 6 mo	49	-0.9 (-2.7 to 0.9)	40	6.0 (4.3 to 7.6)	6.9 (4.9 to 8.9)[b]
Dietary habits, Food Behavior Checklist score[c]					
At baseline	49	59.1 (56.8 to 61.4)	40	59.5 (56.9 to 62.0)	
Change at 8 wk	49	3.3 (0.6 to 5.9)	40	12.0 (9.5 to 14.5)	8.7 (5.7 to 11.7)[b]
Change at 6 mo	49	1.5 (-1.4 to 4.4)	40	9.2 (6.5 to 11.9)	7.7 (4.4 to 10.9)[b]
Per-protocol approach					
Physical activity, km/day					
At baseline	35	5.6 (4.1 to 7.1)	40	6.1 (4.8 to 7.5)	
Change at 8 wk	35	0.2 (-1.4 to 1.9)	40	8.8 (7.2 to 10.4)	8.6 (6.7 to 10.5)[b]
Change at 6 mo	35	-1.1 (-2.9 to 0.8)	40	6.0 (4.3 to 7.7)	7.1 (5.0 to 9.1)[b]
Dietary habits, Food Behavior Checklist score[c]					
At baseline	35	59.6 (57.0 to 62.3)	40	59.5 (57.0 to 62.0)	
Change at 8 wk	35	3.1 (0.4 to 5.9)	40	12.0 (9.5 to 14.5)	8.9 (5.8 to 11.9)[b]
Change at 6 mo	35	1.5 (-1.5 to 4.5)	40	9.2 (6.5 to 11.9)	7.7 (4.4 to 11.0)[b]

Abbreviations: CI confidence interval.

[a] Using the group × visit interaction term from a linear mixed-effects model including study group, time (baseline, 8 weeks and 6 months), and study group × time as fixed effects and participant as random effects.

[b] $P < 0.001$ from the time × study group interactions.

[c] Scores on the Food Behavior Checklist range from 23 to 85, with higher scores indicating healthier dietary pattern.

Supplementary Table S9. Physical activity and dietary behavior endpoints (change from 8 weeks to 6 months)

	Control (n=49)			Intervention (n=40)		
	8 wk Mean (95% CI)	6 mo Mean (95% CI)	Mean change (95% CI)[a]	8 wk Mean (95% CI)	6 mo Mean (95% CI)	Mean change (95% CI)[a]
Physical activity, km/day	5.6 (4.2 to 7.0)	4.3 (2.7 to 5.8)	-1.3 (-3.2 to 0.5)	15.0 (13.6 to 16.3)	12.1 (10.7 to 13.6)	-2.8 (-4.5 to -1.2)[c]
Dietary habits, Food Behavior Checklist score[d]	62.4 (59.9 to 64.9)	60.6 (57.9 to 63.4)	-1.8 (-4.8 to 1.2)	71.5 (68.9 to 74.0)	68.6 (66.0 to 71.3)	-2.8 (-5.5 to -0.1)[b]

Abbreviations: CI, confidence interval.

[a] Using post-hoc test (pairwise comparison) in a linear mixed-effects model including study group, time (baseline, 8 weeks and 6 months), and study group × time as fixed effects and participant as random effects.

[b] $P < 0.01$

[c] $P < 0.001$

[d] Scores on the Food Behavior Checklist range from 23 to 85, with higher scores indicating healthier dietary pattern.

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CHAPTER 4

Effect of an interdisciplinary weight loss and lifestyle intervention on daily functioning and psychiatric symptoms in obstructive sleep apnea: The INTERAPNEA trial (**Study 4**)

ABSTRACT

Impaired daily functioning and psychiatric symptoms are highly prevalent in obstructive sleep apnea (OSA) and represent a substantial cause of disease burden; however, although effective at reducing OSA severity, the effects of weight loss and lifestyle interventions on these symptoms still remain uncertain. This study was aimed at evaluating the efficacy of an interdisciplinary weight loss and lifestyle intervention on impaired functioning, psychological distress, anxiety and depression among overweight/obese men with moderate-to-severe OSA. This ancillary study was based on data from INTERAPNEA; a randomized clinical trial conducted from April 2019 to April 2020. Men aged 18-65 years with moderate-to-severe OSA and a body mass index ≥25 kg/m^2 from a hospital-based referral center were randomly received usual-care (continuous positive airway pressure), or an eight-week weight loss and lifestyle intervention including nutritional behavior change, aerobic exercise, sleep hygiene, and alcohol and tobacco cessation, combined with usual-care. Primary outcomes were changes from baseline to intervention endpoint and 6 months after intervention in daily functioning (measured by the Functional Outcomes of Sleep Questionnaire [FOSQ]); psychological distress (evaluated through the General Health Questionnaire [GHQ]); and anxiety and depression symptoms (measured by the State-Trait Anxiety Inventory [STAI], State-Trait Depression Inventory [STDI], and Beck Depression Inventory [BDI]). Eighty-nine participants underwent randomization (mean [±SD] age, 54±8 years; mean apnea-hypopnea index, 41±22 events/hr); 49 were assigned to usual-care and 40 to the intervention. As compared with usual-care, the intervention group had greater improvements in daily functioning (mean between-group difference in FOSQ score, 2.3; 95% confidence interval, 1.5 to 3.2), psychological distress (GHQ score, -10.3; -15.3 to -5.1), state anxiety (STAI-State score, -7.0; -11.0 to -3.0), trait anxiety (STAI-Trait score, -6.1; -9.5 to -2.8), state depression (STDI-State score, -2.4; -4.3 to -0.4), trait depression (STDI-Trait score, -3.8; -5.6 to -2.1), and general depression (BDI score, -2.0; -3.2 to -0.8) at intervention endpoint. Similar changes were observed at 6 months after intervention. This study provides the first evidence suggesting that an interdisciplinary weight loss and lifestyle intervention outstandingly improves OSA-related impaired daily functioning and psychiatric symptoms. These findings should be considered when evaluating the potential benefits of this behavioral approach for OSA.

Introduction

Obstructive sleep apnea (OSA), a major public health problem affecting up to 38% of adults in the overall population, is characterized by recurrent episodes of complete or partial upper-airway obstructions during sleep resulting in long-term exposure to hypoxia, hypercapnia, sleep fragmentation and increased sympathetic activity.[1,2] With obesity as the leading attributable cause, OSA is closely associated with an increased risk of a wide spectrum of metabolic and cardiovascular diseases, psychiatric/psychological disorders, impaired daily functioning and, thus, diminished quality of life and all-cause mortality.[3-10] Depression and anxiety, similar highly prevalent major causes of disease burden and cardiovascular risk factors, are the most common psychiatric conditions found in OSA.[8-10] These comorbid psychiatric symptoms have been found to adversely impact self-management, treatment adherence and functioning, symptoms perception, and health care costs in chronic medical illnesses and, specifically, in OSA.[9-11]

Continuous positive airway pressure (CPAP), the first line treatment for OSA, is a mechanical device highly effective at reducing the number of apnea and hypopnea episodes per hour of sleep (i.e., apnea-hypopnea index; AHI).[12] However, the effects of CPAP on OSA-related subjective symptoms such as psychological distress, anxiety and depression still remain controversial.[13,14] Gathered evidence in the field has shown that CPAP is not more effective at reducing these psychological comorbidities than placebo or sham CPAP, which evidences the complex process underlying the reciprocal interaction between OSA and psychiatric conditions.[13-16] Although effective at reducing OSA severity, CPAP may not address OSA major risk factors such as obesity and other cardiometabolic diseases associated to both OSA and psychological distress.[17] Therefore, a sole reduction in AHI after CPAP therapy, without other autonomic and/or metabolic changes, may not be sufficient to contribute to a clinically significant improvement in psychological well-being, anxiety, and depression.[13]

Alternative or combined non-surgical and non-pharmacological approaches such as weight loss and lifestyle interventions are highly recommended and appear to substantially improve OSA severity and related cardiometabolic comorbidities.[18-25] There are fairly well-established data indicating that these active interventions significantly reduce comorbid psychiatric symptoms in other chronic medical illnesses such as obesity, type 2 diabetes and cardiovascular diseases. [26-28] However, there is no evidence to date on the efficacy of this approach at addressing the psychiatric symptoms found in OSA.

This ancillary study based on data from the INTERAPNEA trial was aimed at testing the effects of an eight-week interdisciplinary weight loss and lifestyle intervention on daily functioning and psychiatric symptoms in overweight/obese adults with CPAP-treated moderate-to-severe OSA. The INTERAPNEA trial sought to determine the efficacy of this behavioral approach, as compared with usual care alone (i.e. CPAP), on OSA severity, body weight and composition, and cardiometabolic risk in overweight-obese adults with moderate-to-severe OSA.[29] At six months after intervention, AHI reductions in the intervention and control groups were 23.8 and -0.8, respectively; 62% of participants

in the intervention group no longer requiring CPAP therapy.[21] Furthermore, clinically significant differences in body weight and composition, as well as cardiometabolic risk outcomes, were also found in the intervention group as compared with the control group.[21] Therefore, we hypothesized that the intervention group would also have greater improvements in daily functioning, psychological distress, and anxiety and depression symptoms than the control group.

Methods

Study Design and Population

The present study is an ancillary study of the INTERAPNEA; a randomized clinical open-label trial designed to evaluate the effects of an eight-week interdisciplinary weight loss and lifestyle intervention combined with usual-care (i.e. CPAP) on OSA severity, body weight and composition, and cardiometabolic risk among adults with moderate-to-severe OSA. The rationale, design, and methodology of this trial has previously been described in detail (see Annexes for the Trial Protocol).[21,29] In brief, this study was conducted from April 2019 to October 2020, and eligible participants were men aged 18-65 years with CPAP-treated moderate-to-severe OSA (AHI equal or greater than 15 events per hour of sleep), and a body mass index (BMI) equal or greater than 25 kg/m^2. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline for randomized clinical trials. All participants provided written informed consent and the study protocol was registered and approved by appropriate regulatory authorities and ethics committees.

Study Recruitment, Enrollment and Randomization

Potential participants were recruited from the sleep-disordered breathing unit of the collaborating hospital-based referral center. Owing to practical and feasibility reasons, the trial was conducted in three consecutive sets of a maximum of 30 participants. Inclusion feasibility and baseline assessments —including an overnight fasting blood test, an in-laboratory full-night polysomnography, a set of questionnaires measuring subjective variables, and measurements of anthropometric and body composition parameters— were performed on each participant. Eligible participants were randomly assigned to either usual-care (control group) or weight loss and lifestyle intervention combined with usual-care (intervention group) by means of a computer-generated simple (unrestricted) randomization.[30]

Owing to the nature of the intervention, clinicians and participants were aware of trial-group assignments after randomization. Nevertheless, the personnel responsible for data collection and analyses was blinded to allocation assignments at the follow-up.

Study Interventions

The INTERAPNEA interdisciplinary weight loss and lifestyle intervention, meticulously designed and based on existing clinical practice guidelines, lasted eight weeks and was composed of five components/modules: nutritional behavior change; moderate aerobic exercise; smoking cessation; alcohol avoidance; and sleep hygiene. Each component, including

60–90 min group-based weekly sessions, was led by trained professionals in each field. A detailed intervention description has previously been published.[21,29]

The usual-care/control group received, apart from CPAP, a single 30 min session led by a sleep-disordered breathing specialist addressing general advice on weight loss and lifestyle change. In addition, the study intervention was offered to all participants at the end of the trial.

Study Assessments and Outcomes

The primary outcomes of this study were changes from baseline to intervention endpoint in (1) daily functioning, (2) psychological distress; (3) anxiety; (4) and depression; all outcomes being assessed through well-validated questionnaires. Daily functioning was subjectively assessed through the Functional Outcomes of Sleep Questionnaire (FOSQ), a disease-specific quality of life instrument assessing OSA and excessive daytime sleepiness impact on the ability to perform different activities related to daily living. [31,32] This questionnaire is composed of 30 items comprising five subscales including general productivity, social outcome, activity level, vigilance, and sexual relationships and intimacy. Each item rates the difficulty of performing a given activity on a scale from 1 (extreme difficulty) to 4 (no difficulty), mean-weighted item scores for each subscale ranging from 1 to 4 and the total score from 5 to 20, with higher scores indicating greater functioning. A total score less than 18 indicates an impaired functional status.[33,34]

Psychological distress was measured using the General Health Questionnaire (GHQ).[35,36] This 28-item instrument is a widely used measure of psychological distress as the opposite of psychological well-being. It consists of four subscales, each composed of 7 items related to the presence of somatic symptoms, anxiety, social dysfunction and depression. Each item is scored on a Likert-type scale of severity ranging from 0 to 3, with a total score range from 0 to 84. Higher scores indicate greater psychological distress; a total score greater than 23 suggesting the presence of psychological distress and/or a psychiatric disorder.[35,36]

The intensity and frequency of displaying anxiety symptoms were assessed with the State-Trait Anxiety Inventory (STAI).[37-39] This 40-item inventory is composed of two subscales comprising 20 items each, measuring state anxiety and trait anxiety on a scale from 0 (not at all or almost never) to 3 (very much so or almost always); the total scores ranging from 0 to 60 for each subscale with higher scores indicating greater anxiety. The state anxiety subscale evaluates the intensity or current anxiety symptoms including items such as worry, apprehension, nervousness, tension and autonomic nervous system activation. The trait anxiety assesses the anxiety proneness or frequency of feeling anxious, including general states of calmness, confidence, and security. Total scores equal or greater than 21 and 24 suggest clinical levels of state anxiety and trait anxiety, respectively, in this specific sample.[39]

State-trait and general depression were assessed using the State-Trait Depression Inventory (STDI) and the Beck Depression Inventory-Fast Screen (BDI-FS), respectively.[40-42] These questionnaires are highly reliable screening tools of depression among medical patients, both solely including cognitive-affective symptoms of depression and excluding other overlapping symptoms commonly found in medical illnesses such as somatic symptoms. STDI evaluates both state and

trait depression, distinguishing dysthymia (high negative affect) and euthymia (lack of positive affect) components of depression within each subscale. Items are scored from 1 (not at all or almost never) to 4 (very much so or almost always); total scores of each subscale ranging from 10 to 40, with higher scores indicating greater symptoms of depression. A total score equal or greater than 20 and 21 suggests clinical levels of state depression and trait depression, respectively, in this sample.[40] Similarly, the BDI-FS consists of 7 items rated from 0 (never) to 3 (high likelihood) related to sadness, pessimism, past failure, loss of pleasure, self-dislike, self-criticalness, and suicidal thoughts. Total scores range from 0 to 21; a score of 4 or higher suggesting depression.[41,42]

Statistical Analysis

The intervention effects on the study outcomes were estimated in the context of linear mixed-effects models, including trial group, assessment time and their interaction terms as the main effect.[43] Estimations were performed using the restricted maximum-likelihood method and an unstructured covariance matrix in order to adjust for within-participant clustering resulting from the repeated-measures design. This model assumed that missing values were missing-at-random; all values presented in the tables being model-based estimates. Yet, attrition propensity was calculated through a logistic model which predicted attrition based on baseline values of set of participants, allocation group, OSA severity, age and BMI. Owing to the occurrence of the Covid-19 pandemic at the trial endpoint (intervention endpoint assessment of the third set of participants), only the set of participants significantly predicted attrition. Model assumptions of missing values being missing-at-random were therefore sustained, which is also in accordance with recent recommendations for handling missing data in randomized trials affected by a pandemic specific to our case.[44]

All estimations and analyses were performed primarily with an intention-to-treat approach (including all participants as originally allocated after randomization) and an additional per-protocol approach restricted to participants with a CPAP usage equal or greater than four hours per night on 70% of nights and, concerning the intervention group, at least 80% of attendance rate at intervention sessions.

In addition, exploratory analyses using t test were also performed to examine differences on changes on the study outcomes by group and clinical status on the corresponding symptoms at baseline. All analyses were performed using R version 4.0.3 (R Project for Statistical Computing).

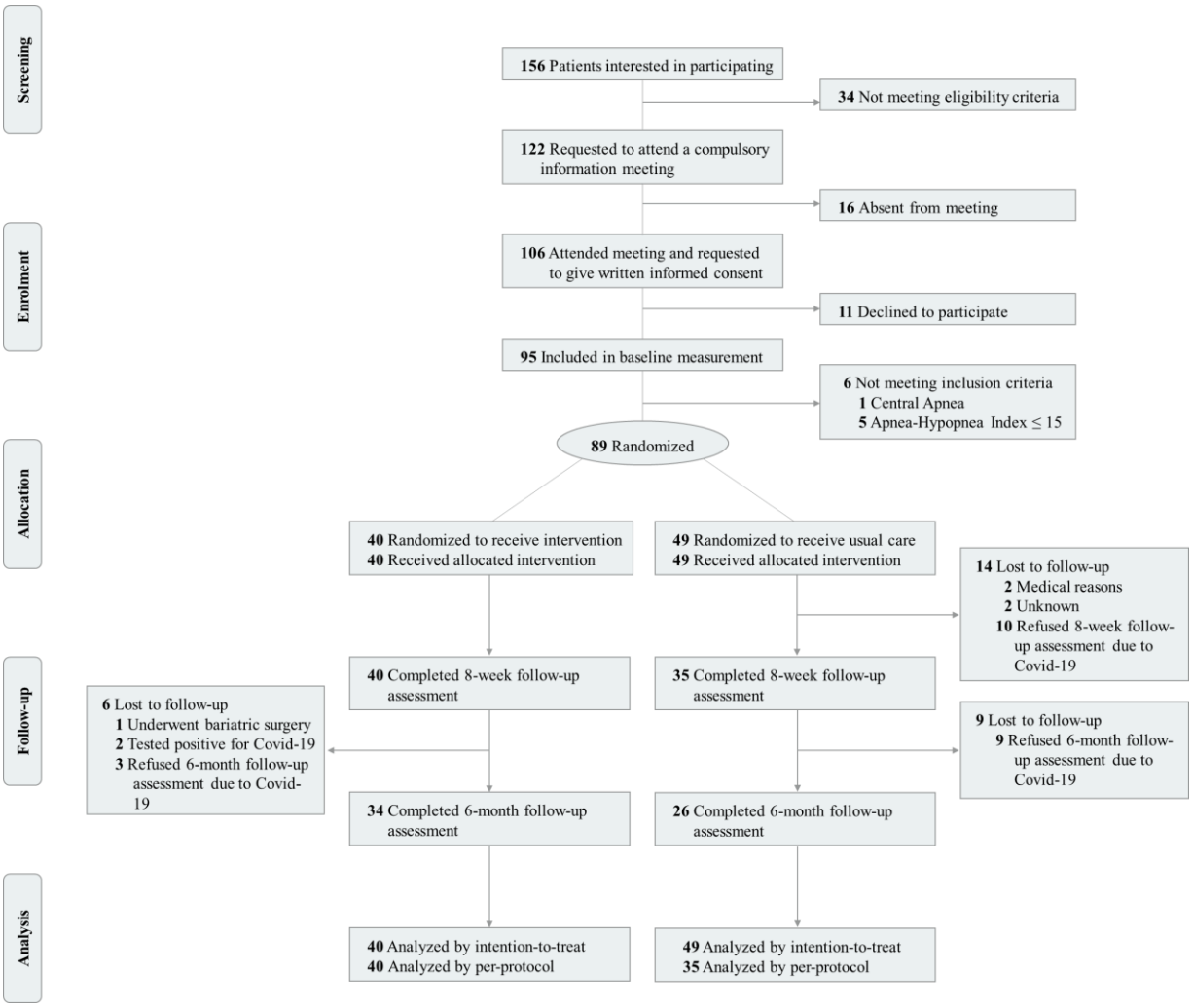
Results

Study Participants

A total of 89 participants with CPAP-treated moderate-to-severe OSA and overweight/obesity were enrolled from April 2019 through February 2020; data collection concluding by October 2020 (Figure 1). Participants were randomly assigned to the control group (49 participants) or the intervention group (40 participants). The loss to follow-up was 14 participants from the control group (15.7%), which was mainly due to the emergence of the Covid-19 pandemic (10 participants). A

total of 89 participants were included in the intention-to-treat analyses, and 75 in the per-protocol approach according to the prespecified adherence criteria. The two randomized groups were well balanced with respect to baseline characteristics; there were no differences in clinical measures at baseline values between the control group and the intervention group (Table 1). The mean (SD) age was 54.1 (8.0) years, the mean (SD) BMI was 34.4 (5.4) kg/m^2, and the mean (SD) AHI was 41.3 (22.2) events/hr. The mean (SD) time since OSA diagnosis and CPAP use was 7.0 (6.1) years. Baseline characteristics were equivalent when adopting a per-protocol approach (Supplementary Table S1).

Figure 1. Flow-Chart Diagram of the INTERAPNEA Randomized Clinical Trial



Daily Functioning

Participants in the intervention group had statistically significant greater improvements from baseline to intervention endpoint and 6 months after intervention in daily functioning than those in the control group, with a mean between-group difference in FOSQ total score of 2.3 (95% confidence interval [CI], 1.5 to 3.2; P < 0.001) and 2.5 (95% CI, 1.5 to 3.4; P < 0.001) (Table 2, Figure 2 and Supplementary Figure S1). Accordingly, participants in the intervention group also had significant greater improvements in general productivity, social function, activity level, vigilance, and sexual and intimacy

Table 1. Baseline Characteristics of the Study Participants

Characteristics[b]	No. (%)[a]	
	Control (n = 49)	Intervention (n = 40)
Age, mean (SD), y	55.3 (8.5)	52.6 (7.1)
Educational level		
Primary Education	13 (26.5)	10 (25.0)
Secondary Education	10 (20.4)	6 (15.0)
Vocational Education	13 (26.5)	17 (42.5)
Higher Education	13 (26.5)	7 (17.5)
Marital status		
Single	7 (14.3)	2 (5.0)
Married	34 (69.4)	34 (85.0)
Divorced	8 (16.3)	4 (10.0)
Occupational status		
Employed	27 (55.1)	21 (52.5)
Self-employed	8 (16.3)	12 (30.0)
Unemployed	4 (8.2)	5 (12.5)
Retired	10 (20.4)	2 (5.0)
Medical Conditions[c]		
Hypertension	33 (67.4)	27 (67.5)
Diabetes Mellitus II	12 (24.5)	10 (25.0)
Cardiovascular disease	9 (18.4)	7 (17.5)
Other medical conditions	29 (59.2)	26 (65.0)
Medication[c]		
Antihypertensive	31 (63.3)	24 (60.0)
Statins	15 (30.6)	7 (17.5)
Oral antidiabetic	5 (10.2)	2 (5.0)
Insulin	3 (6.1)	1 (2.5)
Beta-blockers	7 (14.3)	5 (12.5)
Polymedication[d]	14 (28.6)	6 (15.0)
Body mass index, mean (SD), kg/m^2	33.9 (4.8)	35.0 (6.0)
Body weight status		
Overweight	10 (20.4)	5 (12.5)
Class I obesity	21 (42.9)	19 (47.5)
Class II obesity	16 (32.7)	11 (27.5)
Class III obesity	2 (4.1)	5 (12.5)
Apnea-hypopnea index, mean (SD), events/hr	41.1 (21.3)	41.6 (23.5)
Obstructive sleep apnea severity		
Moderate	20 (40.8)	15 (37.5)
Severe	29 (59.2)	25 (62.5)
Time since obstructive sleep apnea diagnosis, mean (SD), y	7.4 (5.7)	6.5 (6.5)

[a] No. (%) reported unless otherwise specified.

[b] No significant between-group differences were observed in any of the baseline characteristics.

[c] Participants could have more than one condition or medication.

[d] Defined as the use of five or more medications.

Table 2. Daily Functioning, Psychological Distress, Anxiety and Depression Outcomes

Endpoints	Control (n=49)			Intervention (n=40)			Mean difference between groups at 8 weeks (95% CI)	Mean difference between groups at 6 months (95% CI)
	At Baseline (95% CI)[a]	Change at 8 weeks (95% CI)	Change at 6 months (95% CI)	At Baseline (95% CI)[a]	Change at 8 weeks (95% CI)	Change at 6 months (95% CI)		
Functional Outcomes of Sleep Questionnaire[b]								
General productivity score	3.4 (3.3 to 3.6)	0.2 (0.01 to 0.3)	0.04 (-0.1 to 0.2)	3.5 (3.4 to 3.7)	0.4 (0.2 to 0.5)	0.3 (0.2 to 0.5)	0.2 (0.02 to 0.4)[g]	0.3 (0.1 to 0.5)[h]
Social outcome score	3.4 (3.2 to 3.7)	-0.01 (-0.3 to 0.3)	-0.3 (-0.7 to 0.1)	3.5 (3.2 to 3.8)	0.4 (0.1 to 0.7)	0.4 (0.1 to 0.8)	0.4 (0.04 to 0.8)[g]	0.7 (0.3 to 1.1)[i]
Activity level score	3.2 (3.0 to 3.3)	0.1 (-0.04 to 0.3)	0.1 (-0.1 to 0.2)	3.3 (3.1 to 3.5)	0.4 (0.3 to 0.6)	0.5 (0.3 to 0.6)	0.3 (0.1 to 0.5)[h]	0.4 (0.2 to 0.6)[i]
Vigilance score	3.3 (3.1 to 3.5)	-0.1 (-0.3 to 0.2)	0.1 (-0.2 to 0.4)	3.3 (3.1 to 3.5)	0.4 (0.1 to 0.6)	0.5 (0.2 to 0.8)	0.4 (0.1 to 0.7)[h]	0.4 (0.1 to 0.7)[g]
Sexual relationships and intimacy score	3.1 (2.8 to 3.4)	-0.4 (-0.9 to 0.03)	-0.1 (-0.6 to 0.4)	3.3 (3.0 to 3.6)	0.6 (0.2 to 1.0)	0.6 (0.2 to 1.1)	1.0 (0.5 to 1.5)[i]	0.7 (0.2 to 1.3)[g]
Total score	16.5 (15.8 to 17.2)	-0.2 (-0.9 to 0.6)	-0.2 (-1.0 to 0.6)	16.9 (16.2 to 17.7)	2.2 (1.5 to 2.9)	2.3 (1.5 to 3.0)	2.3 (1.5 to 3.2)[i]	2.5 (1.5 to 3.4)[i]
General Health Questionnaire[c]								
Somatic symptoms score	6.1 (5.1 to 7.0)	-1.1 (-2.4 to 0.3)	0.8 (-0.7 to 2.3)	6.6 (5.5 to 7.7)	-5.1 (-6.4 to -3.8)	-3.9 (-5.3 to -2.5)	-4.0 (-5.6 to -2.4)[i]	-4.8 (-6.4 to -3.1)[i]
Anxiety symptoms score	6.6 (5.6 to 7.6)	-1.1 (-2.8 to 0.6)	-0.2 (-2.1 to 1.6)	6.2 (5.1 to 7.3)	-3.6 (-5.3 to -1.9)	-3.7 (-5.5 to -1.9)	-2.5 (-4.5 to -0.5)[g]	-3.5 (-5.6 to -1.4)[h]
Social dysfunction symptoms score	8.8 (8.1 to 9.4)	-1.2 (-2.4 to 0.02)	-0.9 (-2.2 to 0.4)	7.9 (7.2 to 8.6)	-3.1 (-4.3 to -1.8)	-2.7 (-3.9 to -1.4)	-1.9 (-3.3 to -0.4)[g]	-1.8 (-3.3 to -0.3)[g]
Depression symptoms score	2.6 (1.7 to 3.4)	-0.2 (-1.4 to 0.9)	-0.2 (-1.5 to 1.1)	2.7 (1.7 to 3.6)	-2.2 (-3.3 to -1.1)	-2.1 (-3.3 to -0.9)	-1.9 (-3.2 to -0.6)[h]	-1.9 (-3.3 to -0.5)[h]
Total score	24.0 (21.3 to 26.8)	-3.6 (-8.0 to 0.8)	-0.6 (-5.4 to 4.3)	23.4 (20.3 to 26.4)	-13.9 (-18.2 to -9.5)	-12.4 (-17.0 to -7.8)	-10.3 (-15.3 to -5.1)[i]	-11.8 (-17.3 to -6.3)[i]
State-Trait Anxiety Inventory[d]								
Anxiety-state total score	15.7 (13.2 to 18.1)	1.3 (-2.2 to 4.8)	2.2 (-1.7 to 6.0)	16.7 (13.9 to 19.4)	-5.7 (-9.1 to -2.3)	-7.1 (-10.8 to -3.5)	-7.0 (-11.0 to -3.0)[i]	-9.3 (-13.6 to -4.9)[i]
Anxiety-trait total score	19.9 (17.1 to 22.7)	0.05 (-2.9 to 3.0)	0.6 (-2.7 to 3.8)	20.7 (17.5 to 23.8)	-6.1 (-8.9 to -3.3)	-8.2 (-11.2 to -5.2)	-6.1 (-9.5 to -2.8)[i]	-8.8 (-12.4 to -5.2)[i]
State-Trait Depression Inventory[e]								
Euthymia-state score	11.5 (10.5 to 12.4)	-0.5 (-1.7 to 0.8)	0.8 (-0.5 to 2.1)	11.6 (10.6 to 12.7)	-1.9 (-3.0 to -0.7)	-1.6 (-2.9 to -0.4)	-1.4 (-2.8 to -0.02)	-2.4 (-3.9 to -1.0)[h]
Dysthymia-state score	6.0 (5.5 to 6.5)	0.2 (-0.6 to 1.1)	0.7 (-0.2 to 1.6)	6.1 (5.5 to 6.6)	-0.7 (-1.5 to 0.2)	-0.3 (-1.2 to 0.5)	-0.9 (-1.8 to -0.1)	-1.0 (-2.0 to -0.01)
Depression-state total score	17.4 (16.1 to 18.8)	-0.1 (-1.9 to 1.6)	1.5 (-0.4 to 3.5)	17.7 (16.2 to 19.2)	-2.5 (-4.2 to -0.8)	-2.0 (-3.8 to -0.2)	-2.4 (-4.3 to -0.4)[g]	-3.5 (-5.7 to -1.3)[h]
Euthymia-trait score	10.9 (9.9 to 11.9)	-0.4 (-1.5 to 0.8)	0.3 (-1.0 to 1.6)	11.3 (10.2 to 12.4)	-2.6 (-3.7 to -1.4)	-1.6 (-2.8 to -0.4)	-2.2 (-3.5 to -0.8)[h]	-1.9 (-3.4 to -0.5)[g]
Dysthymia-trait score	6.7 (6.1 to 7.4)	0.4 (-0.4 to 1.1)	0.3 (-0.4 to 1.1)	7.0 (6.3 to 7.7)	-1.3 (-1.9 to -0.6)	-1.0 (-1.7 to -0.3)	-1.6 (-2.4 to -0.8)[i]	-1.4 (-2.2 to -0.5)[h]
Depression-trait total score	17.6 (16.1 to 19.1)	0.01 (-1.5 to 1.6)	0.7 (-1.1 to 2.4)	18.3 (16.6 to 20.0)	-3.8 (-5.3 to -2.3)	-2.6 (-4.2 to -1.0)	-3.8 (-5.6 to -2.1)[i]	-3.3 (-5.2 to -1.4)[i]
Beck Depression Inventory-Fast Screen[f]								
Total score	2.8 (2.0 to 3.5)	-0.3 (-1.3 to 0.8)	0.2 (-0.9 to 1.4)	3.2 (2.3 to 4.0)	-2.3 (-3.3 to -1.2)	-1.9 (-3.0 to -0.8)	-2.0 (-3.2 to -0.8)[h]	-2.1 (-3.4 to -0.8)[h]

Abbreviations: CI, confidence interval.

[a] No significant between-group differences were observed in mean baseline values.

[b] The Functional Outcomes of Sleep Questionnaire assess the impact of excessive daytime sleepiness on daily functioning (range, 5-20; higher scores indicate greater functioning; score <18 reflects negative effect of sleepiness on daily functioning).[31-34]

[c] The General Health Questionnaire evaluates psychological distress (range, 0-84; higher scores indicate greater psychological distress; score >23 indicates presence of psychological distress).[35,36]

[d] The State-Trait Anxiety Inventory measures state anxiety and trait anxiety (range, 0-60; higher scores indicate greater anxiety; score ≥21 and ≥24 suggests clinical levels of state and trait anxiety, respectively).[37-39]

[e] The State-Trait Depression Inventory measures state depression and trait depression (range, 10-40; higher scores indicate greater depression; score ≥20 and ≥21 suggests clinical levels of state and trait depression, respectively).[40]

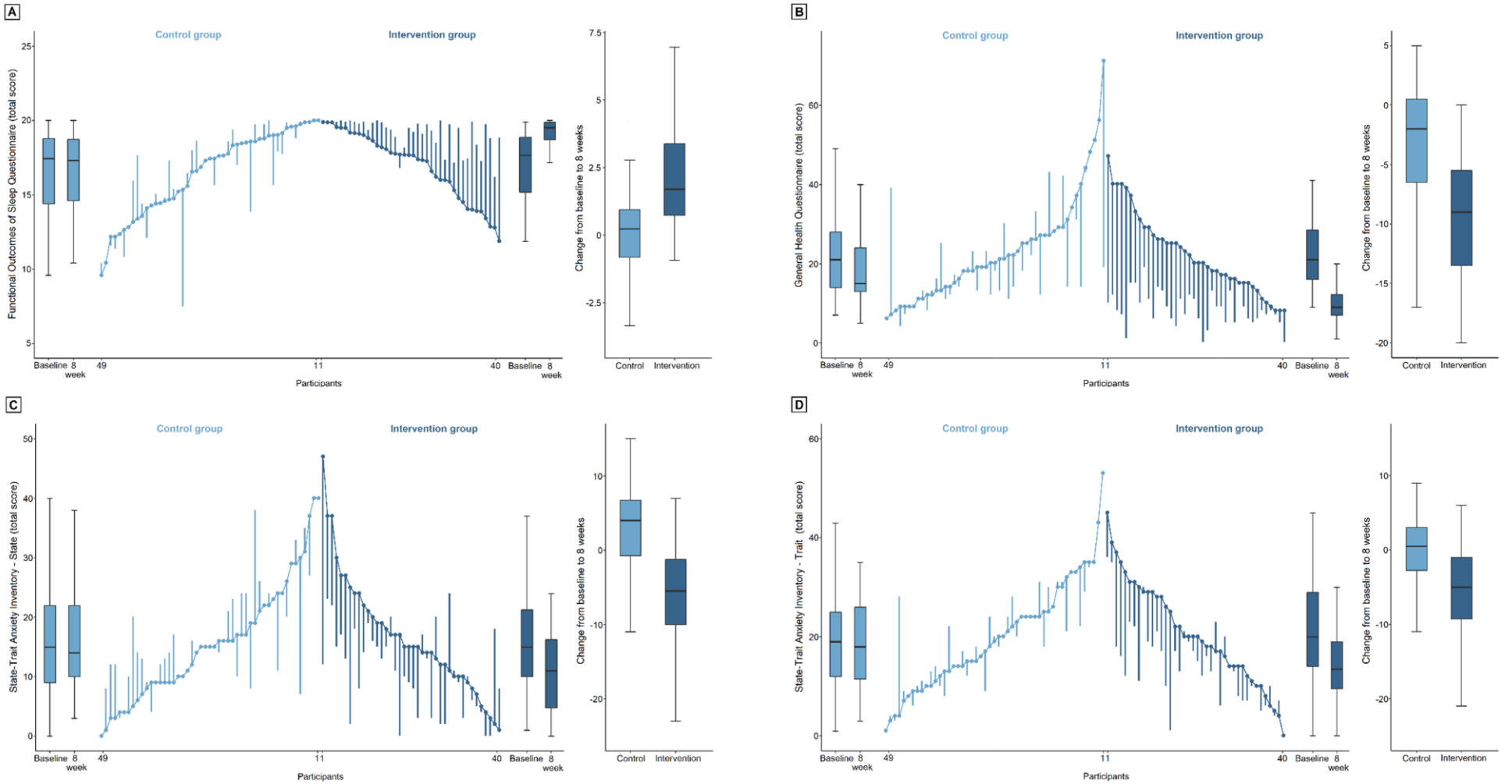
[f] The Beck Depression Inventory-Fast Screen evaluates depression (range, 0-21; higher scores indicate greater depression; score ≥4 suggests presence of depression).[41,42]

[g] $P < 0.05$

[h] $P < 0.01$

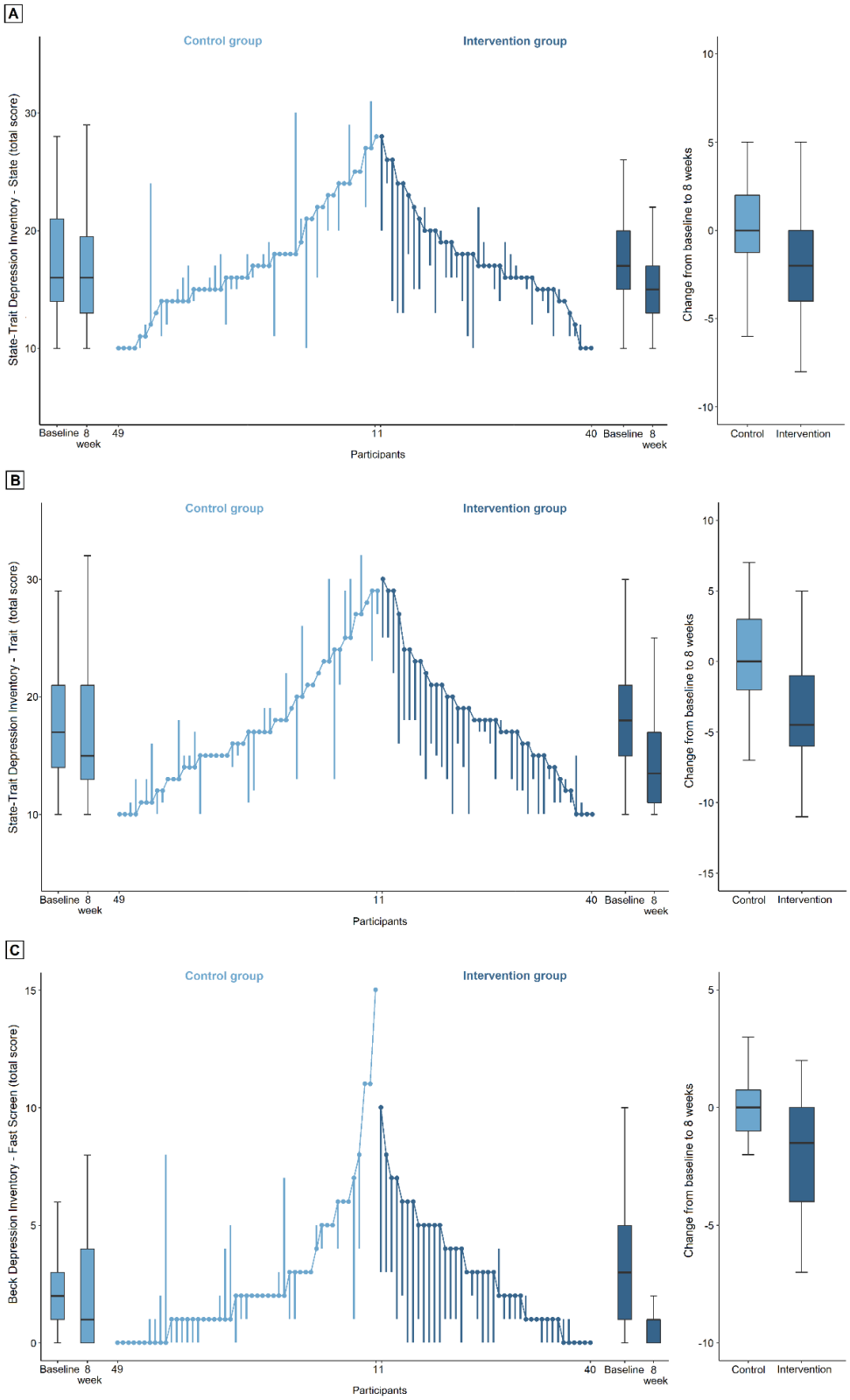
[i] $P < 0.001$

Figure 2. Daily Functioning, Psychological Distress, and Anxiety Outcomes



The ends of the boxes in the boxplots are located at the first and third quartiles, with the black line in the middle illustrating the median. Whiskers extend to the upper and lower adjacent values, the location of the furthest point within a distance of 1.5 interquartile ranges from the first and third quartiles. The parallel line plot contains 1 vertical line for each patient which extends from their baseline value to their 8-week value. Ascending lines indicate an improvement in the outcome (A). Descending lines indicate an improvement in the outcome (B, C, D). Baseline values are placed in ascending order for the control group and descending order for the intervention group. A, The Functional Outcomes of Sleep Questionnaire assess the impact of excessive daytime sleepiness on daily functioning (range, 5-20; higher scores indicate greater functioning; score <18 reflects negative effect of sleepiness on daily functioning).[31-34] B, The General Health Questionnaire evaluates psychological distress (range, 0-84; higher scores indicate greater psychological distress; score >23 indicates presence of psychological distress).[35,36] C,D, The State-Trait Anxiety Inventory measures state anxiety and trait anxiety (range, 0-60; higher scores indicate greater anxiety; score ≥21 and ≥24 suggests clinical levels of state and trait anxiety, respectively).[37-39]

Figure 3. Depression Outcomes



The ends of the boxes in the boxplots are located at the first and third quartiles, with the black line in the middle illustrating the median. Whiskers extend to the upper and lower adjacent values, the location of the furthest point within a distance of 1.5 interquartile ranges from the first and third quartiles. The parallel line plot contains 1 vertical line for each patient which extends from their baseline value to their 8-week value. Descending lines indicate an improvement in the outcome. Baseline values are placed in ascending order for the control group and descending order for the intervention group. A, B, The State-Trait Depression Inventory measures state depression and trait depression (range, 10-40; higher scores indicate greater depression; score ≥20 and ≥21 suggests clinical levels of state and trait depression, respectively).[40] C, The Beck Depression Inventory-Fast Screen evaluates psychological distress (range, 0-21; higher scores indicate greater depression; score ≥4 suggests presence of depression).[41,42]

functioning (FOSQ subscales; all P < 0.05). Similar results were obtained using the per-protocol approach (Supplementary Table S2). According to changes from intervention endpoint to 6 months after intervention, participants in the intervention group maintained improvements in all daily functioning outcomes (Supplementary Table S3).

