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SCIENTIFIC INVESTIGATIONS

Survival benefit of continuous positive airway pressure in Japanese patients with obstructive sleep apnea: a propensity-score matching analysis

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Study Objectives: Continuous positive airway pressure (CPAP) improves quality of life in patients with obstructive sleep apneas. However, the long-term benefit in all-cause mortality and cardiovascular death are limited among Japanese.

Methods: We conducted a retrospective study of patients treated in our sleep clinic in Okinawa, Japan. All patients with full-scale polysomnography from September 1990 to December 2010 were investigated in terms of outcomes such as death (dates and causes of death) between 2012 and 2013 by chart review, telephone calls, and letters of inquiry. Propensity-score matching was performed to balance baseline characteristic differences between a CPAP user group and a nonuser group. The primary outcomes were all-cause mortality and a composite of cardiovascular disease mortality, such as heart disease and stroke, between the two groups.

Results: The CPAP user group, almost double in number, had more severe obstructive sleep apnea, more comorbidities, smoking, and alcohol consumption compared to the nonuser group but no significant difference in Epworth Sleepiness Scale. Propensity-score matching selected 1,274 of 4,519 patients as the CPAP user group and 1,274 of 2,128 as the CPAP nonuser group. Mean age of the patients was 52.3 (±13.5) years and 79% were men. After a median follow-up of 79 (interquartile interval, 24 to 128) months in the CPAP user group and 73.5 (interquartile interval, 26 to 111) in the non-CPAP group, death from all causes occurred in 53 (4.2%) patients in CPAP user group and in 94 (7.4%) patients in CPAP nonuser group. The leading cause of death was malignancy in each group. The hazard ratios for all-cause mortality and cardiovascular disease deaths were 0.56 (95% confidence interval (CI), 0.41–0.78) and 0.54 (95% CI, 0.28–1.03) between CPAP user group and CPAP nonuser group, respectively.

Conclusions: In obstructive sleep apnea patients, CPAP use was associated with lower all-cause mortality.

Keywords: obstructive sleep apnea, continuous positive airway pressure, CPAP, mortality, cardiovascular diseases, malignancy.

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Obstructive sleep apnea is associated with increased risk of mortality, cardiovascular disorders, and recently cancer. But continuous positive airway pressure effectiveness in lowering mortality in patients with obstructive sleep apnea is still uncertain, especially in Japan.

Study Impact: We conducted a retrospective, propensity-matching study with a large number of Japanese patients and a long follow-up period. Continuous positive airway pressure potentially may improve all-cause mortality.

INTRODUCTION

Obstructive sleep apnea (OSA) characterized by partial or total upper airway obstruction during sleep[1] is a common condition and the estimated prevalence in the United States is 4% of middle-age men and 2% of women.[2] Patients with OSA have repetitive intermittent hypoxemia and increased sympathetic nervous system activation while sleeping. Associated conditions include hypertension,[3] diabetes,[4] chronic kidney disease,[5] atrial fibrillation,[6] heart disease,[7] stroke,[8,9] and high overall mortality,[10–12] especially in severe OSA.

Continuous positive airway pressure (CPAP) has been the standard treatment for OSA. Use of CPAP improves such symptoms of OSA as snoring and excessive daytime sleepiness.[13] CPAP also slightly reduces blood pressure in hypertensive patients with OSA.[14] An observational study showed that CPAP prevented fatal and nonfatal cardiovascular disease (CVD) events, especially in men with severe OSA.[15] However, the merits of CPAP in reducing all causes of death and the risk of CVD, a composite of diseases such as heart disease and stroke, have remained unclear. The Sleep Apnea Cardiovascular Endpoints (SAVE) study, a large randomized controlled study (RCT), showed no survival merit of CPAP in patients with moderate to severe OSA.[16] This study excluded OSA patients with severe daytime sleepiness and very severe hypoxemia for safety reasons. In another meta-analysis, CPAP was not effective for prevention of CVD and all-cause mortality.[17]

Data is sparse on the prognosis of OSA in Japanese patients, with or without CPAP use. We previously reported that CPAP contributed to better survival for patients with mild to moderate

OSA in our institution,[18] but several confounding factors were not accounted for. In the present study we added more confounding factors, extended the number of enrolled participants and the follow-up duration, and conducted propensity-score (PS) matching in order to produce more robust evidence of the effects of CPAP in Japanese patients.

