Longitudinal Analysis of Causes of Mortality in Continuous Positive Airway Pressure–treated Patients at the Population Level

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Abstract

Rationale: Randomized controlled trials do not support a role for continuous positive airway pressure (CPAP) in preventing major cardiovascular events or mortality in patients with obstructive sleep apnea (OSA). However, these trials' setting does not apply to most CPAP-treated patients.

Objectives: We aimed to assess the effect of CPAP on mortality in real-world patients.

Methods: We performed a population-based longitudinal observational study including all patients with OSA prescribed CPAP during 2011 in Catalonia, Spain, and non-OSA control subjects matched (1:2) by sex, 5-year age group, and region who were followed from 2011 to 2016.

Results: A total of 9,317 CPAP-treated patients with OSA and 18,370 control subjects without OSA were included (median age, 67 [57–72] years; 74% male). During a median follow-up of 5.5 years, 2,301 deaths were recorded. After adjustment by a composite of diagnosed comorbidities and previous use of healthcare resources, CPAP-treated patients showed a lower risk of death than control subjects (hazard ratio [HR], 0.67; 95% confidence interval [CI], 0.61–0.74), with the association not being statistically significant in women. Cancer-related deaths were the main drivers of this association (men: HR, 0.44; 95% CI, 0.36–0.54; women: HR, 0.44; 95% CI, 0.28–0.68). No significant associations were found for cardiovascular-related deaths. CPAP-treated women had an increased risk of respiratory-related death (HR, 2.41; 95% CI, 1.37–4.23).

Conclusions: CPAP-treated patients had a lower mortality rate than control subjects. This relationship was driven by cancer-related, but not cardiovascular-related, deaths. Results suggest a role for sex when prescribing CPAP, especially considering respiratory-related deaths, and foster a debate on the relationship between OSA and cardiovascular outcomes.

Keywords: obstructive sleep apnea; mortality; CPAP

(Received in original form July 28, 2020; accepted in final form February 19, 2021.

Supported by Instituto de Salud Carlos III through the project PI18/00502, and co-funded by the European Regional Development Fund (ERDF), "A way to make Europe"; Spanish Respiratory Society (SEPAR); Sociedad Española de Sueño (SES); Associació Lleidatana de Respiratori (ALLER); and ResMed. J.d.B. is supported by the Catalan Departament de Salut (Pla Estratègic de Recerca i Innovació en Salut [PERIS] 2016: SLT002/16/00364) and Instituto de Salud Carlos III (Miguel Servet 2019: CP19/00108), co-funded by the European Social Fund (ESF), "Investing in your future." The funders did not play any role in the study design, study analysis, manuscript preparation, or decision to publish this work.

Author Contributions: S.B. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. J.d.B. and S.B. wrote the first draft of the manuscript. J.d.B., S.B., and F.B. defined the study design. All authors contributed to the interpretation of results and critically reviewed the manuscript.

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This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

Ann Am Thorac Soc Vol 18, No 8, pp 1390–1396, Aug 2021

DOI: 10.1513/AnnalsATS.202007-888OC
Internet address: www.atsjournals.org

Obstructive sleep apnea (OSA) is a common disease, caused by the collapse of the upper airway during sleep, that affects 20–30% of the adult population (1). OSA has been associated with increased morbidity and mortality because of its association with hypertension, cancer, and metabolic, cardiovascular, and cerebrovascular diseases (2); in OSA, increased oxidative stress, inflammation, sympathetic activation, and hypercoagulability are the main mechanisms causing these associations.