Participants in the intervention group who reported impaired daily functioning (FOSQ total score less than 18) at baseline (62.5%) had significantly greater improvements in this outcome than those with no/minimal impaired daily functioning at baseline (P < 0.001) (Supplementary Table S4 and Supplementary Figure S2). At the intervention endpoint and 6 months after intervention, impaired daily functioning was only reported by 17.5% and 7.5 of participants in the intervention group, respectively. No discernible differences in daily functioning changes between those with impaired daily functioning (59%) and without it at baseline were found in the control group (P > 0.05).

Psychological Distress

There was a significantly greater reduction in psychological distress in the intervention group than in the control group, with a mean between-group difference in GHQ total score of -10.3 (95% CI, -15.3 to -5.1; P < 0.001) and -11.8 (95% CI, -17.3 to -6.3; P < 0.001) from baseline to intervention endpoint and 6 months after intervention, respectively (Table 2, Figure 2 and Supplementary Figure S1). Correspondingly, participants in the intervention group also significantly reduced somatic, social dysfunction, anxiety and depression symptoms (GHQ subscales; all P < 0.05). Similar results were obtained using the per-protocol approach (Supplementary Table S2). According to changes from intervention endpoint to 6 months after intervention, participants in the intervention group maintained improvements in all psychological distress outcomes (Supplementary Table S3).

Participants in the intervention group who reported psychological distress (GHQ total score greater than 23) at baseline (45%) had significantly greater improvements in this outcome than those with no/minimal impaired daily functioning at baseline (P < 0.001) (Supplementary Table S5 and Supplementary Figure S3). After the intervention, no participants in this group reported psychological distress. No discernible differences in psychological distress changes between those with psychological distress (41%) and without it at baseline were found in the control group (P > 0.05).

Anxiety

Compared with participants in the control group, participants in the intervention group significantly reduced both state anxiety (mean between-group difference in STAI-State, -7.0; 95% CI, -11.0 to -3.0; P < 0.001) and trait anxiety (mean between-group difference in STAI-Trait, -6.1; 95% CI, -9.5 to -2.8; P < 0.001) at intervention endpoint (Table 2 and Figure 2). At 6 months after intervention, mean between-group differences for state anxiety and trait anxiety were -9.3 (95% CI, -13.6 to -4.9; P < 0.001) and -8.8 (95% CI, -12.4 to -5.2; P < 0.001), respectively (Table 2 and Supplementary Figure S1). Similar results were obtained using the per-protocol approach (Supplementary Table S2). According to changes from intervention endpoint to 6 months after intervention, participants in the intervention group maintained improvements in all anxiety outcomes (Supplementary Table S3).

Those participants in the intervention group reporting state anxiety and/or trait anxiety (STAI scores equal or greater than 21 and 24, respectively) at baseline (28% and 38%, respectively) had greater reductions in these outcomes than those with no/minimal state anxiety and/or trait anxiety at baseline (both $P < 0.001$) (Supplementary Table S6 and Supplementary Figure S4). At the intervention endpoint, only 8% of participants in this group reported state and/or trait anxiety symptoms; which was reduced to 5% at 6 months after intervention. In the control group, a significant difference was only found in state anxiety change between those reporting state anxiety at baseline (29%) and those with no/minimal state anxiety at baseline ($P < 0.05$).

Depression

Participants in the intervention group had significantly greater reductions in depression from baseline to intervention endpoint and 6 months after intervention than the control group as shown by the STDI and BDI-FS total scores (Table 2, Figure 3 and Supplementary Figure S5). The mean between-group difference was -2.4 (95% CI, -4.3 to -0.4; $P < 0.05$) in state depression, and -3.8 (95% CI, -5.6 to -2.1; $P < 0.001$) in trait depression at intervention endpoint. At 6 months after intervention, the mean between-group difference was -3.5 (95% CI, -5.7 to -1.3; $P < 0.01$) in state depression and -3.3 (95% CI, -5.2 to -1.4; $P < 0.001$) in trait depression. Consistently, the mean between-group difference in depression as measured by the BDI-FS was -2.0 (95% CI, -3.2 to -0.8; $P < 0.01$) and -2.1 (-3.4 to -0.8; $P < 0.01$) at intervention endpoint and 6 months after intervention, respectively. Similar results were obtained using the per-protocol approach (Supplementary Table S2). According to changes from intervention endpoint to 6 months after intervention, participants in the intervention group maintained improvements in all depression outcomes (Supplementary Table S3).

Participants in the intervention group reporting state, trait and/or general depression (STDI-State score equal or greater than 20; STDI-Trait score equal or greater than 21; BDI-FS score equal or greater than 4) at baseline (28%, 30% and 40%, respectively) had greater reductions in these outcomes than those with no/minimal state, trait and/or general depression at baseline (all $P < 0.001$) (Supplementary Tables S7 and S8, and Supplementary Figures S6 and S7). After the intervention, 12.5% and 7.5% of participants in this group reported state and/or trait depression, respectively; only 3% reporting general depression. At 6 months after intervention, 15% and 17.5% reported state and/or trait depression, respectively; general depression being reported by 5% of participants. In the control group, no significant differences in state, trait and/or general depression changes from baseline to intervention endpoint by depression status at baseline were found (all $P > 0.05$).

Discussion

The current study demonstrates the efficacy of an interdisciplinary weight loss and lifestyle intervention, designed to reduced OSA severity, at improving daily functioning and comorbid psychiatric symptoms in CPAP-treated moderate-to-severe OSA. At intervention endpoint, the intervention group had a significant improvement in daily functioning of 13%

and an outstanding reduction in psychological distress of 59%. Similarly, participants in the intervention group significantly reduced both state anxiety by 34% and trait anxiety symptoms by 29% at intervention endpoint. Regarding depression symptoms, these participants had significant reductions of 14%, 21% and 72% in state depression, trait depression, and general depression, respectively. Remarkably, all improvements were maintained at 6 months after intervention. These results extent previous findings on the efficacy of weight loss and lifestyle interventions at reducing comorbid psychiatric symptoms in obesity and other related medical conditions such as type 2 diabetes, and provide the strongest evidence to date of the effects of this approach on OSA.[26-28]

Furthermore, according to the standard thresholds of the measures used, those participants in the intervention group reporting clinically significant levels of impaired daily functioning, psychological distress, anxiety and/or depression at baseline, had significantly greater improvements in these symptoms than those with no/minimal symptoms at the start of the trial. Remarkably, 72% and 100% of those with clinical levels of impaired daily functioning and/or psychological distress at baseline, respectively, reported resolution of these symptoms after the intervention. Similarly, 82% achieved resolution of state anxiety and 80% of trait anxiety at the intervention endpoint. Of those reporting state, trait, and/or general depression at baseline, 73%, 75% and 100% also reported resolution of these symptoms, respectively, after the intervention. These results, apart from strengthening the evidence supporting that weight loss and lifestyle interventions protect patients from psychiatric disorders rather than precipitating them,[26,45] question the consideration of these symptoms as risk factors that could undermine the effects of or adherence to these interventions.[46-48]

Improvements in functional and psychiatric symptoms after a weight loss and lifestyle intervention, as compared with CPAP alone, may be explained by the underlying biological, metabolic and neurologic dysregulations contributing to both OSA and psychiatric conditions.[7-9,13] According to current models, the functional and psychiatric disturbances found in OSA are not only the result of sleep fragmentation, hypoxia and neurotransmitter alterations, but also secondary to the chronic illness burden and its comorbidities including obesity and cardiometabolic diseases.[7-9,13] As compared to CPAP alone, the INTERAPNEA intervention had significant effects on OSA severity, weight, cardiometabolic risk factors and, thus, health-related quality of life;[21] factors which are well-related to impaired functional status, psychological distress and anxiety and depression symptoms.[49,50] Thus, addressing all these factors, as opposed to OSA severity alone, exacerbates the improvement and even resolution of these symptoms.

Strengths and Limitations

A major strength of this study is that it provides the first evidence to date on the effects of a weight loss and lifestyle approach on daily functioning and psychiatric symptoms in OSA. Given the intervention design and results obtained, this study may be a clear rationale for an effective approach readily adaptable to real-world practice settings. Another noteworthy strength is the use of well-validated questionnaires, measuring depression through instruments adapted to

medical patients by excluding overlapping/somatic symptoms that are commonly found in both OSA and depression and complicate the determination of one condition in the presence of the other.

A main study limitation is the sole inclusion of men with obesity and moderate-to-severe OSA, which limits the generalizability of results to women and men without obesity and/or with mild OSA.

Conclusion

This study provides the first evidence suggesting that an interdisciplinary weight loss and lifestyle intervention is effective at improving and even resolving impaired functioning, psychological distress, and anxiety and depression symptoms comorbid to moderate-to-severe OSA. Given the high prevalence of these psychiatric symptoms and their adverse impact on OSA and related chronic medical illnesses, clinicians and health-care providers should consider combined weight loss and lifestyle approaches to comprehensively address the imperatives of this increasingly common sleep-disordered breathing.

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Supplementary Material

Supplementary Table S1. Baseline characteristics of the study participants (per-protocol approach)

Characteristics[b]	No. (%)[a]	
	Control (n = 49)	Intervention (n = 40)
Age, mean (SD), y	55.4 (8.9)	52.6 (7.2)
Educational level		
Primary Education	8 (22.9)	10 (25.0)
Secondary Education	6 (17.1)	6 (15.0)
Vocational Education	11 (31.4)	17 (42.5)
Higher Education	10 (28.6)	7 (17.5)
Marital status		
Single	4 (11.4)	2 (5.0)
Married	25 (71.4)	34 (85.0)
Divorced	6 (17.1)	4 (10.0)
Occupational status		
Employed	19 (54.3)	21 (52.5)
Self-employed	6 (17.1)	12 (30.0)
Unemployed	3 (8.6)	5 (12.5)
Retired	7 (20.0)	2 (5.0)
Medical Conditions[c]		
Hypertension	22 (62.9)	27 (67.5)
Diabetes Mellitus II	12 (34.3)	10 (25.0)
Cardiovascular disease	8 (22.9)	7 (17.5)
Other medical conditions	18 (51.4)	26 (65.0)
Medication[c]		
Antihypertensive	21 (60.0)	24 (60.0)
Statins	9 (25.7)	7 (17.5)
Oral antidiabetic	4 (11.4)	2 (5.0)
Insulin	3 (8.6)	1 (2.5)
Beta-blockers	5 (14.3)	5 (12.5)
Polymedication[d]	9 (25.7)	6 (15.0)
Body mass index, mean (SD), kg/m^2	33.7 (4.5)	35.0 (6.0)
Body weight status		
Overweight	7 (20.0)	5 (12.5)
Class I obesity	17 (48.6)	19 (47.5)
Class II obesity	10 (28.6)	11 (27.5)
Class III obesity	1 (2.9)	5 (12.5)
Apnea-hypopnea index, mean (SD), events/hr	39.2 (20.7)	41.6 (23.5)
Obstructive sleep apnea severity		
Moderate	15 (42.9)	15 (37.5)
Severe	20 (57.1)	25 (62.5)
Time since obstructive sleep apnea diagnosis, mean (SD), y	8.6 (6.0)	6.5 (6.5)

[a] No. (%) reported unless otherwise specified.
[b] No significant between-group differences were observed in any of the baseline characteristics.
[c] Participants could have more than one condition or medication.
[d] Defined as the use of five or more medications.

Supplementary Table S2. Daily functioning, psychological distress, anxiety and depression outcomes (per-protocol approach)

Endpoints	Control (n=49)			Intervention (n=40)			Mean difference between groups at 8 weeks (95% CI)	Mean difference between groups at 6 months (95% CI)
	At Baseline (95% CI)[a]	Change at 8 weeks (95% CI)	Change at 6 months (95% CI)	At Baseline (95% CI)[a]	Change at 8 weeks (95% CI)	Change at 6 months (95% CI)		
Functional Outcomes of Sleep Questionnaire[b]								
General productivity score	3.4 (3.3 to 3.6)	0.2 (-0.001 to 0.3)	0.04 (-0.1 to 0.2)	3.5 (3.4 to 3.7)	0.4 (0.2 to 0.5)	0.3 (0.2 to 0.5)	0.2 (0.03 to 0.4)[g]	0.3 (0.1 to 0.5)[h]
Social outcome score	3.5 (3.3 to 3.8)	-0.1 (-0.4 to 0.3)	-0.4 (-0.7 to 0.02)	3.5 (3.2 to 3.8)	0.4 (0.1 to 0.8)	0.4 (0.1 to 0.8)	0.5 (0.1 to 0.9)[g]	0.8 (0.4 to 1.2)[i]
Activity level score	3.2 (3.0 to 3.4)	0.1 (-0.1 to 0.3)	0.05 (-0.1 to 0.2)	3.3 (3.1 to 3.5)	0.4 (0.3 to 0.6)	0.5 (0.3 to 0.6)	0.3 (0.1 to 0.5)[h]	0.4 (0.2 to 0.6)[i]
Vigilance score	3.2 (3.0 to 3.5)	-0.03 (-0.3 to 0.3)	0.1 (-0.2 to 0.4)	3.3 (3.1 to 3.5)	0.4 (0.1 to 0.6)	0.5 (0.2 to 0.8)	0.4 (0.1 to 0.7)[g]	0.4 (0.03 to 0.7)[g]
Sexual relationships and intimacy score	3.0 (2.6 to 3.3)	-0.3 (-0.8 to 0.2)	0.02 (-0.5 to 0.6)	3.3 (3.0 to 3.6)	0.6 (0.2 to 1.1)	0.6 (0.2 to 1.1)	0.9 (0.4 to 1.4)[h]	0.6 (0.02 to 1.2)[g]
Total score	16.4 (15.6 to 17.2)	-0.1 (-0.9 to 0.6)	-0.1 (-1.0 to 0.7)	16.9 (16.2 to 17.7)	2.2 (1.5 to 2.9)	2.3 (1.5 to 3.0)	2.3 (1.5 to 3.2)[i]	2.4 (1.5 to 3.4)[i]
General Health Questionnaire[c]								
Somatic symptoms score	5.8 (4.7 to 6.9)	-0.9 (-2.3 to 0.5)	0.9 (-0.6 to 2.5)	6.6 (5.6 to 7.6)	-5.1 (-6.4 to -3.8)	-3.9 (-5.3 to -2.5)	-4.1 (-5.7 to -2.6)[i]	-4.9 (-6.6 to -3.1)[i]
Anxiety symptoms score	5.9 (4.7 to 7.0)	-0.5 (-2.2 to 1.3)	0.5 (-1.4 to 2.4)	6.2 (5.2 to 7.3)	-3.6 (-5.2 to -1.9)	-3.7 (-5.4 to -2.0)	-3.1 (-5.1 to -1.1)[h]	-4.2 (-6.3 to -2.1)[i]
Social dysfunction symptoms score	8.5 (7.8 to 9.3)	-1.0 (-2.2 to 0.3)	-0.7 (-2.1 to 0.7)	7.9 (7.2 to 8.6)	-3.1 (-4.2 to -1.9)	-2.7 (-3.9 to -1.4)	-2.1 (-3.5 to -0.7)[h]	-2.0 (-3.5 to -0.5)[g]
Depression symptoms score	2.1 (1.2 to 3.0)	-0.03 (-1.1 to 1.2)	-0.1 (-1.2 to 1.4)	2.7 (1.8 to 3.5)	-2.2 (-3.3 to -1.1)	-2.1 (-3.3 to -1.0)	-2.2 (-3.5 to -0.9)[h]	-2.2 (-3.6 to -0.8)[h]
Total score	22.3 (19.2 to 25.3)	-2.3 (-6.8 to 2.1)	0.8 (-4.2 to 5.7)	23.4 (20.5 to 26.2)	-13.9 (-18.1 to -9.7)	-12.5 (-16.9 to -8.1)	-11.5 (-16.6 to -6.5)[i]	-13.2 (-18.6 to -7.8)[i]
State-Trait Anxiety Inventory[d]								
Anxiety-state total score	14.5 (11.6 to 17.3)	1.9 (-1.7 to 5.5)	2.8 (-1.2 to 6.8)	16.7 (14.0 to 19.3)	-5.7 (-9.1 to -2.4)	-7.2 (-10.7 to -3.6)	-7.6 (-11.7 to -3.6)[i]	-10.0 (-14.4 to -5.6)[i]
Anxiety-trait total score	18.5 (15.3 to 21.6)	0.5 (-2.5 to 3.5)	1.1 (-2.2 to 4.4)	20.7 (17.7 to 23.6)	-6.1 (-8.9 to -3.3)	-8.2 (-11.2 to -5.3)	-6.6 (-9.9 to -3.2)[i]	-9.3 (-13.0 to -5.7)[i]
State-Trait Depression Inventory[e]								
Euthymia-state score	11.3 (10.2 to 12.4)	-0.3 (-1.6 to 0.9)	1.0 (-0.4 to 2.4)	11.6 (10.6 to 12.7)	-1.9 (-3.0 to -0.7)	-1.6 (-2.9 to -0.4)	-1.5 (-2.9 to -0.1)[g]	-2.6 (-4.1 to -1.1)[i]
Dysthymia-state score	5.7 (5.1 to 6.3)	0.4 (-0.4 to 1.3)	0.9 (-0.1 to 1.8)	6.1 (5.5 to 6.6)	-0.7 (-1.4 to 0.1)	-0.4 (-1.2 to 0.5)	-1.1 (-2.0 to -0.1)[g]	-1.2 (-2.2 to -0.2)[g]
Depression-state total score	17.0 (15.4 to 18.5)	0.1 (-1.7 to 1.9)	1.9 (-0.1 to 3.8)	17.7 (16.2 to 19.1)	-2.5 (-4.2 to -0.8)	-2.0 (-3.7 to -0.2)	-2.6 (-4.6 to -0.6)[g]	-3.8 (-6.0 to -1.6)[i]
Euthymia-trait score	10.9 (9.7 to 12.0)	-0.3 (-1.5 to 0.9)	0.4 (-0.9 to 1.8)	11.3 (10.2 to 12.4)	-2.6 (-3.7 to -1.4)	-1.6 (-2.8 to -0.4)	-2.2 (-3.6 to -0.9)[h]	-2.0 (-3.5 to -0.6)[h]
Dysthymia-trait score	6.5 (5.7 to 7.3)	0.5 (-0.3 to 1.2)	0.5 (-0.3 to 1.3)	7.0 (6.2 to 7.7)	-1.3 (-1.9 to -0.6)	-1.0 (-1.7 to -0.3)	-1.7 (-2.5 to -0.9)[i]	-1.5 (-2.4 to -0.6)[h]
Depression-trait total score	17.4 (15.6 to 19.2)	0.1 (-1.4 to 1.7)	1.0 (-0.8 to 2.7)	18.3 (16.6 to 20.0)	-3.8 (-5.3 to -2.3)	-2.6 (-4.2 to -1.1)	-3.9 (-5.7 to -2.2)[i]	-3.6 (-5.5 to -1.7)[i]
Beck Depression Inventory-Fast Screen[f]								
Total score	2.3 (1.5 to 3.1)	-0.000 (-1.1 to 1.1)	0.6 (-0.6 to 1.7)	3.2 (2.4 to 3.9)	-2.3 (-3.2 to -1.3)	-1.9 (-2.9 to -0.9)	-2.3 (-3.4 to -1.1)[i]	-2.5 (-3.7 to -1.2)[i]

Abbreviations: CI, confidence interval.

[a] No significant between-group differences were observed in mean baseline values.

[b] The Functional Outcomes of Sleep Questionnaire assess the impact of excessive daytime sleepiness on daily functioning (range, 5-20; higher scores indicate greater functioning; score <18 reflects negative effect of sleepiness on daily functioning).[1-4]

[c] The General Health Questionnaire evaluates psychological distress (range, 0-84; higher scores indicate greater psychological distress; score >23 indicates presence of psychological distress).[5,6]

[d] The State-Trait Anxiety Inventory measures state anxiety and trait anxiety (range, 0-60; higher scores indicate greater anxiety; score ≥21 and ≥24 suggests clinical levels of state and trait anxiety, respectively).[7-9]

[e] The State-Trait Depression Inventory measures state depression and trait depression (range, 10-40; higher scores indicate greater depression; score ≥20 and ≥21 suggests clinical levels of state and trait depression, respectively).[10]

[f] The Beck Depression Inventory-Fast Screen evaluates depression (range, 0-21; higher scores indicate greater depression; score ≥4 suggests presence of depression).[11,12]

[g] $P < 0.05$

[h] $P < 0.01$

[i] $P < 0.001$

Supplementary Table S3. Daily Functioning, Psychological Distress, Anxiety and Depression Outcomes (Changes from 8 weeks to 6 months)

Endpoints	Control (n=49)			Intervention (n=40)		
	8 weeks Mean (SE)	6 months Mean (SE)	Mean change (95% CI)	8 weeks Mean (SE)	6 months Mean (SE)	Mean change (95% CI)
Functional Outcomes of Sleep Questionnaire[b]						
General productivity score	3.6 (3.4 to 3.7)	3.5 (3.3 to 3.6)	-0.1 (-0.3 to 0.1)	3.9 (3.7 to 4.0)	3.8 (3.7 to 4.0)	-0.03 (-0.2 to 0.1)
Social outcome score	3.4 (3.1 to 3.7)	3.1 (2.8 to 3.4)	-0.3 (-0.7 to 0.1)	3.9 (3.7 to 4.2)	3.9 (3.6 to 4.2)	0.01 (-0.3 to 0.4)
Activity level score	3.3 (3.1 to 3.5)	3.2 (3.1 to 3.4)	-0.1 (-0.2 to 0.1)	3.7 (3.6 to 3.9)	3.8 (3.6 to 3.9)	0.04 (-0.1 to 0.2)
Vigilance score	3.2 (3.0 to 3.4)	3.4 (3.1 to 3.6)	0.1 (-0.2 to 0.4)	3.7 (3.5 to 3.9)	3.8 (3.6 to 4.0)	0.1 (-0.2 to 0.4)
Sexual relationships and intimacy score	2.7 (2.4 to 3.1)	3.0 (2.7 to 3.4)	0.3 (-0.2 to 0.8)	3.9 (3.6 to 4.2)	3.9 (3.6 to 4.3)	0.02 (-0.4 to 0.5)
Total score	16.3 (15.6 to 17.1)	16.3 (15.5 to 17.1)	-0.02 (-0.9 to 0.8)	19.1 (18.3 to 19.8)	19.2 (18.4 to 20.0)	0.1 (-0.6 to 0.9)
General Health Questionnaire[c]						
Somatic symptoms score	5.0 (3.9 to 6.1)	6.9 (5.7 to 8.1)	1.9 (0.4 to 3.5)[g]	1.5 (0.5 to 2.6)	2.7 (1.6 to 3.8)	1.2 (-0.2 to 2.6)
Anxiety symptoms score	5.5 (4.4 to 6.7)	6.4 (5.1 to 7.7)	0.9 (-1.1 to 2.8)	2.7 (1.5 to 3.8)	2.5 (1.3 to 3.7)	-0.1 (-1.9 to 1.6)
Social dysfunction symptoms score	7.6 (6.8 to 8.4)	7.9 (7.0 to 8.8)	0.3 (-1.1 to 1.7)	4.9 (4.1 to 5.6)	5.2 (4.4 to 6.0)	0.4 (-0.9 to 1.7)
Depression symptoms score	2.4 (1.4 to 3.3)	2.4 (1.3 to 3.4)	0.02 (-1.3 to 1.3)	0.5 (-0.5 to 1.4)	0.5 (-0.4 to 1.5)	0.1 (-1.1 to 1.2)
Total score	20.4 (17.2 to 23.7)	23.5 (19.8 to 27.1)	3.0 (-2.1 to 8.1)	9.5 (6.4 to 12.6)	11.0 (7.7 to 14.2)	1.5 (-3.1 to 6.0)
State-Trait Anxiety Inventory[d]						
Anxiety-state total score	16.9 (14.1 to 19.8)	17.8 (14.7 to 20.9)	0.9 (-3.1 to 4.9)	11.0 (8.2 to 13.7)	9.5 (6.6 to 12.4)	-1.4 (-5.0 to 2.2)
Anxiety-trait total score	19.9 (16.9 to 23.0)	20.5 (17.2 to 23.8)	0.5 (-2.8 to 3.9)	14.6 (11.4 to 17.7)	12.4 (9.2 to 15.7)	-2.1 (-5.1 to 0.9)
State-Trait Depression Inventory[e]						
Euthymia-state score	11.0 (9.9 to 12.1)	12.3 (11.1 to 13.4)	1.3 (-0.1 to 2.6)	9.8 (8.7 to 10.8)	10.0 (8.9 to 11.1)	0.2 (-1.0 to 1.4)
Dysthymia-state score	6.2 (5.6 to 6.8)	6.6 (6.0 to 7.3)	0.4 (-0.5 to 1.4)	5.4 (4.8 to 6.0)	5.7 (5.1 to 6.3)	0.3 (-0.5 to 1.1)
Depression-state total score	17.3 (15.8 to 18.8)	19.0 (17.3 to 20.6)	1.7 (-0.3 to 3.7)	15.2 (13.7 to 16.7)	15.7 (14.1 to 17.3)	0.5 (-1.3 to 2.3)
Euthymia-trait score	10.5 (9.4 to 11.6)	11.2 (10.0 to 12.4)	0.7 (-0.7 to 2.0)	8.8 (7.6 to 9.9)	9.7 (8.5 to 10.9)	0.9 (-0.3 to 2.1)
Dysthymia-trait score	7.1 (6.4 to 7.8)	7.1 (6.3 to 7.8)	-0.02 (-0.8 to 0.8)	5.7 (5.0 to 6.4)	6.0 (5.2 to 6.7)	0.2 (-0.5 to 1.0)
Depression-trait total score	17.6 (16.0 to 19.3)	18.3 (16.5 to 20.0)	0.7 (-1.1 to 2.4)	14.5 (12.8 to 16.2)	15.7 (13.9 to 17.4)	1.2 (-0.4 to 2.8)
Beck Depression Inventory-Fast Screen[f]						
Total score	2.5 (1.7 to 3.4)	3.0 (2.1 to 4.0)	0.5 (-0.7 to 1.7)	0.9 (0.1 to 1.7)	1.3 (0.4 to 2.1)	0.4 (-0.7 to 1.4)

Abbreviations: CI, confidence interval.

[a] No significant between-group differences were observed in mean baseline values.

[b] The Functional Outcomes of Sleep Questionnaire assess the impact of excessive daytime sleepiness on daily functioning (range, 5-20; higher scores indicate greater functioning; score <18 reflects negative effect of sleepiness on daily functioning).[1-4]

[c] The General Health Questionnaire evaluates psychological distress (range, 0-84; higher scores indicate greater psychological distress; score >23 indicates presence of psychological distress).[5,6]

[d] The State-Trait Anxiety Inventory measures state anxiety and trait anxiety (range, 0-60; higher scores indicate greater anxiety; score ≥21 and ≥24 suggests clinical levels of state and trait anxiety, respectively).[7-9]

[e] The State-Trait Depression Inventory measures state depression and trait depression (range, 10-40; higher scores indicate greater depression; score ≥20 and ≥21 suggests clinical levels of state and trait depression, respectively).[10]

[f] The Beck Depression Inventory-Fast Screen evaluates depression (range, 0-21; higher scores indicate greater depression; score ≥4 suggests presence of depression).[11,12]

[g] $P < 0.05$

Supplementary Table S4. Functional Outcomes of Sleep Questionnaire[a] by group and clinical status

	At baseline		At 8 weeks		At 6 months	
Group	No. (%)	Mean (SD)	No. (%)	Mean (SD)	No. (%)	Mean (SD)
Control/usual care						
All	49 (100)	16.48 (2.82)	49 (100)	16.38 (3.16)	49 (100)	16.41 (2.97)
With impaired daily functioning	29 (59.2)	14.65 (2.22)	32 (65.3)	14.78 (2.76)	31 (63.3)	14.72 (2.41)
No impaired in daily functioning	20 (40.8)	19.13 (0.59)	17 (34.7)	19.40 (0.60)	18 (36.7)	19.33 (0.62)
Intervention						
All	40 (100)	16.91 (2.29)	40 (100)	19.09 (1.07)	40 (100)	19.23 (0.93)
With impaired daily functioning	25 (62.5)	15.61 (1.88)	7 (17.5)	17.07 (0.44)	3 (7.5)	16.74 (0.49)
No impaired in daily functioning	15 (37.5)	19.10 (0.61)	33 (82.5)	19.52 (0.52)	37 (92.5)	19.43 (0.60)

[a] The Functional Outcomes of Sleep Questionnaire assess the impact of excessive daytime sleepiness on daily functioning (range, 5-20; higher scores indicate greater functioning; score <18 reflects negative effect of sleepiness on daily functioning).[1-4]

Supplementary Table S5. General Health Questionnaire[a] by group and clinical status

Group	At baseline		At 8 weeks		At 6 months	
	No. (%)	Mean (SD)	No. (%)	Mean (SD)	No. (%)	Mean (SD)
Control/usual care						
All	49 (100)	24.04 (13.54)	49 (100)	22.37 (12.65)	49 (100)	23.63 (11.98)
With psychological distress	20 (40.8)	36.20 (12.79)	19 (38.8)	35.37 (10.22)	21 (42.9)	34.33 (10.68)
No psychological distress	29 (59.2)	15.66 (4.97)	30 (61.2)	14.13 (4.38)	28 (57.1)	15.61 (3.86)
Intervention						
All	40 (100)	23.38 (10.11)	40 (100)	9.5 (4.29)	40 (100)	10.25 (4.02)
With psychological distress	18 (45.0)	32.44 (7.25)	0 (0.0)	-	0 (0.0)	-
No psychological distress	22 (55.0)	15.96 (4.35)	40 (100)	9.5 (4.29)	40 (100)	10.25 (4.02)

[a] The General Health Questionnaire evaluates psychological distress (range, 0-84; higher scores indicate greater psychological distress; score >23 indicates presence of psychological distress).[5,6]

Supplementary Table S6. State-Trait Anxiety Inventory[a] by group and clinical status

		At baseline		At 8 weeks		At 6 months	
		No. (%)	Mean (SD)	No. (%)	Mean (SD)	No. (%)	Mean (SD)
State Anxiety	Control/usual care						
	All	49 (100)	15.65 (9.97)	49 (100)	17.02 (9.54)	49 (100)	17.7 (10.22)
	With state anxiety	14 (28.6)	28.43 (6.58)	16 (32.7)	28.31 (6.66)	19 (38.8)	28.3 (6.50)
	No state anxiety	35 (71.4)	10.54 (5.45)	33 (67.3)	11.55 (4.60)	30 (61.2)	11.0 (5.26)
	Intervention						
	All	40 (100)	16.68 (9.89)	40 (100)	10.95 (6.92)	40 (100)	9.60 (6.21)
	With state anxiety	11 (27.5)	29.18 (8.00)	3 (7.5)	23.00 (1.00)	2 (5.0)	22.00 (0.00)
	No state anxiety	29 (72.5)	11.93 (5.34)	37 (92.5)	9.97 (6.23)	38 (95.0)	8.95 (5.65)
Trait Anxiety	Control/usual care						
	All	49 (100)	19.90 (11.03)	49 (100)	20.25 (10.69)	49 (100)	20.35 (11.64)
	With trait anxiety	19 (38.8)	31.00 (7.59)	20 (40.8)	30.45 (7.24)	19 (38.8)	32.11(7.80)
	No trait anxiety	30 (61.2)	12.87 (5.82)	29 (59.2)	13.20 (5.88)	30 (61.2)	12.90 (6.21)
	Intervention						
	All	40 (100)	20.65 (10.36)	40 (100)	14.55 (8.15)	40 (100)	12.60 (8.19)
	With trait anxiety	15 (37.5)	31.67 (5.35)	3 (7.5)	33.67 (3.21)	2 (5.0)	36.00 (0.00)
	No trait anxiety	25 (62.5)	14.04 (6.03)	37 (92.5)	13.00 (6.20)	38 (95.0)	11.37 (6.29)

[a] The State-Trait Anxiety Inventory measures state anxiety and trait anxiety (range, 0-60; higher scores indicate greater anxiety; score ≥21 and ≥24 suggests clinical levels of state and trait anxiety, respectively).[7-9]

Supplementary Table S7. State-Trait Depression Inventory[a] by group and clinical status

		At baseline		At 8 weeks		At 6 months	
	Group	No. (%)	Mean (SD)	No. (%)	Mean (SD)	No. (%)	Mean (SD)
State Depression	Control/usual care						
	All	49 (100)	17.43 (4.88)	49 (100)	17.49 (5.57)	49 (100)	18.41 (5.81)
	With state depression	14 (28.6)	24.00 (2.22)	15 (30.6)	24.33 (3.64)	17 (34.7)	25.18 (3.66)
	No state depression	35 (71.4)	14.80 (2.61)	34 (69.4)	14.47 (2.98)	32 (65.3)	14.81 (2.61)
	Intervention						
	All	40 (100)	17.68 (4.27)	40 (100)	15.18 (3.48)	40 (100)	15.68 (4.29)
	With state depression	11 (27.5)	23.09 (2.77)	5 (12.5)	21.60 (1.67)	6 (15.0)	24.00 (2.28)
	No state depression	29 (72.5)	15.62 (2.60)	35 (87.5)	14.26 (2.57)	34 (85.0)	14.21 (2.47)
Trait Depression	Control/usual care						
	All	49 (100)	17.59 (5.45)	49 (100)	17.69 (6.08)	49 (100)	18.02 (6.21)
	With trait depression	14 (28.6)	24.86 (2.77)	15 (30.6)	25.47 (3.81)	14 (28.6)	26.36 (3.91)
	No trait depression	35 (71.4)	14.69 (2.94)	34 (69.4)	14.27 (2.83)	35 (71.4)	14.69 (2.93)
	Intervention						
	All	40 (100)	18.28 (5.22)	40 (100)	14.48 (3.88)	40 (100)	15.55 (4.87)
	With trait depression	12 (30.0)	24.50 (3.37)	3 (7.5)	24.00 (1.73)	7 (17.5)	24.14 (3.29)
	No trait depression	28 (70.0)	15.61 (3.19)	37 (92.5)	13.70 (2.82)	33 (82.5)	13.73 (2.70)

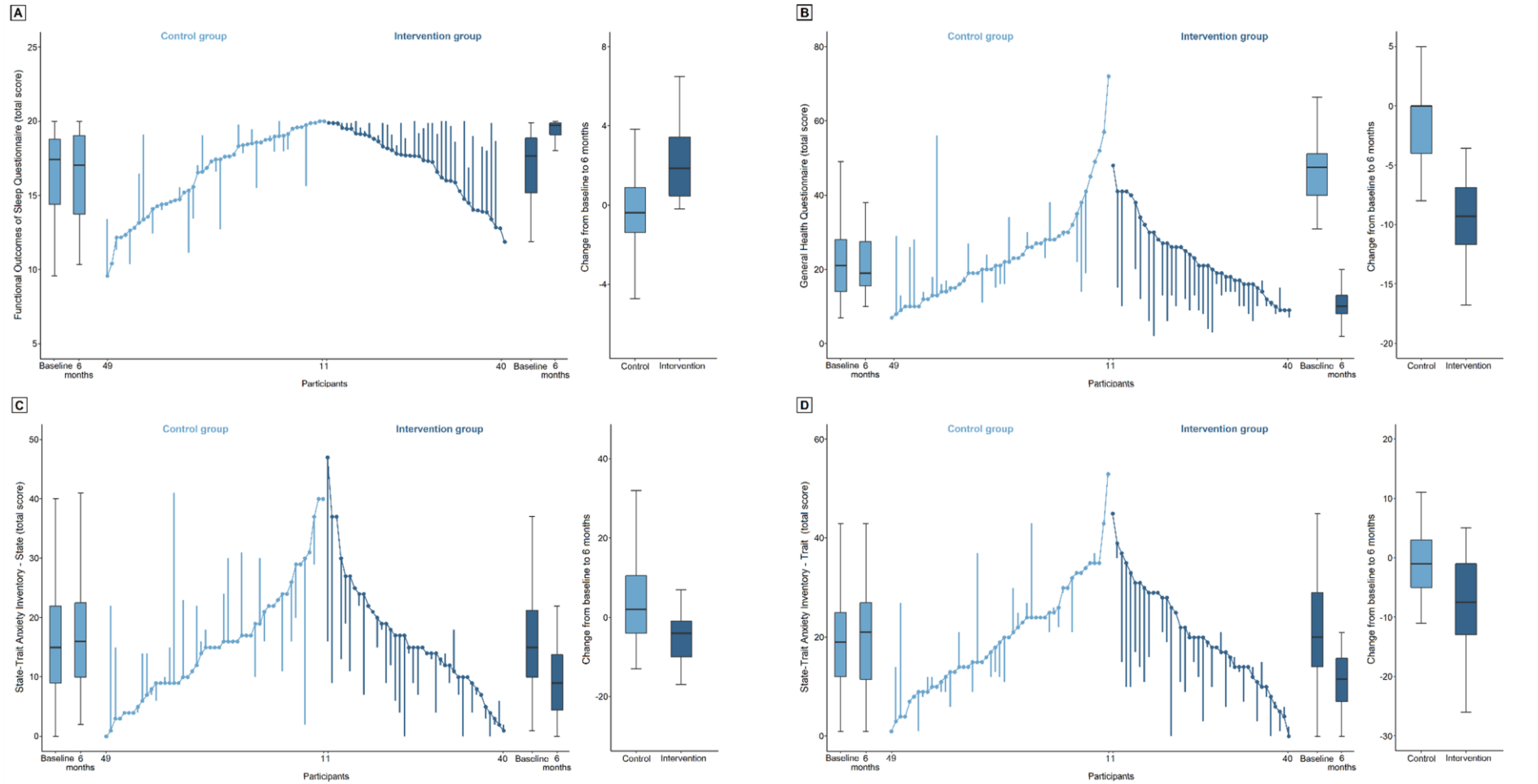
[a] The State-Trait Depression Inventory measures state depression and trait depression (range, 10-40; higher scores indicate greater depression; score ≥20 and ≥21 suggests clinical levels of state and trait depression, respectively).[10]

Supplementary Table S8. Beck Depression Inventory-Fast Screen[a] by group and clinical status

