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SCIENTIFIC INVESTIGATIONS

CPAP increases physical activity in obstructive sleep apnea with cardiovascular disease

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Study Objectives: Uncertainty exists over whether continuous positive airway pressure (CPAP) treatment improves moderate to vigorous physical activity levels in those with obstructive sleep apnea. We aimed to determine effects of CPAP on moderate to vigorous physical activity among participants with co-occurring cardiovascular disease and obstructive sleep apnea.

Methods: The Sleep Apnea cardioVascular Endpoints (SAVE) trial recruited participants with confirmed cardiovascular disease history and obstructive sleep apnea, 45–75 years old. The 2,687 participants (1,346 randomized to CPAP plus usual care and 1,341 to usual care alone) were followed up for a mean of 3.7 years. Self-reported physical activity was recorded at baseline, 6, 24, and 48 months using the Godin-Shepard Leisure Time Exercise Questionnaire (LTEQ). We also determined effects on any limitation of physical activity reported on the physical functioning subscale of the 36-item short form questionnaire (SF-36) and proportions of participants reaching guideline recommended physical activity levels.

Results: Among 2,601 participants with available data, those in the CPAP group reported significantly more physical activity compared to the usual care group, with approximately 20% higher reported moderate activities on the LTEQ during follow-up (adjusted mean 95% confidence interval) scores: 8.7, 7.5–9.9 vs 7.3, 6.1–8.5; $P = .003$). Those in the CPAP group also reported less limitation in physical activity (adjusted between-group difference in SF-36 physical functioning subscale score 1.66, 95% confidence interval 0.87–2.45; $P < 0.001$), and more reported sufficient levels of physical activity to meet recommendations.

Conclusions: CPAP has positive effects on improving physical activity levels, consistent with long-term health benefits.

Clinical Trial Registration: Registry: ClinicalTrials.gov; Name: Continuous Positive Airway Pressure Treatment of Obstructive Sleep Apnea to Prevent Cardiovascular Disease (SAVE); URL: https://clinicaltrials.gov/ct2/show/NCT00738179; Identifier: NCT00738179; and Registry: Australian New Zealand Clinical Trials Registry; Name: Sleep Apnea cardioVascular Endpoints study—An investigation of continuous positive airway pressure for the treatment of obstructive sleep apnea to prevent cardiovascular disease; URL: https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=83062&isReview=true; Identifier: ACTRN12608000409370.

Keywords: physical activity, continuous positive airway pressure, obstructive sleep apnea

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Continuous positive airway pressure (CPAP) therapy for obstructive sleep apnea improves quality of life, yet it is unclear whether this extends to increased physical activity. As regular physical activity is beneficial to cardiovascular health, it was important to examine whether CPAP increased self-reported physical activity in a large prospective cohort.

Study Impact: Prescription of CPAP resulted in increased self-reported physical activity, along with self-report reductions in limitations to undertake physical activity. Therefore, CPAP may encourage positive lifestyle changes consistent with long-term health benefits, complementing CPAP with improvements in health.

INTRODUCTION

Obstructive sleep apnea (OSA) is defined by repetitive episodes of partial (hypopnea) or complete (apnea) upper airway obstruction during sleep that cause oxygen desaturation, sleep fragmentation, and daytime sleepiness. OSA has been linked to cardiometabolic conditions such as type 2 diabetes mellitus,[1] hypertension,[2] cardiovascular (CV) events[3] and neurocognitive dysfunction.[4] Increasing severity of OSA is associated with reduced levels of physical activity,[5] with many affected

individuals classed as overweight or obese.[6] The impact of continuous positive airway pressure (CPAP), the gold standard treatment of OSA, on activity levels is uncertain. Although CPAP reduces daytime sleepiness[7] and improves self-reported quality of life[8,9] and mood,[10] 4 short duration studies (2 uncontrolled and 2 randomized controlled trials), have produced conflicting results for effects on physical activity.[11–14] Diamanti et al[12] showed improved sleepiness and mood in 24 CPAP-adherent participants over 6 months, but no change in objectively measured activity, whereas Jean et al[13] found that both self-reported and objectively measured levels of activity increased in 62 participants on CPAP over 7 months. Batool-Anwar et al[11] showed a small increase in self-reported recreational activity in women, but not men, after 4 months of CPAP vs sham CPAP. West et al[14] failed to show changes in physical activity levels over 3 months between 16 participants who used therapeutic CPAP and 20 participants who had placebo CPAP.