Nocturnal continuous positive airway pressure (CPAP) is the most effective treatment for OSA (3). CPAP improves quality of life and daytime sleepiness, reduces OSA severity markers, such as the apnea–hypopnea index (AHI), and moderately decreases arterial blood pressure (mainly in patients with resistant hypertension) (3, 4). However, the SAVE study (5) and a 2017 meta-analysis (6) did not support a role for CPAP in preventing major cardiovascular events or OSA-related mortality. In this sense, the ISAACC study confirmed that CPAP does not significantly reduce the rate of cardiovascular events and/or deaths among patients with OSA and acute coronary syndrome, and this study questioned the link between OSA and an increased rate of cardiovascular events (7). However, it must be noticed that randomized controlled trials (RCTs) may struggle to capture what happens in real-life scenarios. The tight inclusion and exclusion criteria combined with ethical constrains (i.e., the need of being able to randomize a patient to not receive CPAP treatment) can cause the participants in RCTs to not be representative of the whole population using CPAP. This may have an impact on the generalizability of RCT results. RCTs will always be the gold standard for assessing efficacy but may not be suited for assessing effectiveness. In this sense, more recent studies have shown that CPAP treatment is related to lower overall mortality over long follow-up times (8) or in population-based data (9).

Considering the high prevalence of OSA, and thus the extensive use of CPAP (CPAP use prevalence has reached 1% of the population in Catalonia (9), Spain), it is of paramount relevance to analyze the potential effect of CPAP treatment on mortality at the population level while considering the specific causes of death and potential sex differences.

Methods

This was a longitudinal prospective study of all patients with OSA with a CPAP prescription during 2011 in Catalonia, Spain, that included control subjects without OSA who had contact with the Catalan Health System during the same year and did not use CPAP throughout the whole follow-up. The selection of this comparator group responded to the reality of population-based health registries, in which almost all subjects with an OSA diagnosis have had, are having, or will eventually initiate CPAP treatment during a follow-up period. Therefore, a set of patients with OSA without CPAP treatment could not be used as comparator group. However, given that OSA is a highly prevalent condition with remarkable levels of underdiagnosis, comparisons against patients without OSA at a similar risk of dying indeed include a substantial proportion of nondiagnosed subjects experiencing OSA and not being treated with CPAP (this is further discussed in the discussion section). CPAP prescription was identified on the basis of invoiced services. Patients with OSA and control subjects were matched (1:2) by sex, 5-year age group, and health region. All subjects were followed from 2011 to 2016 or until death. Collected variables included age; sex; health region; date of CPAP prescription; date and cause of death, as coded using *International Classification of Diseases, Tenth Revision* (ICD-10) in the Catalan Statistical Bulletin of Death; comorbidities *International Classification of Diseases, Ninth Revision* (ICD-9); and adjusted morbidity group (AMG), which is a morbidity measurement based on diagnosed comorbidities and previous use of healthcare resources (visits and prescriptions) that allows patient risk stratification (10, 11). An accurate description of how AMG is generated can be found in the online supplement of a manuscript by Monterde and colleagues (10). Briefly, the AMG algorithm is based on identification of neoplasia, identification of diseases associated with pregnancy and/or childbirth, identification of acute diseases, number of chronic diseases, number of organ systems affected by chronic diseases, total relative complexity weight (population-based measures of mortality, healthcare needs, and prescriptions), and the list of relevant disease labels (if any). The output of this algorithm is an average AMG score and a risk stratum (baseline, low, moderate, or high risk). The current analyses included the AMG score as a continuous variable. Patients receiving CPAP treatment via private health services were excluded from the current analyses.

Available data included 72 specific causes of death, which were further grouped into the following five categories: cancer; cardiovascular; nervous system and mental illness; respiratory; and other. Unfortunately, the registry of the specific causes of death started in 2012; therefore, all subjects who died during 2011 had an unspecified cause of death and were grouped together.

Participants' baseline characteristics are described by the number (percentage) or median (interquartile range), as appropriate. Cox proportional hazards regression models were used to estimate hazard ratios (HRs) for the association between CPAP treatment and overall mortality as well as the grouped causes of death. All models were adjusted by the 5-year age group and AMG (continuous) and were stratified by sex. Models including an interaction between CPAP treatment and sex were used to assess potential sex differences in the association between CPAP treatment and mortality. Similarly, adjusted Kaplan-Meier curves of the time to death were plotted. To reduce the chance of reverse causality, all models considering cancer as the main cause of death were also run while excluding the first 2 years of follow-up. In addition, sensitivity analyses excluding patients with an ICD-9 code for cancer at baseline were also performed. The proportional hazards assumption was satisfied in all models. The statistical level of significance was fixed at 0.05. All analyses were performed using R statistical software, version 3.5.2.