Group	At baseline		At 8 weeks		At 6 months	
	No. (%)	Mean (SD)	No. (%)	Mean (SD)	No. (%)	Mean (SD)
Control/usual care						
All	49 (100)	2.78 (3.22)	49 (100)	22.37 (12.65)	49 (100)	3.08 (3.67)
With symptoms of depression	12 (24.5)	7.42 (3.29)	15 (30.6)	6.67 (3.27)	17 (34.7)	6.88 (3.85)
No symptoms of depression	37 (75.5)	1.27 (1.02)	34 (69.4)	1.06 (1.04)	32 (65.3)	1.06 (1.01)
Intervention						
All	40 (100)	3.15 (2.50)	40 (100)	9.5 (4.29)	40 (100)	1.18 (1.74)
With symptoms of depression	16 (40.0)	5.69 (1.66)	1 (2.5)	4 (0.0)	2 (5.0)	7.00 (2.83)
No symptoms of depression	24 (60.0)	1.46 (1.14)	39 (97.5)	0.82 (0.97)	38 (95.0)	0.87 (1.02)

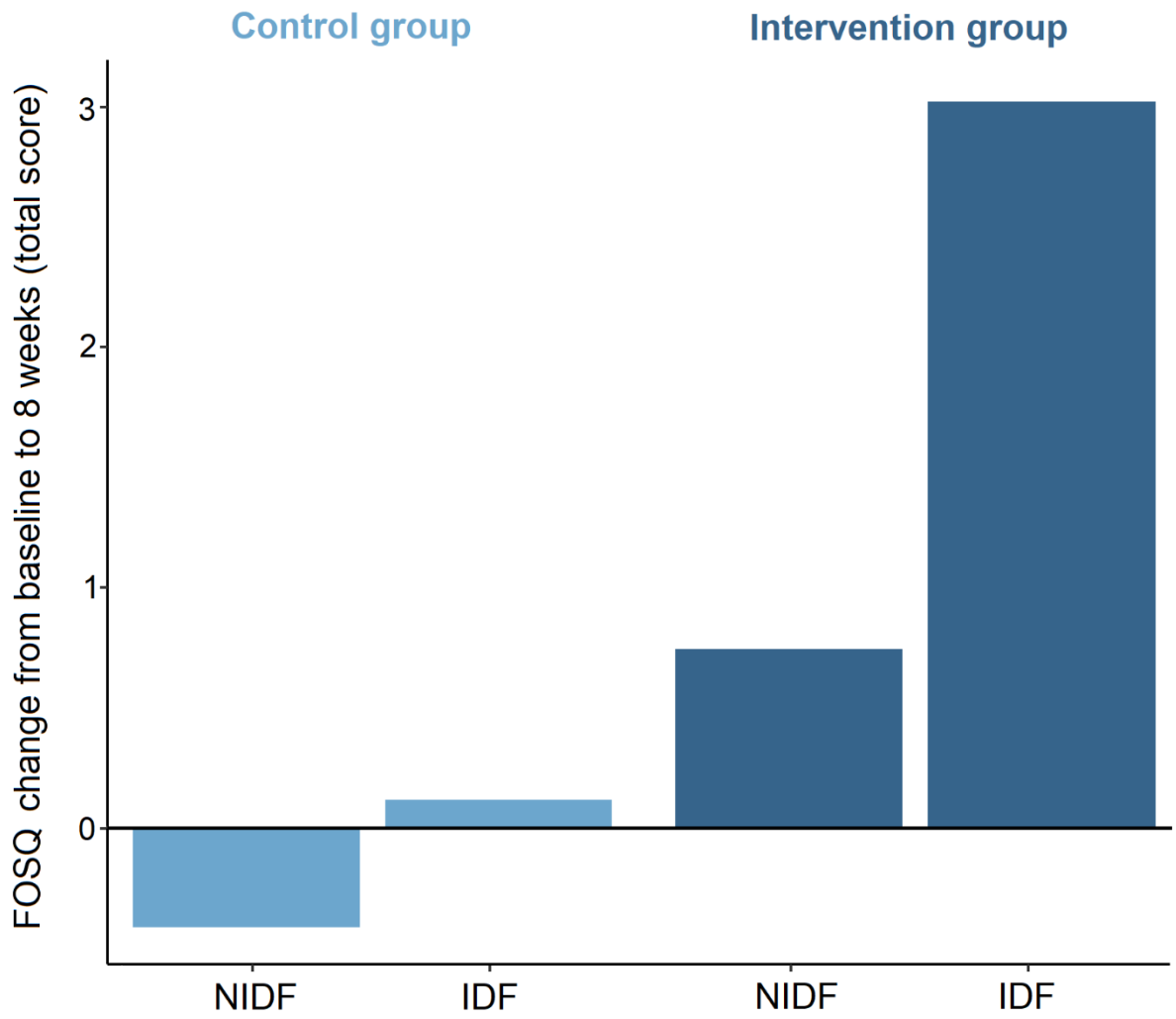
[a] The Beck Depression Inventory-Fast Screen evaluates depression (range, 0-21; higher scores indicate greater depression; score ≥4 suggests presence of depression).[11,12]

Supplementary Figure S1. Daily Functioning, Psychological Distress, and Anxiety Outcomes (Changes from baseline to 6 months)



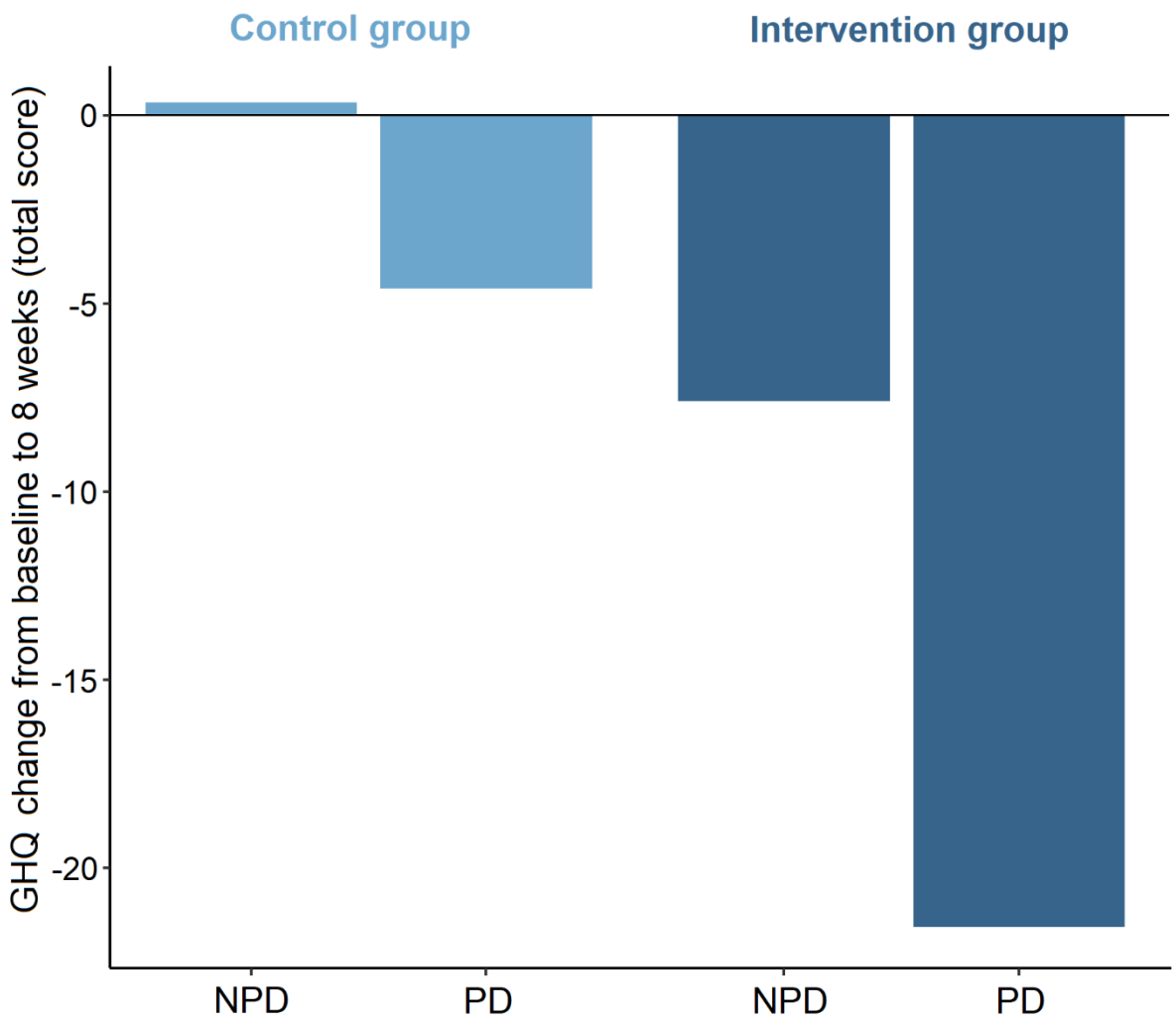
The ends of the boxes in the boxplots are located at the first and third quartiles, with the black line in the middle illustrating the median. Whiskers extend to the upper and lower adjacent values, the location of the furthest point within a distance of 1.5 interquartile ranges from the first and third quartiles. The parallel line plot contains 1 vertical line for each patient which extends from their baseline value to their 6-month value. Ascending lines indicate an improvement in the outcome (A). Descending lines indicate an improvement in the outcome (B, C, D). Baseline values are placed in ascending order for the control group and descending order for the intervention group. A, The Functional Outcomes of Sleep Questionnaire assess the impact of excessive daytime sleepiness on daily functioning (range, 5-20; higher scores indicate greater functioning; score <18 reflects negative effect of sleepiness on daily functioning).[1-4] B, The General Health Questionnaire evaluates psychological distress (range, 0-84; higher scores indicate greater psychological distress; score >23 indicates presence of psychological distress).[5,6] C,D, The State-Trait Anxiety Inventory measures state anxiety and trait anxiety (range, 0-60; higher scores indicate greater anxiety; score ≥21 and ≥24 suggests clinical levels of state and trait anxiety, respectively).[7-9]

Supplementary Figure S2. Changes in the Functional Outcomes of Sleep Questionnaire (FOSQ) by group and daily functioning status at baseline



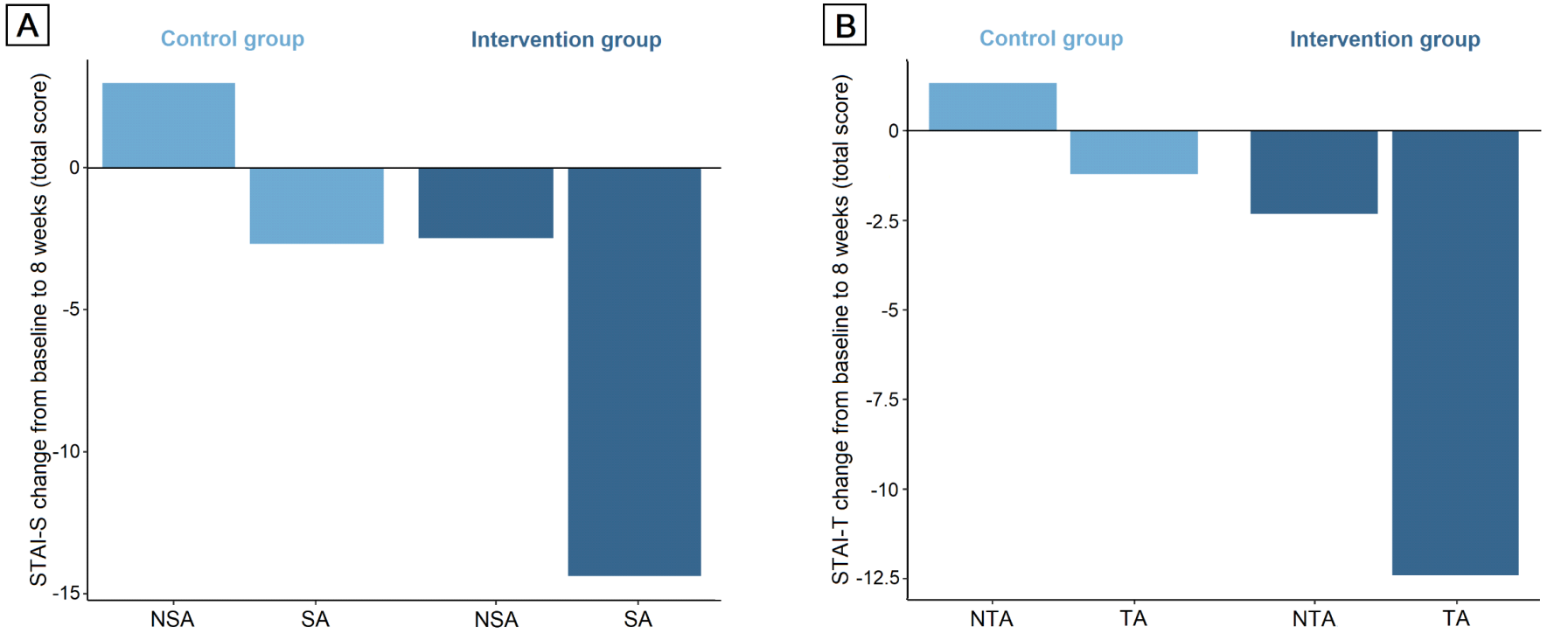
IDF, participants who reported impaired daily functioning at baseline; NIDF, participants with no/minimal impaired daily functioning reported at baseline.

Supplementary Figure S3. Changes in the General Health Questionnaire (GHQ) by group and psychological distress status at baseline



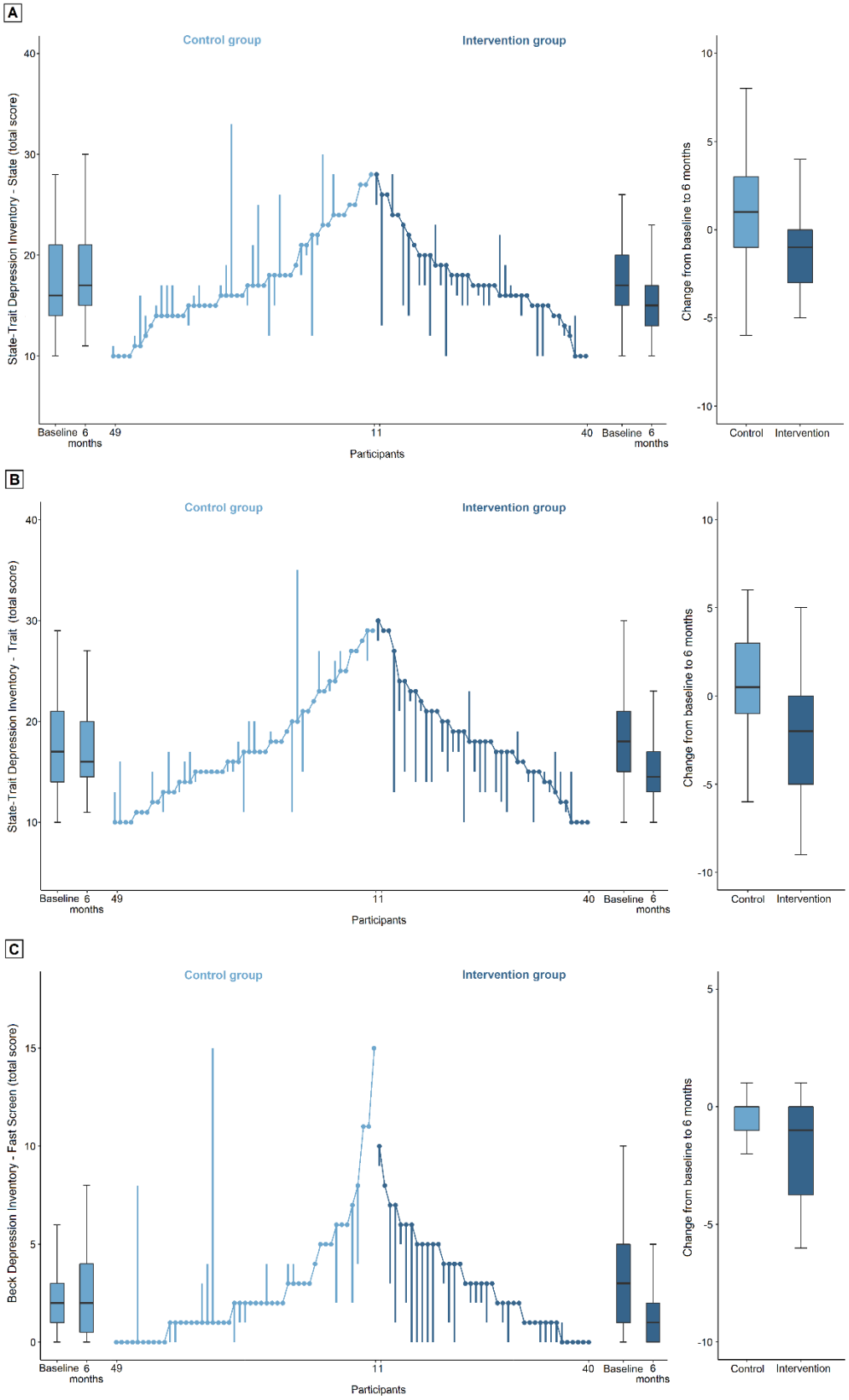
PD, participants who reported psychological distress at baseline; NPD, participants with no/minimal psychological distress reported at baseline.

Supplementary Figure S4. Changes in the State-Trait Anxiety Inventory (STAI) by group and anxiety status at baseline



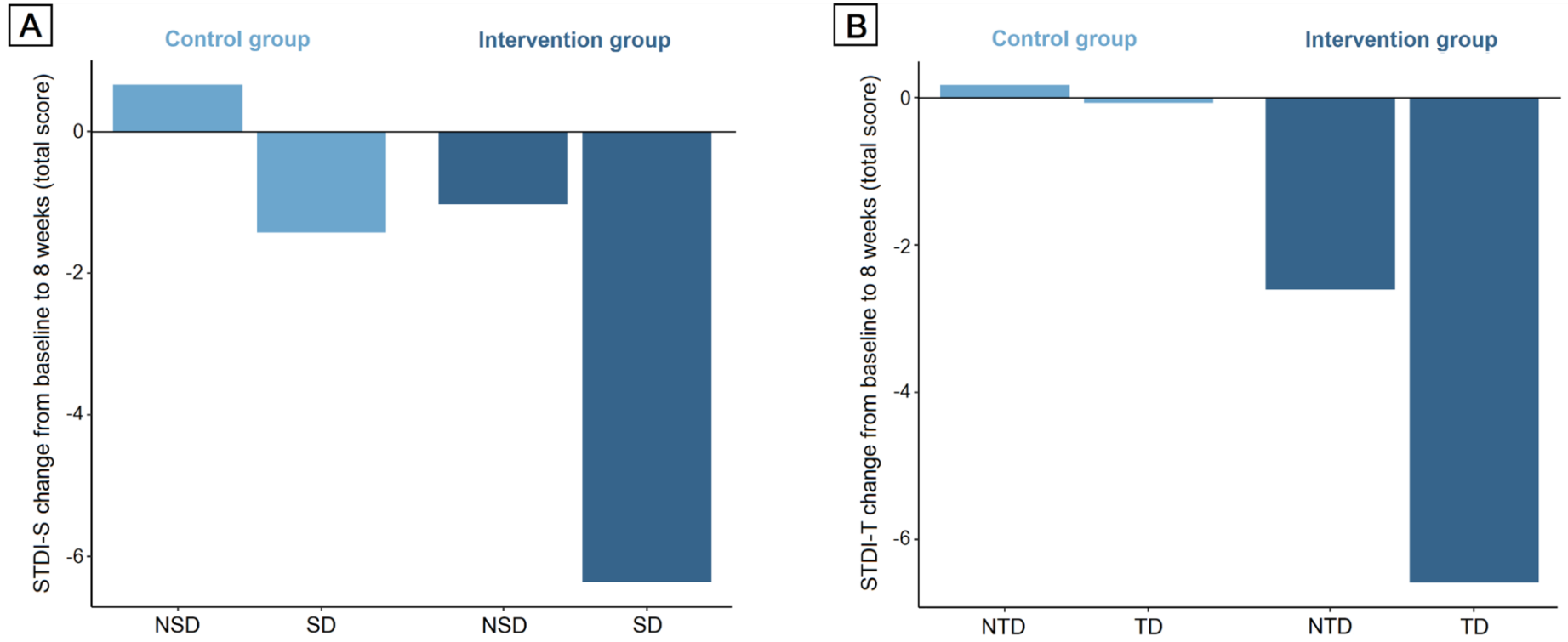
A, State Anxiety (STAI-S); SA, participants who reported state anxiety at baseline; NSA, participants with no/minimal state anxiety reported at baseline. B, Trait Anxiety (STAI-T); TA, participants who reported trait anxiety at baseline; NTA, participants with no/minimal trait anxiety reported at baseline.

Supplementary Figure S5. Depression Outcomes (Changes from baseline to 6 months)



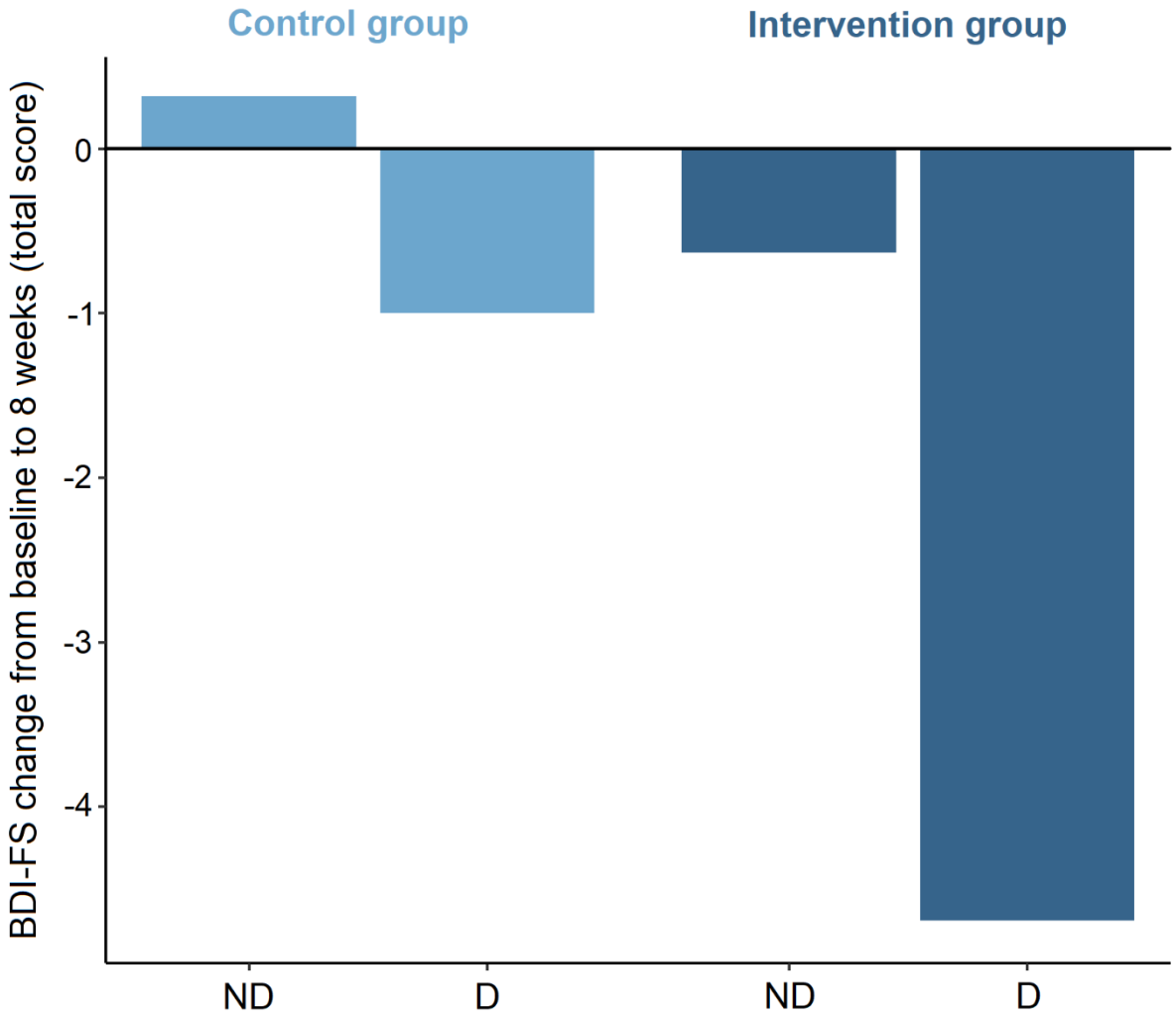
The ends of the boxes in the boxplots are located at the first and third quartiles, with the black line in the middle illustrating the median. Whiskers extend to the upper and lower adjacent values, the location of the furthest point within a distance of 1.5 interquartile ranges from the first and third quartiles. The parallel line plot contains 1 vertical line for each patient which extends from their baseline value to their 6-month value. Descending lines indicate an improvement in the outcome. Baseline values are placed in ascending order for the control group and descending order for the intervention group. A, B, The State-Trait Depression Inventory measures state depression and trait depression (range, 10-40; higher scores indicate greater depression; score ≥20 and ≥21 suggests clinical levels of state and trait depression, respectively).[10] C, The Beck Depression Inventory-Fast Screen evaluates psychological distress (range, 0-21; higher scores indicate greater depression; score ≥4 suggests presence of depression).[11,12]

Supplementary Figure S6. Changes in the State-Trait Depression Inventory (STDI) by group and depression status at baseline



A, State Depression (STDI-S); SD, participants who reported state depression at baseline; NSD, participants with no/minimal state depression reported at baseline. B, Trait Depression (STDI-T); TD, participants who reported trait depression at baseline; NTD, participants with no/minimal trait depression reported at baseline.

Supplementary Figure S7. Changes in the Beck Depression Inventory-Fast Screen (BDI-FS) by group and depression status at baseline



D, participants who reported depression at baseline; ND, participants with no/minimal symptoms of depression reported at baseline.

References

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CHAPTER 5

Effect of an interdisciplinary weight loss and lifestyle intervention on cardiorespiratory fitness in obstructive sleep apnea: The INTERAPNEA trial (**Study 5**)

ABSTRACT

The main objective of this study was to investigate the effects of an interdisciplinary weight loss and lifestyle intervention on cardiorespiratory fitness (CRF) and self-reported physical fitness in adults with moderate-to-severe obstructive sleep apnea (OSA) treated with continuous positive airway pressure (CPAP). This ancillary study was based on data from INTERAPNEA; a randomized clinical trial conducted from April 2019 to April 2020. Men aged 18-65 years with moderate-to-severe OSA and a body mass index ≥25 kg/m^2 were randomly assigned to a usual-care group (CPAP) or an eight-week interdisciplinary weight loss and lifestyle intervention combined with usual-care. Of the 89 participants who underwent randomization, 75 completed the intervention endpoint assessment, 89 participants being therefore included in the intention-to-treat analyses, and 75 in the per-protocol approach. CRF was assessed through the 2-km walking test, and the International Fitness Scale (IFIS) was used to assess self-reported physical fitness. As compared with usual-care, the intervention group had greater improvements at intervention endpoint in objective CRF (6% reduction in 2-km walking test total time, mean between-group difference, -1.7 min; 95% confidence interval, -2.3 to -1.1), and self-reported overall physical fitness (18% increase in IFIS total score, mean between-group difference, 2.3; 95% CI 1.2 to 3.3). At 6 months after intervention, the intervention group also had greater improvements in both 2-km walking test total time (10% reduction) and IFIS total score (22% increase), with mean between-group differences of -2.5 (CI 95%, -3.1 to -1.8) and 3.0 (CI 95%, 1.8 to 4.1), respectively. An eight-week interdisciplinary weight loss and lifestyle intervention resulted in significant and sustainable improvements in CRF and self-reported physical fitness in men with overweight/obesity and moderate-to-severe OSA.

Introduction

Obstructive sleep apnea (OSA), defined by repetitive sleep-state dependent upper-airway obstructions, is the most common sleep-disordered breathing in the overall population affecting 936 million adults aged 30–69 years globally;[1] obesity, increasing age, and male sex being the key risk factors for this condition.[2] Through mechanisms of intermittent hypoxemia, arousal-related sleep fragmentation, and sympathetic overactivity triggered by the recurrent airway collapse during sleep, OSA is closely related to a wide range of negative sequalae including neurocognitive alterations, impaired daily functioning and mood, and cardiometabolic disorders such as dyslipidemia, diabetes, hypertension, and life-threatening cardiovascular diseases.[3-9]

Cardiorespiratory fitness (CRF), is also considered a well-established strong and independent predictor of cardiometabolic morbidity and all-cause mortality.[10-12] Indeed, a growing body of epidemiological and clinical research demonstrates that low CRF is a stronger predictor of adverse cardiovascular outcomes and mortality than recognized risk factors such as obesity, smoking, hypertension, high cholesterol, and type 2 diabetes mellitus.[13-17] In adults with OSA, CRF has been found to be reduced; the cooccurrence of both conditions substantially increasing the risk of major adverse cardiovascular events and reduced survival.[18-21]

Continuous positive airway pressure (CPAP), the standard treatment of OSA, is a mechanical device effective at reducing OSA severity (i.e., the number of apnea and hypopnea episodes per hour of sleep; apnea-hypopnea index, AHI) when used as prescribed.[22] However, the efficacy of this treatment at improving CRF and, thus, the reduction of related cardiovascular and all-cause mortality risk still remains uncertain.[19,23-25] Although some studies reported enhanced CRF after short-term CPAP use,[26,27] other studies found no changes after 1-3 months of treatment.[28,29] Conversely, weight loss and lifestyle interventions including dietary modification and increased physical activity have been shown to not only substantially improve OSA severity,[30-34] but also CRF and related cardiovascular and metabolic morbidity.[31,35-41] Yet, evidence is sparse and results on the association between CRF and OSA severity change are controversial.[37,42-43]

The current study was based on data from the INTERAPNEA trial,[44] a randomized clinical trial designed to determine the effects of a weight loss and lifestyle intervention, as compared with usual-care (i.e., CPAP), on OSA severity, body weight and composition, and cardiometabolic risk in overweight-obese adults with moderate-to-severe OSA.[44] As previously reported, the intervention group had a mean AHI reduction of 57% at 6 months after intervention; 62% of participants no longer requiring CPAP and 29% attaining complete OSA remission.[31] Clinically significant differences between groups in body weight and composition, as well as cardiometabolic risk outcomes, were also found.[31] The present study was primarily aimed at elucidating the effects of this behavioral weight loss and lifestyle intervention on CRF and self-reported physical fitness in adults with overweight/obesity and CPAP-treated moderate-to-severe OSA. Additionally, the associations between changes in CRF, OSA severity and body weight and composition outcomes were also investigated.

We hypothesized that the intervention group would have greater sustainable improvements in CRF and self-reported physical fitness than the control group. We also expected that changes in CRF and self-reported physical fitness would be significantly associated with changes in OSA severity and body weight and composition outcomes.

Methods

Study Design and Participants

The present study is an ancillary study of the INTERAPNEA randomized clinical trial. Detailed descriptions of the rationale, design, and methodology of this trial are available elsewhere.[44] Appropriate regulatory authorities and ethics committees approved the study protocol, and all participants provided written informed consent before participating. The trial was conducted from April 2019 through October 2020. Men aged 18-65 years with CPAP-treated moderate-to-severe OSA (AHI equal or greater than 15 events per hour of sleep), and a body mass index (BMI) equal or greater than 25 kg/m^2 were eligible to participate. Exclusion criteria only included current participation in a weight loss program, presence of any psychological/psychiatric disorder, and/or any other primary sleep disorder which were not secondary to OSA. Due to feasibility reasons, the trial was conducted in three consecutive sets of 30 participants. A total of 89 adults were enrolled in INTERAPNEA and randomly assigned to either the intervention group (40 participants) or the usual-care group (49 participants). A total of 75 participants completed the 8-week assessment (intervention endpoint); the loss to follow-up being therefore 15.7% (14 participants), primarily due to the Covid-19 pandemic (10 participants). Thus, 89 participants were included in the intention-to-treat analyses, and 75 in the per-protocol approach according to prespecified adherence criteria (Supplementary Figure S1).[31]

Study Intervention

The eight-week interdisciplinary weight loss and lifestyle intervention, accurately based on current clinical practice guidelines,[45-48] was composed of five different but complementary components: nutritional behavior change; moderate-intensity aerobic exercise; smoking cessation; alcohol avoidance; and sleep hygiene. Each component included 60–90 min group-based weekly sessions led by trained professionals in each field. A detailed description of the study intervention has been previously reported.[31,44] In brief, key behavioral change techniques used in each intervention component comprised motivation and preparation for action; goal-setting and action-planning; self-monitoring and functional behavioral analysis; review of behavioral goals, action plans, and adherence; problem solving and social skills; and self-efficacy, maintenance, and relapse prevention.

Apart from the CPAP, the usual-care/control group received general advice on weight loss and lifestyle change in a single 30 min session led by a sleep-disordered breathing specialist. The study intervention was also offered to all participants from this group at the end of the trial.

Study Outcomes

Sleep

Objective sleep outcomes including AHI (number of apnea and hypopnea episodes per hour of sleep), oxygen desaturation index (number of oxygen desaturation ≥3% per hour of sleep) and sleep efficiency (%; total sleep time/total time in bed) were measured at baseline, intervention endpoint and 6 months after intervention through a full-night in-laboratory polysomnography using SOMNOScreen™ PSG-Tele (SOMNOmedics, GmbH, Randersacker, Germany), or Somté PSG v2 system (Compumedics Limited, Abbotsford, Australia). Recordings included electroencephalogram (three channels: F4-M1, C4-M1, O2-M1), electrooculogram (two channels: E1 and E2), electromyogram (two channels: submental and anterior tibialis muscles), and electrocardiogram (two channels). Cardiorespiratory measurements included oral and nasal airflow (triple thermistor), oxyhaemoglobin saturation (SpO_2) and pulse-rate (pulse oximeter), respiratory effort (chest and abdomen bands), and body position (sensor). Electrodes were placed following the international 10–20 system,[49] and recordings were automatically and manually scored in 30 s epochs[50] by trained physicians using DOMINO (v2.7, SOMNOmedics, GmbH, Randersacker, Germany), or ProFusion PSG 3 (v3.3, Compumedics Limited, Abbotsford, Australia) associated computer software. Settings, technical specifications, and scorings were executed following the AASM Manual for the Scoring of Sleep and Associated Events.[51]

Body weight and composition

Body weight and composition were also measured at baseline, intervention endpoint and 6 months after intervention. Body weight (kg) was measured using a calibrated scale and stadiometer (model 799, Electronic Column Scale, Hamburg, Germany). Neck, chest, and waist circumferences (cm) were measured following standard procedures recommended by the International Society for the Advancement of Kinanthropometry (ISAK).[52] Fat mass (kg) and visceral adipose tissue (g) were obtained through a full-body DXA scanner (Discovery Wi, Hologic, Inc., Bedford, MA, USA). The manufacturer's recommendations were followed when performing quality controls, positioning of participants and analyses of results, and automatic delineation of anatomic regions was conducted using APEX 4.0.2. software.

Cardiorespiratory fitness

Cardiorespiratory fitness was objectively measured at intervention endpoint and 6 months after intervention by the 2km walking test, which has been widely used and validated for accurate estimation of maximal aerobic power.[53-55] Participants were required to walk over a marked 2 km track on a firm surface wearing a heart rate monitor (Polar RS800cx, Polar Electro, Kempele, Finland). Walking time and heart rate were recorded at the end of the test.

Self-reported physical fitness

The International Fitness Scale (IFIS)[56,57] was also used in order to measure subjective physical fitness at intervention endpoint and 6 months after intervention. This simple and short scale is composed of five questions on perceived overall fitness and its main components—cardiorespiratory fitness, muscular fitness, speed–agility, and flexibility. Each question

is scored on a Likert-type scale that ranges from 0 (very poor) to 5 (very good); higher scores indicating greater physical fitness.

Statistical Analysis

This study was ancillary to a parent study aimed at determining the effects of an interdisciplinary weight loss and lifestyle intervention on OSA severity, which was originally powered to detect changes in AHI. The primary analyses included linear mixed-effects models used to estimate intervention effects on the study outcomes with group, time of assessment and their interaction terms as the main effect.[58] The restricted maximum-likelihood method and an unstructured covariance matrix were used in order to adjust for within-participant clustering resulting from the repeated-measures design. Missing data therefore were assumed to be missing-at-random; all values presented being model-based estimates. Nevertheless, a logistic model predicting attrition based on baseline values of set of participants, allocation group, OSA severity, age and BMI was used in order to calculate attrition propensity. As expected, only set of participants significantly predicted attrition due to the occurrence of the Covid-19 pandemic at the trial endpoint (intervention endpoint assessment of the third set of participants). Thus, assumptions of missing data being missing-at-random were confirmed, which is also in agreement with recent recommendations for handling missing data in randomized trials affected by a pandemic.[59]

An intention-to-treat approach (including all participants as originally allocated after randomization) was primarily used in all estimations and analyses, with an additional per-protocol approach only including participants with a CPAP usage equal or greater than four hours per night on 70% of nights and, regarding the intervention group, at least 80% of attendance rate at intervention sessions.

In addition, association of changes in CRF and self-reported physical fitness over time with changes in sleep and body weight and composition outcomes were examined by repeated measures correlation analysis — a statistical technique used to determine the within-individual association for paired measures assessed on two or more occasions for multiple individuals.[60] All analyses were performed using R version 4.0.3 (R Project for Statistical Computing).

Results

Study Participants

Baseline characteristics of the study participants are summarized in Table 1. On average, participants were middle-aged (mean ± SD age, 54.1±8.0 years), and had obesity (mean ± SD BMI, 34.4±5.4 kg/m^2). The mean ± SD AHI was 41.3±22.2 events/hr; 61% of participants suffering from severe OSA (i.e., AHI ≥ 30). The two randomized groups were well balanced with respect to baseline characteristics; there were no differences in clinical measures at baseline values between the control group and the intervention group.

Changes in CRF and Self-Reported Physical Fitness

Participants in the intervention group significantly reduced 2-km walking test total time from the baseline value of 22.1 min to 20.7 min at intervention endpoint (6% reduction; change in 2-km walking test total time, -1.4 min; 95% confidence

Table 1. Baseline characteristics of the study participants

	No. (%)[a]	
Characteristic[b]	**Control (n = 49)**	**Intervention (n = 40)**
Age, mean (SD), y	55.3 (8.5)	52.6 (7.1)
Educational level		
Primary Education	13 (26.5)	10 (25.0)
Secondary Education	10 (20.4)	6 (15.0)
Vocational Education	13 (26.5)	17 (42.5)
Higher Education	13 (26.5)	7 (17.5)
Marital status		
Single	7 (14.3)	2 (5.0)
Married	34 (69.4)	34 (85.0)
Divorced	8 (16.3)	4 (10.0)
Occupational status		
Employed	27 (55.1)	21 (52.5)
Self-employed	8 (16.3)	12 (30.0)
Unemployed	4 (8.2)	5 (12.5)
Retired	10 (20.4)	2 (5.0)
Medical Conditions[c]		
Hypertension	33 (67.4)	27 (67.5)
Diabetes Mellitus II	12 (24.5)	10 (25.0)
Cardiovascular disease	9 (18.4)	7 (17.5)
Other medical conditions	29 (59.2)	26 (65.0)
Medication[c]		
Antihypertensive	31 (63.3)	24 (60.0)
Statins	15 (30.6)	7 (17.5)
Oral antidiabetic	5 (10.2)	2 (5.0)
Insulin	3 (6.1)	1 (2.5)
Beta-blockers	7 (14.3)	5 (12.5)
Polymedication[d]	14 (28.6)	6 (15.0)
Body mass index, mean (SD), kg/m^2	33.9 (4.8)	35.0 (6.0)
Body weight, mean (SD), kg	99.6 (18.3)	103.3 (17.5)
Fat mass, mean (SD), kg	33.8 (9.0)	34.9 (10.6)
Visceral adipose tissue, mean (SD), g	1049.2 (260.3)	1017.3 (285.2)
Neck circumference, mean (SD), cm	45.5 (3.9)	45.0 (3.8)
Chest circumference, mean (SD), cm	117.4 (9.9)	118.0 (10.3)
Waist circumference, mean (SD), cm	117.9 (12.2)	119.0 (12.4)
Apnea-hypopnea index, mean (SD), events/hr	41.1 (21.3)	41.6 (23.5)
Obstructive sleep apnea severity		
Moderate	20 (40.8)	15 (37.5)
Severe	29 (59.2)	25 (62.5)
Oxygen desaturation index, mean (SD), events/hr	45.4 (21.1)	45.4 (27.7)
Sleep efficiency, mean (SD), %	85.6 (8.1)	86.0 (9.1)

[a] No. (%) reported unless otherwise specified.