As regular exercise reduces the risks of CV events and improves quality of life,[15,16] the American College of Sports Medicine and American Medical Association recommend a minimum of 150 minutes (or 30 minutes on 5 days) of moderate to vigorous physical activity (MVPA) per week for health benefits.[17,18]

The aim of this study was to determine whether long-term CPAP treatment affects self-reported physical activity among participants with moderate-severe OSA and comorbid CV disease of the Sleep Apnea cardioVascular Endpoints (SAVE) study, an international randomized controlled trial of CPAP plus usual care vs usual care alone.[19,20]

METHODS

Design

SAVE was an international, multicenter, randomized controlled trial, the details of which have been described previously.[19,20] In brief, male and female participants, aged 45–75 years old, with a prior diagnosis of coronary and/or cerebrovascular disease, were invited to participate. OSA was defined as an oxygen desaturation index of ≥ 12 events/h with peripheral oxygen saturation reduction at least 4%, measured by respiratory polygraphy (Apnealink, ResMed, San Diego, CA). Participants were excluded from the SAVE study if they had severe excessive daytime somnolence (Epworth Sleepiness Scale score > 15/24), severe nocturnal hypoxemia (oxygen desaturation ≤ 80% for > 10% of the sleep time recording), and/or had predominantly Cheyne-Stokes respiration pattern, indicating central sleep apnea. Those who met the inclusion criteria underwent a 7-day trial of sham CPAP, where pressure was set at subtherapeutic levels, to identify those who would be able to tolerate the CPAP mask and thus be more likely to adhere to study procedures. Those who recorded a nightly sham CPAP use less than 3 hours were excluded.

Randomization and interventions

Eligible participants were randomly assigned centrally to receive either CPAP treatment plus usual care (CPAP group) or usual care alone (Usual Care group). Randomization was performed with the use of a minimization procedure to balance the group assignments according to site, type of CV disease (cardiac, cerebrovascular, or both), and severity of daytime sleepiness (Epworth Sleepiness Scale score < 11 vs ≥ 11). CPAP group patients were provided with an automated positive airway pressure machine (REMstar Auto, M or PR series, Philips Respironics, Murrysville, PA) that was initially set in automatic mode for 1 week and thereafter fixed to the 90th percentile of pressure that was calculated by the automated positive airway pressure device from the recorded data. Concomitant management of CV risk factors was performed in accordance with national guidelines. All participants were given advice on healthful sleep habits and lifestyle changes to minimize OSA symptoms, but there was no specific dietary or exercise intervention.

The SAVE trial was conducted according to the amended Declaration of Helsinki. Local institutional review boards, or independent ethics committees at recruiting sites, approved the protocol. All participants or appropriate surrogate provided written informed consent.

Procedures

Information on demographic and clinical characteristics, medical history, medications, and health behaviors was recorded at the time of enrolment.

Physical activity was reported using the Leisure-Time Exercise Questionnaire (LTEQ)[21] at baseline and at follow-up appointments at 6, 24, and 48 months. The LTEQ records the frequency of vigorous, moderate, and mild intensity of physical activity, of at least 15 minutes duration, during the past week. A total score was calculated by weighted multiplication of the reported number of episodes for each intensity level of exercise: number of vigorous, moderate and mild episodes by × 9, 5, and 3, respectively. Although mild physical activity was recorded, current evidence suggests that moderate and vigorous activity is most likely to convey substantial health benefits,[22] with an LTEQ score of 24 or greater from moderate and vigorous categories shown to equate to the American College of Sports Medicine and American Medical Association recommendations of at least 150 minutes of MVPA per week.[22,23]

Responses to questions on the Medical Outcomes Study 36-item short-form questionnaire (SF-36) physical functioning subscale (PFS, items 3 to 12) at the same timepoints were used to ascertain self-perceived limitations (not limited, somewhat limited, very limited) in undertaking physical activities of differing intensities (eg, walking more than 1 km, walking 500 m, walking 100 m).[24] Responses were converted to a numeric PFS score on a 0 (most disability) to 100 (perfect health) scale.