All the data for the current study were obtained from Agency for Healthcare Quality and Evaluation of Catalonia (AQuAS; Public Data Analytical Program for Health Research and Innovation), which is a public entity attached to the Department of Health of the Government of Catalonia. Patient informed consent was not required because all data were anonymized. The ethics committee of Hospital Arnau de Vilanova approved this study (2015, CEIC-1430).

Results

Table 1 shows the baseline characteristics of the 9,317 patients with OSA prescribed CPAP in 2011 in Catalonia and the 18,369 control subjects without OSA who had contact with the Catalan Health System in 2011. The median age at enrollment was 67 years, and up to 74% of the subjects were male. The morbidity of the two groups is represented by the AMG, which was significantly higher among the subjects prescribed CPAP than among the control subjects; thus, the CPAP-

treated patients had a worse overall health status than the control subjects and were at a higher risk of death during the follow-up. Additional information on the main baseline comorbidities of the subjects in the database can be found in the online supplement (Table E1 in the online supplement).

A total of 2,301 deaths were recorded during a median follow-up of 5.52 years. Table 2 describes the deaths during the follow-up. The main grouped causes of death were cancer (27%), cardiovascular causes (19%), and respiratory causes (11%). Up to 21% of the causes of death were considered unspecified, which corresponded with all deaths during 2011. A full description of the deaths during the follow-up, including all 74 registered causes of death, can be found in the online supplement (Table E2).

The adjusted Kaplan-Meier survival curves for CPAP-treated patients and control subjects as well as the curves for men and women are shown in Figure 1. The Kaplan-Meier survival curves for each of the grouped causes of death can be found in the online supplement (Figure E1). Adjusted Cox proportional hazards regression models assessing the association between CPAP treatment and overall mortality and the grouped causes of death, which were stratified by sex, are shown in Table 3 and Figure 2. CPAP treatment was associated with significantly lower adjusted mortality rates (HR, 0.67; 95% CI, 0.61–0.74), and this relationship was statistically significant in men (HR, 0.61; 95% CI, 0.56–0.69) but not in women (HR, 0.87; 95% CI, 0.73–1.05). This difference was confirmed in a model including a CPAP treatment–sex interaction term ($P = 0.004$). The analysis of the specific causes of death showed that the main drivers of this association were the lower mortality due to cancer and nervous system and mental illnesses. The sensitivity analysis excluding the first 2 years of follow-up in the models considering cancer as the main cause of death showed similar results for men (cancer deaths: 247; HR, 0.59; 95% CI, 0.45–0.78) and women (cancer deaths: 53; HR, 0.61; 95% CI, 0.33–1.14), although the results in women did not reach statistical significance because of the reduced number of recorded events. Similarly, sensitivity analysis excluding the 268 patients with an ICD-9 code for cancer in 2011 showed similar results (HR, 0.47; 95% CI, 0.39–0.56). Finally, the inclusion of baseline smoking status as an additional covariate reported very similar results, as shown in the online supplement (Table E3). Similarly, the inclusion of baseline comorbidities related to each cause of death also reported very similar results, as shown in the online supplement (Table E4).

Discussion

The longitudinal analysis of all patients with OSA prescribed CPAP treatment in Catalonia during 2011 showed that, during the period from 2011 to 2016, these patients had an overall lower mortality rate than the matched control subjects after appropriate adjustments. However, this association was not significant in women. The analysis of the specific causes of death showed that the main drivers of the reported association were the lower mortality from cancer and, to a lesser extent, from nervous system and mental illnesses. Interestingly, no differences were found between CPAP-treated patients and control subjects regarding cardiovascular-related deaths. Finally, CPAP-treated women were at a significantly higher risk of respiratory-related death than control subjects.