[b] No significant between-group differences were observed in any of the baseline characteristics.

[c] Participants could have more than one condition or medication.

[d] Defined as the use of five or more medications.

interval [CI], -1.9 to -0.9); and to 20.0 min at 6 months after intervention (10% reduction; change in 2-km walking test total time, -2.1 min; 95% CI, -2.6 to -1.5) (Table 2 and Figure 1). No differences in 2-km walking test total time were detected in the control group at intervention endpoint (0.3 min; 95% CI, -0.2 to 0.9), nor at 6 months after intervention (-0.4 min; 95% CI, -0.2 to 1.0); the mean difference between groups in 2-km walking test total time change being -1.7 min (95% CI, -2.3 to -1.1) at intervention endpoint, and -2.5 min (95% CI, -3.1 to -1.8) at 6 months after intervention, (both P<0.001).

Similarly, participants in the intervention group had greater improvements in self-reported physical fitness as measured by IFIS at intervention endpoint (change in IFIS total score, 2.5; 95% CI, 1.6 to 3.4) than participants in the control group (0.2; 95% CI, -0.7 to 1.2), with a mean difference of 2.3 (95% CI, 1.2 to 3.3) between groups (P<0.001) (Table 2 and Figure 1). Similar results were found at 6 months after intervention, the mean difference in IFIS total score being 3.0 (95% CI, 1.8 to 4.1) between groups (P<0.001). Accordingly, participants in the intervention group also had significant greater improvements in self-reported overall fitness, CRF, muscular fitness, and speed–agility at both intervention endpoint and 6 months after intervention (IFIS subscales; all P < 0.05).

Regarding changes from intervention endpoint to 6 months after intervention, participants in the intervention group not only significantly continued improving 2-km walking test total time but also maintained improvements achieved in self-reported fitness outcomes (Supplementary Table S2 and Supplementary Figure S2).

Similar results were obtained using the per-protocol approach (Supplementary Table S1 and Supplementary Table S2).

Association of Changes in CRF and Self-Reported Physical Fitness with Changes in OSA and Body Weight and Composition Outcomes

Changes in physical fitness over time as objectively measured by the 2-km walking test were significantly associated with changes in OSA outcomes; a reduction in 2-km walking test total time being related with reduced AHI and oxygen desaturation index, and increased sleep efficiency (all P<0.001; Table 3 and Figure 2). Regarding body composition and anthropometric outcomes, changes over time in 2-km walking test total time were positively associated with changes in body weight, fat mass, visceral adipose tissue, and neck, chest, and waist circumferences (all P<0.001; Table 3 and Figures 3 and 4).

Similarly, changes over time in self-reported physical fitness as measured by IFIS were significantly associated with changes in OSA outcomes; an increase in IFIS total score being related with reduced AHI and oxygen desaturation index, and increased sleep efficiency (all P<0.01; Table 3 and Figure 2). Increases over time in IFIS total score were also negatively associated with changes in body weight, fat mass, visceral adipose tissue, and neck, chest and waist circumferences (all P<0.001; Table 3 and Figures 3 and 4).

Table 2. Physical fitness outcomes

Endpoints	Control (n=49)		Intervention (n=40)		Difference between groups, mean (95% CI)[a]
	Mean (95% CI)	Change from baseline, mean (95% CI)	Mean (95% CI)	Change from baseline, mean (95% CI)	
2-km walking test, min					
At baseline	22.3 (21.5 to 23.2)		22.1 (21.1 to 23.0)		
At 8 weeks	22.6 (21.7 to 23.5)	0.3 (-0.2 to 0.9)	20.7 (19.7 to 21.6)	-1.4 (-1.9 to -0.9)	-1.7 (-2.3 to -1.1)[d]
At 6 months	22.7 (21.8 to 23.6)	0.4 (-0.2 to 1.0)	20.0 (19.0 to 21.0)	-2.1 (-2.6 to -1.5)	-2.5 (-3.1 to -1.8)[d]
International Fitness Scale, total score[e]					
At baseline	12.8 (11.8 to 13.9)		13.7 (12.6 to 14.8)		
At 8 weeks	13.1 (12.0 to 14.2)	0.2 (-0.7 to 1.2)	16.2 (15.1 to 17.3)	2.5 (1.6 to 3.4)	2.3 (1.2 to 3.3)[d]
At 6 months	12.9 (11.8 to 14.1)	0.1 (-1.0 to 1.1)	16.7 (15.6 to 17.9)	3.0 (2.1 to 4.0)	3.0 (1.8 to 4.1)[d]
International Fitness Scale, overall fitness					
At baseline	2.6 (2.4 to 2.9)		2.8 (2.5 to 3.1)		
At 8 weeks	2.9 (2.6 to 3.2)	0.2 (-0.04 to 0.5)	3.5 (3.2 to 3.8)	0.7 (0.4 to 1.0)	0.4 (0.1 to 0.8)[b]
At 6 months	2.8 (2.5 to 3.1)	0.1 (-0.2 to 0.5)	3.6 (3.3 to 3.9)	0.8 (0.5 to 1.1)	0.7 (0.3 to 1.0)[d]
International Fitness Scale, cardiorespiratory fitness					
At baseline	2.2 (1.9 to 2.5)		2.4 (2.1 to 2.7)		
At 8 weeks	2.2 (1.9 to 2.5)	0.01 (-0.3 to 0.3)	3.1 (2.8 to 3.4)	0.7 (0.4 to 1.0)	0.7 (0.3 to 1.1)[d]
At 6 months	2.3 (2.0 to 2.6)	0.1 (-0.3 to 0.5)	3.2 (2.9 to 3.5)	0.8 (0.5 to 1.2)	0.7 (0.3 to 1.1)[d]
International Fitness Scale, muscular fitness					
At baseline	3.0 (2.8 to 3.2)		3.2 (2.9 to 3.4)		
At 8 weeks	2.9 (2.7 to 3.2)	-0.1 (-0.4 to 0.2)	3.5 (3.2 to 3.7)	0.3 (0.1 to 0.6)	0.4 (0.1 to 0.7)[b]
At 6 months	2.9 (2.6 to 3.1)	-0.2 (-0.5 to 0.1)	3.7 (3.4 to 4.0)	0.5 (0.3 to 0.8)	0.7 (0.4 to 1.0)[d]
International Fitness Scale, speed-agility					
At baseline	2.5 (2.3 to 2.8)		2.8 (2.6 to 3.1)		
At 8 weeks	2.6 (2.3 to 2.8)	0.02 (-0.3 to 0.3)	3.3 (3.0 to 3.5)	0.4 (0.1 to 0.7)	0.4 (0.1 to 0.7)[b]
At 6 months	2.5 (2.2 to 2.8)	-0.1 (-0.4 to 0.3)	3.3 (3.0 to 3.5)	0.5 (0.1 to 0.8)	0.5 (0.1 to 0.9)[c]
International Fitness Scale, flexibility					
At baseline	2.4 (2.2 to 2.7)		2.5 (2.2 to 2.8)		
At 8 weeks	2.5 (2.2 to 2.8)	0.1(-0.3 to 0.4)	2.9 (2.6 to 3.2)	0.4 (0.04 to 0.7)	0.3 (-0.1 to 0.7)
At 6 months	2.5 (2.2 to 2.8)	0.1 (-0.3 to 0.4)	3.0 (2.7 to 3.3)	0.4 (0.1 to 0.8)	0.4 (-0.01 to 0.8)

Abbreviations: CI, confidence interval.

[a] Using the group × visit interaction term from a linear mixed-effects model including study group, time (baseline, 8 weeks and 6 months), and study group × time as fixed effects and participant as random effects.

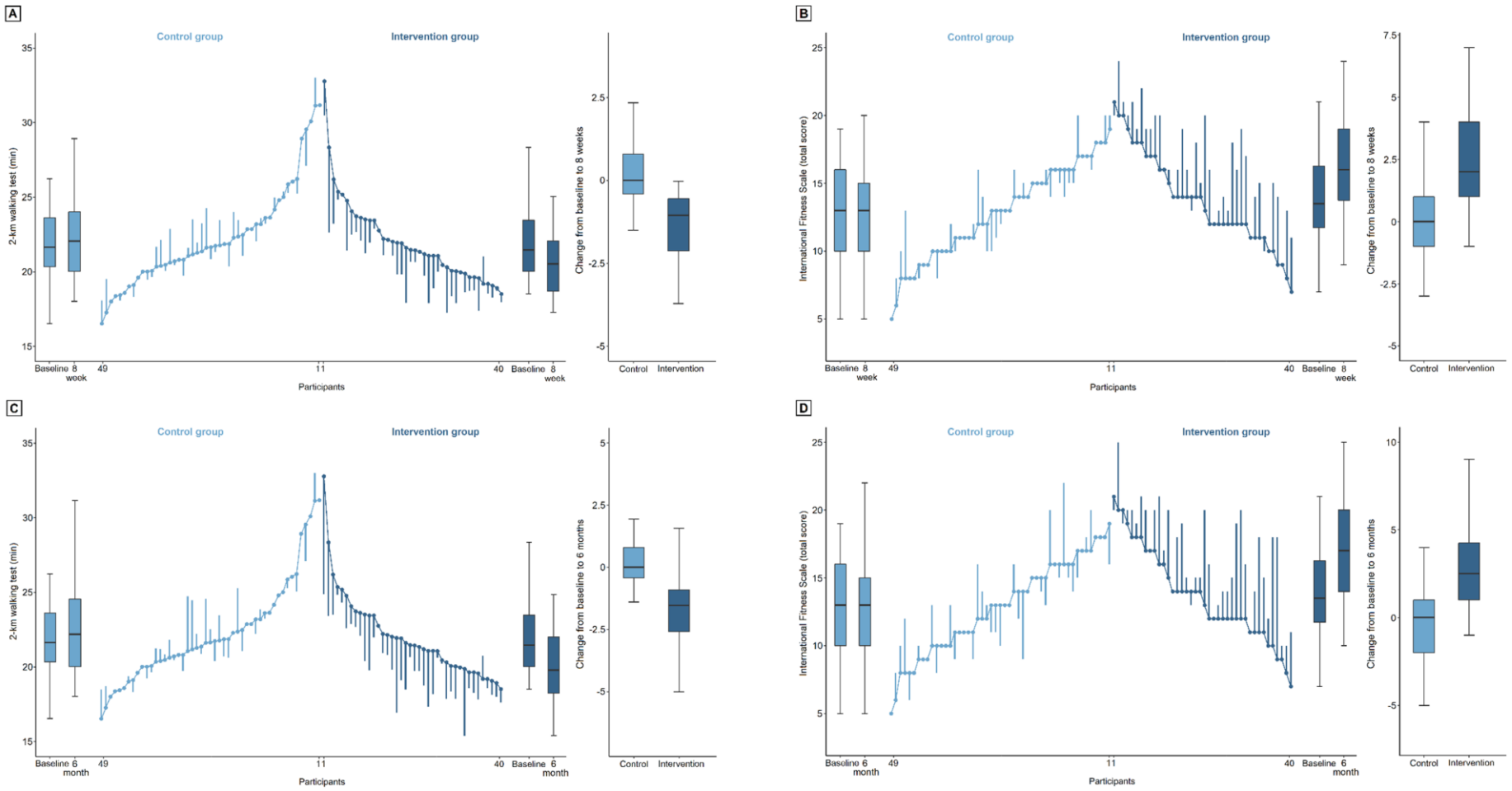
[b] $P < 0.05$ from the time × study group interactions.

[c] $P < 0.01$ from the time × study group interactions.

[d] $P < 0.001$ from the time × study group interactions.

[e] The International Fitness Scale assesses physical fitness and its main components (range, 5-20; higher scores indicate greater functioning).[56,57]

Figure 1. Physical fitness outcomes



The ends of the boxes in the boxplots are located at the first and third quartiles, with the black line in the middle illustrating the median. Whiskers extend to the upper and lower adjacent values, the location of the furthest point within a distance of 1.5 interquartile ranges from the first and third quartiles. The parallel line plot contains 1 vertical line for each patient which extends from their baseline value to their 8-week value (A, B) or 6-month value (C, D). Descending lines indicate an improvement in the outcome (A, C). Ascending lines indicate an improvement in the outcome (B, D). Baseline values are placed in ascending order for the control group and descending order for the intervention group. A, C, The 2-km walking test is a widely used and validated measure of cardiorespiratory fitness.[53-55] B, D, The International Fitness Scale assesses physical fitness and its main components (range, 5-25; higher scores indicate greater levels of physical fitness).[56,57]

Table 3. Repeated measures correlation analyses examining association of changes in physical fitness over time with changes in sleep and body weight and composition outcomes

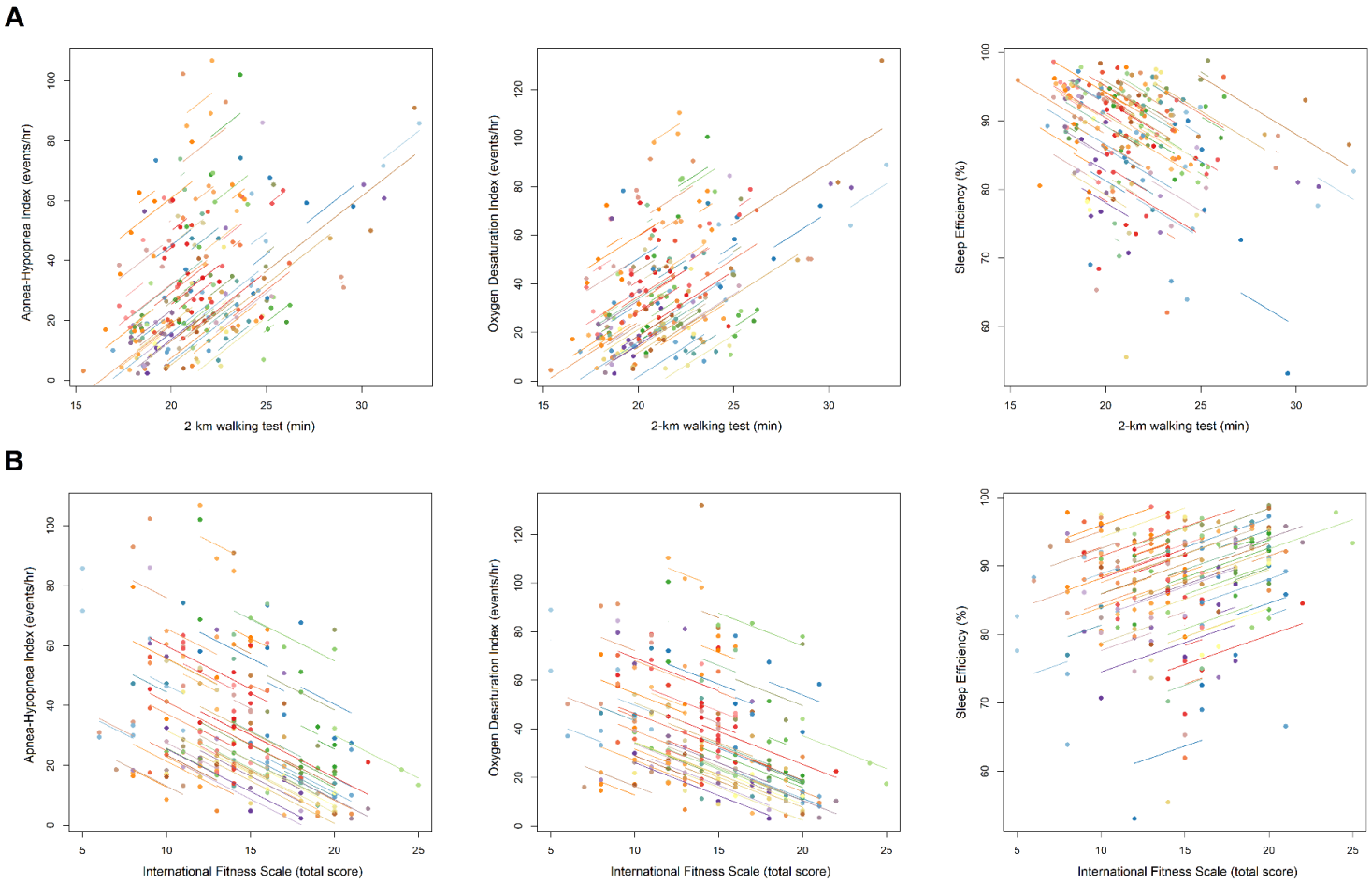
	2-km walking test, min[a]			International Fitness Scale, total score[b]		
Outcomes	**r**	**95% CI**	**P value**	**r**	**95% CI**	**P value**
Changes at 8 weeks and 6 months after intervention						
Apnea-hypopnea index, events/hr	0.50	0.36 to 0.61	< 0.001	-0.47	-0.59 to -0.33	<0.001
Oxygen desaturation index ≥3%, events/hr	0.47	0.33 to 0.59	<0.001	-0.42	-0.55 to -0.27	<0.001
Sleep efficiency, %	-0.32	-0.46 to -0.16	<0.001	0.27	0.10 to 0.42	0.002
Body weight, kg	0.55	0.41 to 0.65	<0.001	-0.47	-0.59 to -0.33	<0.001
Fat mass, kg	0.47	0.33 to 0.60	<0.001	-0.36	-0.50 to -0.21	<0.001
Visceral adipose tissue, g	0.43	0.28 to 0.56	<0.001	-0.27	-0.42 to -0.11	<0.001
Neck circumference, cm	0.50	0.37 to 0.62	<0.001	-0.39	-0.52 to -0.23	<0.001
Chest circumference, cm	0.45	0.31 to 0.58	<0.001	-0.32	-0.46 to -0.16	<0.001
Waist circumference, cm	0.57	0.44 to 0.67	<0.001	-0.48	-0.60 to -0.34	<0.001
Changes from baseline to 8 weeks						
Apnea-hypopnea index, events/hr	0.51	0.32 to 0.66	<0.001	-0.51	-0.66 to -0.31	<0.001
Oxygen desaturation index ≥3%, events/hr	0.42	0.21 to 0.59	<0.001	-0.39	-0.57 to -0.18	<0.001
Sleep efficiency, %	-0.44	-0.61 to -0.24	<0.001	0.32	0.10 to 0.51	0.004
Body weight, kg	0.56	0.38 to 0.70	<0.001	-0.62	-0.74 to -0.45	<0.001
Fat mass, kg	0.37	0.16 to 0.55	<0.001	-0.32	-0.51 to -0.10	0.005
Visceral adipose tissue, g	0.37	0.16 to 0.55	<0.001	-0.21	-0.41 to 0.02	0.07
Neck circumference, cm	0.47	0.27 to 0.63	<0.001	-0.44	-0.61 to -0.24	<0.001
Chest circumference, cm	0.38	0.17 to 0.56	<0.001	-0.37	-0.55 to -0.15	0.001
Waist circumference, cm	0.52	0.33 to 0.67	<0.001	-0.58	-0.71 to -0.40	<0.001
Changes from baseline to 6 months after intervention						
Apnea-hypopnea index, events/hr	0.58	0.38 to 0.73	<0.001	-0.58	-0.72 to -0.37	<0.001
Oxygen desaturation index ≥3%, events/hr	0.60	0.41 to 0.74	<0.001	-0.54	-0.70 to -0.34	<0.001
Sleep efficiency, %	-0.34	-0.55 to -0.10	0.007	0.35	0.10 to 0.55	0.006
Body weight, kg	0.66	0.49 to 0.78	<0.001	-0.52	-0.69 to -0.31	<0.001
Fat mass, kg	0.68	0.51 to 0.79	<0.001	-0.57	-0.72 to -0.37	<0.001
Visceral adipose tissue, g	0.65	0.47 to 0.78	<0.001	-0.57	-0.72 to -0.37	<0.001
Neck circumference, cm	0.61	0.42 to 0.75	<0.001	-0.49	-0.66 to -0.27	<0.001
Chest circumference, cm	0.57	0.37 to 0.72	<0.001	-0.41	-0.60 to -0.18	<0.001
Waist circumference, cm	0.67	0.50 to 0.79	<0.001	-0.56	-0.72 to -0.36	<0.001

Abbreviations: CI, confidence interval.

[a] The 2-km walking test is a widely used and validated measure of cardiorespiratory fitness.[53-55]

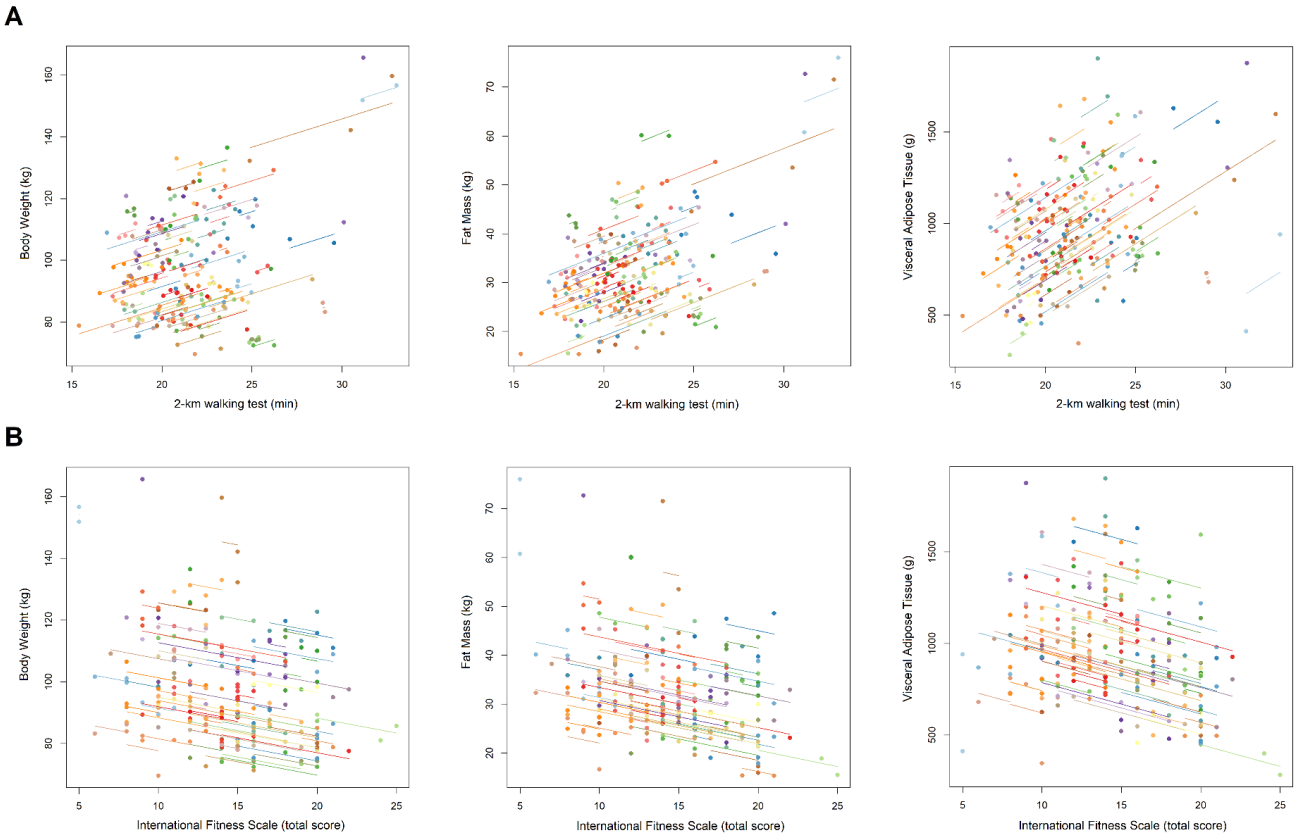
[b] The International Fitness Scale assesses physical fitness and its main components (range, 5-20; higher scores indicate greater functioning).[56,57]

Figure 2. Association of changes in physical fitness over time with changes in sleep outcomes



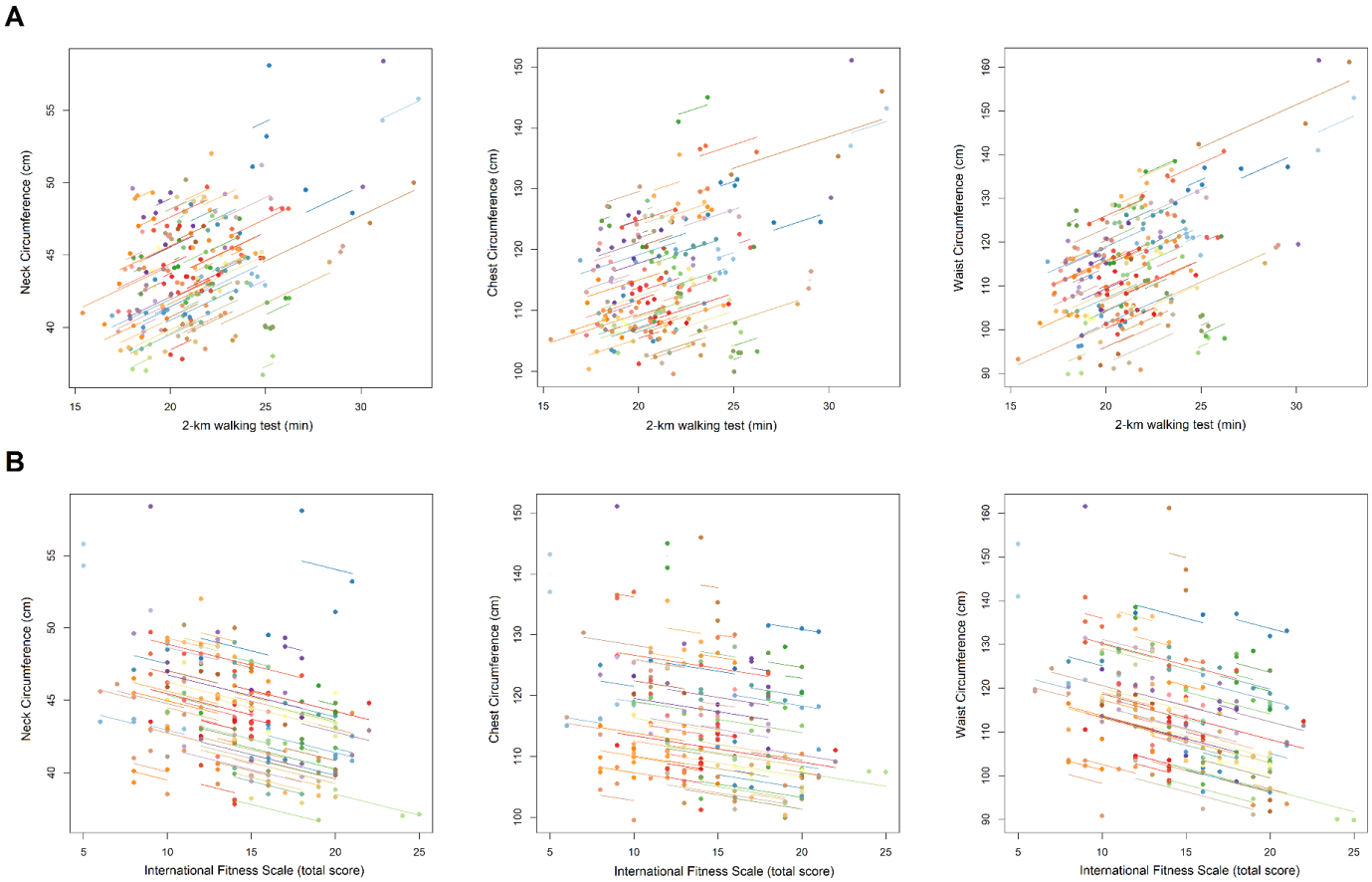
Each dot represents one of three separate observations (baseline, 8 weeks and 6 months after intervention) of physical fitness — as measured by the 2-km walking test (A) and International Fitness Scale (B) — and sleep outcomes for a participant. Observations from the same participant are given the same color, with corresponding lines to show the repeated measures correlation fit for each participant. A, The 2-km walking test is a widely used and validated measure of cardiorespiratory fitness.[53-55] B, The International Fitness Scale assesses physical fitness and its main components (range, 5-25; higher scores indicate greater levels of physical fitness).[56,57]

Figure 3. Association of changes in physical fitness over time with changes in body weight and composition outcomes



Each dot represents one of three separate observations (baseline, 8 weeks and 6 months after intervention) of physical fitness — as measured by the 2-km walking test (A) and International Fitness Scale (B) — and body weight and composition outcomes for a participant. Observations from the same participant are given the same color, with corresponding lines to show the repeated measures correlation fit for each participant. A, The 2-km walking test is a widely used and validated measure of cardiorespiratory fitness.[53-55] B, The International Fitness Scale assesses physical fitness and its main components (range, 5-25; higher scores indicate greater levels of physical fitness).[56,57]

Figure 4. Association of changes in physical fitness over time with changes in body circumferences outcomes



Each dot represents one of three separate observations (baseline, 8 weeks and 6 months after intervention) of physical fitness — as measured by the 2-km walking test (A) and International Fitness Scale (B) — and body circumferences outcomes for a participant. Observations from the same participant are given the same color, with corresponding lines to show the repeated measures correlation fit for each participant. A, The 2-km walking test is a widely used and validated measure of cardiorespiratory fitness.[53-55] B, The International Fitness Scale assesses physical fitness and its main components (range, 5-25; higher scores indicate greater levels of physical fitness).[56,57]

Discussion

CRF has been found to be significantly reduced in patients with OSA, which may be associated with increased cardiovascular disease risk and all-cause mortality.[18-21] The current study demonstrates that an eight-week interdisciplinary weight loss and lifestyle intervention was effective at improving CRF and self-reported physical fitness in patients with overweight/obesity and CPAP-treated moderate-to-severe OSA. In addition, we found that increases in CRF and self-reported physical fitness were significantly associated with improvements not only in OSA outcomes but also in body composition and anthropometric outcomes. According to the results reported herein, the weight loss and lifestyle intervention was associated with 6% and 10% reductions in 2-km walking test total time at intervention endpoint and 6 months after intervention, respectively. Similarly, this behavioral approach was related to 18% and 22% increases at intervention endpoint and 6 months after intervention, respectively, in self-reported overall physical fitness as measured by IFIS.

These results are consistent with the limited existing evidence supporting the beneficial effects of behavioral weight loss interventions promoting increased physical activity on CRF and overall physical fitness in OSA.[36-38] Kline et al.[36] found that a 12-week supervised exercise training intervention led to increased CRF in patients with moderate-to-severe OSA, although improvements in this outcome were not strongly associated to reductions in OSA severity. A meta-analysis conducted by Iftikhar et al.[37] also found that 3 to 6 months of supervised aerobic exercise was associated with an approximated 18% increase in CRF and 32% reduction in AHI. Similarly, in the recently reported Exercise in Sleep Apnea Syndrome (EXESAS) trial,[38] the nine-month supervised exercise intervention group showed significant improvements in both CRF and OSA severity, although improvements in these outcomes were unrelated and transient when long-term adherence to physical activity was not maintained.[43] Yet, results from the aforementioned studies should be interpreted with caution as limitations such as small sample sizes, stringent eligibility criteria, and the sole inclusion of a supervised exercise component may certainly limit generalizability of results.

Substantial evidence suggests that reduced CRF and overall physical fitness found in patients with OSA may be partially explained by multiple underlying mechanisms triggered by the long-lasting exposure to intermittent hypoxia and sympathetic hyperactivity.[19] These potential physiological mechanisms may include chronotropic incompetence,[61] reduced cardiac output secondary to ventricular dysfunction and increased afterload,[28] diastolic hypertension and impaired peripheral vasodilation,[62,63] impaired glycolytic and oxidative metabolism with decreased maximal lactate concentration and delayed lactate elimination,[64] and/or abnormalities of the skeletal muscles.[65] Furthermore, lower physical fitness in OSA may not only be caused by underlying cardiac and metabolic dysfunctions but also increased weight, excessive daytime somnolence, and, in turn, lack of motivation and sedentary lifestyle.[66]

As opposed to usual-care/CPAP therapy alone, behavioral weight loss and lifestyle interventions have been shown to intensely ameliorate not only OSA severity, body weight and composition, and cardiometabolic comorbidities,[30-41] but also

sleep efficiency and architecture, habitual physical activity levels, and even mood and daily functioning.[31,67] Therefore, and consistent with our results, these non-surgical and non-pharmacological approaches may also potentially enhance and even reverse the CRF and physical fitness impairments commonly found in OSA. Improvements in these health-related outcomes would certainly have robust clinical implications, since physical fitness is an increasingly recognized predictor of a wide range of substantial health outcomes, including cardiovascular disease risk factors, morbidity, and all-cause mortality.[10-12,68] Indeed, unequivocal evidence suggests that CRF is a stronger predictor of mortality than established risk factors such as obesity, smoking, hypertension, high cholesterol, and type 2 diabetes.[13-17] According to epidemiological research, an increased physical fitness could in effect even counterbalance the obesity-related risks for type 2 diabetes, cardiovascular disease and mortality.[14]

Considerable strengths of the current study include the balance in the efficacy-effectiveness continuum achieved by our trial, with a satisfactory internal validity being accompanied by a high degree of generalizability; the study design, pioneeringly including an interdisciplinary weight loss and lifestyle intervention readily adaptable to real-world practice settings; and the use of a full-night in-laboratory polysomnography, the gold-standard objective measure of sleep and OSA parameters. Nevertheless, a study limitation is the subjective assessment of physical fitness through IFIS which, although previously validated, is a self-reported questionnaire. The sole inclusion in our sample of men with overweight/obesity and CPAP-treated moderate-to-severe may also certainly limit the generalizability of results to different populations.

Conclusion

Overall, this trial involving overweight/obese participants with CPAP-treated moderate-to-severe OSA demonstrates that an eight-week interdisciplinary weight loss and lifestyle intervention resulted in significant and sustainable improvements in CRF and self-reported physical fitness. Increased CRF and self-reported physical fitness were closely related to improvements in OSA severity and sleep outcomes, body weight and composition, and neck, chest, and waist circumferences. Future research should further examine longer-term adherence to the acquired lifestyle habits and, in turn, the maintenance of increased CRF and physical fitness levels. Meanwhile, given the high prevalence of OSA, the close association of this condition with reduced CRF and physical fitness, and the widening range of adverse consequences of both OSA and physical fitness impairment, a behavioral weight loss, and lifestyle change approach should be considered an effective strategy to address OSA and related comorbidities.

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Supplementary Material

Supplementary Table S1. Physical fitness outcomes (per-protocol approach)

	Control (n=35)		Intervention (n=40)		Difference between groups, mean (95% CI)[a]
	Mean (95% CI)[a]	Change from baseline, mean (95% CI)	Mean (95% CI)[a]	Change from baseline, mean (95% CI)	
2-km walking test, min					
At baseline	22.0 (21.0 to 22.9)		22.1 (21.2 to 23.0)		
At 8 weeks	22.3 (21.4 to 23.2)	0.3 (-0.2 to 0.9)	20.7 (19.8 to 21.5)	-1.4 (-1.9 to -0.9)	-1.7 (-2.4 to -1.1)[d]
At 6 months	22.4 (21.4 to 23.3)	0.4 (-0.2 to 1.0)	20.0 (19.1 to 20.9)	-2.2 (-2.6 to -1.5)	-2.5 (-3.2 to -1.8)[d]
International Fitness Scale, total score[e]					
At baseline	13.0 (11.8 to 14.2)		13.7 (12.6 to 14.8)		
At 8 weeks	13.2 (12.0 to 14.4)	0.2 (-0.7 to 1.2)	16.2 (15.1 to 17.3)	2.5 (1.6 to 3.4)	2.3 (1.2 to 3.4)[d]
At 6 months	13.1 (11.9 to 14.4)	0.1 (-0.9 to 1.2)	16.7 (15.6 to 17.9)	3.0 (2.1 to 4.0)	2.9 (1.7 to 4.1)[d]
International Fitness Scale, overall fitness					
At baseline	2.7 (2.4 to 3.0)		2.8 (2.5 to 3.1)		
At 8 weeks	2.9 (2.6 to 3.2)	0.3 (-0.03 to 0.6)	3.5 (3.2 to 3.8)	0.7 (0.4 to 1.0)	0.4 (0.1 to 0.7)[b]
At 6 months	2.8 (2.5 to 3.2)	0.2 (-0.1 to 0.5)	3.6 (3.3 to 3.9)	0.8 (0.5 to 1.1)	0.6 (0.3 to 1.0)[d]
International Fitness Scale, cardiorespiratory fitness					
At baseline	2.2 (1.9 to 2.5)		2.4 (2.1 to 2.7)		
At 8 weeks	2.2 (1.9 to 2.6)	0.02 (-0.3 to 0.4)	3.1 (2.8 to 3.4)	0.7 (0.4 to 1.0)	0.7 (0.3 to 1.1)[d]
At 6 months	2.3 (2.0 to 2.7)	0.1 (-0.2 to 0.5)	3.2 (2.9 to 3.5)	0.8 (0.5 to 1.2)	0.7 (0.3 to 1.1)[c]
International Fitness Scale, muscular fitness					
At baseline	3.0 (2.8 to 3.3)		3.2 (2.9 to 3.4)		
At 8 weeks	2.9 (2.7 to 3.2)	-0.1 (-0.4 to 0.2)	3.5 (3.2 to 3.7)	0.3 (0.1 to 0.6)	0.4 (0.1 to 0.7)[b]
At 6 months	2.9 (2.6 to 3.2)	-0.1 (-0.5 to 0.2)	3.7 (3.4 to 4.0)	0.5 (0.3 to 0.8)	0.7 (0.3 to 1.0)[d]
International Fitness Scale, speed-agility					
At baseline	2.6 (2.3 to 2.9)		2.8 (2.6 to 3.1)		
At 8 weeks	2.6 (2.3 to 2.9)	-0.00 (-0.3 to 0.3)	3.3 (3.0 to 3.5)	0.4 (0.1 to 0.7)	0.4 (0.1 to 0.8)[b]
At 6 months	2.6 (2.3 to 2.8)	-0.05 (-0.4 to 0.3)	3.3 (3.0 to 3.5)	0.5 (0.1 to 0.8)	0.5 (0.1 to 0.9)[b]
International Fitness Scale, flexibility					
At baseline	2.5 (2.2 to 2.8)		2.5 (2.2 to 2.8)		
At 8 weeks	2.5 (2.2 to 2.8)	0.03(-0.3 to 0.4)	2.9 (2.6 to 3.2)	0.4 (0.05 to 0.7)	0.3 (-0.04 to 0.7)
At 6 months	2.6 (2.3 to 2.9)	0.07 (-0.3 to 0.4)	3.0 (2.7 to 3.3)	0.4 (0.1 to 0.8)	0.4 (-0.01 to 0.8)

Abbreviations: CI, confidence interval.

[a] Using the group × visit interaction term from a linear mixed-effects model including study group, time (baseline, 8 weeks and 6 months), and study group × time as fixed effects and participant as random effects.

[b] $P < 0.05$ from the time × study group interactions.

[c] $P < 0.01$ from the time × study group interactions.

[d] $P < 0.001$ from the time × study group interactions.