Statistical analysis

Linear mixed models were used to assess differences between the CPAP and Usual Care groups during follow-up for each intensity level of exercise and the total LTEQ score. Baseline age, sex (male vs female), ethnicity (Caucasian vs Asian vs other), presence of diabetes mellitus, smoking status (current vs former vs never), body mass index, oxygen desaturation index, daytime sleepiness (measured by the Epworth Sleepiness Scale), baseline physical activity (on the LTEQ) and type of

co-occurring CV disease (coronary, cerebral, or combination) were included in the models based on clinical relevance to prognosis and levels of physical activity. To test whether there were effects in subgroups of participants, interaction terms for variables of interest with CPAP treatment were each added to the linear mixed model.

To assess the importance of adherence to CPAP therapy, we assessed LTEQ outcomes in comparison to average nightly adherence to CPAP to 24 months as a continuous value. We also assessed outcomes according to per-protocol treatment adherence groups: participants who achieved good adherence to CPAP (average ≥ 4 h/night to 24 months), those allocated to CPAP with poor use (average < 4 h/night to 24 months), and Usual Care participants who never used CPAP, identified as previously described.[20]

Linear mixed models were used to assess whether SF-36 PFS scores differed by treatment group during follow up. Ordinal regression analyses were subsequently used to determine whether responses to component questions of the SF-36 PFS differed according to treatment allocation, adjusted for age, ethnicity, diabetes mellitus, smoking status, CV event type, baseline body mass index, oxygen desaturation index, Epworth Sleepiness Scale, and SF-36 scores. Adjusted ordinal regression was also used to determine effects of CPAP on guideline recommended levels of physical activity based on the MVPA LTEQ score, where participants were classed as no (score 0), insufficient or some benefit (score 1–23; combining insufficient [1–14] or some [15–23] benefit), and active (score ≥ 24, substantial health benefits) of MVPA.

A two-tailed standard significance level ($P < .05$) was used. All analyses were performed in SPSS (v23, IBM, Armonk, NY).

Data availability

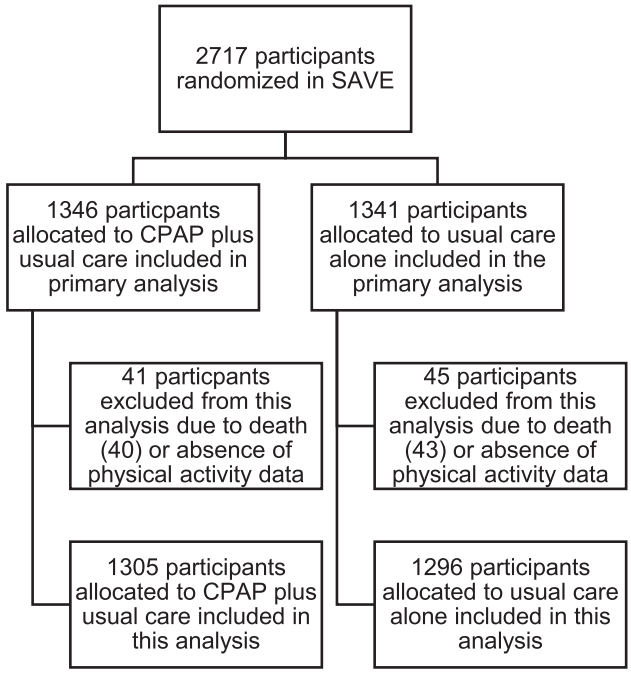
Individual deidentified participant data used in these analyses may be shared by request from qualified investigators with approval of a protocol and signed data access agreement via contacting the chief investigators or the research office of The Adelaide Institute for Sleep Health, South Australia.

RESULTS

After exclusion of participants who died or lacked LTEQ or SF-36 data during follow-up, there were 2601 included with available data (**Figure 1**). **Table 1** shows there were no significant differences in characteristics between the CPAP and Usual Care groups at baseline.