The results from the 18 years of follow-up of the Wisconsin Sleep Cohort established that untreated patients with severe (AHI $\geqslant$ 30) sleep-disordered breathing (SDB) were at a higher risk of overall mortality (HR, 3.8; 95% CI, 1.6–9.0) and cardiovascular mortality (HR, 5.2; 95% CI, 1.4–19.2) than subjects without SDB after adjustment (12). On the other hand, the 20 years of follow-up of the Busselton Health Study cohort showed that moderate to severe OSA was related to an increased risk of all-cause mortality (HR, 4.2; 95% CI, 1.9–9.2) and cancer mortality (HR, 3.4; 95% CI, 1.1–10.2) but not to an increased number of cardiovascular events (13). Finally, the results from the Sleep Heart Health Study were significantly milder, with patients with severe SDB showing increased all-cause mortality (HR, 1.5; 95% CI, 1.1–1.9) and cardiovascular mortality being significantly increased only in men with moderate to severe OSA (HR, 1.7; 95% CI, 1.1–2.5) but not in women (14). In this sense, most of the RCTs assessing the effect of CPAP on cardiovascular mortality reported null results (6, 7). The current study shows lower adjusted mortality rates among CPAP-treated patients with OSA than population-based matched control subjects without OSA treated by the Catalan Health System, but, most interestingly, this study shows that the overall reduction in mortality was not driven by an effect on cardiovascular mortality. These results, together with a report that OSA is not associated with an increased rate of cardiovascular events among patients with acute coronary syndrome (7) and the heterogeneity reported in observational studies, (in terms of the impact of CPAP on cardiovascular mechanisms, cardiovascular diseases, and mortality) (15), should foster a profound debate on the relationship between OSA and cardiovascular outcomes.

The reported lower mortality rates among CPAP-treated patients in the current study were driven by an effect on cancer-related deaths and, to a lesser extent, on nervous system– and mental illness–related

Table 1. Baseline characteristics

	All (*N = 27,686*)	Control (*n = 18,369*)	CPAP (*n = 9,317*)	*P* Value
Male sex, *n* (%)	20,472 (73.9)	13,574 (73.9)	6,898 (74.0)	0.813
Age, median (IQR), yr	67 (57–72)	67 (57–72)	67 (57–72)	0.746
AMG, median (IQR)	4.14 (1.47–9.25)	3.31 (1.12–7.35)	6.42 (2.86–13.4)	<0.001
AMG stratified, *n* (%)				<0.001
Baseline risk	12,366 (44.7)	9,510 (51.8)	2,856 (30.7)	—
Low risk	8,487 (30.7)	5,454 (29.7)	3,033 (32.6)	—
Moderate risk	5,049 (18.2)	2,680 (14.6)	2,369 (25.4)	—
High risk	1,784 (6.44)	725 (3.95)	1,059 (11.4)	—

Definition of abbreviations: AMG = adjusted morbidity group; CPAP = continuous positive airway pressure; IQR = interquartile range. Baseline risk [0–3.503]; Low risk [3.504–9.360]; Moderate risk [9.361–22.098]; High risk [22.099–100].

Table 2. Main causes of death in the studied population in each group and stratified by sex

	All [*n* (%)] *N* = 2,301	Men [*n* (%)]		Women [*n* (%)]	
		Control *n* = 1,123	CPAP *n* = 601	Control *n* = 298	CPAP *n* = 279
Cancer	629 (27.3)	369 (32.9)	150 (25.0)	73 (24.5)	37 (13.3)
Cardiovascular	447 (19.4)	187 (16.7)	131 (21.8)	57 (19.1)	72 (25.8)
Respiratory	244 (10.6)	88 (7.84)	89 (14.8)	21 (7.05)	46 (16.5)
Nervous system and mental illness	175 (7.61)	88 (7.84)	28 (4.66)	42 (14.1)	17 (6.09)
Metabolic	63 (2.74)	27 (2.40)	16 (2.66)	7 (2.35)	13 (4.66)
Other	254 (11.0)	120 (10.7)	55 (9.15)	34 (11.4)	45 (16.1)
Unspecified*	489 (21.3)	244 (21.7)	132 (22.0)	64 (21.5)	49 (17.6)