[e] The International Fitness Scale assesses physical fitness (range, 5-25; higher scores indicate greater physical fitness).[31-34]

Supplementary Table S2. Fitness Outcomes (Change from 8 weeks to 6 months)

	Control				Intervention			
	N	8 weeks Mean (95% CI)	6 months Mean (95% CI)	Mean change (95% CI)[a]	N	8 weeks Mean (95% CI)	6 months Mean (95% CI)	Mean change (95% CI)[a]
Intention-to-treat approach								
2-km walking test								
Total time, min	49	22.6 (21.7 to 23.5)	22.7 (21.8 to 23.6)	0.1 (-0.5 to 0.7)	40	20.7 (19.7 to 21.6)	20.0 (19.0 to 21.0)	-0.7 (-1.2 to -0.1)[b]
International Fitness Scale[c]								
Total score	49	13.1 (12.0 to 14.2)	12.9 (11.8 to 14.1)	-0.2 (-1.2 to 0.9)	40	16.2 (15.1 to 17.3)	16.7 (15.6 to 17.9)	0.5 (-0.4 to 1.5)
Overall fitness	49	2.9 (2.6 to 3.2)	2.8 (2.5 to 3.1)	-0.1 (-0.4 to 0.2)	40	3.5 (3.2 to 3.8)	3.6 (3.3 to 3.9)	0.1 (-0.2 to 0.4)
Cardiorespiratory fitness	49	2.2 (1.9 to 2.5)	2.3 (2.0 to 2.6)	0.1 (-0.3 to 0.5)	40	3.1 (2.8 to 3.4)	3.2 (2.9 to 3.5)	0.1 (-0.2 to 0.4)
Muscular fitness	49	2.9 (2.7 to 3.2)	2.9 (2.6 to 3.1)	-0.1 (-0.4 to 0.2)	40	3.5 (3.2 to 3.7)	3.7 (3.4 to 4.0)	0.2 (-0.1 to 0.5)
Speed-agility	49	2.6 (2.3 to 2.8)	2.5 (2.2 to 2.8)	-0.1 (-0.4 to 0.3)	40	3.3 (3.0 to 3.5)	3.3 (3.0 to 3.5)	0.02 (-0.3 to 0.3)
Flexibility	49	2.5 (2.2 to 2.8)	2.5 (2.2 to 2.8)	0.02 (-0.3 to 0.4)	40	2.9 (2.6 to 3.2)	3.0 (2.7 to 3.3)	0.1 (-0.2 to 0.4)
Per-protocol approach								
2-km walking test								
Total time, min	35	22.3 (21.4 to 23.2)	22.4 (21.4 to 23.3)	0.1 (-0.6 to 0.7)	40	20.7 (19.8 to 21.5)	20.0 (19.1 to 20.9)	-0.7 (-1.2 to -0.1)[b]
International Fitness Scale[c]								
Total score	35	13.2 (12.0 to 14.4)	13.1 (11.9 to 14.4)	-0.1 (-1.2 to 1.0)	40	16.2 (15.1 to 17.3)	16.7 (15.6 to 17.9)	0.5 (-0.4 to 1.5)
Overall fitness	35	2.9 (2.6 to 3.2)	2.8 (2.5 to 3.2)	-0.1 (-0.4 to 0.3)	40	3.5 (3.2 to 3.8)	3.6 (3.3 to 3.9)	0.1 (-0.2 to 0.4)
Cardiorespiratory fitness	35	2.2 (1.9 to 2.6)	2.3 (2.0 to 2.7)	0.1 (-0.3 to 0.5)	40	3.1 (2.8 to 3.4)	3.2 (2.9 to 3.5)	0.1 (-0.2 to 0.4)
Muscular fitness	35	2.9 (2.7 to 3.2)	2.9 (2.6 to 3.2)	-0.1 (-0.4 to 0.3)	40	3.5 (3.2 to 3.7)	3.7 (3.4 to 4.0)	0.2 (-0.1 to 0.5)
Speed-agility	35	2.6 (2.3 to 2.9)	2.6 (2.3 to 2.8)	-0.05 (-0.4 to 0.3)	40	3.3 (3.0 to 3.5)	3.3 (3.0 to 3.5)	0.03 (-0.3 to 0.3)
Flexibility	35	2.5 (2.2 to 2.8)	2.6 (2.3 to 2.9)	0.04 (-0.3 to 0.4)	40	2.9 (2.6 to 3.2)	3.0 (2.7 to 3.3)	0.1 (-0.2 to 0.4)

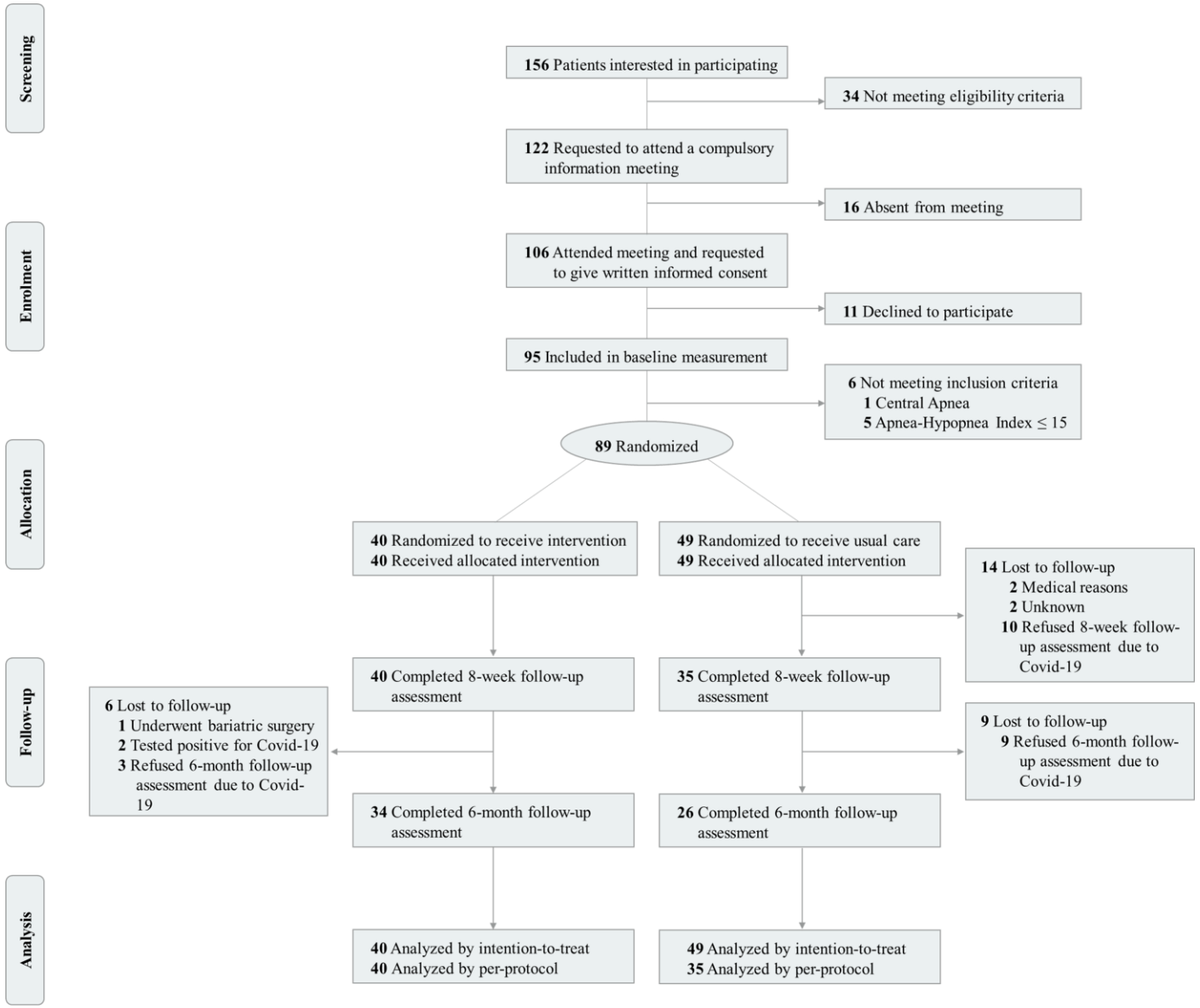
Abbreviations: CI, confidence interval.

[a] Using post-hoc test (pairwise comparison) in a linear mixed-effects model including study group, time (baseline, 8 weeks and 6 months), and study group × time as fixed effects and participant as random effects.

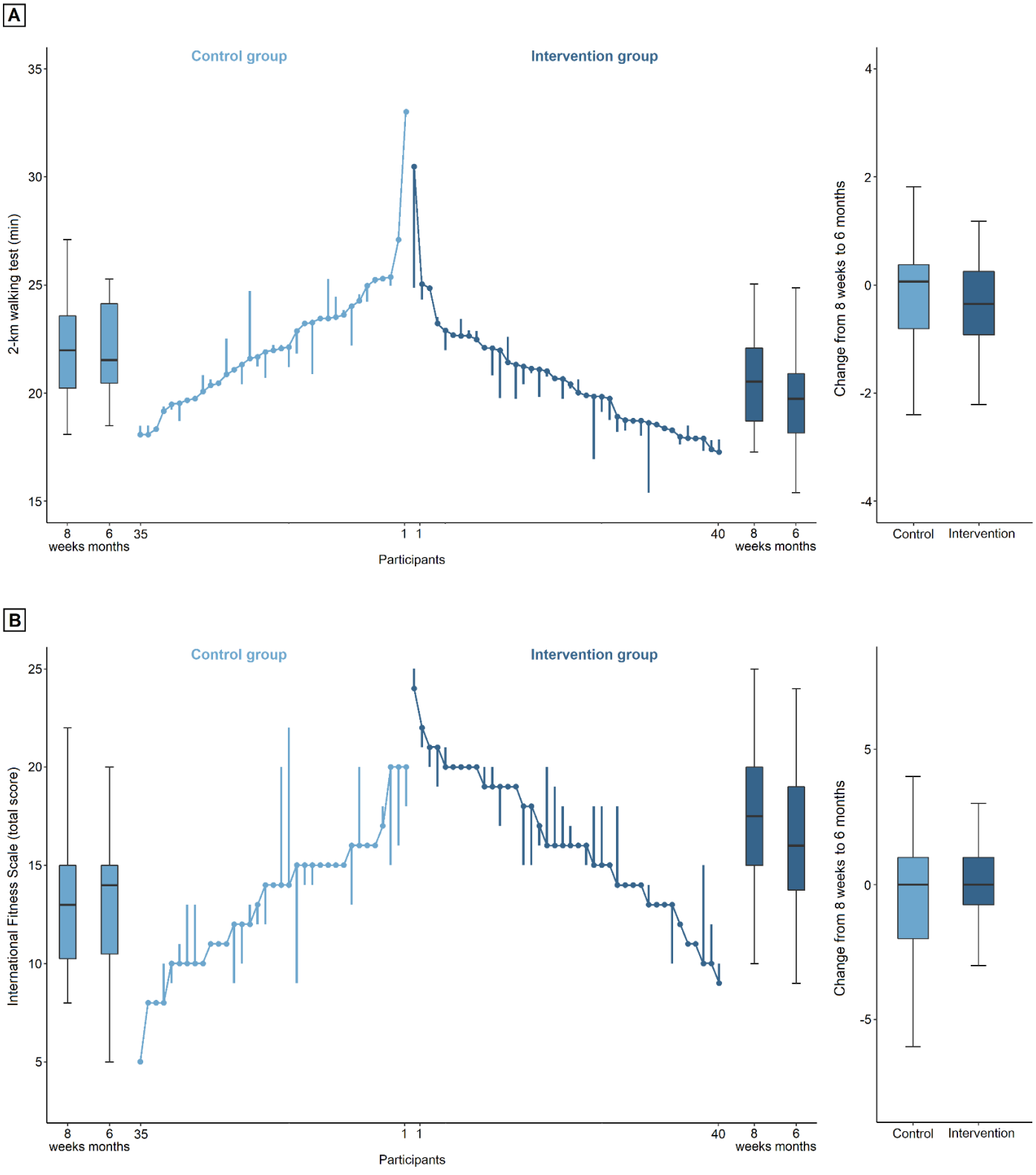
[b] $P < 0.05$.

[c] The International Fitness Scale assesses physical fitness and its main components (range, 5-20; higher scores indicate greater functioning).[56,57]

Supplementary Figure S1. Flow-chart diagram of the INTERAPNEA randomized clinical trial



Supplementary Figure S2. Physical fitness outcomes (Change from 8 weeks to 6 months)



The ends of the boxes in the boxplots are located at the first and third quartiles, with the black line in the middle illustrating the median. Whiskers extend to the upper and lower adjacent values, the location of the furthest point within a distance of 1.5 interquartile ranges from the first and third quartiles. The parallel line plot contains 1 vertical line for each patient which extends from their 8-week value to their 6-month value. Descending lines indicate an improvement in the outcome (A). Ascending lines indicate an improvement in the outcome (B). Eight-week values are placed in ascending order for the control group and descending order for the intervention group. A, The 2-km walking test is a widely used and validated measure of cardiorespiratory fitness.[53-55] B, The International Fitness Scale assesses physical fitness and its main components (range, 5-25; higher scores indicate greater levels of physical fitness).[56,57]

CHAPTER 6

Effect of an interdisciplinary weight loss and lifestyle intervention on dietary behavior in obstructive sleep apnea: The INTERAPNEA trial (**Study 6**)

ABSTRACT

The objective of this study was to investigate the effects of an eight-week interdisciplinary weight loss and lifestyle intervention on dietary behavior in adults with overweight/obesity and moderate-to-severe obstructive sleep apnea (OSA) treated with continuous positive airway pressure (CPAP). This ancillary study was based on data from INTERAPNEA; a randomized clinical trial conducted from April 2019 to April 2020. Men aged 18-65 years with moderate-to-severe OSA and a body mass index ≥25 kg/m^2 were randomly assigned to a usual-care group (CPAP) or an eight-week interdisciplinary weight loss and lifestyle intervention combined with usual-care. Of the 89 participants who underwent randomization, 75 completed the intervention endpoint assessment, 89 participants being therefore included in the intention-to-treat analyses, and 75 in the per-protocol approach. Dietary behavior was assessed through the Food Behavior Checklist (FBC) and the Mediterranean Diet Adherence Screener (MEDAS). As compared with usual-care, the intervention group had greater improvements at intervention endpoint in dietary behavior as measured by FBC total score (20% increase in FBC total score, mean between-group difference, 8.7; 95% confidence interval, 5.7 to 11.7), and MEDAS total score (33% increase in MEDAS total score, mean between-group difference, 2.1; 95% CI 1.3 to 2.9). At 6 months after intervention, the intervention group also had greater improvements in both FBC total score (15% increase) and MEDAS total score (25% increase), with mean between-group differences of 7.7 (CI 95%, 4.4 to 10.9) and 1.7 (CI 95%, 0.9 to 2.6), respectively. An eight-week interdisciplinary weight loss and lifestyle intervention resulted in meaningful and sustainable improvements in dietary behavior, including adherence to the Mediterranean diet, in men with overweight/obesity and CPAP-treated moderate-to-severe OSA.

Introduction

Obstructive sleep apnea (OSA), characterized by episodic upper-airway obstructions during sleep, affects nearly a billion adults aged 30–69 years globally[1] and is strongly associated with neurocognitive impairment, diminished quality of life and an increased likelihood of hypertension, cancer, and metabolic, cardiovascular, and cerebrovascular diseases.[2-10] Although continuous positive airway pressure (CPAP) is the first-line treatment for OSA — a device serving to reduce upper-airway collapse during sleep[11] — CPAP adherence rates are suboptimal,[12] and long-term benefits beyond reduction of apnea-hypopnea events per hour of sleep (i.e., apnea-hypopnea index; AHI) remain uncertain.[13-15]

Given the complex and reciprocal interaction between OSA and obesity,[16] weight loss and lifestyle interventions including dietary change and exercise are strongly recommended[17-18] and appear to significantly improve OSA severity, cardiometabolic comorbidities and, thus, health-related quality of life.[19-24] Yet, most previous studies in this regard only included calorie-restricted diets,[25] which may not be the most-efficient approach for long-lasting and sustainable dietary behavior change.[26,27] Instead, alternative approaches such as Mediterranean diets and other dietary strategies focusing on nutritional education and behavior change have been proposed as potential strategies of choice for OSA management.[26-28] Still, although effective at improving dietary behaviors in persons with and without cardiovascular risk factors and other conditions,[29-33] there is no evidence to date on the effects of this approach on the unhealthy dietary behaviors and poor quality of diet commonly found in patients with OSA.[34-36]

The Interdisciplinary Weight Loss and Lifestyle Intervention (INTERAPNEA) trial is an open-label, parallel-group, randomized controlled trial aimed at testing the efficacy of an eight-week weight loss and lifestyle intervention for the improvement of OSA severity, body weight and composition, and cardiometabolic comorbidities in adults with OSA and overweight/obesity.[37] This study included two arms: a usual-care/control group, which received CPAP as the standard care of OSA; and a weight loss and lifestyle intervention group, which received an eight-week interdisciplinary intervention including nutritional behavior change, aerobic exercise, sleep hygiene, and alcohol and tobacco cessation, combined with usual-care. Changes in OSA severity and body weight at 6 months after intervention indicated that participants in the intervention group reduced a significantly greater amount of their initial AHI and body weight (57% and 7%, respectively) than those in the usual-care/control group (2% and 1%).[20] INTERAPNEA provides an opportunity to examine the effects of a behavior-induced weight loss intervention on dietary behavior and diet quality in adults with moderate-to-severe OSA who received, among other intervention components, nutritional education and behavior change. The aim of this study was therefore to examine the effects of an eight-week interdisciplinary weight loss and lifestyle intervention, as compared with usual-care (i.e., CPAP), on dietary behavior in adults with moderate-to-severe OSA and overweight/obesity. Additionally, we pursued to investigate the associations of changes in dietary behavior and adherence to the Mediterranean diet with changes in OSA severity and body weight and composition outcomes. We

hypothesized that the intervention group would have greater sustainable improvements in these dietary outcomes than the control group. Similarly, we expected that changes in dietary behavior and adherence to the Mediterranean diet would be significantly associated with changes in OSA severity and body weight and composition outcomes.

Methods

Study design

The present work is an ancillary study of the INTERAPNEA randomized clinical trial,[37] conducted from April 2019 to October 2020. Detailed information on the study rationale, design and methodology has previously been published[37] and is also provided in the Supplementary Appendix Study Protocol. This trial is in compliance with the Consolidated Standards of Reporting Trials (CONSORT); was approved by the Clinical Research Ethics Committees of the University of Granada (Granada, Spain), Virgen de las Nieves University Hospital (Granada, Spain), and Junta de Andalucía (Spain) (0770-N-19); and is registered in the National Institutes of Health database (ClinicalTrials.gov NCT03851653).

Participants

Participants were recruited from the sleep-disordered breathing unit of the collaborating hospital (Virgen de las Nieves University Hospital). Potential participants were men aged 18-65 years with CPAP-treated moderate-to-severe OSA (i.e., AHI equal or greater than 15 events per hour of sleep), and a body mass index (BMI) equal or greater than 25 kg/m^2. Exclusion criteria included present participation in a weight loss program, presence of any psychological/psychiatric disorder, and/or any other primary sleep disorder which were not secondary to OSA. Upon providing written informed consent, potential participants were clinically/physically examined to ensure feasibility of inclusion in the study. Successively, screening/baseline measurements including an overnight fasting blood test; complete full-night polysomnography; a set of questionnaires measuring subjective variables; and measurements of anthropometric and body composition parameters were conducted on each participant. The trial was conducted in three consecutive sets of 30 participants. A total of 89 adults were finally randomly assigned to either the intervention group (40 participants) or the usual-care group (49 participants) by means of a computer-generated simple (unrestricted) randomization (Supplementary Figure S1). The 8-week assessment (intervention endpoint) was completed by 75 participants; 15.7% (14 participants) being lost to follow-up, mainly due to the Covid-19 pandemic (10 participants).

Interventions

The eight-week interdisciplinary weight loss and lifestyle intervention was precisely designed following the latest clinical practice guidelines for OSA[17,18] and obesity management.[38,39] It lasted eight weeks and was composed of five components: nutritional behavior change; moderate-intensity aerobic exercise; smoking cessation; alcohol avoidance; and sleep hygiene. Participants received 60-90 min sessions weekly per component, each session being led by qualified personnel in the field (human nutrition and dietetics, physical activity and sport sciences, psychology and sleep medicine). Briefly, the cornerstone of this interdisciplinary intervention was the use of the Transtheoretical Model of Health Behavior Change,[40]

a well-recognized biopsychosocial model based on integrating key strategies, processes and principles of behavior change theories into a comprehensive interventional approach for the achievement of sustainable health-related behaviors. Consciousness raising, self-reevaluation, stimulus control, goal-setting, self-monitoring, and self-efficacy were some of the behavioral change processes and strategies used. Details of the content of the intervention is provided in the Supplementary Appendix Study Protocol.

The usual-care/control group received CPAP therapy together with a single session of 30 min addressing general advice on weight loss and lifestyle change. Nevertheless, the weight loss and lifestyle intervention was offered to all participants from this group at trial completion.

Assessments

Assessments at baseline, intervention endpoint and 6 months after intervention were completed over a one to two-week period including a fasting blood test, a full-night ambulatory polysomnography, a set of questionnaires, and a full-body dual energy X-ray absorptiometry (DXA) scanner. All participants were instructed to refrain from using CPAP for seven days before each study assessment. A detailed description of the INTERAPNEA trial assessments has previously been published[37] and is precisely provided in the Supplementary Appendix Study Protocol.

The primary outcomes of this study were changes from baseline to intervention endpoint and 6 months after intervention in self-reported dietary behavior as measured by the Food Behavior Checklist (FBC) questionnaire,[41] and adherence to the Mediterranean diet, which was assessed through the Mediterranean Diet Adherence Screener (MEDAS).[42]

The FBC is composed by 22 items and seven sub-scales related to fruit and vegetables consumption (nine items), milk/dairy consumption (two items), food security (one item), diet quality (four items), fast food consumption (three items), sweetened beverages consumption (two items), and meat consumption (one item). Scores range from 23 to 85; higher scores indicating healthier dietary behavior.

Similarly, the MEDAS is a widely-used 14-item screener to assess adherence to the Mediterranean dietary pattern through questions related to food intake habits and food consumption frequency. Total scores range from 1 to 14; higher scores indicating greater compliance with the Mediterranean diet. Scores equal or greater than 10 indicate high adherence to the Mediterranean diet.

Objective sleep outcomes included in this study were AHI, defined as the number of apnea and hypopnea episodes per hour of sleep; oxygen desaturation index, which is the number of oxygen desaturation ≥3% per hour of sleep; and sleep efficiency (%), calculated as the ratio of total sleep time to total time in bed. These sleep outcomes were measured through a full-night in-laboratory polysomnography.

Body weight and composition outcomes included body weight (kg), which was measured with a calibrated scale and stadiometer (model 799, Electronic Column Scale, Hamburg, Germany); neck, chest and waist circumferences (cm); and

fat mass (kg) and visceral adipose tissue (g), which were measured through a full-body DXA scanner (Discovery Wi, Hologic, Inc., Bedford, MA, USA).

Statistical analysis

Linear mixed-effects models[43] were used in order to estimate intervention effects on the study outcomes. These models included group, assessment time, and their interaction terms; estimations being conducted through the restricted maximum-likelihood method and an unstructured covariance matrix adjusting for within-participant clustering resulting from the repeated-measures design. All values presented in the tables are model-based estimates, this model assuming that missing values were missing-at-random. Nevertheless, a logistic model predicting attrition propensity based on baseline values of set of participants, trial group, OSA severity, age and BMI was used. Only set of participants predicted attrition due to the occurrence of the Covid-19 pandemic at the trial endpoint, which was the intervention endpoint assessment of the third set of participants.

Analyses and estimations were performed with both an intention-to-treat approach (including all participants as originally allocated after randomization) and a per-protocol approach restricted to participants with a CPAP usage equal or greater than four hours per night on 70% of nights and, regarding the intervention group, at least 80% of attendance rate at intervention sessions.

In addition, association of changes in dietary behavior over time with changes in sleep and body weight and composition outcomes were examined by repeated measures correlation analysis — a statistical technique used to determine the within-individual association for paired measures assessed on two or more occasions for multiple individuals.[44] All analyses were performed using R version 4.0.3 (R Project for Statistical Computing).

Results

Participants' characteristics

Baseline characteristics of the study participants by group are presented in Table 1. The majority of participants enrolled were middle-aged men (mean ± SD age, 54.1 ± 8.0 years), with severe OSA (mean ± SD AHI, 41.3 ± 22.2 events/hr) and obesity (mean ± SD BMI, 34.4±5.4 kg/m^2). There were no significant between-group differences in any of the baseline values.

Changes in dietary behavior

There was a significantly greater improvement in dietary behavior in the intervention group than in the control group, with a mean between-group difference in FBC total score of 8.7 (95% CI, -5.7 to -11.7; P < 0.001) and 7.7 (95% CI, -4.4 to 10.9; P < 0.001) from baseline to intervention endpoint and 6 months after intervention, respectively (Table 2 and Figure 1). Correspondingly, participants in the intervention group also significantly reduced consumption of sweetened beverages (P < 0.05), increased consumption of fruits and vegetables (P < 0.001) and, thus, enhanced diet quality (P < 0.001) (FBC subscales). Similar results were obtained using the per-protocol approach (Supplementary Table S1). According to

Table 1. Baseline characteristics of the study participants

Characteristics[b]	No. (%)[a]	
	Control (n = 49)	Intervention (n = 40)
Age, mean (SD), y	55.3 (8.5)	52.6 (7.1)
Educational level		
Primary Education	13 (26.5)	10 (25.0)
Secondary Education	10 (20.4)	6 (15.0)
Vocational Education	13 (26.5)	17 (42.5)
Higher Education	13 (26.5)	7 (17.5)
Marital status		
Single	7 (14.3)	2 (5.0)
Married	34 (69.4)	34 (85.0)
Divorced	8 (16.3)	4 (10.0)
Occupational status		
Employed	27 (55.1)	21 (52.5)
Self-employed	8 (16.3)	12 (30.0)
Unemployed	4 (8.2)	5 (12.5)
Retired	10 (20.4)	2 (5.0)
Medical Conditions[c]		
Hypertension	33 (67.4)	27 (67.5)
Diabetes Mellitus II	12 (24.5)	10 (25.0)
Cardiovascular disease	9 (18.4)	7 (17.5)
Other medical conditions	29 (59.2)	26 (65.0)
Medication[c]		
Antihypertensive	31 (63.3)	24 (60.0)
Statins	15 (30.6)	7 (17.5)
Oral antidiabetic	5 (10.2)	2 (5.0)
Insulin	3 (6.1)	1 (2.5)
Beta-blockers	7 (14.3)	5 (12.5)
Polymedication[d]	14 (28.6)	6 (15.0)
Body mass index, mean (SD), kg/m^2	33.9 (4.8)	35.0 (6.0)
Body weight, mean (SD), kg	99.6 (18.3)	103.3 (17.5)
Fat mass, mean (SD), kg	33.8 (9.0)	34.9 (10.6)
Visceral adipose tissue, mean (SD), g	1049.2 (260.3)	1017.3 (285.2)
Neck circumference, mean (SD), cm	45.5 (3.9)	45.0 (3.8)
Chest circumference, mean (SD), cm	117.4 (9.9)	118.0 (10.3)
Waist circumference, mean (SD), cm	117.9 (12.2)	119.0 (12.4)
Apnea-hypopnea index, mean (SD), events/hr	41.1 (21.3)	41.6 (23.5)
Obstructive sleep apnea severity		
Moderate	20 (40.8)	15 (37.5)
Severe	29 (59.2)	25 (62.5)
Oxygen desaturation index, mean (SD), events/hr	45.4 (21.1)	45.4 (27.7)
Sleep efficiency, mean (SD), %	85.6 (8.1)	86.0 (9.1)

[a] Results are presented as mean (standard deviation) for normally distributed numerical variables, and as absolute number (relative frequency) for categorical variables.
[b] No significant between-group differences were observed in any of the baseline characteristics.
[c] Participants could have more than one condition or medication.
[d] Defined as the use of five or more medications.

Table 2. Dietary behavior outcomes

Outcomes	Control (n=49)		Intervention (n=40)		Difference between groups, mean (95% CI)[a]
	Mean (95% CI)	Change from baseline, mean (95% CI)	Mean (95% CI)	Change from baseline, mean (95% CI)	
Food Behavior Checklist, total score[d]					
At baseline	59.1 (56.8 to 61.4)		59.5 (56.9 to 62.0)		
At 8 weeks	62.4 (59.9 to 64.9)	3.3 (0.6 to 5.9)	71.5 (68.9 to 74.0)	12.0 (9.5 to 14.5)	8.7 (5.7 to 11.7)[c]
At 6 months	60.6 (57.9 to 63.4)	1.5 (-1.4 to 4.4)	68.6 (66.0 to 71.3)	9.2 (6.5 to 11.9)	7.7 (4.4 to 10.9)[c]
Fruit and vegetables consumption score					
At baseline	21.5 (20.0 to 22.9)		22.6 (21.0 to 24.2)		
At 8 weeks	23.1 (21.5 to 24.7)	1.6 (-0.2 to 3.4)	29.5 (27.9 to 31.1)	6.9 (5.2 to 8.6)	5.2 (3.2 to 7.3)[c]
At 6 months	22.4 (20.7 to 24.2)	0.9 (-1.0 to 2.9)	27.5 (25.8 to 29.1)	4.9 (3.0 to 6.7)	3.9 (1.7 to 6.1)[c]
Milk/dairy consumption score					
At baseline	6.0 (5.5 to 6.4)		5.8 (5.3 to 6.3)		
At 8 weeks	5.6 (5.1 to 6.2)	-0.3 (-0.9 to 0.2)	5.7 (5.2 to 6.2)	-0.1 (-0.6 to 0.4)	0.2 (-0.4 to 0.8)
At 6 months	5.9 (5.3 to 6.4)	-0.1 (-0.7 to 0.5)	5.4 (4.9 to 6.0)	-0.4 (-0.9 to 0.2)	-0.3 (-1.0 to 0.4)
Food security score					
At baseline	3.1 (2.9 to 3.4)		3.1 (2.8 to 3.3)		
At 8 weeks	3.3 (3.0 to 3.5)	0.1 (-0.2 to 0.4)	3.1 (2.8 to 3.4)	0.1 (-0.2 to 0.4)	-0.1 (-0.4 to 0.3)
At 6 months	3.2 (3.0 to 3.5)	0.1 (-0.2 to 0.4)	3.2 (2.9 to 3.5)	0.2 (-0.2 to 0.5)	0.1 (-0.3 to 0.5)
Diet quality score					
At baseline	9.9 (9.3 to 10.5)		9.7 (9.0 to 10.4)		
At 8 weeks	10.5 (9.9 to 11.2)	0.7 (-0.1 to 1.4)	12.2 (11.5 to 12.8)	2.5 (1.8 to 3.2)	1.8 (1.0 to 2.6)[c]
At 6 months	10.3 (9.5 to 11.0)	0.4 (-0.4 to 1.2)	11.8 (11.1 to 12.5)	2.1 (1.4 to 2.9)	1.7 (0.8 to 2.6)[c]
Fast food consumption score					
At baseline	7.4 (7.0 to 7.9)		7.2 (6.7 to 7.7)		
At 8 weeks	8.2 (7.6 to 8.8)	0.8 (-0.1 to 1.6)	8.6 (8.1 to 9.1)	1.4 (0.6 to 2.2)	0.6 (-0.3 to 1.6)
At 6 months	7.7 (7.1 to 8.4)	0.3 (-0.6 to 1.2)	8.3 (7.8 to 8.9)	1.1 (0.3 to 2.0)	0.8 (-0.2 to 1.9)
Sweetened beverages consumption score					
At baseline	6.7 (6.5 to 7.0)		6.6 (6.3 to 6.9)		
At 8 weeks	7.1 (6.8 to 7.4)	0.3 (-0.1 to 0.7)	7.5 (7.2 to 7.8)	0.9 (0.5 to 1.3)	0.5 (0.1to 1.0)[b]
At 6 months	6.9 (6.5 to 7.2)	0.1 (-0.3 to 0.6)	7.4 (7.1 to 7.7)	0.7 (0.3 to 1.1)	0.6 (0.1to 1.1)[b]
Meat consumption score					
At baseline	1.9 (1.6 to 2.1)		1.9 (1.6 to 2.2)		
At 8 weeks	2.1 (1.8 to 2.5)	0.3 (-0.2 to 0.8)	2.3 (2.0 to 2.6)	0.4 (-0.1 to 0.9)	0.1 (-0.5 to 0.7)
At 6 months	2.0 (1.7 to 2.4)	0.2 (-0.4 to 0.7)	2.5 (2.1 to 2.8)	0.6 (0.1 to 1.1)	0.4 (-0.2 to 1.0)
Mediterranean Diet Adherence Screener, total score[e]					
At baseline	8.2 (7.7 to 8.7)		8.1 (7.6 to 8.6)		
At 8 weeks	8.8 (8.2 to 9.4)	0.6 (-0.1 to 1.3)	10.7 (10.2 to 11.3)	2.7 (1.9 to 3.3)	2.1 (1.3 to 2.9)[c]
At 6 months	8.5 (7.9 to 9.1)	0.3 (-0.5 to 1.1)	10.1 (9.6 to 10.7)	2.0 (1.3 to 2.8)	1.7 (0.9 to 2.6)[c]

Abbreviations: CI, confidence interval.

[a] Using the group × visit interaction term from a linear mixed-effects model including study group, time (baseline, 8 weeks and 6 months), and study group × time as fixed effects and participant as random effects.

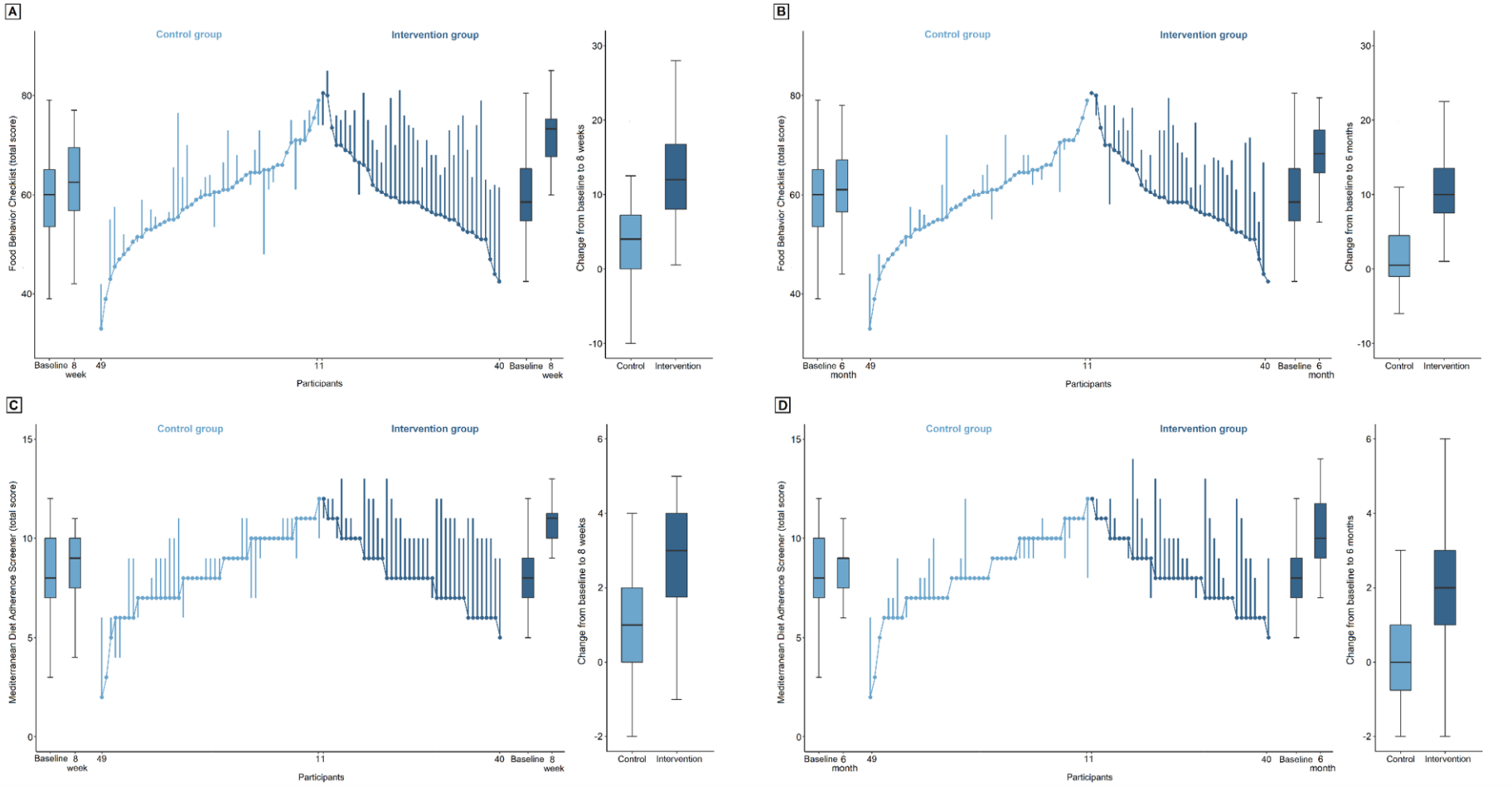
[b] $P < 0.05$ from the time × study group interactions.

[c] $P < 0.001$ from the time × study group interactions.

[d] The Food Behavior Checklist assesses dietary behavior (range, 23-85; higher scores indicate healthier dietary behavior).[41]

[e] The Mediterranean Diet Adherence Screener assesses adherence to the Mediterranean diet (range, 0-14; higher scores indicate greater adherence; scores ≥10 indicate high adherence to the Mediterranean diet).[42]

Figure 1. Dietary behavior outcomes



The ends of the boxes in the boxplots are located at the first and third quartiles, with the black line in the middle illustrating the median. Whiskers extend to the upper and lower adjacent values, the location of the furthest point within a distance of 1.5 interquartile ranges from the first and third quartiles. The parallel line plot contains 1 vertical line for each patient which extends from their baseline value to their 8-week value (A, C) or 6-month value (B, D). Ascending lines indicate an improvement in the outcome. Baseline values are placed in ascending order for the control group and descending order for the intervention group. A, B, The Food Behavior Checklist assesses dietary behavior (range, 23-85; higher scores indicate healthier dietary behavior).[41] C, D, The Mediterranean Diet Adherence Screener assesses adherence to the Mediterranean diet (range, 0-14; higher scores indicate greater adherence; scores ≥10 indicate high adherence to the Mediterranean diet).[42]

changes from intervention endpoint to 6 months after intervention, participants in the intervention group preserved improvements in these dietary behavior and diet quality outcomes, although a slight reduction in fruits and vegetables consumption was found (Supplementary Table S2 and Supplementary Figure S2).

Regarding adherence to the Mediterranean diet, participants in the intervention group also had a greater increase in the compliance with the Mediterranean diet as measured by MEDAS at both intervention endpoint and 6 months after intervention, with mean between-group differences of 2.1 (95% CI, 1.3 to 2.9; P<0.001) and 1.7 (95% CI, 0.9 to 2.6; P<0.001), respectively (Table 2 and Figure 1). Similar results were obtained using the per-protocol approach (Supplementary Table S1). Improvements in the adherence to the Mediterranean diet at intervention endpoint were maintained at 6 months after intervention (Supplementary Table S2 and Supplementary Figure S2).

Association of changes in dietary behavior over time with changes in sleep and body weight and composition outcomes

Changes in dietary behavior over time as measured by FBC total score were significantly associated with changes in sleep outcomes; an increase in FBC total score being related with reduced AHI and oxygen desaturation index, and increased sleep efficiency (all P<0.05; Table 3 and Figure 2). With regards to body composition and anthropometric outcomes, changes over time in FBC total score were inversely associated with changes in body weight, fat mass, visceral adipose tissue, and neck, chest, and waist circumferences (all P<0.05; Table 3 and Figures 3 and 4).

Similarly, changes over time in adherence to the Mediterranean diet as measured by MEDAS total score were significantly associated with changes in sleep outcomes; an increase in MEDAS total score being related with reduced AHI and oxygen desaturation index and increased sleep efficiency (all P≤0.01; Table 3 and Figure 2). Increases over time in MEDAS total score were also associated with reductions in body weight, fat mass, visceral adipose tissue, and neck, chest and waist circumferences (all P<0.001; Table 3 and Figures 3 and 4).

Discussion

The present study demonstrates that a novel eight-week interdisciplinary weight loss and lifestyle intervention, incorporating not only a nutritional behavior change component but also increased physical activity, sleep hygiene and alcohol and tobacco avoidance, is effective at significantly improving dietary behavior in adults with CPAP-treated moderate-to-severe OSA and overweight/obesity. According to the results reported herein, the weight loss and lifestyle intervention group had 20% and 15% increases in healthful dietary behavior as measured by FBC at intervention endpoint and 6 months after intervention, respectively. Similarly, participants from this group reported 33% and 25% increases at intervention endpoint and 6 months after intervention, respectively, in adherence to the Mediterranean diet as measured by MEDAS. Furthermore, these improvements in dietary behavior and increases in adherence to the Mediterranean diet over time were closely related to improvements in sleep, body composition and anthropometric outcomes.