METHODS

Patient enrollment

We started nocturnal, attended fully monitored polysomnography (PSG) in 1990, preserved electronically the basic PSG data from the first test onwards, and have compiled the Okinawa Nakamura Sleep Registry (ONSLEEP) at the Nakamura clinic in the Okinawa islands, which have a population of 1.35 million and are located in southernmost Japan. In our clinic, most patients are evaluated by PSG when suspected of sleep breathing disorder, especially OSA. PSGs were performed and scored manually by 1 and later 2 registered polysomnographic technologists and several trained technologists using 4 different devices. The full methods for test devices were described in our original paper.[18] From the ONSLEEP dataset, we included only patients who underwent PSG from September 1990 to December 2010. The results consisted of an electroencephalogram, electro-oculogram, submental and tibial electromyogram, airflow at the nose or mouth, thoraco-abdominal movement, and percutaneous arterial oxygen saturation (SpO_2). An apnea event was defined as the complete cessation of airflow at the nose or mouth for at least 10 seconds, classified as obstructive or central in accordance with the presence or absence of respiratory movement. Hypopnea was defined according to the criteria at that time, which was a reduction of more than 50% in airflow for more than 10 seconds, a decrease of more than 3% in oxygen saturation, or the presence of arousal from sleep. The apnea-hypopnea index (AHI), lowest SpO_2, and the percentage of time $SpO_2 < 90\%$ during the PSG was extracted for each patient. In case of multiple PSG examinations, we enrolled only the first PSG result. Exclusion criteria were insufficient data, such as a total sleep time < 2 hours, total time in bed < 4 hours, under the age of 20 years, AHI < 5 events/h, and those with follow-up periods < 30 days. Patients with central sleep apnea, defined as ≥ 5 central apneas per hour, which dominated more than half of all apnea events, were also excluded. Severity of OSA was stratified by AHI into mild (≥ 5 events/h), moderate (≥ 15 events/h), and severe (≥ 30 events/h).

CPAP treatment

From September 1990 to March 1998, patients with an AHI ≥ 5 events/h and daytime clinical signs and symptoms of OSA were provided with CPAP on a fee-for-service basis ($90/mo) in our clinic. The Japanese national insurance provided full coverage for CPAP treatment after April 1998 for patients with AHI ≥ 20 events/h and who required regular monthly visits. Patients who could continuously use CPAP for more than 30 days after CPAP implementation made up the CPAP user group, and those who could not made up the CPAP nonuser group. Patient qualified and eligible but who had refused CPAP were also included in the CPAP nonuser group. Main reasons for refusal of CPAP were inability to tolerate devices within 30 days, expected financial problems, and difficulty adjusting to the required monthly visit.

Our institutional management of CPAP therapy was the same throughout the research years. Educational programs on treatment and fitting of devices were done by doctors and mainly trained nurses at the first trial session. We set the initial pressure at a fixed mode decided empirically by the severity (AHI score) and bodyweight. When necessary this was changed to auto-mode or another device was substituted according to subjective complaints in order to maintain the patient's use of CPAP and the flow of monitoring data. Titration prior to CPAP was not common in Japan because of patients' financial conditions and the insurance regulations. It was performed within 3 months and repeated when the patient had problems of adherence or any difficulties in reaching optimal AHI goals. Following the start of CPAP, the first clinic consultation was usually around 2 weeks later, and thereafter the patients were required to visit every month to have adherence checked and pressure adjusted. On every visit they were asked the frequency per month and hours per day of usage; we used the monitoring data when available and adjusted the pressure. Mask fitting, humidification, and device problems were solved by our staff. When the patient could not continue using CPAP or attend clinics monthly, they had to return their CPAP equipment. Every process-associated therapy was recorded systematically on the chart.

