CHEST

The Effects of Long-term CPAP on Weight Change in Patients With Comorbid OSA and Cardiovascular Disease

Data From the SAVE Trial

Qiong Ou, MD; Baixin Chen, MMed; Kelly A. Loffler, PhD; Yuanming Luo, MD, PhD; Xilong Zhang, PhD; Rui Chen, PhD; Qian Wang, MMed; Luciano F. Drager, MD, PhD; Geraldo Lorenzi-Filho, MD, PhD; Michael Hlavac, PhD; Nigel McArdle, MD; Sutapa Mukherjee, MD, PhD; Olga Mediano, MD; Ferran Barbe, MD; Craig S. Anderson, MD, PhD; R. Doug McEvoy, MD; Richard J. Woodman, PhD; on behalf of the SAVE investigators[*]

BACKGROUND: Although recent evidence suggests that OSA treatment may cause weight gain, the long-term effects of CPAP on weight are not well established.

METHODS: This study was a post hoc analysis of the Sleep Apnea Cardiovascular Endpoints (SAVE) study, a multicenter, randomized trial of CPAP plus standard care vs standard care alone in adults with a history of cardiac or cerebrovascular events and moderate to severe OSA. Participants with weight, BMI, and neck and waist circumferences measured at baseline and during follow-up were included. Linear mixed models were used to examine sex-specific temporal differences, and a sensitivity analysis compared high CPAP adherers (≥ 4 h per night) with propensity-matched control participants.

RESULTS: A total of 2,483 adults (1,248 in the CPAP group and 1,235 in the control group) were included (mean 6.1 ± 1.5 measures of weight available). After a mean follow-up of 3.78 years, there was no difference in weight change between the CPAP and control groups, for male subjects (mean [95% CI] between-group difference, 0.07 kg [–0.40 to 0.54]; $P = .773$) or female subjects (mean [95% CI] between-group difference, –0.14 kg [–0.37 to 0.09]; $P = .233$). Similarly, there were no significant differences in BMI or other anthropometric measures. Although male participants who used CPAP ≥ 4 h per night gained slightly more weight than matched male control subjects without CPAP (mean difference, 0.38 kg [95% CI, 0.04 to 0.73]; $P = .031$), there were no between-group differences in other anthropometric variables, nor were there any differences between female high CPAP adherers and matched control subjects.

CONCLUSIONS: Long-term CPAP use in patients with comorbid OSA and cardiovascular disease does not result in clinically significant weight change.

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ABBREVIATIONS: AHI = apnea-hypopnea index; CV = cardiovascular; ESS = Epworth Sleepiness Scale; ODI = oxygen desaturation index

AFFILIATIONS: From the Sleep Center (Drs Ou, B. Chen, and Wang), Respiratory and Critical Medical Department, Guangdong Geriatric Institute, Guangdong General Hospital, Guangdong Academy of Medical Sciences, Guangzhou, Guangdong, China; Adelaide Institute for Sleep Health (Drs Loffler and McEvoy), Flinders University, Adelaide, SA, Australia; The First Affiliated Hospital of Guangzhou Medical University (Dr Luo), State Key Laboratory of Respiratory Disease, Guangzhou, Guangdong, China; The First Affiliated Hospital of Nanjing Medical University (Dr Zhang), Nanjing, Jiangsu, China;

Obesity is one of the main causes of OSA. The resultant narrowing of the pharyngeal airway predisposes to airflow obstruction during sleep, when compensatory dilator neuromuscular reflexes are suppressed.[1-3] It is likely that obesity in OSA is due to a complex interaction of environmental, socioeconomic, and hereditary factors. However, recently reviewed evidence suggests that the relationship may be reciprocal, whereby OSA leads to weight gain by inducing behavioral, metabolic, and/or hormonal changes that adversely affect the balance between energy intake and expenditure.[4] Compared with BMI-matched control subjects, patients with OSA have increased circulating levels of leptin and ghrelin, which together may predispose to increased food (energy) intake.[5] Studies that have used dietary questionnaires suggest that patients with severe OSA are predisposed toward eating high-fat foods,[6] although no studies have objectively measured actual food intake in those with OSA. Physical activity seems to decline with increasing severity of OSA, associated with excessive sleepiness and obesity,[7-9] which may not be reversed with treatment.[10] Conversely, resting metabolic rate, a major determinant of energy expenditure, seems to be increased in OSA.[11-13] Thus, uncertainty persists regarding the effects of OSA on energy balance (energy intake vs energy expenditure).