Table 3. Repeated measures correlation analyses examining association of changes in dietary behavior over time with changes in sleep and body weight and composition outcomes

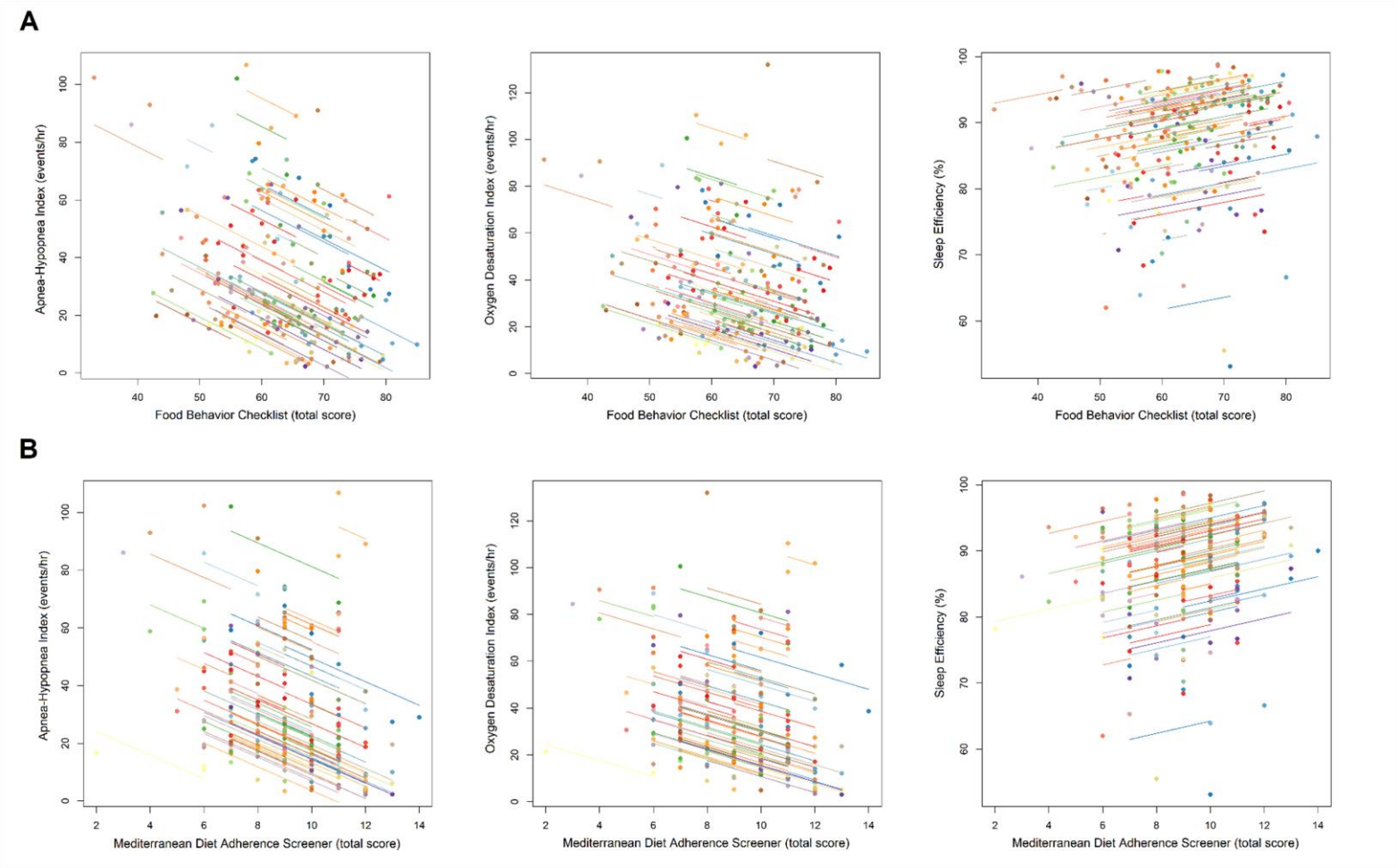
	Food Behavior Checklist, total score[a]			Mediterranean Diet Adherence Screener, total score[b]		
Outcomes	**r**	**95% CI**	**P value**	**r**	**95% CI**	**P value**
Changes at 8 weeks and 6 months after intervention						
Apnea-hypopnea index, events/hr	-0.59	-0.69 to -0.47	< 0.001	-0.54	-0.65 to -0.41	<0.001
Oxygen desaturation index ≥3%, events/hr	-0.43	-0.56 to -0.28	<0.001	-0.43	-0.56 to -0.28	<0.001
Sleep efficiency, %	0.19	0.02 to 0.34	0.03	0.23	0.07 to 0.39	0.01
Body weight, kg	-0.61	-0.71 to -0.49	<0.001	-0.57	-0.67 to -0.44	<0.001
Fat mass, kg	-0.38	-0.51 to -0.22	<0.001	-0.44	-0.56 to -0.29	<0.001
Visceral adipose tissue, g	-0.30	-0.44 to -0.14	<0.001	-0.38	-0.51 to -0.22	<0.001
Neck circumference, cm	-0.58	-0.69 to -0.46	<0.001	-0.53	-0.64 to -0.40	<0.001
Chest circumference, cm	-0.43	-0.56 to -0.28	<0.001	-0.42	-0.55 to -0.27	<0.001
Waist circumference, cm	-0.54	-0.65 to -0.41	<0.001	-0.54	-0.65 to -0.40	<0.001
Changes from baseline to 8 weeks						
Apnea-hypopnea index, events/hr	-0.67	-0.78 to -0.53	<0.001	-0.63	-0.75 to -0.47	<0.001
Oxygen desaturation index ≥3%, events/hr	-0.47	-0.63 to -0.27	<0.001	-0.47	-0.63 to -0.27	<0.001
Sleep efficiency, %	0.24	0.01 to 0.44	0.04	0.20	-0.03 to 0.41	0.08
Body weight, kg	-0.74	-0.83 to -0.62	<0.001	-0.69	-0.79 to -0.55	<0.001
Fat mass, kg	-0.39	-0.56 to -0.17	<0.001	-0.46	-0.62 to -0.25	<0.001
Visceral adipose tissue, g	-0.30	-0.49 to -0.08	0.01	-0.36	-0.55 to -0.15	0.001
Neck circumference, cm	-0.69	-0.80 to -0.55	<0.001	-0.67	-0.78 to -0.51	<0.001
Chest circumference, cm	-0.52	-0.67 to -0.33	<0.001	-0.52	-0.67 to -0.33	<0.001
Waist circumference, cm	-0.62	-0.74 to -0.46	<0.001	-0.65	-0.76 to -0.49	<0.001
Changes from baseline to 6 months after intervention						
Apnea-hypopnea index, events/hr	-0.71	-0.81 to -0.55	<0.001	-0.58	-0.73 to -0.38	<0.001
Oxygen desaturation index ≥3%, events/hr	-0.66	-0.79 to -0.49	<0.001	-0.53	-0.69 to -0.31	<0.001
Sleep efficiency, %	0.31	0.06 to 0.53	0.01	0.36	0.12 to 0.57	0.004
Body weight, kg	-0.67	-0.79 to -0.51	<0.001	-0.60	-0.74 to -0.41	<0.001
Fat mass, kg	-0.66	-0.78 to -0.49	<0.001	-0.61	-0.75 to -0.42	<0.001
Visceral adipose tissue, g	-0.65	-0.78 to -0.47	<0.001	-0.61	-0.75 to -0.43	<0.001
Neck circumference, cm	-0.63	-0.76 to -0.44	<0.001	-0.54	-0.70 to -0.33	<0.001
Chest circumference, cm	-0.48	-0.65 to -0.26	<0.001	-0.40	-0.59 to -0.16	<0.001
Waist circumference, cm	-0.66	-0.78 to -0.48	<0.001	-0.57	-0.72 to -0.36	<0.001

Abbreviations: CI, confidence interval.

[a] The Food Behavior Checklist assesses dietary behavior (range, 23-85; higher scores indicate healthier dietary behavior).[41]

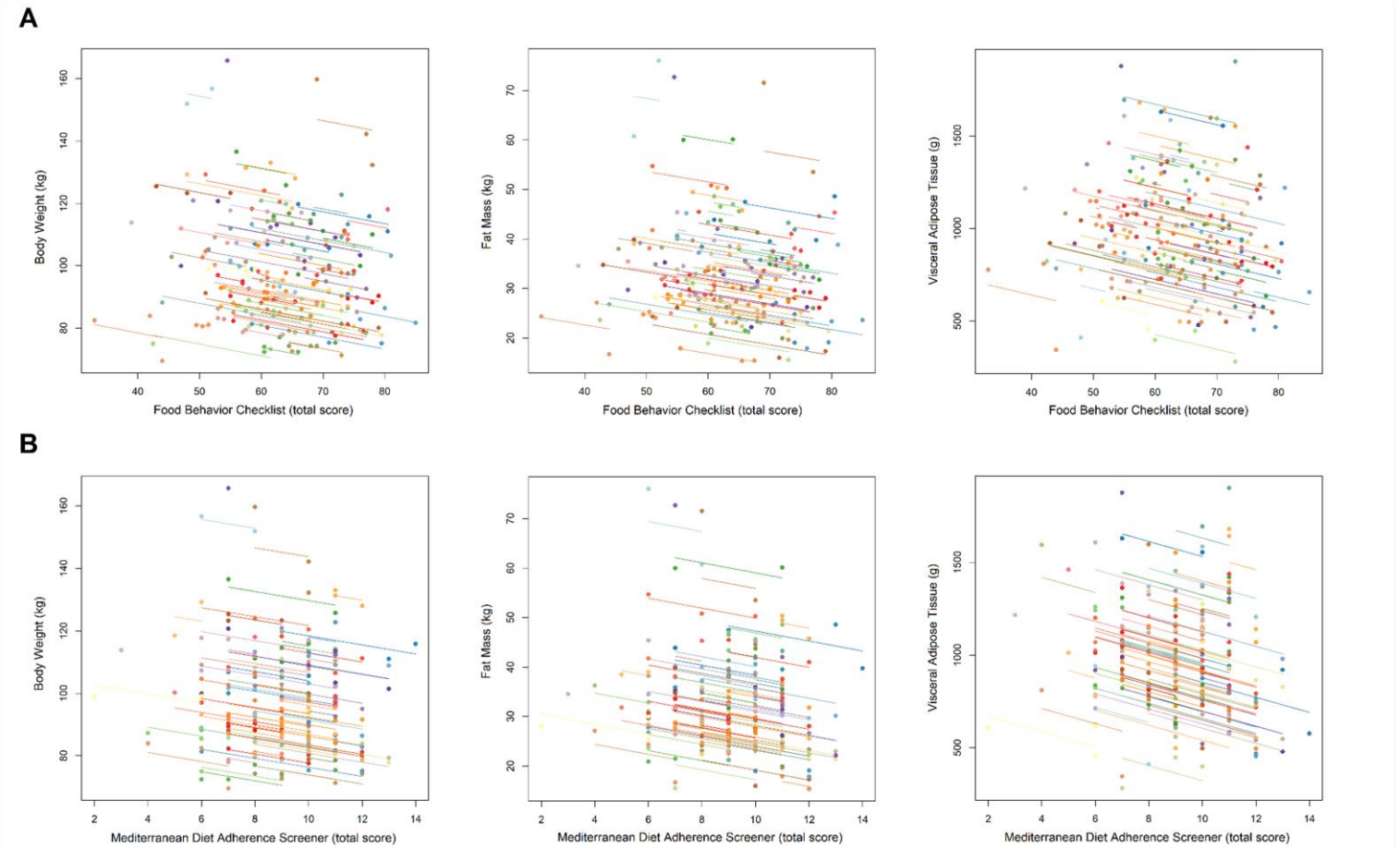
[b] The Mediterranean Diet Adherence Screener assesses adherence to the Mediterranean diet (range, 0-14; higher scores indicate greater adherence; scores ≥10 indicate high adherence to the Mediterranean diet).[42]

Figure 2. Association of changes in dietary behavior over time with changes in sleep outcomes



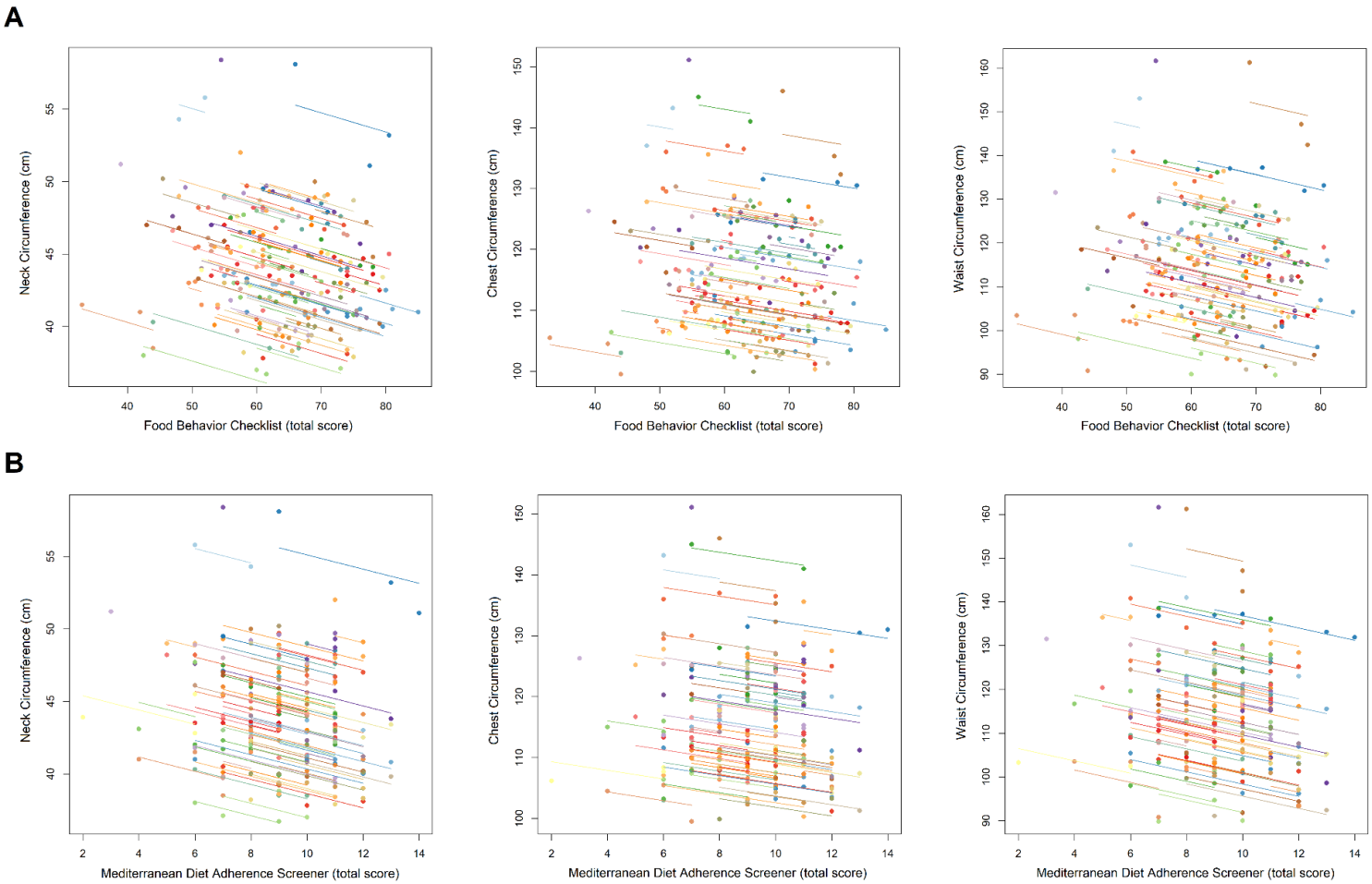
Each dot represents one of three separate observations (baseline, 8 weeks and 6 months after intervention) of dietary behavior — as measured by the Food Behavior Checklist (A) and Mediterranean Diet Adherence Screener (B) — and sleep outcomes for a participant. Observations from the same participant are given the same color, with corresponding lines to show the repeated measures correlation fit for each participant. A, The Food Behavior Checklist assesses dietary behavior (range, 23-85; higher scores indicate healthier dietary behavior).[41] B, The Mediterranean Diet Adherence Screener assesses adherence to the Mediterranean diet (range, 0-14; higher scores indicate greater adherence; scores ≥10 indicate high adherence to the Mediterranean diet).[42]

Figure 3. Association of changes in dietary behavior over time with changes in body weight and composition outcomes



Each dot represents one of three separate observations (baseline, 8 weeks and 6 months after intervention) of dietary behavior — as measured by the Food Behavior Checklist (A) and Mediterranean Diet Adherence Screener (B) — and body weight and composition outcomes for a participant. Observations from the same participant are given the same color, with corresponding lines to show the repeated measures correlation fit for each participant. A, The Food Behavior Checklist assesses dietary behavior (range, 23-85; higher scores indicate healthier dietary behavior).[41] B, The Mediterranean Diet Adherence Screener assesses adherence to the Mediterranean diet (range, 0-14; higher scores indicate greater adherence; scores ≥10 indicate high adherence to the Mediterranean diet).[42]

Figure 4. Association of changes in dietary behavior over time with changes in body circumferences outcomes



Each dot represents one of three separate observations (baseline, 8 weeks and 6 months after intervention) of dietary behavior — as measured by the Food Behavior Checklist (A) and Mediterranean Diet Adherence Screener (B) — and body circumferences outcomes for a participant. Observations from the same participant are given the same color, with corresponding lines to show the repeated measures correlation fit for each participant. A, The Food Behavior Checklist assesses dietary behavior (range, 23-85; higher scores indicate healthier dietary behavior).41 B, The Mediterranean Diet Adherence Screener assesses adherence to the Mediterranean diet (range, 0-14; higher scores indicate greater adherence; scores ≥10 indicate high adherence to the Mediterranean diet).[42]

These results are consistent with the limited existing evidence supporting the beneficial effects of behavioral weight loss interventions promoting nutritional education and behavior change on dietary behavior, diet quality and/or adherence to the Mediterranean diet.[29-33] Patnode et al.,[29] in a systematic review for the U.S. Preventive Services Task Force, found that healthful diet interventions in adults without known cardiovascular disease risk factors were related to reduced total energy and saturated fat intake, and increased fiber and fruits and vegetables consumption. Similarly, a systematic review by Lin et al.[30,31] based on a large body of evidence (76 trials) also determined that an intensive combined lifestyle counseling significantly improved dietary behavior in participants with cardiovascular disease risk factors.

Studies exploring the effects of these dietary and/or lifestyle approaches on dietary patterns and quality of diet in adults with moderate-to-severe OSA are currently lacking. Most previous studies in this regard only included calorie-restricted diets[25] which, as shown by the Look AHEAD (Action for Health in Diabetes) study[45] — the largest randomized trial in this field of research —, may not be the most-efficient approach for diet quality and sustainable dietary behavior change.[26,27] According to corroborative evidence, caloric restriction may result in compensatory changes that cause increased hunger and, in turn, increased energy intake as a homeostatic response to fat loss.[26,46] Furthermore, caloric restriction has also been associated with a compensatory reduction in energy expenditure that prevents weight loss in the long term.[46] Most importantly, this approach is not focused on changing dietary patterns and diet quality in the long term, which are the key factors for weight loss and benefits maintenance.

The current study is the first to report the beneficial effects of an interdisciplinary weight loss and lifestyle intervention on dietary behavior in adults with moderate-to-severe OSA. Remarkably, those participants who achieved healthier dietary behavior and greater adherence to the Mediterranean diet also exhibited lower OSA severity, greater weight loss and enhanced body composition and anthropometric parameters. Therefore, nutritional education and behavior change, focusing on macronutrients intake and promoting the Mediterranean diet, is an important intervention component to be considered and included in weight loss and lifestyle interventions for the management of OSA. The Mediterranean diet has been shown to have greater beneficial effects on weight and waist circumference than low-fat and calorie-restricted diets among individuals with type 2 diabetes and other cardiovascular risk factors.[47] In adults with OSA, the Mediterranean diet has also been shown to be related with reductions in body weight and abdominal fat, which is associated with reductions in OSA severity.[28] Furthermore, given its anti-inflammatory and antioxidant properties, the Mediterranean diet may potentially combat the inflammation and oxidative stress found in OSA, improving thereby the upper-airway neuromuscular control and muscle force-generating capacity and, thus, preventing the occurrence of the upper-airway obstructions during sleep.[26]

The main strength of the current study is the design and implementation of a novel interdisciplinary weight loss and lifestyle intervention readily adaptable to real-world clinical practice. Another notable strength is the measurement of sleep and OSA severity through a full-night in-laboratory polysomnography — the gold-standard for the measurement of

these outcomes — at each study assessment (baseline, intervention endpoint and 6 months after intervention). Nevertheless, a limitation of the study design is the sole inclusion of men with moderate-to-severe OSA and overweight/obesity in our sample, which restricts generalization of our findings. Another limitation is the subjective assessment of dietary behavior and adherence to the Mediterranean diet through the FBC and MEDAS which, although widely used, are self-reported questionnaires.

Conclusion

In this study involving adults with moderate-to-severe OSA and overweight/obesity, an eight-week interdisciplinary weight loss and lifestyle intervention including dietary behavior change, moderate-intensity aerobic exercise, sleep hygiene and tobacco and alcohol avoidance, was related to significant improvements in dietary behavior and adherence to the Mediterranean diet. Given the beneficial effects of dietary behavior change interventions and the Mediterranean diet on weight loss and OSA severity, approaches including these dietary components should be the strategy of choice for the comprehensive management of this increasingly common sleep-disordered breathing.

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Supplementary Material

Supplementary Table S1. Dietary behavior outcomes (per-protocol approach)

	Control (n=35)		Intervention (n=40)		Difference between groups, mean (95% CI)[a]
	Mean (95% CI)[a]	Change from baseline, mean (95% CI)	Mean (95% CI)[a]	Change from baseline, mean (95% CI)	
Food Behavior Checklist, total score[c]					
At baseline	59.6 (57.0 to 62.3)		59.5 (57.0 to 62.0)		
At 8 weeks	62.8 (60.1 to 65.5)	3.1 (0.4 to 5.9)	71.5 (69.0 to 74.0)	12.0 (9.5 to 14.5)	8.9 (5.8 to 11.9)[b]
At 6 months	61.1 (58.2 to 64.0)	1.5 (-1.5 to 4.5)	68.6 (66.1 to 71.2)	9.2 (6.5 to 11.9)	7.7 (4.4 to 11.0)[b]
Fruit and vegetables consumption score					
At baseline	21.8 (20.0 to 22.9)		22.6 (21.0 to 24.2)		
At 8 weeks	23.3 (21.5 to 24.7)	1.5 (-0.4 to 3.3)	29.5 (27.8 to 31.1)	6.9 (5.1 to 8.6)	5.4 (3.3 to 7.4)[b]
At 6 months	22.7 (20.7 to 24.2)	0.8 (-1.2 to 2.9)	27.5 (25.8 to 29.2)	4.9 (3.0 to 6.7)	4.0 (1.8 to 6.3)[b]
Milk/dairy consumption score					
At baseline	6.1 (5.5 to 6.6)		5.8 (5.3 to 6.3)		
At 8 weeks	5.7 (5.2 to 6.3)	-0.3 (-0.9 to 0.2)	5.7 (5.2 to 6.2)	-0.1 (-0.6 to 0.4)	0.2 (-0.4 to 0.8)
At 6 months	6.0 (5.4 to 6.6)	-0.1 (-0.7 to 0.5)	5.4 (4.9 to 5.9)	-0.4 (-0.9 to 0.2)	-0.3 (-1.0 to 0.4)
Food security score					
At baseline	3.1 (2.9 to 3.4)		3.1 (2.8 to 3.3)		
At 8 weeks	3.3 (3.0 to 3.5)	0.1 (-0.2 to 0.4)	3.1 (2.9 to 3.4)	0.1 (-0.2 to 0.4)	-0.03 (-0.4 to 0.3)
At 6 months	3.2 (2.9 to 3.5)	0.1 (-0.3 to 0.4)	3.2 (2.9 to 3.5)	0.2 (-0.2 to 0.5)	0.1 (-0.3 to 0.5)
Diet quality score					
At baseline	9.8 (9.1 to 10.5)		9.7 (9.0 to 10.3)		
At 8 weeks	10.5 (9.8 to 11.2)	0.7 (-0.03 to 1.5)	12.2 (11.5 to 12.8)	2.5 (1.8 to 3.2)	1.8 (0.9 to 2.6)[b]
At 6 months	10.3 (9.5 to 11.0)	0.5 (-0.3 to 1.3)	11.8 (11.1 to 12.5)	2.1 (1.4 to 2.9)	1.6 (0.7 to 2.6)[b]
Fast food consumption score					
At baseline	7.7 (7.1 to 8.2)		7.2 (6.7 to 7.7)		
At 8 weeks	8.3 (7.7 to 8.8)	0.6 (-0.3 to 1.4)	8.6 (8.1 to 9.1)	1.4 (0.6 to 2.2)	0.8 (-0.1 to 1.8)
At 6 months	7.9 (7.2 to 8.5)	0.2 (-0.8 to 1.1)	8.3 (7.8 to 8.9)	1.1 (0.3 to 2.0)	1.0 (-0.1 to 2.0)
Sweetened beverages consumption score					
At baseline	6.7 (6.5 to 7.0)		6.6 (6.3 to 6.9)		
At 8 weeks	7.1 (6.8 to 7.4)	0.4 (0.002 to 0.9)	7.5 (7.2 to 7.8)	0.9 (0.5 to 1.3)	0.4 (-0.03 to 0.9)
At 6 months	6.9 (6.5 to 7.2)	0.2 (-0.2 to 0.7)	7.4 (7.1 to 7.7)	0.7 (0.3 to 1.1)	0.5 (-0.02 to 1.0)
Meat consumption score					
At baseline	1.9 (1.6 to 2.1)		1.9 (1.6 to 2.2)		
At 8 weeks	2.1 (1.8 to 2.5)	0.2 (-0.3 to 0.8)	2.3 (2.0 to 2.6)	0.4 (-0.1 to 0.9)	0.2 (-0.4 to 0.8)
At 6 months	2.0 (1.7 to 2.4)	0.2 (-0.4 to 0.8)	2.5 (2.1 to 2.8)	0.6 (0.1 to 1.1)	0.4 (-0.2 to 1.1)
Mediterranean Diet Adherence Screener, total score[d]					
At baseline	8.1 (7.6 to 8.7)		8.1 (7.6 to 8.6)		
At 8 weeks	8.7 (8.2 to 9.3)	0.6 (-0.1 to 1.3)	10.7 (10.2 to 11.3)	2.6 (1.9 to 3.3)	2.0 (1.2 to 2.9)[b]
At 6 months	8.5 (7.8 to 9.1)	0.3 (-0.5 to 1.1)	10.1 (9.6 to 10.7)	2.0 (1.3 to 2.8)	1.7 (0.8 to 2.6)[b]

Abbreviations: CI, confidence interval.

[a] Using the group × visit interaction term from a linear mixed-effects model including study group, time (baseline, 8 weeks and 6 months), and study group × time as fixed effects and participant as random effects.

[b] $P < 0.001$ from the time × study group interactions.

[c] The Food Behavior Checklist assesses dietary behavior (range, 23-85; higher scores indicate healthier dietary behavior).

[d] The Mediterranean Diet Adherence Screener assesses adherence to the Mediterranean diet (range, 0-14; higher scores indicate greater adherence; scores ≥10 indicate high adherence to the Mediterranean diet).

Supplementary Table S2. Dietary behavior outcomes (change from 8 weeks to 6 months after intervention)

	Control				Intervention			
	N	8 weeks Mean (95% CI)	6 months Mean (95% CI)	Mean change (95% CI)[a]	N	8 weeks Mean (95% CI)	6 months Mean (95% CI)	Mean change (95% CI)[a]
Intention-to-treat approach								
Food Behavior Checklist[c]								
Total score	49	62.4 (59.9 to 64.9)	60.6 (57.9 to 63.4)	-1.8 (-4.8 to 1.2)	40	71.5 (68.9 to 74.0)	68.6 (66.0 to 71.3)	-2.8 (-5.5 to -0.1)[b]
Fruit and vegetables consumption score	49	23.1 (21.5 to 24.7)	22.4 (20.7 to 24.2)	-0.7 (-2.7 to 1.3)	40	29.5 (27.9 to 31.1)	27.5 (25.8 to 29.1)	-2.0 (-3.8 to -0.2)[b]
Milk/dairy consumption score	49	5.6 (5.1 to 6.2)	5.9 (5.3 to 6.4)	0.2 (-0.4 to 0.8)	40	5.7 (5.2 to 6.2)	5.4 (4.9 to 6.0)	-0.3 (-0.8 to 0.3)
Food security score	49	3.3 (3.0 to 3.5)	3.2 (3.0 to 3.5)	-0.03 (-0.4 to 0.3)	40	3.1 (2.8 to 3.4)	3.2 (2.9 to 3.5)	0.1 (-0.2 to 0.4)
Diet quality score	49	10.5 (9.9 to 11.2)	10.3 (9.5 to 11.0)	-0.3 (-1.1 to 0.6)	40	12.2 (11.5 to 12.8)	11.8 (11.1 to 12.5)	-0.3 (-1.1 to 0.4)
Fast food consumption score	49	8.2 (7.6 to 8.8)	7.7 (7.1 to 8.4)	-0.5 (-1.4 to 0.5)	40	8.6 (8.1 to 9.1)	8.3 (7.8 to 8.9)	-0.3 (-1.1 to 0.6)
Sweetened beverages consumption score	49	7.1 (6.8 to 7.4)	6.9 (6.5 to 7.2)	-0.2 (-0.7 to 0.3)	40	7.5 (7.2 to 7.8)	7.4 (7.1 to 7.7)	-0.1 (-0.6 to 0.3)
Meat consumption score	49	2.1 (1.8 to 2.5)	2.0 (1.7 to 2.4)	-0.1 (-0.7 to 0.5)	40	2.3 (2.0 to 2.6)	2.5 (2.1 to 2.8)	0.2 (-0.3 to 0.7)
Mediterranean Diet Adherence Screener[d]								
Total score	49	8.8 (8.2 to 9.4)	8.5 (7.9 to 9.1)	-0.3 (-1.1 to 0.5)	40	10.7 (10.2 to 11.3)	10.1 (9.6 to 10.7)	-0.6 (-1.3 to 0.1)
Per-protocol approach								
Food Behavior Checklist[c]								
Total score	49	62.8 (60.1 to 65.5)	61.1 (58.2 to 64.0)	-1.7 (-4.7 to 1.4)	40	71.5 (68.9 to 74.0)	68.6 (66.0 to 71.3)	-2.8 (-5.5 to -0.1)[b]
Fruit and vegetables consumption score	49	23.3 (21.5 to 24.7)	22.7 (20.7 to 24.2)	-0.7 (-2.7 to 1.4)	40	29.5 (27.9 to 31.1)	27.5 (25.8 to 29.1)	-2.0 (-3.8 to -0.2)[b]
Milk/dairy consumption score	49	5.7 (5.2 to 6.3)	6.0 (5.4 to 6.6)	0.3 (-0.4 to 0.9)	40	5.7 (5.2 to 6.2)	5.4 (4.9 to 6.0)	-0.3 (-0.8 to 0.3)
Food security score	49	3.3 (3.0 to 3.5)	3.2 (2.9 to 3.5)	-0.1 (-0.4 to 0.3)	40	3.1 (2.8 to 3.4)	3.2 (2.9 to 3.5)	0.1 (-0.2 to 0.4)
Diet quality score	49	10.5 (9.8 to 11.2)	10.3 (9.5 to 11.0)	-0.2 (-1.1 to 0.6)	40	12.2 (11.5 to 12.8)	11.8 (11.1 to 12.5)	-0.3 (-1.1 to 0.4)
Fast food consumption score	49	8.3 (7.7 to 8.8)	7.9 (7.2 to 8.5)	-0.4 (-1.3 to 0.6)	40	8.6 (8.1 to 9.1)	8.3 (7.8 to 8.9)	-0.3 (-1.1 to 0.6)
Sweetened beverages consumption score	49	7.1 (6.8 to 7.4)	6.9 (6.5 to 7.2)	-0.2 (-0.7 to 0.3)	40	7.5 (7.2 to 7.8)	7.4 (7.1 to 7.7)	-0.1 (-0.6 to 0.3)
Meat consumption score	49	2.1 (1.8 to 2.5)	2.0 (1.7 to 2.4)	-0.1 (-0.6 to 0.5)	40	2.3 (2.0 to 2.6)	2.5 (2.1 to 2.8)	0.2 (-0.3 to 0.7)
Mediterranean Diet Adherence Screener[d]								
Total score	49	8.7 (8.2 to 9.3)	8.5 (7.8 to 9.1)	-0.3 (-1.1 to 0.5)	40	10.7 (10.2 to 11.3)	10.1 (9.6 to 10.7)	-0.6 (-1.3 to 0.1)

Abbreviations: CI, confidence interval.

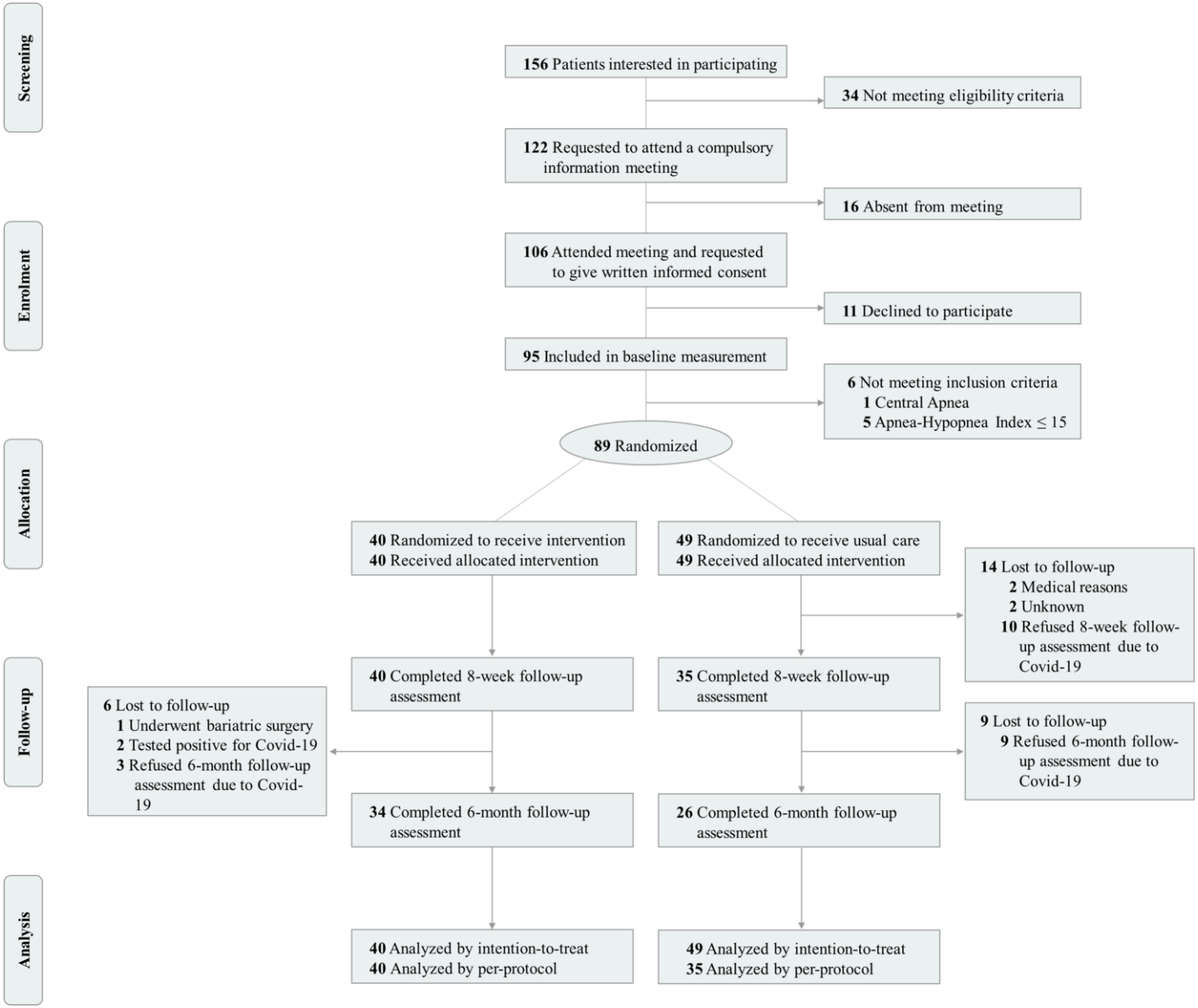
[a] Using post-hoc test (pairwise comparison) in a linear mixed-effects model including study group, time (baseline, 8 weeks and 6 months), and study group × time as fixed effects and participant as random effects.

[b] $P < 0.05$.

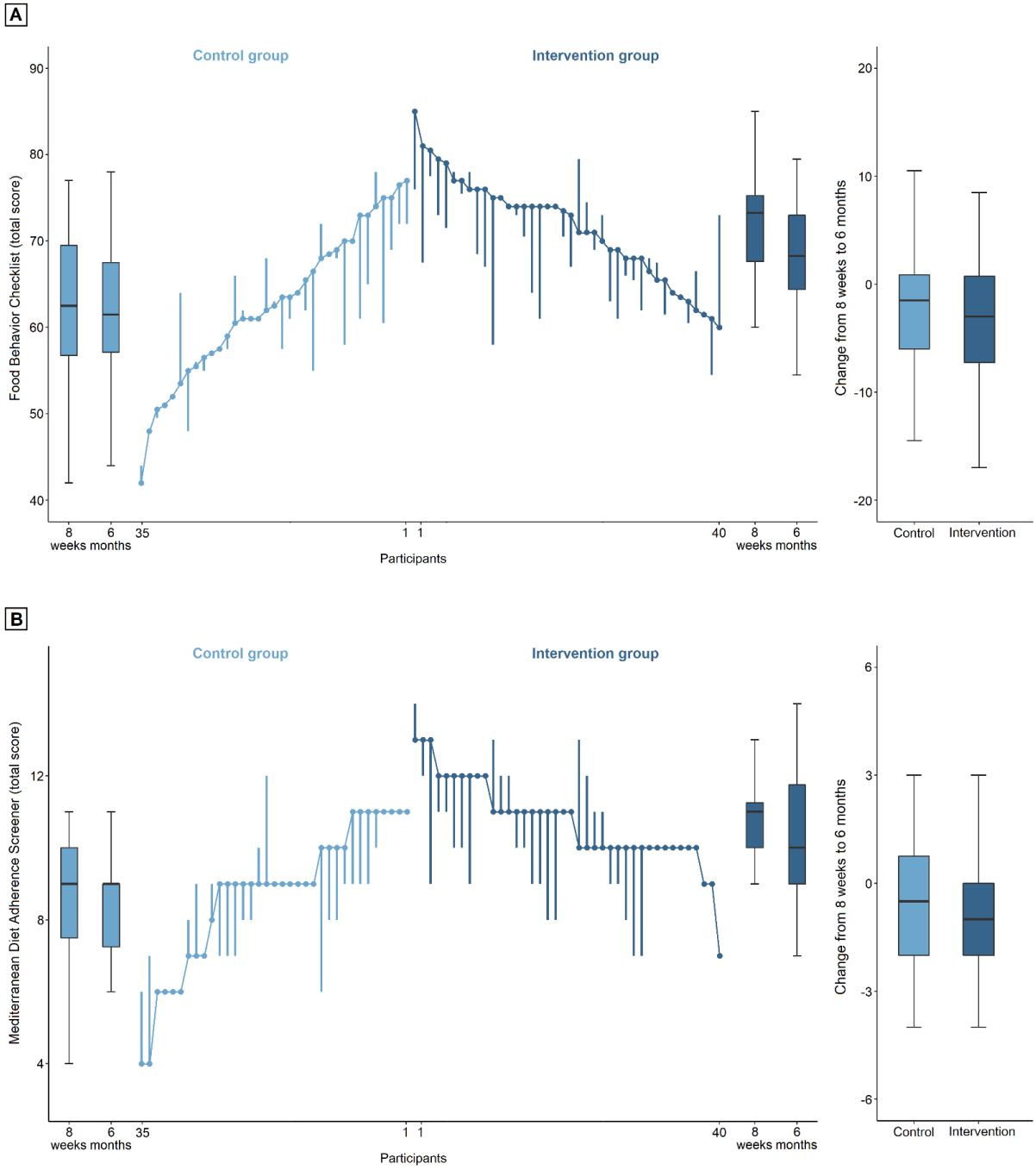
[c] The Food Behavior Checklist assesses dietary behavior (range, 23-85; higher scores indicate healthier dietary behavior).