Baseline assessment

Anthropometric features, age, sex, body mass index (BMI), lifestyle-related factors, alcohol habits, and smoking status were recorded at the first visit for PSG. Drinking habits and smoking status were recorded on the questionnaire as "Yes" or "No," for brevity. The Epworth Sleepiness Scale (ESS) was used to assess somnolence level. Comorbid medical conditions, such as history of heart disease (coronary heart disease and heart failure), stroke, hypertension, diabetes mellitus, and dyslipidemia were also confirmed at the first visit and by the endpoint's questionnaire. As most of the patients had 1 or more comorbidities, blood tests were performed at an optimal interval per the usual practice. In Japan, general screening programs, such as annual medical check-ups that include basic blood tests for metabolic syndrome, are common, and we adopted those data also.

Follow-up and outcomes

In April 2012 through December 2013, we collected information on the date patients stopped using or returned the CPAP device and investigated date and causes of death by chart review, letters of inquiry, and phone calls as needed. The patients who were confirmed to be deceased were removed from follow-up at the date of their deaths, and if they were lost at the endpoint of the study, even after a search, they were also removed as of the date of last contact. Duration of follow-up was calculated from the first PSG to the last visit, date of return the device or death, or the date of the last response. The primary outcomes were all-cause and CVD deaths. Causes of deaths were categorized into heart disease, stroke, malignancy, respiratory disease, infection, sudden death, accident, and unknown.

We obtained written or oral informed consent from the patients or their family members at the time of follow-up. This study was approved by the institutional review board at the Nakamura Clinic.

Statistical analysis

The baseline characteristics of patients are shown as percentages for dichotomous variables, mean with standard deviations for continuous variables following normal distribution, and median with interquartile interval for continuous variables following non-normal distribution. To investigate the characteristic differences between the CPAP user group and CPAP nonuser group, we used Pearson's χ^2 tests for dichotomous variables, 2 sample *t* tests for continuous variables following normal distribution, and Wilcoxon test for continuous variables following non-normal distribution.

Outcomes, such as all-cause mortality and CVD deaths, were first analyzed in the unmatched cohorts. Then we conducted propensity-score matching to balance baseline characteristics between the CPAP user group and CPAP nonuser group.[19] We calculated a PS to predict whether patients were treated with CPAP or not. Each CPAP user group was matched to 1 CPAP nonuser group, adapting nearest neighbor matching without replacement. A caliper was set to 0.1 of the standard deviation of the PS. Covariates were selected according to a previous study: age, sex, BMI, ESS ≥ 11, alcohol habit, smoking status, history of diabetes mellitus, heart disease, stroke, AHI, and proportion of the total sleep time with SpO_2 < 90%. An absolute standard difference below 0.1 for all covariates was considered as well-balanced in a matched cohort. To achieve a more balanced matched cohort, we included some interaction terms (sex*alcohol habit, sex*stroke, sex*heart disease, age*sex, age*heart disease, age*stroke, heart disease*stroke, BMI*heart disease, AHI*heart disease). Kaplan-Meier curves were drawn for the CPAP user group and nonuser group. Hazard ratios (HR) and 95% confidence intervals (CI) of all-cause mortality and CVD deaths were estimated for CPAP user vs nonuser groups.

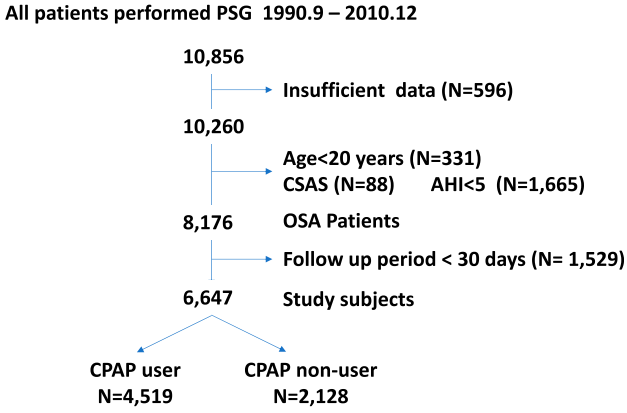
As a sensitivity analysis, we also conducted a stratified Cox regression analysis for all-cause mortality in the PS matched cohort. In unadjusted analyses, we considered the following variables as potentially independent factors of all-cause mortality: age, sex (male), BMI, ESS ≥ 11, history of diabetes mellitus, heart disease, stroke, smoking status, AHI ≥ 30, and proportion of the total sleep time with SpO_2 < 90%. Variables which were significant factors for all-cause mortality were then fitted in a multivariable analysis.