Because CPAP, the first-line treatment for OSA, improves sleep disturbance, nocturnal hypoxia, sympathetic nervous system activity, and daytime sleepiness, measuring the course of body weight after this treatment may provide insight into the effects of OSA on overall energy balance. Early reports produced conflicting results, with studies indicating weight loss[14] and weight gain.[15,16] In an attempt to resolve this uncertainty, Drager et al[17] undertook a meta-analysis of 25 randomized controlled trials with 3,181 patients. The median study duration in this meta-analysis was 3 months, with follow-up exceeding 6 months in only one of the 25 studies. CPAP treatment was found to promote a small increase in BMI and weight, raising the concern that CPAP might have an unintended detrimental effect on cardiometabolic health if such weight gain were to continue with long-term use.

The Sleep Apnea Cardiovascular Endpoints (SAVE) study was a large, international, randomized controlled trial that compared the effects of CPAP treatment plus usual care vs usual care alone on the secondary prevention of serious cardiovascular (CV) events in patients with co-occurring moderate to severe OSA.[18] Secondary analysis of the SAVE dataset provides an ideal opportunity to assess whether long-term CPAP treatment promotes weight gain in patients with OSA, as participants had regular anthropometric measurements for a mean follow-up period of 3.78 years. The present article reviews the changes in weight and other anthropometric measurements compared between the CPAP-treated and usual care groups.

Patients and Methods

Design

The SAVE study was an international, multicenter, randomized, open-label clinical trial, the details of which have been outlined elsewhere.[18,19] In brief, patients aged 45 to 75 years, with a diagnosis

The Second Affiliated Hospital of Soochow University (Dr R. Chen), Suzhou, Jiangsu, China; Instituto do Coracao and Hospital Universitario (Drs Drager and Lorenzi-Filho), Faculty of Medicine, University of São Paulo, São Paulo, Brazil; Christchurch Hospital (Dr Hlavac), Christchurch, New Zealand; West Australian Sleep Disorders Research Institute (Drs McArdle and Mukherjee), Department of Pulmonary Physiology and Sleep Medicine, Sir Charles Gairdner Hospital, Nedlands, WA, Australia; University Hospital of Guadalajara (Dr Mediano), Guadalajara, Spain; Centro de Investigacion Biomedica en Red de Enfermedades Respiratorias (CIBERES) (Drs Mediano and Barbe), Madrid, Spain; Respiratory Department (Dr Barbe), Institut de Recerca Biomedica de Lleida, Lleida, Spain; The George Institute for Global Health (Dr Anderson), Faculty of Medicine, University of New South Wales, Sydney, NSW, Australia; Neurology Department (Dr Anderson), Royal Prince Alfred Hospital, Sydney Health Partners, Sydney, NSW, Australia; Sleep Health Service (Dr McEvoy), Respiratory and Sleep Services, Southern Adelaide Local Health Network, Bedford Park, SA, Australia; and Flinders Centre for Epidemiology and Biostatistics (Dr Woodman), College of Medicine and Public Health, Flinders University, Adelaide, SA, Australia.

*The SAVE trial was conducted by a large team of investigators. Details and affiliations are given in e-Appendix 2 collaborators list.

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Dr Mukherjee is currently with the Adelaide Institute for Sleep Health, Flinders University, Adelaide, SA, Australia; and the Sleep Health Service, Respiratory and Sleep Services, Southern Adelaide Local Health Network, Bedford Park, SA, Australia.