During follow-up, the CPAP group reported higher total LTEQ scores compared to the Usual Care group (adjusted mean 26.6 points, 95% confidence interval [CI] 24.7–28.5 vs 24.4 points, 95% CI 22.5–26.3; $P = 0.003$). Individual components of the LTEQ (**Figure 2**) demonstrated that the CPAP group reported significantly higher levels of moderate physical activity during follow-up compared to the Usual Care group (adjusted mean 8.7 points, 95% CI 7.5–9.9 vs 7.3, 95% CI 6.1–8.5; $P = 0.003$). There were no significant differences between treatment groups for vigorous physical activity (adjusted mean during follow-up 3.4 points, 95% CI 2.6–4.2 vs 2.9 points, 95% CI 2.1–3.7; $P = 0.125$) or mild physical activity (adjusted mean 14.4 points, 95% CI 13.5-15.3 vs 14.2 points, 95% CI 13.3–15.1; $P = 0.599$). Interaction testing between treatment and follow-up timepoint was not significant ($P_{interaction} = .252$ for total exercise score), suggesting that, considering the variable length of follow-up, the reported activity at an individual level plateaued after early improvement.

Figure 1—Flow diagram of included participants.



A full CONSORT diagram for the main SAVE study is available in McEvoy et al.[17] Participants were excluded from this secondary analysis if they died during the course of follow-up or had no physical activity data from the LTEQ or SF-36 questionnaires during follow-up. LTEQ = Leisure Time Exercise Questionnaire, SAVE = Sleep Apnea cardioVascular Endpoints, SF-36 = Medical Outcomes Study 36-item short-form questionnaire.

Interaction testing also showed no indication that the effect of CPAP on physical activity levels during follow-up differed according to sex ($P_{interaction} = .516$), ethnicity ($P_{interaction} = .804$), diabetes status ($P_{interaction} = .513$), category of CV disease history (cardiac/cerebrovascular/both; $P_{interaction} = .628$), or age ($P_{interaction} = .516$). There was a negative association evident with body mass index ($P_{interaction} = .020$), suggesting that higher follow-up physical activity was more likely to be reported during follow-up in participants with lower baseline body mass index.

When CPAP participants were divided into 2 groups using a threshold of 4 h treatment use per night (**Table S1** in the supplemental material), only the group with good adherence to treatment had significantly higher total and moderate activity LTEQ scores compared with Usual Care participants who never used CPAP (**Table S2**). Similar to the primary analysis, there were no significant differences between adherence groups for either vigorous or mild activity scores (data not shown). However, the association between nightly CPAP adherence level in hours per night as a continuous measure and reported

Table 1—Baseline characteristics of included SAVE participants.

	Allocated Treatment	
	CPAP (1,305)	Usual Care (1,296)
Male	1,058 (81.1%)	1,039 (80.2%)
Cardiovascular disease history		
Coronary	662 (50.7%)	648 (50.0%)
Cerebral	597 (45.7%)	592 (45.7%)
Combination	46 (3.5%)	56 (4.3%)
Diabetes mellitus	389 (29.9%)	377 (29.2%)
Smoking status		
Never	572 (43.9%)	590 (45.6%)
Previous	526 (40.4%)	516 (39.9%)
Current	204 (15.7%)	187 (14.5%)
Ethnicity		
Caucasian	326 (25.0%)	324 (25.0%)
Asian	828 (63.4%)	820 (63.3%)
Other	151 (11.6%)	152 (11.7%)
Age, mean (range), years	61.2 (45.0–75.7)	61.1 (44.7–75.8)
BMI, kg/m^2	28.8 ± 4.6	28.5 ± 4.3
ODI, events/h, 4% Spo_2	28 ± 14	28 ± 14
Epworth Sleepiness Scale score	7.3 ± 3.6	7.5 ± 3.6
LTEQ moderate-vigorous physical activity		
Score	11.9 ± 23.1	12.8 ± 29.3
Minutes/w conversion	31.7 ± 57.9	34.0 ± 71.7
SF-36 PFS	76 ± 20	75 ± 21
CPAP adherence, average hours/night to 24 months	3.49 ± 2.22	-

Continuous data are presented as means ± SD, except age. Count variables are presented as *n* (%). BMI = body mass index, CPAP = continuous positive airway pressure, ODI = oxygen desaturation index, LTEQ = Leisure Time Exercise Questionnaire, PFS = physical functioning subscale, SD = standard deviation, SF-36 = short-form health survey 36 item.

moderate exercise did not reach statistical significance (0.23 points improvement per hour of adherence, 95% CI −0.06–0.53, $P = .118$).