All statistical analyses used Stata version 15.1 for Windows (StataCorp LLC, College Station, TX). A $P < .05$ was set as statistically significantly different for all analyses.

RESULTS

A total of 10,856 Japanese patients received PSG from September 1990 to December 2010 (**Figure 1**). Of these, 596 were excluded because of insufficient data, 1,665 for an AHI < 5 events/h, 331 were < 20 years of age, and 88 had been diagnosed with central sleep apnea syndrome. Of the remaining 8,176 patients, 1,529 patients with a short follow-up < 30 days were further excluded. A total of 6,647 patients were analyzed in this study: 4,519 constituted the CPAP user group and 2,128 were the CPAP nonuser group. Outcomes for all of these patients were completed.

Figure 1—Flow chart of patient selection.



AHI = apnea-hypopnea index, CPAP = continuous positive airway pressure, CSAS = central sleep apnea syndrome, OSA = obstructive sleep apnea syndrome, PSG = polysomnography.

Many baseline characteristic variables were significantly different between CPAP user group and CPAP nonuser group, such as sex, BMI, alcohol habit, smoking status, and medical history, such as hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, stroke, and heart disease (**Table 1**). Mean AHI was 51.6 in CPAP user group and 21.3 in CPAP nonuser group ($P < .001$).

The number and causes of deaths are shown in **Table 2**. The total number of deaths was 209 in the CPAP user group and 144 in the CPAP nonuser group. The risk of death was significantly lower among CPAP user group (HR 0.64, 95% confidence interval [CI] 0.51–0.79). The leading cause of death was malignancy in both CPAP user group (51 patients, 24%) and CPAP nonuser group (28 patients, 19%). The second leading cause of death was heart disease (42 patients, 20%) in CPAP user group and infection (24 patients, 17%) in CPAP nonuser group.

The PS matching procedure selected 1,274 patients in each group. The median follow-up was 79 (interquartile interval, 24 to 128) months in the CPAP user group and 73.5 (interquartile interval, 26 to 111) months in the non-CPAP group. The characteristics in matched cohorts are shown in **Table 3**. Standard differences revealed that the characteristics of each group (sex, age, BMI, ESS score, medical histories of heart disease, alcohol habits, smoking status, AHI, and percentage of time SpO_2 was < 90% of the total sleep time) were well balanced. On the other hand, medical history of diabetes mellitus and stroke were marginally balanced.

The number of all-cause of deaths was 53 (4.2%) in CPAP user group and 94 (7.4%) in CPAP nonuser group in the matched cohort. The CPAP user group had a significantly better survival compared to CPAP nonuser group (HR 0.56, 95% CI 0.41–0.78; **Figure 2A**). The total number of deaths from CVD were 14 (1.1%) in the CPAP user group and 26 (2.0%) in CPAP nonuser group. The difference was not statistically significant (HR 0.54, 95% CI 0.28–1.03; **Figure 2B**).

Table 1—Baseline characteristics of CPAP user group and nonusers.