CORRESPONDENCE TO: R. Doug McEvoy, MD, Adelaide Institute for Sleep Health, Flinders University, GPO Box 2100, Adelaide SA 5001, Australia; e-mail: doug.mcevoy@flinders.edu.au

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of moderate to severe OSA (defined as an oxygen desaturation index [ODI] of ≥ 12 of ≥ 4% oxygen desaturation events per hour during a home overnight screening sleep test [ApneaLink, ResMed]) and a previous diagnosis of coronary or cerebrovascular disease were included from 89 clinical centers in seven countries between December 2008 and November 2013. Patients were excluded if they had severe daytime sleepiness (Epworth Sleepiness Scale [ESS] score > 15), very severe nocturnal hypoxemia (oxygen saturation < 80% for > 10% of the monitoring time), or a predominantly Cheyne-Stokes respiration pattern. Potential participants were required to undergo a 1-week trial of sham CPAP delivered at subtherapeutic pressure to identify those most likely to tolerate mask CPAP treatment and adhere to procedures; those who recorded a daily average sham CPAP usage < 3 h on the machine recording card were excluded. The SAVE trial was conducted in accordance with the amended Declaration of Helsinki. Local institutional review boards or independent ethics committees at recruiting sites approved the protocol (e-Table 1), and all participants provided written informed consent. The trial is registered with ClinicalTrials.gov.[20]

Procedures

Eligible participants were randomly assigned via a secure central server to receive either CPAP treatment plus usual CV care (CPAP group) or usual CV care alone (control group).[18] All participants were advised on healthy sleep habits and lifestyle changes (including advice on healthy eating and weight control) to minimize OSA symptoms. In the CPAP group, home pressure titration on an auto-PAP machine (REMstar Auto, M or PR series, Philips Respironics) was undertaken over the first week postrandomization. Data were extracted from recording cards to guide further therapy, with CPAP pressure fixed for long-term use at the 90th percentile of pressure achieved during the 1-week auto-PAP trial period.

Clinic visits were scheduled for all participants at 1, 3, 6, and 12 months and annually thereafter; participants were also contacted by telephone at 6 months between the annual clinic visits. Additional end-of-study visits were performed between September 2015 and January 2016 on all participants who remained actively enrolled in the trial.

Following randomization, baseline anthropometric measurements of weight, height, and neck, waist, and hip circumferences were taken, and the BMI and waist-to-hip ratio (WHR) were calculated (e-Appendix 1). OSA characteristics included apnea-hypopnea index (AHI), ODI, mean nocturnal oxygen saturation, and lowest nocturnal oxygen saturation, computed from an overnight recording. Information was also obtained on ESS score, medical history, country of residence, and ethnicity. Anthropometric measurements were repeated at 6 and 12 months, and then annually for the duration of follow-up, with CPAP usage time downloaded from machine data cards at each clinic visit for patients allocated to CPAP.

TABLE 1] Baseline Characteristics

Characteristic	CPAP Group (n = 1,248)		Control Group (n = 1,235)	
	Male (n = 1,010)	Female (n = 238)	Male (n = 996)	Female (n = 239)
Age, y	60.8 ± 7.7	63.0 ± 7.1	60.7 ± 8.1	63.4 ± 7.0
Obese	307 (30.4)	92 (38.7)	286 (28.7)	82 (34.3)
OSA characteristics				
AHI, events/h	29 ± 16	28 ± 16	30 ± 16	27 ± 15
ODI, events/h	28 ± 14	27 ± 14	29 ± 15	27 ± 14
Average SpO_2, %	93.4 ± 1.9	93.3 ± 2.2	93.4 ± 1.9	93.2 ± 2.2
Lowest SpO_2, %	77.1 ± 6.0	76.9 ± 5.7	77.3 ± 6.0	76.3 ± 6.7
ESS score	7.4 ± 3.6	7.1 ± 3.8	7.5 ± 3.5	7.5 ± 3.9
Medical history				
Coronary artery disease	544 (53.9)	89 (37.4)	525 (52.7)	97 (40.6)
Cerebrovascular disease[a]	424 (42.0)	144 (60.5)	425 (42.7)	132 (55.2)
Coronary and cerebrovascular disease	42 (4.2)	5 (2.1)	46 (4.6)	10 (4.2)
Diabetes mellitus	292 (28.9)	79 (33.1)	284 (28.5)	79 (33.1)
Country				
Australia	92 (9.1)	11 (4.6)	95 (9.5)	13 (5.4)
Brazil	88 (8.7)	37 (15.5)	90 (9.0)	35 (14.6)
China	643 (63.7)	155 (65.1)	615 (61.7)	156 (65.3)
India	45 (4.5)	9 (3.8)	44 (4.4)	14 (5.9)
New Zealand	40 (4.0)	8 (3.4)	41 (4.1)	2 (0.8)
Spain	101 (10.0)	18 (7.6)	109 (10.9)	19 (7.9)
United States	1 (0.1)	0	2 (0.2)	0