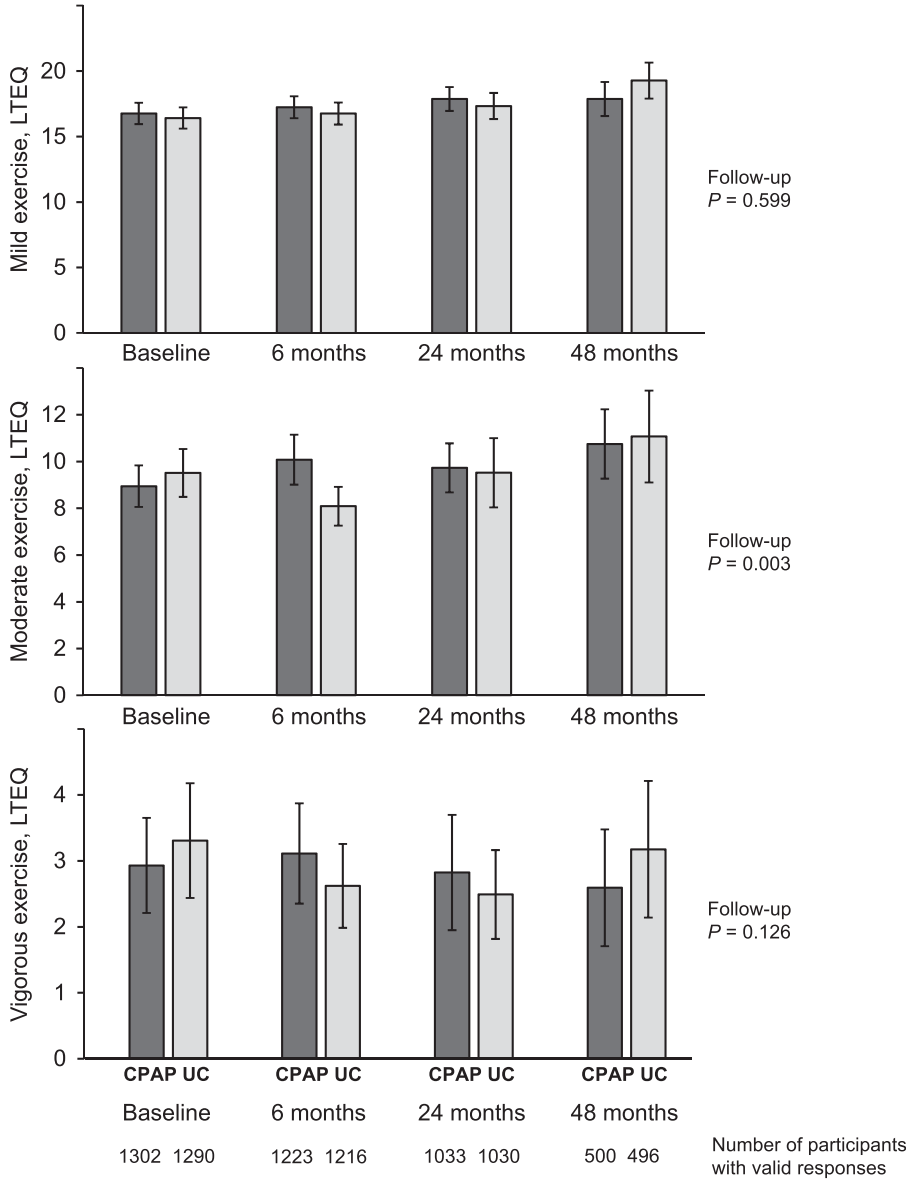
Figure 3 shows health benefit classifications of participant LTEQ responses during follow-up. Although many participants in each group reported no strenuous physical activity, those allocated to CPAP were more likely to report MVPA levels consistent with recommendations for more health benefits during follow-up compared to those in the Usual Care group (odds ratio for CPAP treatment 1.20, 95% CI 1.07–1.35; $P = .002$).

SF-36 PFS scores were higher in the CPAP group during follow-up (adjusted between-group difference 1.66, 95% CI 0.87–2.45; $P < .001$). To assess whether this difference may have been driven by particular items, responses to individual questions in the PFS were examined at all-timepoints (**Figure S1**). Ordinal regression analyses indicated that the CPAP group was significantly positively associated with responses to several of these questions, as shown in **Table 2**. The activities for which CPAP users reported fewer limitations generally corresponded to more vigorous or demanding activities, whereas no significant differences in limitations were found between the treatment groups for less intense activities, for which most participants in both groups reported no limitations.