	CPAP User (n = 4,519)	CPAP Nonuser (n = 2,128)	*P*-Value#
Male (%)	3775 (83.5)	1510 (70.9)	< .001
Age, year (SD)	51.6 (13.2)	51.6 (14.1)	.99
BMI (SD)	28.9 (5.1)	26.8 (4.5)	< .001
ESS (SD)	8.7 (5.2)	8.7 (5.1)	.98
ESS > 11 (%)	2332 (51.6)	1150 (54.0)	.063
Medical history (%)			
Hypertension	2498 (55.3)	554 (26.0)	< .001
Diabetes mellitus	1050 (23.2)	193 (9.1)	< .001
Dyslipidemia	1268 (28.1)	252 (11.8)	< .001
Chronic kidney disease	1053 (23.3)	191 (9.0)	< .001
Stroke	358 (8.0)	80 (3.7)	< .001
Heart disease	872 (19.3)	184 (8.7)	< .001
Respiratory disease	120 (2.7)	92 (4.3)	< .001
Smoking (%)	1068 (23.7)	420 (19.8)	< .001
Alcohol consumption (%)	2889 (64.1)	1115 (54.8)	< .001
Polysomnography			
AHI, mean (SD)	51.6 (32.5)	21.3 (22.5)	< .001
AHI, median (25%, 75%)	43.4 (27.4, 70.8)	13.8 (8.9, 22.5)	< .001
AHI < 15 (%)	320 (7.1)	1178 (55.4)	< .001
15 ≤ AHI < 30 (%)	1033 (22.9)	573 (26.9)	< .001
AHI ≥ 30 (%)	3166 (70.1)	377 (17.7)	< .001
SpO_2 < 90% of total sleeping time % (25%, 75%)	5.9 (1.5, 19)	0.8 (0, 3.3)	< .001

#ESS, AHI, and SpO_2 were analyzed by Mann-Whitney test. All other factors were analyzed by *t*-test. AHI = apnea-hypopnea index, BMI = body mass index, CPAP = continuous positive airway pressure, ESS = Epworth Sleepiness Scale, SD = standard deviation, SpO_2 = percutaneous arterial oxygen saturation.

In the sensitivity analysis by stratified Cox regression, male sex (HR 2.15, 95% CI 1.31–3.53), age (HR 1.08; 95% CI 1.07–1.10), BMI 0.96 (0.92–1.00), ESS ≥ 11 (HR 1.58, 95% CI 1.11–2.24), AHI ≥ 30 (HR 1.72, 95% CI 1.24–2.40), and percentage of time SpO_2 was < 90% of the total sleep time (HR 1.02, 95% CI 1.01–1.02) were risk factors for all-cause mortality in unadjusted analysis, but not history of diabetes mellitus (HR 0.85, 95% CI 0.50–1.43), heart disease (HR 1.06, 95% CI 0.68–1.66), stroke (HR 0.61, 95% CI 0.27–1.39), or smoking status (HR 0.75, 95% CI 0.48–1.19). Adjusting for the set of unadjusted significant factors, the CPAP user group was (as in the primary analysis) a significant predictor for better survival (HR 0.47, 95% CI 0.33–0.66), as was male sex (HR 3.27, 95% CI 1.97–5.41), age (HR 1.08, 95% CI 1.07–1.10), ESS ≥ 11 (HR 1.56, 95% CI 1.10–2.22), AHI ≥ 30 (HR 1.56, 95% CI 1.10–2.22), and percentage of time SpO_2 was < 90% of the total sleep time (HR 1.02, 95% CI 1.01–1.02) (**Table 4**).

Table 2—Causes of death.

Cause	CPAP User (n = 4,519)	CPAP Nonuser (n = 2,128)	Total (n = 6,647)	*P*-Value#
Malignancy	51	28	79	.51
Heart disease	42	22	64	.68
Stroke	24	11	35	.94
Sudden death	14	3	17	.2
Respiratory disease	16	21	37	< .01
Infection	24	24	48	< .01
Others	17	16	33	< .01
Unknown	20	16	36	.11
Accident	1	3	4	.07
Total	209	144	353	< .01

#All factors were analyzed by Pearson χ^2 tests. CPAP = continuous positive airway pressure.

DISCUSSION

In this study to determine the survival benefit of CPAP use in patients with OSA, we gathered more information compared to our previously published study[18] by incorporating propensity-score matching analysis to circumvent several statistical pitfalls of a retrospective observational study. These approaches intensified the strength of our conclusions on CPAP benefit.