Data are presented as mean ± SD or No. (percentiles). Subjects indicated as obese had a BMI ≥ 30 kg/m^2. AHI = apnea-hypopnea index; ESS = Epworth sleepiness scale; ODI = oxygen desaturation index; SpO_2 = peripheral blood oxygen saturation by pulse oximetry.
[a]Stroke or transient ischemic attack.

Statistical Analysis

Summary data for each group are presented as mean ± SD for normally distributed variables, and median (interquartile range) for non-normally distributed variables. We excluded participants with extreme outlying values for any of the five anthropometric variables (weight, BMI, neck or waist circumference, or WHR) at any time point according to a change across the study duration of > 4 SDs; the goal was to eliminate probable typographical errors or effects of unrelated health issues and to ensure a consistent case base for all analyses. A linear mixed effects model was used to determine the mean difference between treatments for each of the variables during follow-up, with fixed effect terms used for baseline values, treatment, sex, visit (categorical), and interactions for sex × baseline value, treatment × visit, treatment × sex, visit × sex, and treatment × visit × sex. Interaction effects between treatment and each of the main effects included in the final model were also tested. A random intercept term for each participant was also included, and the estimated mean between-group differences were estimated with the marginal treatment effect for each sex included in the same model.

The predictors of weight change were also determined for end-of-study minus baseline weight. A simple linear regression was first tested for crude associations, with inclusion of age, sex, follow-up duration, country, baseline weight, AHI, ODI, ESS score, and presence of coronary or cerebrovascular CV disease, previous or current CV medications, hypertension, diabetes mellitus, myocardial infarction, angina, heart failure, valvular heart disease, percutaneous coronary revascularization with or without a stent, coronary artery bypass graft, stroke and transient ischemic attack, and treatment group allocation. Variables that were significant at $P < .20$ were then entered into a multivariate linear regression model that a priori included follow-up duration as a predictor to determine the independent predictors of weight change. All estimated differences were considered significant for $P < .05$ using two-tailed hypothesis tests.

Finally, a sensitivity analysis was conducted to determine whether higher levels of CPAP adherence were associated with weight change. Anthropometric values were compared between the two previously reported groups of propensity score-matched patients[19] after excluding those with unsatisfactory anthropometric measurements. Details of the method whereby "CPAP-adherent" patients (defined as a mean ≥ 4 h of treatment per day) were matched 1:1 with control patients who never used CPAP are provided in e-Table 2 of the main SAVE study report.[19] All analyses were performed by using Stata version 14.2 (StataCorp).

Results

There were 2,717 participants in the SAVE study, but 30 were excluded because of withdrawal of consent, nonadherence to the protocol, or data irregularities identified during monitoring at one site. Eight patients were removed from these analyses because their baseline anthropometric measurements were incomplete, and another 196 were excluded because of extreme values (> 4 SDs) recorded during follow-up. Thus, a total of 2,483 subjects (1,248 in the CPAP group and 1,235 in the control group) were included with a mean 6.1 ± 1.5 (range, 1-8) measures of weight, including the baseline visit. Their mean length of follow-up was 3.78 ± 1.46 years. Table 1 outlines the baseline characteristics of participants according to sex; male and female subjects in the CPAP group used their device for a daily mean of 3.33 ± 2.29 h and 3.15 ± 2.19 h, respectively, over the study duration.

Table 2 describes the summary measures for each of the anthropometric variables and shows that there were no significant differences in the estimated mean differences between treatment groups for either male or female subjects. Figure 1 illustrates that median weights remained stable for both CPAP and control participants, in both male and female subjects. There were no significant treatment × time interactions.