Definition of abbreviation: CPAP = continuous positive airway pressure.
*Corresponding with all deaths during 2011, as the registry of causes of death began in 2012.

deaths. Although in a cohort of ~5.6 million individuals, patients with OSA had increased cancer risk for only a very limited number of cancer types (16), epidemiological and clinical studies have established an association between OSA and cancer in humans (17–19). Interestingly, experimental studies using the intermittent hypoxia model in mice (20) not only confirmed that this association is biologically plausible but also indicated a three-part effect of intermittent hypoxia on tumors, as follows: *1*) accelerated tumor progression, *2*) promotion of metastases, and *3*) increased resistance to treatment. Therefore, CPAP treatment could effectively reduce cancer-related mortality. When considering the present results, the possibility of patients with life-threatening advanced tumors not being referred for sleep tests and thus not being prescribed CPAP should be considered. However, the sensitivity analysis excluding the first 2 years of follow-up or patients with a baseline ICD-9 code for cancer in models considering cancer as the main cause of death showed similar results and supports the validity of these results. Finally, the fact that all control subjects had contacted the Catalan Health System during 2011 makes it unlikely that patients prescribed with CPAP could have greater odds of having an early diagnosis of cancer, and thus have a better prognosis, given the higher interaction with the health system. On the other hand, concerning the findings for the nervous system– and mental illness–related deaths, CPAP treatment has long been suggested to have an effect on cognitive function and early cognitive decline in patients with OSA. In this sense, although the evidence so far has not been sufficiently strong (21), it could be hypothesized that CPAP effect would be more relevant in those patients with the most severe cognitive decline. Therefore, the current results focusing on mortality would precisely target those subjects at a higher risk of dying of nervous system– and mental illness–related causes that constitute the most severe patients with such pathologies.

The current results, together with previous nonlongitudinal results from a similar population (9), suggest a role for sex in OSA, especially in terms of treatment effectiveness and mortality. OSA is a predominantly male disease, with the most recent reviews estimating a male:female ratio of 1.5:1 (22). Women have a more stable upper airway and a less OSA-prone body fat