Table 3—Comparison of baseline characteristics used for PS matching.

Variable	CPAP User (n = 1,274)	CPAP Nonuser (n = 1,274)	Standard Differences#
Male (%)	958 (75)	1003 (79)	–0.084
Age, year (SD)	51.7 (13.1)	52.9 (13.9)	–0.089
BMI (SD)	27.3 (4.3)	27.4 (4.6)	–0.007
ESS ≥ 11 (%)	692 (54.3)	697 (54.7)	–0.008
Medical history (%)			
Diabetes mellitus	100 (7.9)	173 (13.6)	–0.186
Stroke	48 (3.8)	76 (6.0)	–0.102
Heart diseases	131 (10.3)	167 (13.1)	–0.088
Smoking (%)	258 (20.3)	249 (19.5)	0.018
Alcohol consumption (%)	672 (52.8)	723 (56.8)	–0.08
Polysomnography			
AHI, median (25%, 75%)	23.9 (16.7, 34)	18.4 (11.7, 33.7)	0.009
SpO_2 < 90% of total sleeping time % (25%, 75%)	2.3 (0.7, 7.8)	1.0 (0.1, 5.0)	0.06
Median follow-up months (25%, 75%)	79.0 (24, 128)	73.5 (26, 111)	
Deaths (%)	53 (4.2)	94 (7.4)	

#Standard differences below 0.1 were considered well-balanced between CPAP user group and CPAP nonuser group. Covariates: age, sex, BMI, ESS ≥ 11, alcohol habit, smoking status, history of diabetes mellitus, heart disease, stroke, AHI, and proportion of total sleep time SpO_2 < 90%. AHI = apnea-hypopnea index, BMI = body mass index, CPAP = continuous positive airway pressure, ESS = Epworth sleepiness scale, PS = propensity matching, SD = standard deviation, SpO_2 = percutaneous arterial oxygen saturation.

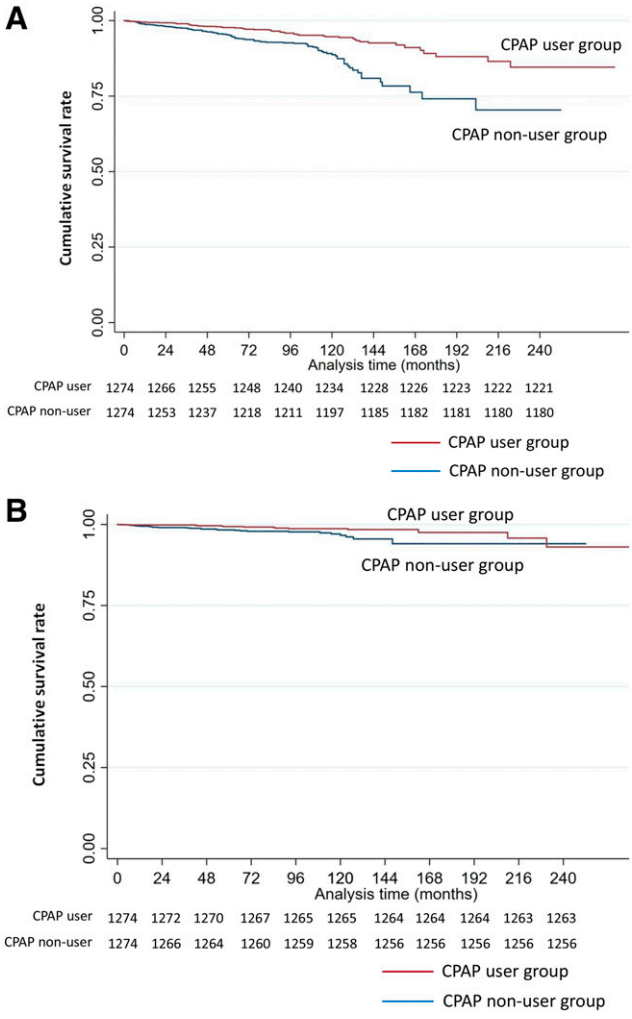
The main cause of death in both cohorts was malignancy, followed by heart disease in CPAP user group and infection in CPAP nonuser group in this study. A potential association between OSA and malignancy has been reported; OSA was a risk factor in several kinds of malignancies,[20] and a risk in 3 of 12 cancer types in a large national health insurance database.[21] The presumptive mechanism in both in vitro and in vivo studies[22]was intermittent hypoxia–induced tumor growth. In this study, whether malignancy was already present before CPAP use or developed after CPAP use was not clear, so it is difficult to confirm the effect of CPAP use on malignancy. In Japan since 1982, malignancy has been the leading cause of death in those older than 45 years, which may be relevant to our findings.[23] In Japan, several general screening programs have suggested that the metabolic syndrome is related to cancer mortality.[24] Although the populations of people with OSA and with metabolic syndrome may overlap to some extent, this association remains to be investigated.