Table 3 presents the results of the multivariate linear regression analysis for the change in weight between baseline and the end of follow-up. Older age ($P < .001$), higher baseline weight ($P < .001$), and recruitment in China ($P < .001$) or India ($P = .007$) vs Australia were associated with significant weight loss. Being male ($P = .003$), having previous percutaneous coronary revascularization with or without a stent ($P = .001$), and recruitment in New Zealand ($P = .006$ compared with Australia) were associated with significant weight gain. Interactions between treatment status and other variables were not significant, indicating that there was no subgroup in which CPAP had a significant effect. Despite different patterns of weight change indicated by the regression coefficients according to country, there is no evidence that CPAP treatment had a differential effect on weight between countries.

A sensitivity analysis compared good CPAP adherers (≥ 4 h per night; n = 516) with propensity-matched control subjects (n = 531) (e-Table 2). Each individual contributed 6.1 ± 1.5 weight measures (range, 1-8), including the baseline visit. Table 4 describes the summary measures for each anthropometric outcome as well as the estimated mean difference between groups. There was a significantly higher weight gain after CPAP treatment compared with control for male subjects: the mean (95% CI) baseline-adjusted difference was 0.38 kg (0.04-0.73) ($P = .031$). No significant differences were found for any of the other anthropometric measures, either in male or female subjects.

TABLE 2] Anthropometric Variables for Each Treatment Group, Separated According to Sex

Variable	CPAP Group		Control Group		Adjusted Δ in Change From Baseline (CPAP vs Control), Mean (95% CI)	*P*
	Baseline	Follow-up	Baseline	Follow-up		
	Median (IQR) (No.)	Median (IQR) (No.)	Median (IQR) (No.)	Median (IQR) (No.)		
Weight, kg						
Female	70 (64-80) (238)	70 (63-79) (1,049)	70 (62-77) (239)	69.5 (61-76) (1,084)	0.07 (−0.40 to 0.54)	.773
Male	80 (73-90) (1,010)	80 (73-90) (4,737)	80 (73-90) (996)	80 (74-89) (4,684)	−0.14 (−0.37 to 0.09)	.233
	Mean ± SD (No.)	Mean ± SD (No.)	Mean ± SD (No.)	Mean ± SD (No.)		
BMI, kg/m^2						
Female	29.58 ± 5.78 (238)	29.35 ± 5.62 (1,049)	28.71 ± 4.99 (239)	28.34 ± 4.94 (1,084)	0.035 (−0.13 to 0.20)	.682
Male	28.43 ± 3.96 (1,010)	28.38 ± 4.06 (4,737)	28.39 ± 3.93 (996)	28.45 ± 4.07 (4,684)	−0.05 (-0.13 to 0.030)	.216
Neck circumference, cm						
Female	37.5 ± 3.8 (235)	37.3 ± 3.8 (679)	36.9 ± 3.9 (239)	36.8 ± 4.0 (695)	0.124 (−0.104 to 0.352)	.286
Male	41.5 ± 3.6 (1,004)	41.2 ± 3.5 (3,008)	41.5 ± 3.7 (995)	41.4 ± 3.8 (2,989)	−0.108 (−0.218 to 0.002)	.054
Waist circumference, cm						
Female	98.5 ± 13.3 (236)	98.5 ± 13.8 (681)	96.2 ± 13.2 (239)	96.1 ± 13.6 (696)	0.013 (−0.58 to 0.61)	.966
Male	101.5 ± 11.1 (1,009)	101.4 ± 11.2 (3,007)	101.3 ± 11.1 (996)	101.4 ± 11.6 (2,995)	−0.015 (−0.30 to 0.27)	.917
WHR						
Female	0.92 ± 0.08 (235)	0.93 ± 0.09 (679)	0.90 ± 0.08 (239)	0.92 ± 0.08 (696)	−0.002 (−0.007 to 0.004)	.553
Male	0.97 ± 0.06 (1,003)	0.97 ± 0.07 (3,005)	0.96 ± 0.07 (995)	0.97 ± 0.07 (2,990)	−0.0004 (−0.003 to 0.002)	.782

No. indicates the total number of measurements performed during either baseline or follow-up. A single measure per subject was performed at baseline, but multiple measures were performed during follow-up.
IQR = interquartile range; WHR = waist-to-hip ratio.