[d] The Mediterranean Diet Adherence Screener assesses adherence to the Mediterranean diet (range, 0-14; higher scores indicate greater adherence; scores ≥10 indicate high adherence to the Mediterranean diet).

Supplementary Figure S1. Flow-Chart Diagram of the INTERAPNEA Randomized Clinical Trial



Supplementary Figure S2. Dietary Behavior Outcomes (Change from 8 weeks to 6 months after intervention)



The ends of the boxes in the boxplots are located at the first and third quartiles, with the black line in the middle illustrating the median. Whiskers extend to the upper and lower adjacent values, the location of the furthest point within a distance of 1.5 interquartile ranges from the first and third quartiles. The parallel line plot contains 1 vertical line for each patient which extends from their 8-week value to their 6-month value. Ascending lines indicate an improvement in the outcome. Eight-week values are placed in ascending order for the control group and descending order for the intervention group. A, The Food Behavior Checklist assesses dietary behavior (range, 23-85; higher scores indicate healthier dietary behavior). C, The Mediterranean Diet Adherence Screener assesses adherence to the Mediterranean diet (range, 0-14; higher scores indicate greater adherence; scores ≥10 indicate high adherence to the Mediterranean diet).

GENERAL DISCUSSION

CHAPTER 7
An integrative discussion of the International Doctoral Thesis

Obstructive sleep apnea (OSA), with obesity as the leading attributable cause, is a major global health problem that has become the prime focus of clinical research and practice owing not only to its high and increasing prevalence,[1] but also to its wide-range of adverse health-related consequences.[2-4] According to the most recent epidemiological and clinical research, this condition affects nearly a billion adults aged 30–69 years globally,[1] and is strongly associated with an increased likelihood of neurocognitive alterations, impaired daily functioning and mood, cardiometabolic disorders including dyslipidemia, diabetes, hypertension, life-threatening cardiovascular diseases, and all-cause mortality.[5-10]

The first-line treatment for OSA is continuous positive airway pressure (CPAP); a mechanical device effective at maintaining upper-airway patency and, thus, reducing the apnea-hypopnea events per hour of sleep (i.e., apnea-hypopnea index; AHI).[11] However, CPAP adherence rates are suboptimal,[12] and long-term benefits beyond reduction of the upper-airway occlusions during sleep remain uncertain. Indeed, large observational and experimental studies in this field have found no significant reductions in metabolic risk or cardiovascular events after long-term CPAP therapy.[13-15]

Given the robust and reciprocal interaction between OSA and obesity,[16] alternative or combined non-surgical and non-pharmacological approaches such as weight loss and lifestyle interventions are currently highly recommended and appear to substantially improve OSA severity and coexisting conditions.[17-19] Yet, previous studies in this regard, although enlightening, contained limitations inherent to the study design or methodology including, but not limited to, stringent eligibility criteria, limited reported outcomes, and/or non-randomized allocation; which restrict generalizability of results.[18,19] Furthermore, weight loss had only been addressed through calorie-restricted diets or exercise, without either a combination of both components or behavioral approaches pursuing maintenance of benefits.[19] Most remarkably, there was no study in the field addressing alcohol avoidance and/or smoking cessation;[19] which are well-evidenced behavioral risk factors closely associated with the occurrence and worsening of OSA.[20,21]

This International Doctoral Thesis and, thus, the Interdisciplinary Weight Loss and Lifestyle Intervention for Obstructive Sleep Apnea (INTERAPNEA) randomized clinical trial,[22] was aimed at designing, implementing and testing the efficacy of an interdisciplinary weight loss and lifestyle intervention for the improvement of OSA severity and related comorbidities in adults with CPAP-treated moderate-to-severe OSA and overweight/obesity. Accordingly, we firstly systematically contrasted, combined, and synthesized the available evidence in the field in order to determine the potential beneficial effects of lifestyle interventions on OSA and, in turn, elucidate which intervention and participant characteristics were related with the greatest effectiveness (**Study 1**).[19] Subsequently, and based on our findings from this systematic review and meta-analysis, we designed the INTERAPNEA randomized clinical trial (**Study 2**),[22] with the aforementioned essential aim of elucidating the beneficial effects of an eight-week interdisciplinary weight loss and lifestyle intervention not only on OSA severity, body weight and composition, cardiometabolic risk, and health-related quality of life (**Study 3**), but also on daily functioning and psychiatric symptoms (**Study 4**), cardiorespiratory fitness (**Study 5**), and dietary behavior (**Study 6**), in men with CPAP-treated moderate-to-sever OSA and overweight/obesity.

ROLE OF WEIGHT LOSS AND LIFESTYLE CHANGE ON OBSTRUCTIVE SLEEP APNEA SEVERITY, BODY WEIGHT AND COMPOSITION, AND CARDIOMETABOLIC RISK

Weight loss and lifestyle changes may intensely ameliorate OSA and coexisting conditions by means of multifactorial mechanisms. Gathered evidence suggests that nearly 60% of moderate-to-severe OSA is attributable to obesity,[23] which contributes to alterations of the airway anatomy and collapsibility, and respiratory modulation.[16] Simultaneously, adverse lifestyles such as poor diet, low physical activity, smoking and alcohol intake, have also been shown to be closely related to OSA independent of body habitus.[20-22,24] Thus, a combination of both weight loss and lifestyle change may even resolve OSA in overweight/obese populations.[3,18] Yet, weight loss and lifestyle interventions for OSA treatment, although recommended, are rarely implemented in the care of patients with this condition owing to the modest quality of evidence and the methodological weaknesses found in this field of research.[18,19] According to our systematic review and meta-analysis (**Study 1**),[19] the number of reported randomized controlled trials addressing both diet and exercise components as a combination was significantly low and only included effects on specific OSA outcomes such as AHI, oxygen desaturation index, and excessive daytime sleepiness. Additionally, there was no original study actively focusing on the cessation of tobacco and alcohol intake,[19] factors which have been shown to be common in patients with OSA and associated with the occurrence and worsening of this condition.[20,21]

The INTERAPNEA randomized clinical trial (**Study 2**),[22] overcoming all the shortcomings found in the field and involving 89 adults with CPAP-treated moderate-to-severe OSA and overweight/obesity, demonstrates that an eight-week interdisciplinary weight loss and lifestyle intervention resulted in clinically meaningful and sustainable improvements not only in specific OSA-related outcomes and cardiometabolic comorbidities, but also in health-related quality of life (**Study 3**). The weight loss and lifestyle intervention group had a clinically meaningful reduction in AHI of 51% at intervention endpoint; 15% of participants attaining complete remission of OSA, and 45% no longer requiring CPAP therapy. After 6 months, the reduction in AHI was 57%; the complete remission of OSA being attained by 29% of participants; 62% no longer requiring CPAP therapy. Similarly, the intervention group notably exhibited 7%, 19% and 26% reductions in body weight, fat mass and visceral adipose tissue at 6 months after intervention, respectively. Furthermore, these results were strengthened by the evidence of significant improvements in key cardiometabolic endpoints involved in the pathogenesis of cardiovascular diseases, including blood pressure, fasting blood glucose and lipid, and liver function. Simply considering reductions in systolic and diastolic blood pressure at intervention endpoint — which were not only sustained but also significantly enlarged at 6 months after intervention — our intervention group may have lowered risk of stroke death by 40% and risk of death from ischemic heart disease or other vascular causes by 30%.[25]

ROLE OF WEIGHT LOSS AND LIFESTYLE CHANGE ON DAILY FUNCTIONING AND PSYCHIATRIC SYMPTOMS IN OBSTRUCTIVE SLEEP APNEA

Impaired daily functioning and psychiatric symptoms including psychological distress, depression and anxiety, are highly prevalent in OSA and represent a substantial cause of disease burden.[26-28] Apart from being significant cardiovascular risk factors,[26-28] these comorbid psychiatric symptoms have been found to adversely impact self-management, treatment adherence and functioning, symptoms perception, and health care costs in chronic medical illnesses and, specifically, in OSA.[27-29] Gathered evidence in the field has shown that CPAP is not more effective at reducing these psychological comorbidities than placebo or sham CPAP.[6,30-32] Although effective at reducing OSA severity, CPAP may not address OSA major risk factors such as obesity and other cardiometabolic diseases associated to both OSA and psychological distress.[33] There is fairly well-established data indicating that weight loss and lifestyle interventions significantly reduce comorbid psychiatric symptoms in other chronic medical illnesses such as obesity, type 2 diabetes and cardiovascular diseases.[34-36] However, there was no evidence to date on the efficacy of this approach at addressing the psychiatric symptoms found in OSA.

This International Doctoral Thesis and, thus, the INTERAPNEA trial, demonstrates the efficacy of an interdisciplinary weight loss and lifestyle intervention at improving daily functioning and comorbid psychiatric symptoms in CPAP-treated moderate-to-severe OSA (**Study 4**). Remarkably, 72% and 100% of those participants in the intervention group with clinical levels of impaired daily functioning and/or psychological distress at baseline, respectively, reported resolution of these symptoms after the intervention. Similarly, 82% achieved resolution of state anxiety and 80% of trait anxiety at the intervention endpoint. Of those reporting state, trait, and/or general depression at baseline, 73%, 75% and 100% also reported resolution of these symptoms, respectively, after the intervention. These results, apart from strengthening the evidence supporting that weight loss and lifestyle interventions protect patients from psychiatric disorders rather than precipitating them,[34,37] question the consideration of these symptoms as risk factors that could undermine the effects of or adherence to these interventions.[38-40]

These findings may be explained by the underlying biological, metabolic and neurologic dysregulations contributing to both OSA and psychiatric conditions.[26,27,30,41] According to current models, the functional and psychiatric disturbances found in OSA are not only the result of sleep fragmentation, hypoxia and neurotransmitter alterations, but also secondary to the chronic illness burden and its comorbidities including obesity and cardiometabolic diseases.[26,27,30,41] As compared to CPAP alone, the INTERAPNEA intervention had significant effects on OSA severity, weight, cardiometabolic risk factors and, thus, health-related quality of life (**Study 3**); factors which are well-related to impaired functional status, psychological distress and anxiety and depression symptoms.[42-43]

ROLE OF WEIGHT LOSS AND LIFESTYLE CHANGE ON CARDIORESPIRATORY FITNESS IN OBSTRUCTIVE SLEEP APNEA

Cardiorespiratory fitness has been found to be significantly reduced in patients with OSA, which may be associated with increased cardiovascular disease risk and all-cause mortality.[44-47] Substantial evidence suggests that these alterations may be partially explained by multiple underlying mechanisms triggered by the long-lasting exposure to intermittent hypoxia and sympathetic hyperactivity.[45] Potential physiological mechanisms may include chronotropic incompetence,[48] reduced cardiac output secondary to ventricular dysfunction and increased afterload,[49] diastolic hypertension and impaired peripheral vasodilation,[50,51] impaired glycolytic and oxidative metabolism with decreased maximal lactate concentration and delayed lactate elimination,[52] and/or abnormalities of the skeletal muscles.[53] Furthermore, lower physical fitness in OSA may not only be caused by underlying cardiac and metabolic dysfunctions but also increased weight, excessive daytime somnolence, and, in turn, lack of motivation and sedentary lifestyle.[54]

Therefore, weight loss and lifestyle interventions including dietary modification and increased physical activity, which have been shown to substantially improve OSA severity and related cardiovascular and metabolic morbidity,[18,19] may also be effective at improving CRF and physical fitness. Yet, evidence was sparse and results on the association between CRF and OSA severity change were controversial.[55-57]

The INTERAPNEA study demonstrates that an eight-week interdisciplinary weight loss and lifestyle intervention was effective at improving CRF and self-reported physical fitness in adults with overweight/obesity and CPAP-treated moderate-to-severe OSA (**Study 5**). In addition, we found that increases in CRF and self-reported physical fitness were significantly associated with improvements not only in OSA outcomes but also in body composition and anthropometric outcomes. According to the results reported herein, the weight loss and lifestyle intervention was associated with 6% and 10% reductions in 2-km walking test[58-60] total time at intervention endpoint and 6 months after intervention, respectively. Similarly, this behavioral approach was related to 18% and 22% increases at intervention endpoint and 6 months after intervention, respectively, in self-reported overall physical fitness as measured by the International Fitness Scale (IFIS).[61,62] Improvements in these health-related outcomes would certainly have robust clinical implications, since physical fitness is an increasingly recognized predictor of a wide range of substantial health outcomes, including cardiovascular disease risk factors, morbidity, and all-cause mortality.[63-66] Indeed, unequivocal evidence suggests that CRF is a stronger predictor of mortality than established risk factors such as obesity, smoking, hypertension, high cholesterol, and type 2 diabetes.[67-71] According to epidemiological research, an increased physical fitness could in effect even counterbalance the obesity-related risks for type 2 diabetes, cardiovascular disease and mortality.[68]

ROLE OF WEIGHT LOSS AND LIFESTYLE CHANGE ON DIETARY BEHAVIOR IN OBSTRUCTIVE SLEEP APNEA

Studies exploring the effects of weight loss and lifestyle approaches on dietary patterns and quality of the diet in adults with moderate-to-severe OSA are currently lacking. Most previous studies in this regard only included calorie-restricted diets,[72] which may not be the most-efficient approach for diet quality and sustainable dietary behavior change.[73,74] According to corroborative evidence, caloric restriction may result in compensatory changes that cause increased hunger and, in turn, increased energy intake as a homeostatic response to fat loss.[73,75] Furthermore, caloric restriction has also been associated with a compensatory reduction in energy expenditure that prevents weight loss in the long term.[75] Most importantly, this approach is not focused on changing dietary patterns and diet quality in the long term, which are the key factors for weight loss and benefits maintenance.

Instead, alternative approaches such as Mediterranean diets and other dietary strategies focusing on nutritional education and behavior change have been proposed as potential strategies of choice for OSA management.[73,74,76] In adults with OSA, the Mediterranean diet has been shown to be related with reductions in body weight and abdominal fat, which is associated with reductions in OSA severity.[76] Still, although effective at improving OSA severity, there is no evidence to date on the effects of these behavioral approaches on the unhealthy dietary behaviors and poor quality of the diet commonly found in patients with OSA.[77-79]

This International Doctoral Thesis demonstrates that a novel eight-week interdisciplinary weight loss and lifestyle intervention, incorporating not only a nutritional behavior change component but also increased physical activity, sleep hygiene and alcohol and tobacco avoidance, is effective at significantly improving dietary behavior in adults with CPAP-treated moderate-to-severe OSA and overweight/obesity (**Study 6**). According to our findings, the weight loss and lifestyle intervention group had 20% and 15% increases in healthful dietary behavior as measured by the Food Behavior Checklist[80] at intervention endpoint and 6 months after intervention, respectively. Similarly, participants from this group reported 33% and 25% increases at intervention endpoint and 6 months after intervention, respectively, in adherence to the Mediterranean diet as measured by the Mediterranean Diet Adherence Screener.[81] Remarkably, those participants who achieved healthier dietary behavior and greater adherence to the Mediterranean diet also exhibited lower OSA severity, greater weight loss and enhanced body composition and anthropometric parameters. Therefore, nutritional education and behavior change, focusing on macronutrients intake and promoting the Mediterranean diet, is an important intervention component to be considered and included in weight loss and lifestyle interventions for the comprehensive management of OSA.

GENERAL LIMITATIONS

The findings presented in this International Doctoral Thesis should be interpreted with caution since certain limitations inherent to the study design should be addressed:

- Given the higher incidence and prevalence of OSA in men,[82] and the well-evidenced differences between men and women in OSA phenotypes[83] and the effectiveness of weight loss interventions,[19,84-86] only men with CPAP-treated moderate-to-severe OSA and overweight/obesity were included in the INTERAPNEA sample; the generalization of our findings being therefore limited to this population.
- The INTERAPNEA trial, although rigorously designed and executed, was a single-center study; which may also potentially limit the external validity and generalization of our findings to a broader population.
- Due to ethical considerations, the INTERAPNEA study did not include any group in which no therapy for OSA was implemented; CPAP is the standard care for moderate-to-severe OSA and the inclusion of a group without CPAP is not feasible.

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87.

CONCLUSIONS

GENERAL CONCLUSION

The present International Doctoral Thesis demonstrates that an eight-week interdisciplinary weight loss and lifestyle intervention involving adults with moderate-to-severe obstructive sleep apnea (OSA) and overweight/obesity resulted in clinically meaningful and sustainable improvements not only in OSA severity and comorbidities but also in health-related quality of life, daily functioning and mood, physical fitness and dietary behavior. Given the high prevalence of OSA, its complex and reciprocal interaction with obesity, and the fact that both conditions are readily treatable through an integrated behavioral intervention, health-care providers and policy-makers should, at the very least, consider this approach as a central strategy to comprehensively address the staggering impact of OSA on the health and welfare of our society.

SPECIFIC CONCLUSIONS

Interdisciplinary weight loss and lifestyle intervention for obstructive sleep apnea severity and related comorbidities

- An eight-week interdisciplinary weight loss and lifestyle intervention involving adults with overweight/obesity and moderate-to-severe OSA treated with continuous positive airway pressure (CPAP) not only resulted in clinically meaningful and sustainable improvements in OSA severity, other specific OSA-related outcomes, and cardiometabolic comorbidities but also pragmatically increased health-related quality of life.

Interdisciplinary weight loss and lifestyle intervention for daily functioning and psychiatric symptoms in obstructive sleep apnea

- An eight-week interdisciplinary weight loss and lifestyle intervention combined with CPAP, as compared with CPAP alone, significantly improved and even resolved OSA-related impaired daily functioning, psychological distress, and anxiety and depression symptoms in adults with moderate-to-severe OSA and overweight/obesity.

Interdisciplinary weight loss and lifestyle intervention for cardiorespiratory fitness in obstructive sleep apnea

- An eight-week interdisciplinary weight loss and lifestyle intervention including adults with CPAP-treated moderate-to-severe OSA and overweight/obesity resulted in significant and sustainable improvements in cardiorespiratory fitness and self-reported physical fitness.
- Increases in cardiorespiratory fitness and self-reported physical fitness over time were closely related to improvements in OSA severity and sleep outcomes, body weight and composition, and neck, chest, and waist circumferences.

Interdisciplinary weight loss and lifestyle intervention for dietary behavior in obstructive sleep apnea

- An eight-week interdisciplinary weight loss and lifestyle intervention was related to significant improvements in dietary behavior and adherence to the Mediterranean diet in adults with CPAP-treated moderate-to-severe OSA and overweight/obesity.
- Improvements in dietary behavior and adherence to the Mediterranean diet over time were closely related to improvements in OSA severity and sleep outcomes, body weight and composition, and neck, chest, and waist circumferences.

FUTURE PERSPECTIVES

FUTURE PERSPECTIVES

- Future large collaborative multi-center studies should be conducted in order to determine and compare the effects of interdisciplinary weight loss and lifestyle interventions on obstructive sleep apnea (OSA) severity and related comorbidities across adults from different locations/centers/population groups, which would certainly increase the external validity and generalizability of findings.

- Future well-designed trials should investigate the effects of interdisciplinary weight loss and lifestyle interventions on OSA severity and related comorbidities in women suffering from this sleep-disordered breathing.

- Future original investigations examining the effects of interdisciplinary weight loss and lifestyle interventions on OSA severity and related comorbidities in adults should include longer-term follow-ups, which would definitely provide robust estimations of longer-term effects of the intervention and maintenance of benefits.

ANNEXES

INTERAPNEA Trial
Procotocol

An investigator-initiated and conducted, randomized, controlled trial of INTERdisciplinary weight loss and lifestyle intervention for the treatment of moderate-to-severe obstructive sleep APNEA

PROTOCOL

CONTACT DETAILS

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1. BACKGROUND AND RATIONALE

1.1. OSA — A Major Public Health Problem

Obstructive sleep apnea (OSA), produced by repeated upper airway collapse during sleep, has increasingly become the focus of numerous current interdisciplinary research attributed not only to its high prevalence but also to the wide range of adverse health consequences of this condition [1]. The repeated events of complete (apnea) or partial (hypopnea) pharyngeal obstruction occurred while sleeping lead to intermittent hypoxic episodes, hypercapnia, sleep fragmentation, and upsurges of sympathetic activity [2]. Driven by these short-term consequences, OSA is closely related to increased morbidity and mortality [3], including cardio-metabolic disorders [4], neurocognitive abnormalities [5], impaired daily functioning and mood [6], and greater risk of vehicle and occupational accidents [7,8].

It has recently been estimated that up to 38% of adults suffer from OSA, being more prevalent in the male sex, the elderly, and in those who are obese [9]. OSA risk factors, therefore, include obesity, sex, age, and adverse lifestyle habits such as sedentariness, poor nutrition, smoking, and alcohol intake [10]. According to epidemiological studies, nearly 60% of moderate to severe OSA is attributable to obesity [11], which contributes to alterations of the airway anatomy and collapsibility, respiratory modulation, resting lung volume, and neurohormonal mediators on ventilation [12]. Given the exponential increase of obesity prevalence in the overall population, which has nearly tripled since 1975 — 39% of adults aged 18 years and over in 2016 —, OSA prevalence is not only worryingly high but also likely to rise in upcoming years [13].

1.2. CPAP — First-Line Treatment for OSA

The current treatment of choice is continuous positive airway pressure (CPAP) [14], a mechanical device used to maintain upper airway patency, thereby improving OSA main symptoms and consequences through the reduction of the number of apnea-hypopnea episodes per hour of sleep (i.e. apnea-hypopnea index, AHI) [15-17]. However, CPAP is a chronic day-to-day treatment — it does not cure OSA in the long-term —, and its use may be rejected or abandoned due to discomfort and/or other inconveniences [18]. Most importantly, CPAP does not address the major high-risk factors of OSA, i.e. obesity and adverse lifestyles.

1.3. Weight Loss and Lifestyle Intervention for OSA

Alternative or combined behavioral interventions including weight loss through dietary approaches and exercise, sleep hygiene, and avoidance of alcohol and tobacco consumption are required and strongly recommended in the most recent practical guidelines from the American Academy of Sleep Medicine (AASM) [14,19]. According to our recently published systematic review

and meta-analysis on the effectiveness of these interventions [1], the combination of diet and exercise may be an effective treatment in improving OSA outcomes in middle-aged males with moderate to severe OSA.

Yet, the number of reported randomized controlled trials addressing both weight loss components as a combination was significantly low and only included effects on specific OSA outcomes such as AHI, oxygen desaturation index, and excessive daytime sleepiness [1]. Furthermore, no original studies actively focusing on the cessation of tobacco and alcohol consumption were found [1], factors which have been shown to be common in patients with OSA and associated with the worsening of this condition [20-21]. Thus, the actual effectiveness of potential interdisciplinary interventions for the improvement of OSA main symptoms and consequences still remains unclear. Considering the vast and severe OSA consequences and comorbidities, with obesity being a major risk factor for this condition, there is a need for well-designed studies comprising all these aspects and evaluating the potential clinical and economic relevance of these interventions for OSA and related diseases.

2. AIMS AND OBJECTIVES

The interdisciplinary weight loss and lifestyle intervention for OSA (INTERAPNEA) trial aims to determine the efficacy of a novel eight-week interdisciplinary weight loss and lifestyle intervention for the improvement of OSA and comorbidities in overweight/obese adults with CPAP-treated moderate-to-severe OSA.

2.1. Primary Aim

The primary aim of the INTERAPNEA trial is to design, implement and test the efficacy of an eight-week interdisciplinary weight loss and lifestyle intervention combined with usual-care (i.e. CPAP) to improve OSA severity (i.e. reduction of AHI) in overweight/obese adults with moderate-to-severe OSA. We hypothesize that the eight-week interdisciplinary weight loss and lifestyle intervention will lead to a greater and significant reduction of AHI and/or even remission of OSA as compared with usual-care alone (i.e. CPAP).

2.2. Secondary Aims

The secondary aims of this trial include the determination of the efficacy of the eight-week interdisciplinary weight loss and lifestyle intervention combined with usual-care (i.e. CPAP) to improve other sleep-related outcomes, body weight and composition, OSA-related coexisting conditions/comorbidities (cardiometabolic risk), health-related quality of life, and daily functioning and mood, in overweight/obese adults with moderate-to-severe OSA. Accordingly, we hypothesize that:

- Relative to usual-care alone (i.e. CPAP), an eight-week interdisciplinary weight loss and lifestyle intervention combined with usual-care will lead to a significant improvement of oxyhemoglobin saturation outcomes, sleep efficiency and maintenance, sleep architecture, and subjective sleep quality and sleepiness.
- Relative to usual-care alone (i.e. CPAP), an eight-week interdisciplinary weight loss and lifestyle intervention combined with usual-care will lead to a significant reduction of body weight and improvement of other anthropometric and body composition outcomes (neck, chest and waist circumferences, fat mass, and visceral adipose tissue).
- Relative to usual-care alone (i.e. CPAP), an eight-week interdisciplinary weight loss and lifestyle intervention combined with usual-care will lead to a significant improvement of OSA-related cardiovascular risk outcomes (hypertension, dyslipidemia, insulin resistance, and liver diseases).
- Relative to usual-care alone (i.e. CPAP), an eight-week interdisciplinary weight loss and lifestyle intervention combined with usual-care will lead to a significant improvement of health-related quality of life and overall psychological health including daily functioning and mood.

3. METHODS

3.1. Design

The INTERAPNEA study (ClinicalTrials.gov ID: NCT03851653) is an investigator-initiated, randomized, parallel-group, open-label trial designed to evaluate the effects of an eight-week interdisciplinary weight loss and lifestyle intervention combined with usual-care (i.e. CPAP), as compared with usual-care alone, on OSA severity (i.e. apnea-hypopnea index [AHI]; number of apneas and hypopneas per hour of sleep), and OSA-related comorbidities among adults with moderate-to-severe OSA.

3.2. Eligibility Criteria

Eligible participants will be adults previously diagnosed with moderate-to-severe OSA (AHI equal or greater than 15 [22]) from the province of Granada (Spain). They must be between 18 and 65 years old, and have a body mass index (BMI) equal to or greater than 25 kg/m^2. A full list of the study's inclusion and exclusion criteria are exposed in Table 1. Due to the well-evidenced higher incidence and prevalence of OSA in the male sex [9] and the differences in OSA phenotypes between men and women [23], we will only include male participants in the study. Furthermore, non-pharmacological and non-surgical weight loss interventions have been shown to be less effective in women [1,24], such that different approaches are needed in this population with OSA.

Table 1. Eligibility criteria.

Inclusion criteria	Exclusion criteria
• Men aged 18–65 years • CPAP-treated moderate to severe OSA (AHI equal to or greater than 15 events/hour) • BMI equal to or greater than 25 kg/m^2 • Not participating in a weight loss program • Willing to provide informed consent and acceptance of random group assignment	• Presence of any other primary sleep disorder • Presence of any mental disorder (including depression, anxiety, and addiction to alcohol or other substances) • Presence of any other severe organic disease, except for those comorbid to OSA • Regular use of neuroleptic, sedative or hypnotic drugs, or any other medication that may cause sleep disturbances or increased daytime sleepiness

AHI = apnea-hypopnea index; BMI = body mass index; CPAP, continuous positive airway pressure; OSA, obstructive sleep apnea.

Potential participants will be medically examined and must complete a health history revision prior to their inclusion in the study in order to ensure no hindrance/harm related to the assessment and intervention protocols. Should any incident or medical problem arise during the intervention, participants will be physically and psychologically examined and, if necessary, excluded from the study. Clinical trial liability insurance will be contracted for the INTERAPNEA study, providing legal and financial protection to the sponsor-investigators, and compensation to participants in the case of an injury or any damage incurred in and as a result of the study.

3.3. Recruitment, Enrollment and Randomization

Recruitment

The recruitment of participants will be performed using different strategies including enrollment from the collaborating hospital sleep unit, and use of mass media (e.g. press, magazines, radio and television news, and websites). A brief in-person or phone screening will be conducted on potentially interested participants to provide general information about the study and determine suitability of inclusion. Patients willing to participate and appearing to meet the inclusion criteria will be required to attend an in-person briefing on the rationale and study aims, inclusion and exclusion criteria, assessments to be performed, and components and characteristics of the intervention. After clarification by the research staff of any participant's doubts or questions, signatures of informed consent will be obtained from participants that meet the eligibility criteria, and appointments for the baseline assessment will be given. Participant flow from recruitment to randomization stages are shown in Figure 1.

Enrollment

Upon obtaining signed informed consents, participant demographics and medical history will be collected, and a medical/physical examination will be performed to ensure feasibility of participant

inclusion in the study. Subsequently, a sleep study through a complete full-night polysomnography and other sleep measurements (daytime sleepiness, sleep quality, circadian preference, and functional outcomes of OSA) will be conducted on and taken from each participant. Furthermore, lifestyle habits such as diet, exercise and tobacco and alcohol consumption will also be measured, as well as subjective health-related quality of life, and depressive and anxiety symptoms related to OSA. After completion of participant's medical and sleep studies, objective measurements of cardiorespiratory fitness and body composition will be taken from each participant. All test trials will therefore be performed over three different days during a one to two-week period.

Randomization

After completing baseline measurements, eligible participants will be randomly assigned to either a control group or an interdisciplinary intervention group using a computer generated simple (unrestricted) randomization [25]. Each participant will be specifically informed of which arm they have been assigned to and requested not to reveal their allocation to the research staff involved in further assessments. Bias related to unblinded participants, treatment counsellors and/or outcome assessors affecting data validity will be addressed by achieving different levels of blinding across the study personnel and participants where feasible. Therefore, study personnel responsible for data collection and analysis will be blinded to allocation assignments at the follow-ups, and blinding of participants to details of study manuals and hypothesis will be attained. When blinding is not possible, rigorous procedures of standardization of data collection and intervention, through study manuals and continuous assessment of fidelity, will be followed to avoid potential bias and ensure internal and external validity of the study [26].

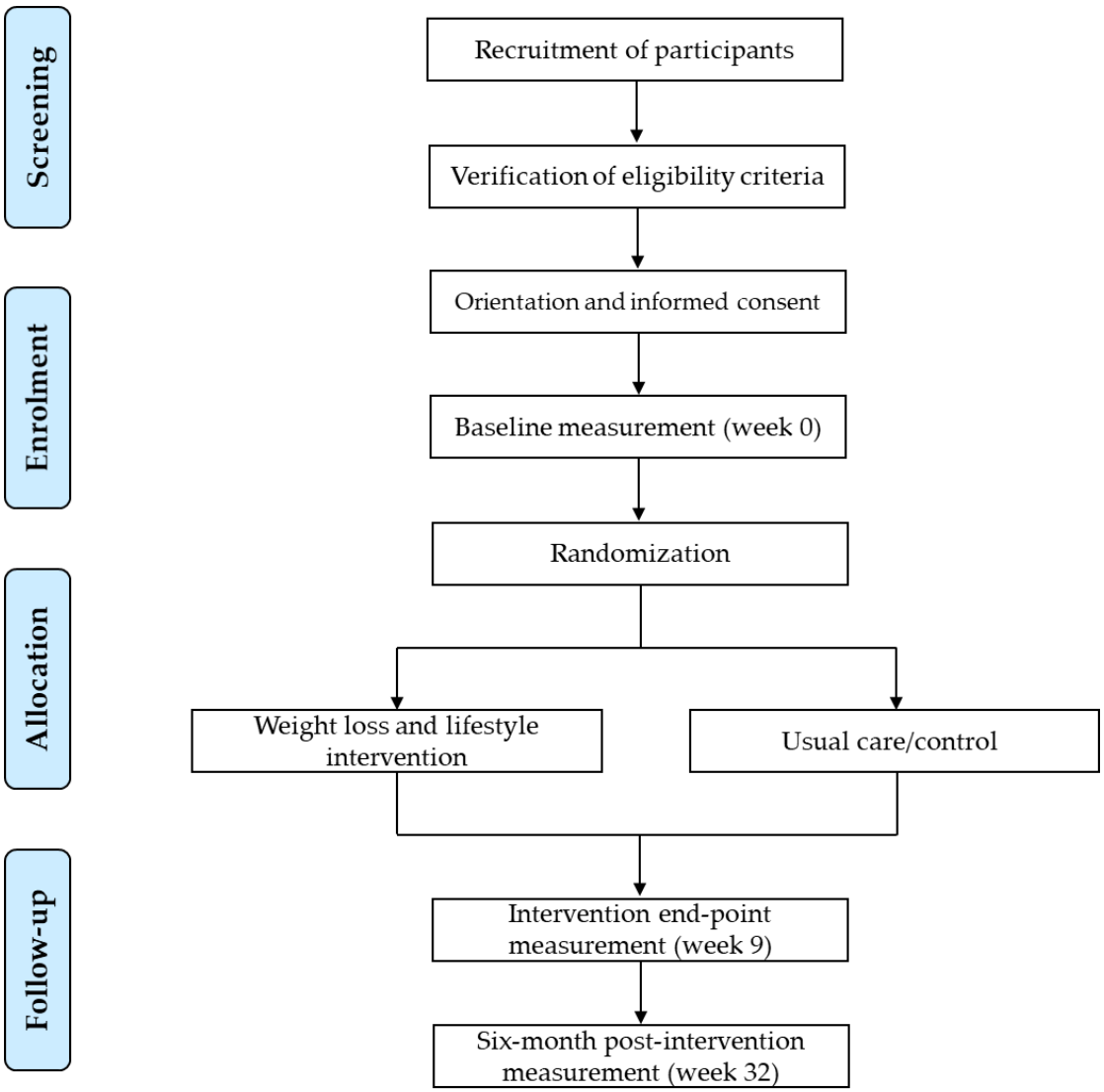

Figure 1. Flow diagram of the INTERAPNEA study participants.

3.4. Assessments

The primary outcome of INTERAPNEA study is the reduction in the number of apnea and/or hypopnea episodes per hour, i.e. AHI, assessed using a full-night ambulatory polysomnography. The main secondary outcomes include other neurophysical and cardiorespiratory polysomnographic outcomes, body weight and composition, physical fitness/cardiorespiratory fitness, and health blood biomarkers. Other variables of interest are subjective measurements of depressive and anxiety symptomatology related to OSA, impaired sleep (i.e. daytime sleepiness, sleep quality, and functional outcomes of OSA), health-related quality of life, and other lifestyle habit measurements (i.e. diet, physical activity, alcohol and tobacco consumption). All outcomes will be measured at baseline (week 0), intervention end-point (week 9), and 6 months post-intervention (week 32).

Assessment of primary and secondary outcomes will be organized and completed over three different days during a one to two-week period:

- Day 1: Potential participants will attend a medical examination and a blood test after a 12-hour overnight fast at the Sleep Unit of Virgen de las Nieves University Hospital.
- Day 2: Eligible participants will complete a full-night in-laboratory polysomnography (PSG; the gold-standard objective testing recommended by the AASM [27]), at the Sleep and Health Promotion Laboratory (CIMCYC). In order to avoid potential CPAP influence on PSG outcomes, participants will be required to withdraw from CPAP during the week prior to the PSG at baseline and follow-ups [28]. Prior to the PSG, participants will also complete a set of questionnaires assessing subjective variables related to sleep, general physical and psychological health, and lifestyle habits including diet, physical exercise, and alcohol and tobacco consumption.
- Day 3: During the third and last assessment day, participants will be required to attend the iMUDS for the measurement of anthropometric parameters, body composition and cardiorespiratory fitness.

Baseline physical activity and sleep habits will also be obtained through a seven-day self-reported daily step log and sleep diary. See Table 2 for study outcomes and measurements.

Table 2. INTERAPNEA study outcomes and measurements.

Variable	Measurement	Assessment
General health history and sociodemographic information	General medical examination (i.e. anamnesis, physical exploration, vital measurements, etc.)	Week 0
	Clinical and socio-demographic interview	Week 0, 9, 32
	Fasting blood test	Week 0, 9, 32
Sleep quality and health-related quality of life		
Sleep habits	Sleep diary	Week 0, 9, 32
Circadian preference/chronotype	Morningness/Eveningness Questionnaire	Week 0, 9, 32
Sleep quality	The Pittsburgh Sleep Quality Index	Week 0, 9, 32
Daytime sleepiness	Epworth Sleepiness Scale	Week 0, 9, 32
Perceived health-related quality of life	Sleep Apnea Quality of Life	Week 0, 9, 32
	Short-Form 36 Health Survey	Week 0, 9, 32
	General Health Questionnaire	Week 0, 9, 32
Objective sleep		
Neurophysiological outcomes	Polysomnography equipment	Week 0, 9, 32
Cardiorespiratory outcomes	Polysomnography equipment	Week 0, 9, 32
Body weight and composition		
BMI and anthropometric measurements	Weight and height measurement, and neck, chest and waist circumferences	Week 0, 9, 32
Body composition	Dual Energy X-ray Absorptiometry	Week 0, 9, 32
Lifestyle habits		
Physical exercise habits	Spring-levered pedometer and daily step logs	Week 0, 9, 32
Dietary habits	Food Behavior Checklist	Week 0, 9, 32
	Mediterranean Diet Adherence Screener	Week 0, 9, 32
Tobacco dependence and consumption	Self-reported tobacco consumption logs	Week 0, 9, 32
	The Fagerstrom Test for Nicotine Dependence	Week 0, 9, 32
Alcohol consumption	Self-reported alcohol consumption logs	Week 0, 9, 32
Physical fitness		
Cardiorespiratory fitness	2-km walk test	Week 0, 9, 32
Subjective physical fitness	International Fitness Scale	Week 0, 9, 32
Daily functioning and mood		
Functional outcomes related to sleepiness	Functional Outcomes of Sleep Questionnaire	Week 0, 9, 32
Subthreshold anxiety symptoms	State-Trait Anxiety Inventory	Week 0, 9, 32
Subthreshold depression symptoms	Beck Depression Inventory-Fast Screen	Week 0, 9, 32
	Inventario de Depresión Estado-Rasgo	Week 0, 9, 32

3.5. Endpoints

Primary endpoint

The primary outcome of the INTERAPNEA study is AHI, defined as the number of apnea (90% or greater drop in airflow for 10 seconds or longer) and hypopneas (30% or greater drop in airflow for 10 seconds or longer associated with ≥ 3% oxygen desaturation or an arousal) episodes per hour of sleep [29].

We will measure this outcome and other neurophysical and cardiorespiratory secondary outcomes through an in-laboratory PSG using SOMNOScreen™ PSG-Tele (SOMNOmedics, GmbH, Randersacker, Germany), or Somté PSG v2 system (Compumedics Limited, Abbotsford, Australia).

The recordings will include all recommended physiologic signals such as electroencephalogram (three channels: F4-M1, C4-M1, O2-M1), electrooculogram (two channels: E1 and E2), electromyogram (two channels: submental and anterior tibialis muscles), and electrocardiogram (two channels). Cardiorespiratory measurements will include oral and nasal airflow (triple thermistor), oxyhaemoglobin saturation (SpO2) and pulse-rate (pulse oximeter), respiratory effort (chest and abdomen bands), and body position (sensor). All electrodes will be placed in accordance with the international 10-20 system [30], and recordings will be automatically and manually scored in 30-second epochs [31] by trained physicians using DOMINO (v2.7, SOMNOmedics, GmbH, Randersacker, Germany), or ProFusion PSG 3 (v3.3, Compumedics Limited, Abbotsford, Australia) associated computer software. All parameters, settings, filters, technical specifications, sleep stage scoring and event scoring will be performed in accordance with the AASM Manual for the Scoring of Sleep and Associated Events [29].