DISCUSSION

This secondary analysis of the SAVE trial has shown that in patients with co-occurring OSA and CV disease, the addition of CPAP treatment to usual guideline-directed CV care results in higher levels of self-reported physical activity and fewer self-reported limitations to activities of daily living. The observed self-reported increase in physical activity as a result of CPAP treatment is likely be real: the findings from the 2 questionnaires (ie, the LTEQ and SF-36 PFS) were consistent with each other, the effect was evident after adjusting for potential confounders, and no exercise intervention was explicitly prescribed for any of the trial participants. Moreover, participants who were able to adhere well to CPAP therapy (ie, used CPAP for 4 or more hours per night) showed greater benefit compared with their counterparts who did not adhere well to treatment, although this improvement did not appear to have a strictly linear relationship with adherence measured in hours per night.

Figure 2—Physical activity scores from LTEQ.

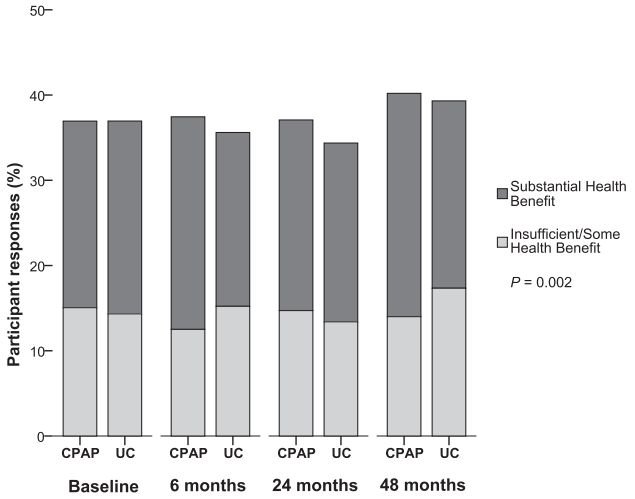


Mild, moderate, and vigorous physical activity point scores from the Leisure Time Exercise Questionnaire (LTEQ) in Continuous Positive Airway Pressure (CPAP, dark gray) and Usual Care (UC, light gray) treatment groups at the indicated timepoints. Data are observed mean and 95% confidence interval scores, with significance from linear mixed models.

Baseline activity levels in this older, overweight, comorbid population were low, in keeping with previous reports in patients with CV disease[25–29] and also some populations with noncomorbid OSA[30,31]: only 22% of participants met current health guidelines for 150 minutes or more of moderate or vigorous physical activity per week at baseline.[22,23,32] The proportion of participants in the Usual Care group meeting this threshold declined during follow-up, whereas it increased among CPAP group participants, suggesting a net benefit of CPAP treatment.

Results of previous studies have been mixed: our results are in agreement with Jean and colleagues, [13] who, in a small uncontrolled 7-month study, found that CPAP-adherent patients with OSA reported increased physical activity, which was confirmed by daily pedometer step counts. On the other hand, in a similar, albeit small and shorter-duration study, Diamanti and colleagues[12] showed no increase in actigraphy-measured physical activity. Batool-Anwar et al,[11] using self-reported physical activity, found women using therapeutic CPAP reported significant increases in recreational physical activity compared to those using sham CPAP. In contrast, men using therapeutic CPAP reported no change in recreational physical activity; however, those using sham CPAP reported a significant reduction in recreational physical activity. Our finding of CPAP-related improvement in the SF-36 physical function subscale is consistent with some,[33,34] but not all,[35,36] previous studies. None of these above studies were, however, conducted in a population with co-occurring OSA and CV disease and low baseline levels of physical functioning.

Figure 3—Participants meeting guidelines from LTEQ.



Percentage of valid participant responses with moderate-vigorous Leisure Time Exercise Questionnaire (LTEQ) scores consistent with substantial health benefits (dark gray, ≥ 24 points) or insufficient or some health benefits (light gray, 1–23 points) at the indicated timepoints in Continuous Positive Airway Pressure (CPAP) and Usual Care (UC) treatment groups. Participants reporting no leisure time physical activity are not shown.