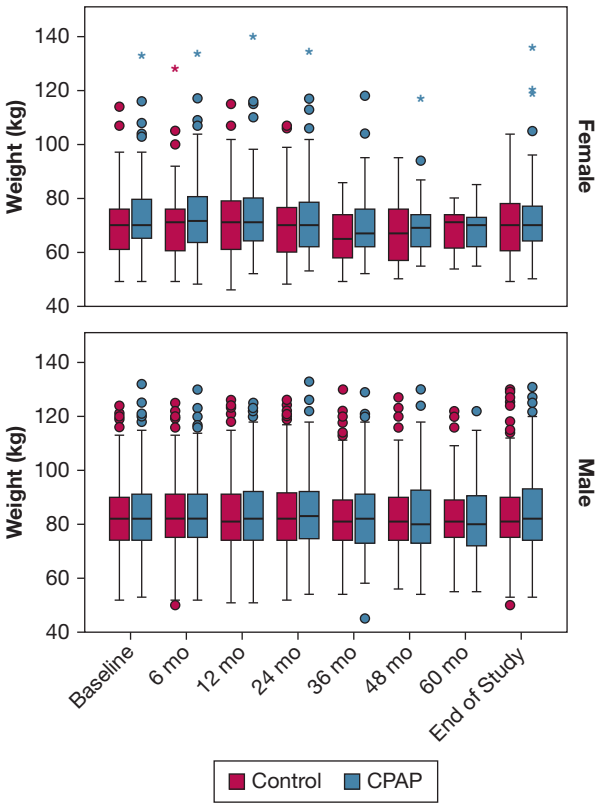

Figure 1 – *Boxplots of observed weight at baseline and during follow-up according to treatment group and sex. The end-of-study visit indicates the last measurement for each individual. Each box shows median and 25th to 75th percentiles.*

Discussion

The principal finding of this large clinical trial was that there was no clinically significant weight change in patients with established CV disease and comorbid OSA over several years, and there was no differential effect of CPAP on other anthropometric measures. In a subanalysis, male subjects, but not female subjects, who achieved high use of CPAP each night had a small (< 400 g) but statistically significant increase in weight compared with matched control patients but without changes in other anthropometric indices such as BMI or neck or waist circumference. Taken together, these results indicate that long-term CPAP treatment is unlikely to exacerbate the problems of overweight and obesity that are common among patients with OSA. Such a small change in weight, even with good adherence over several years, is highly unlikely to have any serious clinical ramifications.

Only one other randomized controlled trial of CPAP vs usual care in overweight or obese patients with moderate to severe OSA recorded weight and BMI over a similar period (median follow-up, 4 years)[21] as our study. Patients allocated to the control group were found to have had a significant decrease in BMI, whereas those allocated to CPAP treatment experienced no significant change in BMI over time. The reported between-group mean difference in change in BMI for CPAP vs control in that trial was 0.25 kg/m^2 (95% CI, 0.04-0.46), and the corresponding difference in change in weight (F. Barbe, personal communication, March 2018) was 0.51 kg (95% CI, 0.13-1.25). Neither the study by

TABLE 3] Regression Coefficients From a Multivariate Linear Regression for Change in Weight

Variable	β (95% CI)[a]	*P*[a]
Age (y)	−0.058 (−0.084 to −0.031)	< .001
Sex (1 = female, 2 = male)	0.789 (0.268 to 1.310)	.003
Baseline weight (kg)	−0.049 (−0.065 to −0.032)	< .001
Treatment group (1 = CPAP, 2 = control)	0.105 (−0.281 to 0.491)	.594
Duration in study (y)	−0.103 (−0.278 to 0.072)	.249
PCR (yes vs no)	0.698 (0.270 to 1.126)	.001
Country		
Australia	1.00	
Brazil	−0.821 (−1.819 to 0.178)	.107
China	−1.594 (−2.383 to −0.808)	< .001
India	−1.810 (−3.120 to −0.502)	.007
New Zealand	1.758 (0.509 to 3.007)	.006
Spain	0.157 (−0.841 to 1.154)	.758
United States	3.734 (−2.743 to 10.211)	.258

The β-coefficients are adjusted for all other variables in the table. Age, sex, treatment group, and duration in study were included in the model a priori. PCR = percutaneous coronary revascularization with or without a stent.