In this study, the number of CVD deaths was small, and a significant difference in deaths from CVD between the 2 groups was not demonstrated.

OSA is related to various complications, especially CVD and all-cause deaths.[7–9] CPAP potentially reduced the incidence of CVD and deaths in an observational study. Marin et al reported a prospective cohort study in which patients with untreated severe OSA were at a higher risk for fatal and nonfatal CVD, and CPAP decreased the risk of CVD for a mean of 10 years of follow-up.[15] We also reported that OSA with an AHI ≥ 30 events/h was negatively correlated to survival, and the use of CPAP significantly improved the survival rate for a mean of 64 months of follow-up.[18] On the other hand, several RCTs have shown no effectiveness of CPAP on CVD and mortality. Barbe et al reported that use of CPAP did not reduce the incidence of hypertension and CVD events in nonsleepy (ESS ≤ 10) patients with OSA for a median of 4 years of follow-up.[25] McEvoy et al also reported that in the SAVE study, the largest RCT to investigate the effect of CPAP and CVD events in patients with OSA, CPAP did not prevent CVD events after a mean of 3.7 years of follow-up.[16]

Both observational studies and RCTs have inherent limitations. Although the follow-up was longer in the observational studies, there are substantial selection biases. RCT can control such biases, but the follow-ups of earlier studies were shorter and some patients, especially those with excessive sleepiness, were excluded due to ethical concerns. Mazzotti et al recently revealed that the excessively sleepy subtype of patients with OSA was at significantly higher risk of CVD compared to patients with OSA with similar AHI but not excessively sleepy.[26] In RCT, long follow-up of the 2 groups with and without treatment are an essential measure. As the prevalence of OSA is high and is possibly a risk for CVD and mortality, there is a serious ethical concern if patients, including the sleepy patients, remain untreated for a long period in order to investigate whether CPAP improves survival and decreases the risk of fatal cardiovascular events. Therefore, we adopted the PS-matching analysis to circumvent the above-mentioned problems. The Cox regression analysis showed age, male sex, ESS ≥ 11, AHI ≥ 30 events/h, and the proportion of total sleep time that SpO_2 < 90% were independent risk factors for all-cause mortality. This suggests that patients with severe and/or sleepy OSA are at high risk for mortality, a conclusion similar to Mazzotti's.

Figure 2—Kaplan-Meier curves.



(A) Kaplan-Meier curve for all-cause mortality after propensity-score matching. **(B)** Kaplan-Meier curve for cardiovascular disease deaths after propensity-score matching. CPAP = continuous positive airway pressure.

Table 4—Sensitivity analysis by multivariable stratified Cox regression.

Variable	HR	95% CI
Age	1.08	1.07–1.10
Male	3.27	1.97–5.41
BMI	0.97	0.93–1.01
ESS ≥ 11	1.56	1.10–2.22
AHI ≥ 30	1.56	1.10–2.22
SpO_2 < 90% of total sleeping time %	1.02	1.01–1.02
CPAP user group	0.47	0.33–0.66

AHI = apnea-hypopnea index, BMI = body mass index, CI = confidence interval, CPAP = continuous positive airway pressure, ESS = Epworth Sleepiness Scale, HR = hazard ratio, SpO_2 = percutaneous arterial oxygen saturation.