Recent studies have challenged the assumption that health benefits occur linearly with increasing volumes of exercise. A pooled analysis of over 650,000 participants over 14 years showed a 20% lower mortality risk for people performing less than the recommended 150 minutes of MPVA per week compared to those who undertook no exercise at all.[37] Evidence assessed for the formulation of US physical activity guidelines also highlight that there appears to be no minimum threshold duration of MVPA for health benefits.[38] Thus, the 20% higher self-reported MVPA shown in the CPAP group compared to Usual Care group here would likely convey substantial health benefits over longer periods of time beyond the duration of follow-up in SAVE.

The strengths of this study were the large, international cohort; the relatively long duration of follow-up; and the systematic prospective collection of the LTEQ and SF-36 data. The LTEQ questionnaire used in this study has been validated against the recommended 150 minutes of moderate vigorous physical activity per week recommendations.[39,40] Furthermore, the LTEQ has been utilized in other chronic disease populations, including CV disease,[41,42] cancer,[43] and multiple sclerosis.[44]

There are some shortcomings of this study. There was no objective measure of physical activity. It would have been logistically difficult to collect such information in the international SAVE trial in which participants were recruited from diverse socioeconomic and health care settings and were followed for several years. Future studies of CPAP treatment of OSA should take advantage of recent technological advances and the widespread availability of activity tracking devices to incorporate objective measurement of physical activity and sedentary behavior levels. The LTEQ itself only examined leisure time physical activity and did not examine incidental physical activity, such as gardening or housework, meaning CPAP-induced improvements in incidental physical activity have not been captured. Incidental physical activity, such as gardening, conveys health benefits to older adults.[45] Other questionnaires, such as the Active Australia,[46] examine for incidental physical activity, along with leisure time physical activity, and could be used in future studies. Finally, as individuals with severe hypoxemia or excessive sleepiness were excluded from SAVE, the results of this study may not be generalizable to all patients with OSA.

CONCLUSIONS

This study shows that individuals with moderate-severe OSA and co-occurring CV disease when treated with CPAP therapy

Table 2—Effect of CPAP treatment on SF-36 physical functioning subscale scores during follow-up (6, 24, and 48 months).

SF36 Question	Does your health now limit you in these activities?	Odds Ratio (95% CI) for CPAP	*P*
3	Vigorous activities, eg, running, lifting heavy objects, participating in strenuous sports	1.28 (1.14–1.43)	< .001
4	Moderate activities, eg, moving a table, pushing a vacuum cleaner, bowling, playing golf	1.31 (1.18–1.47)	8.58×10^{-7}
5	Lifting or carrying groceries	1.12 (0.98–1.28)	.098
6	Climbing several flights of stairs	1.23 (1.10–1.37)	< .001
7	Climbing one flight of stairs	1.10 (0.93–1.29)	.268
8	Bending, kneeling, or stooping	1.15 (1.02–1.29)	.018
9	Walking more than one kilometer	1.26 (1.11–1.42)	< .001
10	Walking half a kilometer	1.22 (1.04–1.43)	.016
11	Walking 100 meters	1.08 (0.87–1.34)	.473
12	Bathing or dressing yourself	1.24 (0.99–1.55)	.057

Odds ratios for allocation to CPAP treatment arm; from ordinal regression for higher responses during follow-up, to the SF-36 physical functioning subscale questionnaire items. Adjusted for cardiovascular disease history (coronary, cerebrovascular, or both), ethnicity, sex, corresponding baseline value for the question of interest, and Epworth Sleepiness Scale score, body mass index, diabetes and smoking status at baseline. CI = confidence interval, CPAP = continuous positive airway pressure, SF-36 = short form health survey 36 item.

report higher levels of physical activity and fewer physical health limitations than their counterparts receiving usual CV care alone. Therefore, although CPAP did not directly reduce the risk of secondary CV events during the SAVE trial,[19] the results of this analysis suggest that CPAP users are more likely to engage in physical activity that, if sustained over a longer time horizon and confirmed by objective activity measures, could reduce the recurrence of CV events as well as provide other long term positive benefits for health and wellbeing.

ABBREVIATIONS

CI, confidence interval
CPAP, continuous positive airway pressure
CV, cardiovascular
LTEQ, Leisure Time Exercise Questionnaire
MVPA, moderate-vigorous physical activity
PFS, physical functioning scale
SAVE, Sleep Apnea cardioVascular Endpoints
OSA, obstructive sleep apnea
SF-36, Medical Outcomes Study 36-item short-form questionnaire

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