[a]Using a multivariate linear regression for change in weight between baseline and end of follow-up.

TABLE 4] Change in Anthropometric Variables in Patients With Good CPAP Compliance and Propensity-Matched Control Subjects, Separated According to Sex

Variable	CPAP Group		Control Group		Adjusted Δ in Change From Baseline (CPAP vs Control), Mean (95% CI)	*P*
	Baseline	Follow-up	Baseline	Follow-up		
	Median (IQR) (No.)	Median (IQR) (No.)	Median (IQR) (No.)	Median (IQR) (No.)		
Weight, kg						
Female	70.0 (65.0-79.50) (92)	70.0 (63.0-78.0) (445)	70.0 (61.0-76.0) (99)	70.0 (60.0-76.0) (415)	−0.217 (−0.966 to 0.531)	.569
Male	82.0 (74.0-91.0) (439)	82.0 (74.0-92.0) (2,196)	82.0 (74.0-90.0) (417)	82.0 (74.0-90.0) (1,955)	0.383 (0.035 to 0.730)	.031[a]
	Mean ± SD (No.)	Mean ± SD (No.)	Mean ± SD (No.)	Mean ± SD (No.)		
BMI, kg/m^2						
Female	29.5 ± 5.0 (92)	29.3 ± 5.1 (445)	29.0 ± 4.9 (99)	28.7 ± 4.9 (415)	−0.059 (−0.324 to 0.207)	.665
Male	28.8 ± 4.1 (439)	28.9 ± 4.2 (2,196)	28.8 ± 4.2 (417)	28.8 ± 4.3 (1,955)	0.123 (−0.001 to 0.246)	.052
Neck circumference, cm						
Female	37.4 ± 3.8 (90)	37.1 ± 3.6 (285)	36.3 ± 3.6 (99)	36.2 ± 3.7 (272)	0.122 (−0.239 to 0.483)	.507
Male	41.8 ± 3.6 (438)	41.6 ± 3.6 (1,387)	41.8 ± 3.6 (416)	41.6 ± 3.7 (1,267)	0.043 (−0.123 to 0.209)	.610
Waist circumference, cm						
Female	98.5 ± 12.7 (91)	98.9 ± 14.2 (285)	97.0 ± 12.9 (99)	95.9 ± 13.2 (272)	0.889 (−0.064 to 1.842)	.068
Male	102.0 ± 11.1 (439)	102.5 ± 11.3 (1,386)	102.4 ± 11.8 (417)	102.5 ± 12.2 (1,269)	0.290 (−0.154 to 0.733)	.200
WHR						
Female	0.92 ± 0.08 (90)	0.93 ± 0.09 (285)	0.91 ± 0.09 (99)	0.91 ± 0.09 (272)	0.004 (−0.005 to 0.013)	.357
Male	0.97 ± 0.06 (438)	0.97 ± 0.07 (1,386)	0.97 ± 0.07 (416)	0.97 ± 0.07 (1,268)	−0.000 (−0.004 to 0.004)	.862

No. indicates the total number of measurements performed during either baseline or follow-up. A single measure per subject was performed at baseline, but multiple measures were performed during follow-up. See Table 1 legend for expansion of abbreviations.

[a] $P < .05$.

Barbe et al[21] nor the present study found evidence of clinically significant weight gain among CPAP-treated patients with long-term follow-up. The small differences in weight change noted between the CPAP and control groups in the two studies may relate to differences in the patient characteristics and levels of CPAP adherence achieved; for example, mean age (52 vs 61 years), prevalence of preexisting CV disease (0% vs 100%), and median CPAP use (5.00 h [interquartile range, 2.18-6.25 h] vs 3.26 h [interquartile range, 1.26-5.08 h]) per night.