OSA per se may not have been the cause for the symptoms. Attesting that a subjective symptom like excessive daytime sleepiness is caused by OSA or by other comorbidities seems impossible in fact. In patients with OSA, sleepiness has been a major sign to be assessed, and regardless of cause, patients with OSA presenting with sleepiness require treatment. This may have resulted in a selection bias in our study. However, we consider the large number of patients and the long follow-up of a matching cohort enough to have covered this factor.

The proportions of respiratory disease and infection as causes of death were higher in the CPAP nonuser group. As our clinic specializes in both respiratory and sleep medicine, we have treated a lot of COPD patients with home oxygen therapy and pneumonia. Thus, selection bias in both disorders is conceivable, and one of the limitations. Many baseline differences between the two groups were present, including that the severity of OSA was lower in the CPAP nonuser group and that the frequency of comorbidities such as hypertension and diabetes were significantly higher in the CPAP user group. It is conceivable that patients with any disease that is severe and combined with comorbidities would be more motivated to accept and stay on treatment than patients with less severe conditions and fewer comorbidities. This would be the case with our study. Most of our patients were already diagnosed with one or more comorbidities at the first visit and those with the most severe OSA, and more comorbidities, may well have been more willing to choose CPAP.

The frequency of such other comorbidities as hypertension and diabetes were higher and concurrently the prognosis for OSA was better in the CPAP user group. We did not ascertain the severity of, or treatments for, each comorbidity in our study. Consequently, it would be misleading to conclude that OSA played a more important role in the prognosis than other comorbidities.

This study has several strengths that consolidate our findings. First, we included a large sample size with a long follow-up, adjusted by PS matching for many important confounders of survival. Second, our study included more than 50% sleepy patients even after matching, those who tended to be excluded in other recent RCT.[16] Third, this study was based on single center–based observation over the past 2 decades, and the medical care and the related supports were quite consistent, regardless of CPAP use, with standards under the national health insurance in Japan. Finally, we were able to confirm the outcomes of 10,411 of 10,856 (95.9%) patients who received basic PSG in our clinic.

Limitations are: First, this was a retrospective study and not a random population sample. As an observational study, the possibility of residual confounding having affected our findings cannot be ruled out. We cannot be sure that all excess deaths in the CPAP group were a consequence of OSA but have no reason to assume any additional difference between the CPAP user and CPAP nonuser groups beyond the factors we have controlled for. Second, adherence to CPAP treatment is an important factor in the prognosis of OSA patients.[27] But CPAP devices with monitoring were not fully provided in an early stage of this study, resulting in a gap in adherence data. Since the late 1990s, we have been checking adherence rates. In this study,

795 monitored patients, 17.6% of the CPAP user group, provided data on days using CPAP and usage time. In this subgroup the adherence rate, defined as the ratio of usage days divided by all follow-up days, was 0.76, and the mean usage time was 265 minutes per night. Third, some comorbidities, such as diabetes mellitus and stroke, were only marginally balanced. Finally, we did not take into consideration the influence of additional OSA treatments, such as surgical intervention and oral appliances.

In conclusion, we found that the all-cause mortality rate was lower among the CPAP user group than in the nonuser group of Japanese patients. However, no significant difference was found in the number of CVD deaths. The present study supports the current strategy of CPAP treatment. However, more research is needed to investigate the effectiveness of CPAP, especially in excessively sleepy patients with OSA.

ABBREVIATIONS

AHI, apnea-hypopnea index
BMI, body mass index
CI, confidential interval
CPAP, continuous positive airway pressure
CVD, cardiovascular diseases
ESS, Epworth Sleepiness Scale
HR, hazard ratio
OSA, obstructive sleep apnea
PS, propensity-score matching
PSG, polysomnography
RCT, randomized controlled study
SBD, sleep-related disorder
SD, standard deviations
SpO_2, percutaneous arterial oxygen saturation

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