We will also specifically analyze AHI in rapid eye movement (REM) and non-REM sleep stages (N1, N2, and N3). Although it has been shown that REM apnea episodes may yield to more adverse cardiovascular consequences than non-REM obstructions [32], previous similar RCTs have rarely included the reduction in AHI differentiated by these sleep stages [1].

Secondary Endpoints

Neurophysical and cardiorespiratory polysomnographic outcomes

Secondary polysomnographic outcomes related to OSA, measured by PSG as above mentioned, are oxygen desaturation index (number of oxygen desaturation ≥ 3% per hour), SpO2 mean (average of oxygen saturation), SpO2 nadir (minimum oxygen saturation), sleep efficiency (total sleep time/total time in bed), sleep latency, wake after sleep onset, REM sleep stage, and nonREM sleep stages (N1, N2, and N3).

Physical fitness

Cardiorespiratory fitness will be measured through a 2-km walking test, which has been widely used and validated for accurate estimation of maximum oxygen uptake (VO_{2max}) [33]. Participants will be required to walk over a marked 2 km track on a firm surface wearing a heart rate monitor (Polar RS800cx, Polar Electro, Kempele, Finland). Walking time and heart rate (HR) will be recorded at the end of the test. The maximal aerobic power will then be calculated considering age, BMI, performance time, and HR with the following formula VO_{2max} (ml/min/kg) = 116.2 - 2.98 * walking time (sec) - 0.11 * HR -0.14 * age - 0.39 * BMI [34]. Participant's scores will be obtained and placed within a fitness category. Subjective physical fitness will also be measured using the International Fitness Scale (IFIS) [35].

Body weight and composition

Body weight and height will be measured using a calibrated scale and stadiometer (model 799, Electronic Column Scale, Hamburg, Germany) with participants wearing undergarments. Neck, chest and waist circumferences will also be measured following standard procedures recommended by the International Society for the Advancement of Kinanthropometry (ISAK) [36]. Body composition measurements including fat mass (kg), fat free mass, lean mass (kg), visceral adipose tissue (kg), and bone mineral density (g/cm2) will be obtained through a full-body dual energy X-ray absorptiometry (DXA) scanner (Discovery Wi, Hologic, Inc., Bedford, MA, USA). An additional two-dimensional lumbar spine DXA scanner will also be performed in order to obtain the trabecular bone score (TBS); an index of bone microarchitecture that consistently and significantly predicts bone fracture risk. Quality controls, positioning of participants and analyses of results will be performed following the manufacturer's recommendations. Automatic delineation of anatomic regions will be performed using APEX 4.0.2. software.

Blood biomarkers

Blood biomarkers will include glucose metabolism (glucose [mg/dl], insulin [IU/ml] and insulin resistance as indicated by the homeostasis model assessment of insulin resistance [HOMA-IR] index), lipid metabolism (total cholesterol [mg/dl], high-density lipoprotein cholesterol [HDL-C; mg/dl], low-density lipoprotein cholesterol [LDL-C; mg/dl], triglycerides [mg/dl], and apolipoproteins A1 and B [mg/dl]), and liver function (aspartate aminotransferase [AST; IU/l], alanine aminotransferase [ALT; IU/l], γ-glutamyltransferase [γ-GT], and fatty liver index [FLI]). These variables will be measured through blood samples obtained from participants' antecubital vein in a supine position during the morning in a fasting state. Samples will be collected into prechilled ethylene diamine tetra-acetic acid-containing tubes (Vacutainer SST, Becton Dickinson, Plymouth, UK) and immediately centrifuged (i.e. 15 minutes at 3,000 rpm), aliquoted and stored at −80°C for further plasma analysis. Glucose levels will be measured by spectrophotometric techniques (AU5800, Beckman Coulter, Brea, California, USA). Insulin will be assessed by chemiluminescence immunoassay with paramagnetic particles (UniCel DxI 800, Beckman Coulter, Brea, California, USA). HOMA-IR will be calculated as fasting glucose (mmol/l) times the level of fasting insulin (UU/ml) divided by 22.5. Total cholesterol, HDL-C, triglycerides, and apolipoproteins A1 and B will be automatically evaluated by spectrophotometric techniques (AU5800, Beckman Coulter, Brea, California, USA). LDL-C will be calculated as the level of total cholesterol minus the level of HDL-C minus 0.45 times the level of triglycerides. AST, ALT and γ-GT will be calculated by absorption spectrophotometric techniques (Beckman Coulter, Brea, California, USA). FLI will be calculated with the formula FLI = ((e 0.953·loge (Triglycerides) + 0.139·BMI + 0.718·loge (γ-GT) + 0.053·Waist Circumference -

15.745)) / ((1 + e 0.953·loge (Triglycerides) + 0.139·BMI + 0.718·loge (γ-GT) + 0.053·Waist Circumference - 15.745)) ·100.

Systolic blood pressure (mm Hg), diastolic blood pressure (mm Hg) and mean blood pressure (mm Hg) will also be considered as cardiometabolic risk outcomes. Blood pressure will be measured with an ambulatory blood pressure monitor (Omron M3 Blood Pressure Monitor, OMRON Healthcare, Hoofddorp, Netherlands) in a sitting position after at least 5 minutes of rest. The mean of two measurements will be recorded. Mean blood pressure will be calculated at each reading as one third of systolic pressure plus two thirds of diastolic pressure.

Lifestyle habits: Dietary habits, physical activity, smoking, and alcohol intake

Participants' dietary habits will be evaluated using the validated 14-item Mediterranean diet screener (MEDAS), which evaluates food consumption frequency (12 items) and characteristic dietary habits of the Mediterranean diet (2 items) [37]. MEDAS items are scored with 0 or 1, the total score ranging from 0 to 14 points. The 22-item Food Behavior Checklist (FBC) will also be used to assess participants' food intake and habits [38]. FBC comprises seven subscales including consumption of fruit and vegetables (9 items), diet quality (4 items), fast food (3 items), dairy/calcium (2 items), sweetened beverages (2 items), meat (1 item) and food security (1 item). This instrument has been shown to be effective at evaluating dietary behavior changes after nutrition education interventions promoting healthy diets [38].

Physical activity will be measured using daily step logs recorded by participants with a spring-levered pedometer (OcioDual, Alicante, Spain). Participants will be required to wear the pedometer all day and register the number of steps achieved per day in a seven-day step log. The average steps per day will then be calculated at baseline and follow-ups.

Regarding the remaining lifestyle habits, smoking and alcohol intake will be measured at baseline and follow-ups using seven-day self-reported tobacco and alcohol consumption logs. Recordings will include number of cigarettes/alcoholic units consumed per day, cigarette brand/type of alcoholic drink, time, situation, and perceived pleasure (from 0 to 10). The validated form of the Fagerström Test for Nicotine Dependence [39] will also be used to assess participants' nicotine dependence in all assessments.

Daily functioning and mood

OSA impact on daily functioning and mood will be measured through validated versions of the Functional Outcomes of Sleep Questionnaire (FOSQ) [40], Beck Depression Inventory-Fast Screen (BDI-FS) [41], State-Trait Anxiety Inventory (STAI) [42] and State-Trait Depression Inventory [43]. It has been shown that impaired daytime functioning and depressive and anxiety symptoms are very common in patients with OSA, being higher in patients with more severe OSA and a greater BMI

[44]. Hence, participants will complete a set of questionnaires on these symptoms not only to measure inclusion/exclusion criteria but also to analyze potential changes in daily functioning and mood driven by the INTERAPNEA study intervention.

Daytime sleepiness, sleep quality and health-related quality of life

The Epworth Sleepiness Scale (ESS) [45], an 8-item Likert-based scale, will be used to obtain subjective measurements of participant's daytime sleepiness. Excessive daytime sleepiness is the most common consequence of OSA due to sleep fragmentation and deprivation, and one of the mediating factors for other OSA outcomes such as daily functioning, social and occupational disturbances [6-8].

As sleep quality is also closely related to daily functioning, mood and, thus, participant's general quality of life and well-being [46,47], we will measure potential benefits of the INTERAPNEA study intervention on these variables through the validated versions of the Pittsburgh Sleep Quality Index (PSQI) [48], Sleep Apnea Quality of Life (SAQLI) [49], Short-Form 36 Health Survey (SF-36) [50], and General Health Questionnaire (GHQ-28) [51].

In addition, we will subjectively measure circadian preference or individual's chronotype using the validated reduced 5-item version of the Morningness-Eveningness Questionnaire (MEQ) [52], an outcome which has been closely related to age, BMI and, in turn, OSA [53]. Evidence suggests that evening-type chronotype may be highly associated with greater unhealthy eating behaviors, sleep disruption, poor sleep quality and mood disturbances, all playing a part in the development and severity of OSA [53,54].

3.6. Weight Loss and Lifestyle Intervention Arm

The design, implementation and evaluation of the INTERAPNEA study intervention components and characteristics are based on results of previous epidemiological and clinical research [1,10] as well as on international evidenced-based clinical practice guidelines for the management of OSA [14,19]. Considering our previous research [1] and with the final aim of the intervention being adaptable to actual primary health-care settings, the intervention will last eight weeks, and will be composed of five different modules (i) nutritional behavior change, (ii) moderate aerobic exercise, (iii) smoking reduction and cessation, (iv) alcohol intake avoidance, and (v) sleep hygiene (see Table 3). Each component will include group-based weekly sessions of 60-90 minutes lead and supervised by a trained professional in the field (i.e. human nutrition and dietetics, physical activity and sport sciences, and psychology).

The key-factor of this interdisciplinary intervention will be the use of the Transtheoretical Model of Health Behavior Change (TM) by Prochaska and Diclemente [55]. This well-evidenced model of

behavior change is based on integrating different intervention theories into an interventional approach that considers different stages, processes and principles of change with the premise of establishing sustainable health-related behaviors or habits [55]. Consciousness raising, self-reevaluation, counterconditioning, stimulus control, contingency management, goal-setting, self-monitoring, self-efficacy, and decisional balance are some of the processes and principles of change addressed by this theory and, therefore, included in the five different INTERAPNEA intervention components. Physical and dietary interventions for weight loss using strategies of TM and, thus, psychological support, have been shown to be more effective than other approaches in overweight and obese patients [56] and, specifically, in those with OSA [1].

Table 3. Description and timing of the INTERAPNEA intervention modules and components.

Module	Objectives/Description	Number of sessions	Frequency of sessions	General behavioral change techniques
Nutritional behavior change	Nutrition education and dietary patterns change	8	Once a week	• Motivation and preparation for action • Goal-setting and action-planning • Self-monitoring and functional behavioral analysis • Review of behavioral goals, action plans, and adherence • Problem solving and social skills • Self-efficacy, maintenance, and relapse prevention
Physical exercise	Supervised moderate aerobic exercise and increase daily steps by 15% each week	8	Once a week	
Sleep hygiene	Change of inappropriate sleep habits: insufficient sleep, consumption of coffee, alcohol and tobacco, and inappropriate sleep schedule and environment	4	Once each two weeks	
Tobacco cessation	Nicotine and cigarette fading: reduction of nicotine and number of cigarettes by 30% each week	8	Once a week	
Alcohol avoidance	Alcohol consumption fading: reduction of alcohol consumption by 30% each week	4	Once each two weeks	

Nutritional behavior change

Diet quality and dietary patterns have been shown to be closely related to biologic pathways involved in chronic disease etiology [57] and, specifically, to sleep disruption, fragmentation and poor sleep quality found in OSA [58]. Recent studies have shown that high-fat intake is associated with lower sleep efficiency and REM sleep and higher arousal index, whereas high-carbohydrate intake may improve sleep duration and architecture by producing reductions in sleep-onset latency and higher proportions of REM sleep [58]. Regarding intake of micronutrients, vitamin D — which has been associated with insulin resistance in OSA [59] — and magnesium deficiencies have also been related to shorter sleep duration, poorer sleep quality and higher daytime sleepiness [60,61]. Therefore, dietary components including milk, fish, fruit and vegetables may yield beneficial effects on sleep and, in turn, OSA [58].

Furthermore, evidence suggests that sleep disturbances occurred in OSA, in turn, have adverse consequences on calorie intake and expenditure, exposing therefore a two-way relationship between dietary habits and sleep [62]. Empirical studies have revealed that sleep fragmentation and deprivation are related to higher energy intake of unhealthy food due to increased hunger, food craving, food reward and portion size selection [63-65]. Neurocognitive impairments found in patients with OSA such as attention and episodic memory deficits [66] have also been associated with higher intake of saturated fats, loss of control over food intake, and thus uncontrolled eating [67].

Hence, The INTERAPNEA intervention includes a nutrition module comprising eight sessions (once a week) of 60-90 minutes in a group format addressing dietary patterns using integrated techniques of nutrition education and behavioral change such as specific goal-setting, cognitive restructuring, stimulus control, progressive muscle relaxation, social skills and assertiveness, and problem solving skills. The nutrition education is based on the World Health Organization (WHO) latest recommendations on food intake and healthy diet (see Table 4 for detailed topics) and each session will follow a three-part format: i) Brief review of previous session and participant's adherence to recommendations; ii) Development of the main nutrition education component of each session using an interactive group discussion layout; iii) Resolution of participant's questions and/or concerns, and setting of specific goals. No specific or individualized diet will be indicated to participants.

Table 4. Description of nutrition education per session.

Session	Nutrition education topics
Session 1	Adverse consequences of obesity, importance of healthy nutrition and body composition on health, and positive effects of changes in nutrition.
Session 2	Maintenance of a healthy nutrition based on the Harvard Plate model: increasing consumption of healthy food (vegetables, fruits, legumes, nuts, extra olive virgin oil, fish and shellfish, white meat, eggs and herbs) and decreasing consumption of unhealthy food (ultra-processed foods, excessive salt consumption, processed meats, red meat, alcohol, and high-calorie foods and beverages).
Session 3	Food myths and health risks of miracle diets.
Session 4	Strategies to improve satiety and decrease appetite: decreasing dishes dietary energy density, choosing food with low dietary energy density, managing dietary fat intake, including enough fibre and protein quantity, limiting sugar and ultra-processed foods, choosing water and low-calorie beverages, and managing portion sizes.
Session 5	Healthy breakfast and snacks: avoiding unhealthy breakfast and snacks and turning them into healthy.
Session 6	Healthy cooking, food purchase and choices when eating out.
Session 7	How to read nutritional labels of food and distinguish between healthy and unhealthy food.
Session 8	Nutritional strategies to improve sleep quality.

Physical exercise

Physical exercise has been shown to be effective in enhancing OSA outcomes and health-related consequences [1,68,69]. Due to the close association between OSA and obesity, a significant and sustainable increase of physical activity could lead to a reduced body weight and, in turn, improvement of the upper airway structure, function, and resting lung volume [12]. Furthermore, physical exercise could also assist the balance of energy intake and expenditure [70], and improve respiratory center modulation through a reduction of the high leptin and ghrelin hormone levels, abnormalities linked to excessive energy intake and found in OSA patients [71]. Yet, some research found that exercise benefits on OSA were independent to weight loss [69], suggesting that there are other related mechanisms potentially leading to OSA enhancement such as the increase of sleep efficiency and slow wave sleep [72], and a decrease of fluid accumulation implicated in the upper airway collapse [73], both due to the direct association between physical exercise and sleep.

Therefore, the INTERAPNEA study will include an eight-week physical exercise program consisting of weekly 60 min-sessions of supervised moderate intensity aerobic exercise (i.e. 55-65% of the heart rate reserve) and individualized goal-setting of increasing daily steps per week. Previous studies have emphasized that walking may be the exercise modality, achieving higher levels of weight loss and increased cardiorespiratory fitness in adults with obesity and CPAP-treated OSA [74]. Thus, in the weekly supervised training sessions, participants will be required to walk at a moderate intensity for 60 minutes wearing a heart rate monitor in order to train themselves to walk at that intensity during the rest of the week. With respect to goal-setting, they will be advised to increase their daily steps by 15% per week, based on their daily steps logs.

Sleep hygiene

Sleep hygiene refers to the practice of certain behaviors that facilitate sleep onset and maintenance (e.g. regular sleep schedule, appropriate sleep environment, exercise-training, and healthy nutrition), and avoidance of habits interfering with sleep (e.g. daytime napping, smoking, alcohol intake, and use of hypnotics) [75]. Patients with OSA frequently exhibit poor sleep hygiene including voluntary sleep restriction, irregular sleep schedule, inappropriate sleep environment, and excessive consumption of alcohol, nicotine and/or caffeine [76]. Accordingly, previous studies have supported the inclusion of this component on the treatment of OSA as effective in improving sleep quantity and efficiency, and therefore daytime sleepiness [1,77,78].

The INTERAPNEA study intervention will include a sleep hygiene module comprising 60 min sessions supervised by a psychologist specialized in the evaluation and treatment of sleep disorders. As most sleep hygiene topics will be covered in simultaneous modules, there will be four sessions distributed over the eight weeks of the intervention, consisting of sleep hygiene education on causes

of sleep disturbances and mistaken sleep related knowledge (see Table 5). Sessions will also be based on treating those frequent inadequate sleep habits found in patients with OSA, i.e. sleep restriction, irregular schedule and inappropriate sleep environment.

Table 5. Summary of components of the sleep hygiene module per session.

Session	Intervention objectives/components
Session 1	• Goal-setting and action-planning: Objective specification and commitment • Self-monitoring: Sleep diary • Psychoeducation: What is sleep hygiene? • Cognitive restructuring: Irrational, false or inaccurate beliefs about sleep • Breathing and relaxation techniques: Diaphragmatic breathing and progressive muscle relaxation
Session 2	• Review of behavioral goals, action plans, and compliance (participant's homework) • Self-monitoring: Sleep diary • Psychoeducation: Voluntary sleep restriction; coffee, alcohol and tobacco consumption before sleep; and irregular sleep schedule and environment. • Cognitive restructuring: Irrational, false or inaccurate beliefs about sleep • Review of diaphragmatic breathing and progressive muscle relaxation
Session 3	• Review of behavioral goals, action plans, and compliance (participant's homework) • Self-monitoring: Sleep diary • Vicarious and self-reinforcement: Changes in sleep habits achieved and benefits • Stimulus control and bedtime restriction • Review of diaphragmatic breathing and progressive muscle relaxation
Session 4	• Review of behavioral goals, action plans, and compliance (participant's homework) • Self-monitoring: Sleep diary • Vicarious and self-reinforcement: Changes in sleep habits achieved and benefits • Review of all intervention components: Main factors of sleep hygiene, diaphragmatic breathing and progressive muscle relaxation, stimulus control and bedtime restriction • Maintenance and relapse prevention: Analysis of high risk situations for unhygienic sleep.

Reduction and avoidance of tobacco consumption

Smoking has been related to the worsening of OSA via different mechanisms such as changes in sleep architecture and increase of arousal threshold from sleep, reduction of the upper airway muscle tones and neural reflexes, and increased inflammation of the upper airway, all due to nicotine and smoke inhalation [21]. In turn, OSA could also be a predisposing factor for smoking addiction, nicotine acting as a reward or self-medication related to the depressive and anxiety symptoms commonly found in OSA [79]. Although this association has been well elucidated, there are no empirical evidences of the potential beneficial effects of smoking cessation on OSA as, surpringsily, there are no studies focusing on active smoking cessation interventions in patients with this condition [1].

Therefore, we will include a smoking reduction and avoidance module in the INTERAPNEA study intervention. Participants with smoking addiction and willing to quit will be required to attend a weekly 60-90 minute session over eight weeks lead by two clinical psychologists. The specific intervention is based on the group behavior therapy for smoking cessation by Becoña et al. [80]. This therapy seeks the progressive reduction of tobacco consumption through the use of nicotine and

cigarette fading [81], and behavior-change techniques such as information on smoking, self-monitoring, stimulus control, avoidance of withdrawal symptoms, and relapse prevention (see Table 6). Nicotine and cigarette fading has been shown to be the most effective method to reduce and stop smoking with abstinence rates of 86% at the end of treatment and nearly 60% at a 12 month follow-up [82].

Thus, participants will be mainly required to keep a daily record of number of cigarettes smoked and triggers for smoking (self-monitoring), change the type of cigarette smoked to a lesser nicotine content brand each week (30%, 60% and 90% nicotine reductions from baseline), reduce the number of cigarettes smoked by 30% weekly, and avoid smoking in three different situations per week (stimulus control). Through the sessions, other behavior change techniques will be used such as discussion of health consequences of smoking and quitting (motivation), muscle and cognitive relaxation techniques to address withdrawal symptoms, and identification of high-risk situations for smoking and problem-solving skills (relapse prevention).

Table 6. Summary of components of the smoking cessation module per session.

Session	Intervention objectives/components
Session 1	• Goal-setting and action-planning: Objective specification and commitment • Self-monitoring: Cigarette consumption logs • Psychoeducation: Cigarette components and smoking consequences • Cognitive restructuring: Irrational, false or inaccurate beliefs about smoking cessation • Stimulus control: Reduction strategies • Nicotine and cigarette fading: Reduction of nicotine/number of cigarettes by 30% from baseline • Breathing and relaxation techniques: Diaphragmatic breathing and progressive muscle relaxation
Session 2	• Review of behavioral goals, action plans, and compliance (participant's homework) • Self-monitoring: Cigarette consumption logs • Cognitive restructuring: Irrational, false or inaccurate beliefs about smoking cessation • Stimulus control: Smoking avoidance in three different situations and other reduction strategies • Nicotine and cigarette fading: Reduction of nicotine/number of cigarettes by 30% from week 1 • Maintenance and relapse prevention: Avoidance of withdrawal symptoms • Review of diaphragmatic breathing and progressive muscle relaxation
Session 3	• Review of behavioral goals, action plans, and compliance (participant's homework) • Self-monitoring: Cigarette consumption logs • Vicarious and self-reinforcement: Changes in smoking achieved and benefits • Stimulus control: Smoking avoidance in six different situations and other reduction strategies • Nicotine and cigarette fading: Reduction of nicotine/number of cigarettes by 30% from week 2 • Maintenance and relapse prevention: Avoidance of withdrawal symptoms • Review of diaphragmatic breathing and progressive muscle relaxation
Session 4	• Review of behavioral goals, action plans, and compliance (participant's homework) • Self-monitoring: Cigarette consumption logs • Vicarious and self-reinforcement: Changes in smoking achieved and benefits • Stimulus control: Smoking avoidance in nine different situations and other reduction strategies • Nicotine and cigarette fading: Reduction of nicotine/number of cigarettes by 30% from week 3 • Maintenance and relapse prevention: Avoidance of withdrawal symptoms • Review of diaphragmatic breathing and progressive muscle relaxation

Session 5	• Review of behavioral goals, action plans, and compliance (participant's homework) • Self-monitoring: Cigarette consumption logs • Vicarious and self-reinforcement: Changes in smoking achieved and benefits • Abstinence planning: Setting the day when abstinence starts • Problem solving and social skills: High risk situations for smoking and alternative behaviors • Maintenance and relapse prevention: Avoidance of withdrawal symptoms • Review of diaphragmatic breathing and progressive muscle relaxation
Sessions 6, 7, 8	• Review of behavioral goals, action plans, and compliance (participant's homework) • Self-monitoring: Cigarette consumption logs/Review of abstinence • Abstinence planning: Setting the day when abstinence starts • Vicarious and self-reinforcement: Changes in smoking achieved and benefits • Problem solving and social skills: High risk situations for smoking and alternative behaviors • Review of diaphragmatic breathing and progressive muscle relaxation • Maintenance and relapse prevention: Difference between lapse and relapse

Reduction and avoidance of alcohol intake

Alcohol intake has also been related to the development and worsening of OSA not only for its direct and indirect effects on weight gain but also due to its negative impact on breathing parameters during sleep [20]. Recent meta-analyses on alcohol and risk of sleep apnea emphasized that alcohol intake increases the risk of breathing cessation episodes by 25%, thus increasing AHI and reducing mean SaO2 during sleep [83]. Potential explanations of these adverse consequences may be the alcohol-related hypotonia of oropharyngeal muscles during sleep, and depression of the arousal response to asphyxia, both caused by the alcohol depressant effects on the central nervous system [84].

Therefore, the INTERAPNEA study intervention will include an alcohol intake reduction and avoidance module supervised by two clinical psychologists. As we will be treating excessive alcohol intake as opposed to alcohol dependence, this module will last eight weeks comprising fortnightly sessions of 60 minutes. Similar to the smoking cessation module, the main content of this specific component is the progressive reduction of alcohol intake in those participants with no alcohol addiction but excessive consumption (see Table 7). Thus, participants will be indicated to reduce the number of units of alcohol consumed per day/week by 30% each week, keeping a log of alcohol-consumption per day including units of alcohol consumed and triggers of consumption. During the sessions, participants will receive detailed information of alcohol general and specific to OSA health-related consequences. Furthermore, behavior change techniques such as stimulus control, muscle and cognitive relaxation and problem-solving skills related to alcohol consumption will be used.

Table 7. Summary of components of the alcohol avoidance module per session.

Session	Intervention objectives/components
Session 1	• Goal-setting and action-planning: Objective specification and commitment • Self-monitoring: Alcohol-consumption logs • Psychoeducation: Alcohol consumption and adverse consequences for obstructive sleep apnea • Cognitive restructuring: Irrational, false or inaccurate beliefs about alcohol consumption • Alcohol fading: Reduction of alcohol consumption/number of alcoholic drinks by 30% from baseline • Breathing and relaxation techniques: Diaphragmatic breathing and progressive muscle relaxation
Session 2	• Review of behavioral goals, action plans, and compliance (participant's homework) • Self-monitoring: Alcohol-consumption logs • Cognitive restructuring: Irrational, false or inaccurate beliefs about smoking cessation • Alcohol fading: Reduction of alcohol consumption/number of alcoholic drinks by 30% from week 1 • Stimulus control: Reduction/abstinence strategies • Review of diaphragmatic breathing and progressive muscle relaxation
Session 3	• Review of behavioral goals, action plans, and compliance (participant's homework) • Self-monitoring: Alcohol-consumption logs • Vicarious and self-reinforcement: Changes in alcohol consumption achieved and benefits • Abstinence planning: Setting the day when abstinence starts • Stimulus control: Reduction/abstinence strategies • Review of diaphragmatic breathing and progressive muscle relaxation
Session 4	• Review of behavioral goals, action plans, and compliance (participant's homework) • Self-monitoring: Alcohol-consumption logs • Vicarious and self-reinforcement: Changes in alcohol consumption achieved and benefits • Problem solving and social skills: High risk situations for drinking alcohol and alternative behaviors • Review of all intervention components: diaphragmatic breathing and progressive muscle relaxation, stimulus control • Maintenance and relapse prevention: Difference between lapse and relapse

3.7. Assessment of Intervention Compliance and Integrity

Integrity of the intervention and treatment fidelity will be evaluated and ensured through the design and implementation of different strategies of process assessment, monitoring and enhancement in order to guarantee internal and external validity of the trial [85].

Firstly, regarding the study design and provider of intervention training, we developed a comprehensive hand-book for the qualified INTERAPNEA study intervention providers/professionals/training personnel of each module (nutrition, physical exercise, sleep hygiene, and tobacco and alcohol consumption). Each intervention manual identifies the theoretical model of the intervention and provides detailed descriptions of session objectives, treatment guidelines in accordance with each objective (i.e. contents, tasks and activities, recommendations, and timing), participant's homework, and material needed for each session. We will also provide each participant with an adapted patient-handbook for each intervention component including descriptions of sessions, and work and logging sheets.

Secondly, we will ensure fidelity in the treatment delivery, receipt, and enactment through the use of these intervention protocols/manuals and monitoring of the implementation. Regarding the

treatment delivery, the standardization of the intervention will support the protocol adherence of providers and the treatment differentiation (i.e. the delivery of the target treatment and no other). Furthermore, we will include a check-list for provider's self-report concerning the achievement of session objectives. With respect to the treatment receipt and enactment, fidelity will be assessed and confirmed through different strategies such as the structuring of the intervention around achievement-based objectives, collecting and reviewing of participants self-monitored data (daily steps log, sleep diaries, alcohol and tobacco consumption records), and information delivery in different formats (e.g. written in the handbooks, and verbal and visual in the sessions).

Finally, apart from the above mention strategies, we will consider complementary approaches in order to reduce participant drop-out rates and increase adherence such as prevention of commitments or vacation periods, use of well-equipped and conditioned facilities, and supervision by a qualified and certified pair of providers in each session motivating and supporting participants. Participants' attendance to each intervention session will be recorded by providers, and phone-calls will be made to assess causes of absence and determine further participation in the intervention.

3.7. Usual Care Arm

Participants with moderate-severe OSA randomly assigned to the usual care group (control) will receive, apart from CPAP treatment, a 30 min session of general advice on weight loss and lifestyle change from a sleep disordered-breathing specialist. Informative leaflets describing the positive effects of healthy nutrition, physical activity, sleep hygiene and tobacco and alcohol avoidance for OSA will also be provided to these participants. Additionally, the opportunity to receive the INTERAPNEA study intervention will be offered to this control group after the six month follow-up.

3.8. Serious Adverse Events

Serious adverse events occurring to participants from baseline to intervention endpoint and/or 6-month follow-up, related or unrelated to the study intervention or participation, will be collected and registered over the course of the trial by the study personnel. These are defined as events that lead to death, life-threatening illness, permanent impairment, or hospitalization with a serious health condition.

3.9. Power and Sample Size

The sample size calculation and power of the study are based on the data of previously reported studies contrasted, combined, and synthesized in our recent systematic review and meta-analysis [1]. We considered following the formula $\boldsymbol{n = \frac{2(Z_{\alpha} + Z_{1-\beta})^2 \sigma^2}{\Delta^2}}$, where n is the required sample size, Zα and Z(1-β) are the constants set by convention according to the accepted α error and power of the study, respectively, σ is the estimated standard deviation, and Δ is the expected effect size. Therefore,

we expect to detect an effect size of -8.36 on AHI (pooled raw mean difference of previous trials) [1], considering a type 1 error/α error of 5%, and a statistical power of 90%. Regarding the estimated AHI variability, we established an σ of 11.98, considering the AHI pooled standard deviation of all independent samples included in our previous research [1]. As a result, the expected sample size is of ≈ 35 participants per arm of our controlled clinical trial. However, assuming a maximum of a 17.25% drop-out rate (based on the average drop-out rate of previous studies [1]), we decided to recruit a total sample size of ≈ 42 participants for each study group. Thus, a total of ≈ 84 patients with moderate to severe OSA will be enrolled in the INTERAPNEA study. For practical and feasibility reasons, and based on our previous experience [86,87], the study will be conducted in sets of a maximum of 30 persons.

3.10. Statistical Analysis

We will perform descriptive and exploratory preliminary analyses of all the study variables to reveal violations of statistical assumptions, distributions, imbalances between the study groups, associations between study variables, covariates/confounders, amount of missing data, and drop-out patterns.

Intervention effects on primary and secondary outcomes will be assessed based on linear mixed-effects models using the package *lme4* [88] from the R statistical program, with individual measures of growth being modeled as the function of randomly assigned group, assessment time, and the interaction between group and time (fixed variables). If required, effects of set of participants will also be included in the model as a random cluster factor. Estimations will be performed using the restricted maximum-likelihood method, including an unstructured covariance matrix to adjust for within-participant clustering resulting from the repeated-measures design. The model will assume that missing values are missing-at-random. Nevertheless, attrition propensity will be calculated using a logistic model predicting attrition with baseline values of set of participants, allocation group, OSA severity, age and BMI [89].

All estimations and analyses will be performed with an intention-to-treat approach (including all participants as originally allocated after randomization) and an additional per-protocol approach restricted to participants with a CPAP usage greater or equal to 4 hours per night on 70% of nights and, regarding the intervention group, at least 80% of attendance rate at intervention sessions.

4. ORGANIZATION

The Sleep and Health Promotion Laboratory of the Mind, Brain and Behavior Research Center (CIMCYC) from the University of Granada (Granada, Spain) was responsible for the study design and organization, participant recruitment process, data collection and management, randomization and participant allocation, trial monitoring, and reporting of the study process and results. Participants previously diagnosed with moderate-to-severe OSA and potentially meeting the inclusion criteria were recruited from the collaborating sleep-disordered breathing unit of the Virgen de las Nieves University Hospital (Granada, Spain). Data collection at baseline and intervention endpoint, as well as implementation of the weight loss and lifestyle intervention, was performed in two different settings of the University of Granada (Granada, Spain): the Sleep and Health Promotion Laboratory (CIMCYC) and the Sport and Health University Research Institute (iMUDS). General and specific OSA standard care (i.e. continuous positive airway pressure [CPAP]) of all participants enrolled in the trial continued being provided by their primary care team from the Virgen de las Nieves University Hospital.

5. ETHICAL ISSUES

5.1. Institutional Ethics Committee Approval

This study conforms to the last revised Ethical Principles for Medical Research Involving Human Subjects comprised in the Declaration of Helsinki and written approvals were obtained from all relevant Research Ethics Committees (i.e., Institutional Review Board) before the recruitment of participants. Specifically, approval were obtained from the Research Ethics Committees of: (a) University of Granada (Granada, Spain); (b) Virgen de las Nieves University Hospital (Granada, Spain); and (c) Junta de Andalucía (Spain) (0770-N-19).

5.2. Participant Consent

All participants will receive accurate information on the study assessments and intervention, and written informed consent from each participant will be obtained prior to any data collection. Signed copies of the Consent Form and a Patient Information Sheet will be given to participants. Those participants unable or not willing to give informed consent will not be eligible for enrollment in this study.

The Patient Information Sheet will also clearly state that participants have the right to withdraw from the study at any time without prejudice or explanation.

5.3. Confidentiality and Privacy

The confidentiality and privacy of all participants will be cautiously respected and ensured throughout the conduct of the study. All data will only be identified by a unique identification

number/code given to each participant at the beginning of the trial; all data treatment and analyses being correspondingly blinded.

5.4. Provision of the Trial Intervention to All Participants

The interdisciplinary weight loss and lifestyle intervention will be offered to all participants randomly assigned to the usual-care/control group (i.e., CPAP alone) at the conclusion of the trial. This information is included in the patient information and consent forms.

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Short- Curriculum Vitae

SHORT CURRICULUM VITAE

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Research experience

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2018-present ACTIBATE project: Activating Brown Adipose Tissue through Exercise. Effects of an exercise intervention on activity and quantity of Brown adipose tissue: A Randomized Controlled Trial. Funded by the Spanish Ministry of Economy and competitiveness among others: ≈600000€.

Publications

Journal Articles

1. **Carneiro-Barrera, A.,** Mochón-Benguigui, S., Castillo, M. J., & Amaro-Gahete, F. J. (2021). Role of physical activity and fitness on sleep in sedentary middle-aged adults: the FIT-AGEING study. *Scientific reports, 11*, 539. doi:10.1038/s41598-020-79355-2
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Books

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1. Buela-Casal, G., **Carneiro-Barrera, A., &** de Almondes, K. M. (2020). Sleep-Wake Disorders. En *A Psychological Approach to Diagnosis Using the ICD-11 as a Framework. IUPsyS-APA Book Project.* American Psychological Association (APA). Book in editing process.

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13. **Carneiro-Barrera, A.**, Díaz-Román, A., Guillén-Riquelme, A., Ruiz-Herrera, N., & Buela-Casal, G. (2018). Eficacia de la intervención en ejercicio físico para el síndrome de apnea obstructiva del sueño: Meta-análisis [Effectiveness of physical exercise interventions for obstructive sleep apnea syndrome: Meta-analysis]. In M. Badenes-Sastre y N. Ruiz-Herrera (Comps.), *Avances en Psicología Clínica. 2018. Libro de Capítulos del XI Congreso Internacional y XVI Nacional de Psicología* in *Clínica* [Advances Clinical Psychology, 2018. Book of Chapters of the 11th International Congress and 16th National of Clinical Psychology] (pp. 451-460). Granada, Spain: Spanish Association of Behavioural Psychology (AEPC). ISBN: 978-84-09-13322-2.

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of Chapters of the 11th International Congress and 16th National of Clinical Psychology] (pp. 526-535). Granada, Spain: Spanish Association of Behavioural Psychology (AEPC). ISBN: 978-84-09-13322-2.

16. Guillén-Riquelme, A., Ruiz-Herrera, N., **Carneiro-Barrera, A.**, Díaz-Román, A., & Buela-Casal, G. (2018). Diferencias en la calidad objetiva del sueño en niños con diagnóstico de TDAH en función del subtipo [Differences in objective sleep quality in children diagnosed with ADHD based on subtype]. In M. Badenes-Sastre y N. Ruiz-Herrera (Comps.), *Avances en Psicología Clínica. 2018. Libro de Capítulos del XI Congreso Internacional y XVI Nacional de Psicología Clínica* [Advances in Clinical Psychology, 2018. Book of Chapters of the 11th International Congress and 16th National of Clinical Psychology] (pp. 451-460). Granada, Spain: Spanish Association of Behavioural Psychology (AEPC). ISBN: 978-84-09-13322-2.

Scientific and Organising Committee Member Activities

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3. Member of the Organising Committee of the 7th International Congress of Educational Sciences and Development. Granada (Spain), 24-26 April, 2019.
4. Member of the Organising Committee of the X International Congress and XV National Congress of Clinical Psychology. Santiago de Compostela (Spain), 16-19 de November, 2017.

Other merits

2019- Editorial board member of the scientific journal *Frontiers in Psychology*

2017- Reviewer of several scientific indexed journal: *Nutrients, PLoS One, Journal of Clinical Medicine, Frontiers in Psychology, Nature and Science of Sleep, BMC Public Health,* and *Journal of Aging and Physical Activity*

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Acknowledgements/ Agradecimientos

ACKNOWLEDGEMENTS

The realization of this International Doctoral Thesis would not have been possible without the economic, technical and material support of the Ministry of Science, Innovation and Universities, and Ministry of Education and Vocational Training of the Government of Spain; Andalusian Health Service-Junta de Andalucía; University of Granada; Virgen de las Nieves University Hospital; University of Granada-LoMonaco S.L. Sleep Research Cathedra; TEA Ediciones S.A.; and research groups of Clinical Psychophysiology and Health Promotion (CTS-261), and PROmoting FITness and Health through Physical Activity (PROFITH; CTS-977).

Equally, the development and completion of this International Doctoral Thesis would not have been achieved without the unquestionable support, direction and guidance of doctors Gualberto Buela Casal and Jonatan Ruiz Ruiz; the significant collaboration of the pulmonologists of the Sleep Respiratory Disorders Unit of the Virgen de las Nieves University Hospital, doctors Germán Sáez Roca and Carlos Martín Carrasco; and, in general, the assistance of the members, doctors and professionals of the INTERAPNEA research group, especially Francisco J. Amaro Gahete, Alejandro Guillén Riqueleme and Lucas Jurado Fasoli.

Finally, this thesis has been possible thanks to the necessary and extraordinary collaboration, participation and support of all the patients who have generously participated in the INTERAPNEA study.

AGRADECIMIENTOS

La realización de esta tesis doctoral no hubiera sido posible sin el soporte económico, técnico y material del Ministerio de Ciencias, Innovación y Universidades y Ministerio de Educación y Formación Profesional del Gobierno de España; Servicio Andaluz de Salud-Junta de Andalucía; Universidad de Granada; Hospital Universitario Virgen de las Nieves; Cátedra de Investigación del Sueño Universidad de Granada-Grupo LoMonaco; TEA Ediciones S.A.; y grupos de investigación de Psicofisiología Clínica y Promoción de la Salud (CTS-261) y PROmoting FITness and Health through Physical Activity (PROFITH; CTS-977).

Así mismo, el desarrollo y finalización de esta tesis doctoral no se hubiera logrado sin el incuestionable respaldo, dirección y orientación de los doctores Gualberto Buela Casal y Jonatan Ruiz Ruiz; la significativa colaboración de los neumólogos de la Unidad de Trastornos Respiratorios del Sueño del Hospital Universitario Virgen de las Nieves, los doctores Germán Sáez Roca y Carlos Martín Carrasco; y, en general, la asistencia de los miembros, doctores y profesionales del grupo de investigación INTERAPNEA, especialmente, Francisco J. Amaro Gahete, Alejandro Guillén Riqueleme y Lucas Jurado Fasoli.

Finalmente, esta tesis ha sido realizable gracias a la necesaria y extraordinaria colaboración, participación y apoyo de todos los pacientes que han participado generosamente en el estudio INTERAPNEA.