The meta-analysis by Drager et al[17] had raised concern that CPAP may cause an increase in weight gain, although the scale of the effect was small (0.17 kg; 95% CI, 0.10-0.24). It is possible that this difference between our observations and that of the previous shorter studies in the meta-analysis may be related to differences in study populations such as baseline obesity, ethnicity, age, and chronic comorbidities. Encouragingly, the relatively small short-term changes seen in the meta-analysis[17] do not seem to have been compounded during long-term follow-up.

It is reassuring that we found no clinically significant weight gain in CPAP-treated patients with OSA who, in the main, were overweight or obese and had proven (mainly atherosclerotic) CV disease. Conversely, it is noteworthy and arguably disappointing from a clinical perspective that weight did not decrease in the male or female subjects in either the CPAP or the control group. All SAVE participants had their CV risk factors managed according to national clinical guidelines, including advice on weight loss for secondary CV prevention in overweight/obese patients.[22-25] They were also given verbal lifestyle advice regarding weight control to minimize the severity of OSA. The absence of weight loss likely reflects the widely acknowledged dual problems of suboptimal adherence to clinical guidelines by practitioners[26] and the difficulties that patients experience in adopting the lifestyle changes that are necessary to achieve sustained weight loss, as discussed elsewhere.[25,27]

Most people with OSA are overweight or obese and have a high frequency of CV risk factors (eg, hypertension,[28] diabetes mellitus[29]) and disease.[30] Results of the Wisconsin Sleep Cohort Study highlight the potential benefit of weight loss in the management of OSA: a 10% reduction in weight was associated with a 26% drop in AHI,[31] and weight loss is recommended in OSA management guidelines[32,33] and for CV risk reduction.[23,25,27] Our study findings indicate that CPAP, and the symptom benefits that flow from it, cannot be relied upon to lead to meaningful weight loss.[17] Enhanced weight management is therefore needed for overweight patients with OSA receiving long-term CPAP treatment and is ideally delivered as part of a personalized chronic disease management program.[34] Indeed, combining weight loss with CPAP therapy for OSA seems necessary to improve CV risk markers.[35] The importance of encouraging weight loss in those with OSA and CV disease living in affluent societies is emphasized in our multivariable regression model, which showed that male subjects were less likely to lose weight than female subjects, as were those from Australia and New Zealand compared with India and China, independent of CPAP status. These differences observed irrespective of CPAP treatment may relate to national differences in dietary patterns, health-care systems, socioeconomic status, or other unknown lifestyle factors.[36]

We recognize that our study has several limitations. First, the study population was restricted to older patients with moderate to severe OSA and established CV disease but with very severe cases (nocturnal oxygen desaturation $< 80\%$ for $> 10\%$ of recording time) and marked self-reported daytime sleepiness (ESS score > 15) excluded. Thus, our results may not be generalizable to all patients with OSA. However, the large size of the study and prospective recording of weight, CPAP adherence, and other measures over several years allowed sensitivity analyses to be undertaken according to levels of adherence to CPAP.

Conclusions

The present study showed that patients with moderate to severe OSA and co-existing CV or cerebrovascular disease had no significant changes in BMI or neck or

waist circumference from the use of CPAP over several years. We found no evidence that patients with moderate to severe OSA and coexisting CV disease are susceptible to clinically concerning long-term weight change from the use of CPAP therapy.

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Author contributions: R. J. W. and K. A. L. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Q. O., B. C., C. S. A., R. D. M., and R. J. W. planned the study. Q. O., Y. L., X. Z., R. C., Q. W., L. F. D., G. L.-F., M. H., N. M., S. M., O. M., F. B., C. S. A., and R. D. M. recruited participants and collected data and samples. R. J. W. and K. A. L. conducted statistical analyses. Q. O., B. C., R. D. M., R. J. W., K. A. L., and C. S. A. interpreted data and drafted the manuscript. All authors contributed to drafting the manuscript, and read and approved the manuscript for submission.

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Additional information: The e-Appendixes and e-Tables can be found in the Supplemental Materials section of the online article.

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