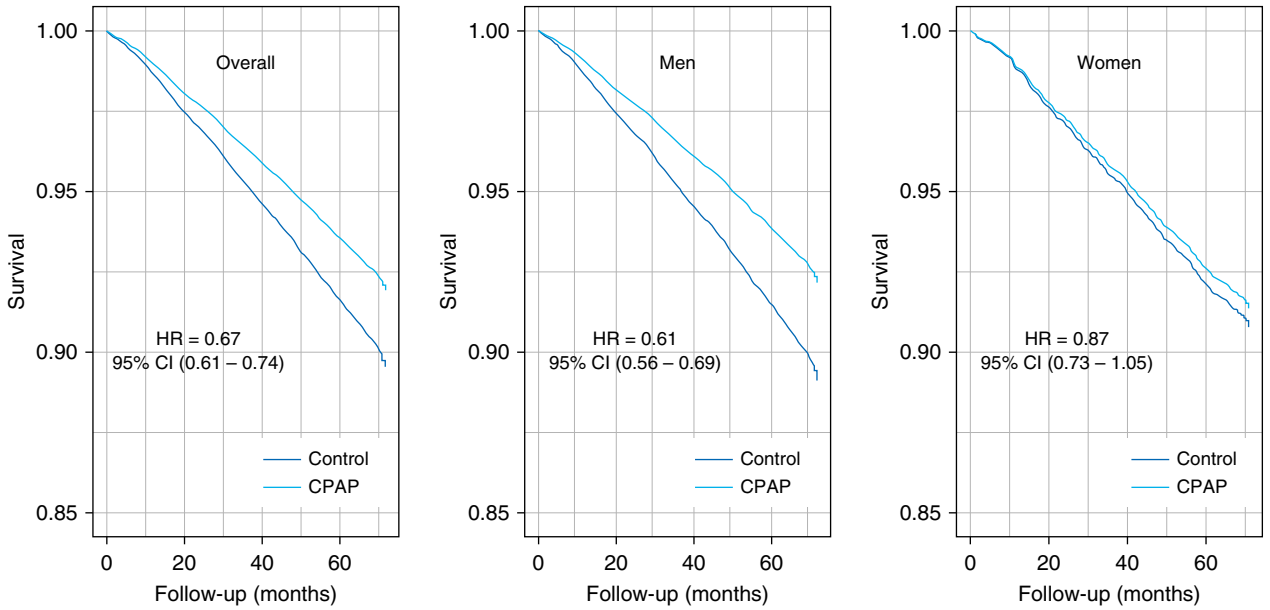

Figure 1. Adjusted Kaplan-Meier survival curves for CPAP-treated patients and control subjects, stratified by sex. All models were adjusted by the 5-year age group and adjusted morbidity group. CI = confidence interval; CPAP = continuous positive airway pressure; HR = hazard ratio.

Table 3. Cox proportional hazard models for all causes of death and for each specific cause of death and CPAP treatment, stratified by sex

	Men (*n* = 20,472)				Women (*n* = 7,214)			
	Crude		Adjusted		Crude		Adjusted	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
All causes of death	1.06 (0.96–1.17)	0.285	0.62 (0.56–0.69)	<0.001	1.91 (1.63–2.25)	<0.001	0.87 (0.73–1.05)	0.146
Cancer	0.80 (0.66–0.97)	0.022	0.44 (0.36–0.54)	<0.001	1.03 (0.69–1.53)	0.879	0.44 (0.28–0.68)	<0.001
Cardiovascular	1.38 (1.10–1.73)	0.005	0.82 (0.65–1.04)	0.098	2.57 (1.82–3.64)	<0.001	0.99 (0.67–1.46)	0.961
Respiratory	1.99 (1.48–2.68)	<0.001	1.05 (0.77–1.43)	0.775	4.45 (2.65–7.45)	<0.001	2.41 (1.37–4.23)	0.002
Nervous system and mental illness	0.63 (0.41–0.96)	0.032	0.45 (0.29–0.7)	<0.001	0.83 (0.47–1.45)	0.505	0.48 (0.26–0.88)	0.019
Metabolic	1.17 (0.63–2.17)	0.622	0.52 (0.27–1.00)	0.050	3.78 (1.51–9.46)	0.005	1.28 (0.46–3.57)	0.640
Other	0.90 (0.66–1.24)	0.532	0.50 (0.36–0.70)	<0.001	2.69 (1.73–4.21)	<0.001	1.13 (0.69–1.87)	0.621
Unspecified	1.07 (0.87–1.32)	0.534	0.74 (0.59–0.92)	0.007	1.60 (1.10–2.32)	0.014	0.85 (0.56–1.28)	0.441

Definition of abbreviations: CI = confidence interval; CPAP = continuous positive airway pressure; HR = hazard ratio.
Adjusted for age and adjusted morbidity group.

distribution than men, and both factors could protect women from OSA to a certain extent (22). Symptom differences among sexes, combined with the reluctance toward seeking treatment and the male-driven diagnosis of OSA by medical professionals, result in a significant underdiagnosis and undertreatment of OSA among women, with the current results showing a 3:1 male:female ratio in CPAP prescription. Overall, these factors have caused women to be underrepresented in most CPAP treatment effectiveness trials. After appropriate adjustment, our results show an overall lower mortality rate among CPAP-treated patients than in matched control subjects, but this result was not observed in women. This difference was driven by respiratory mortality.

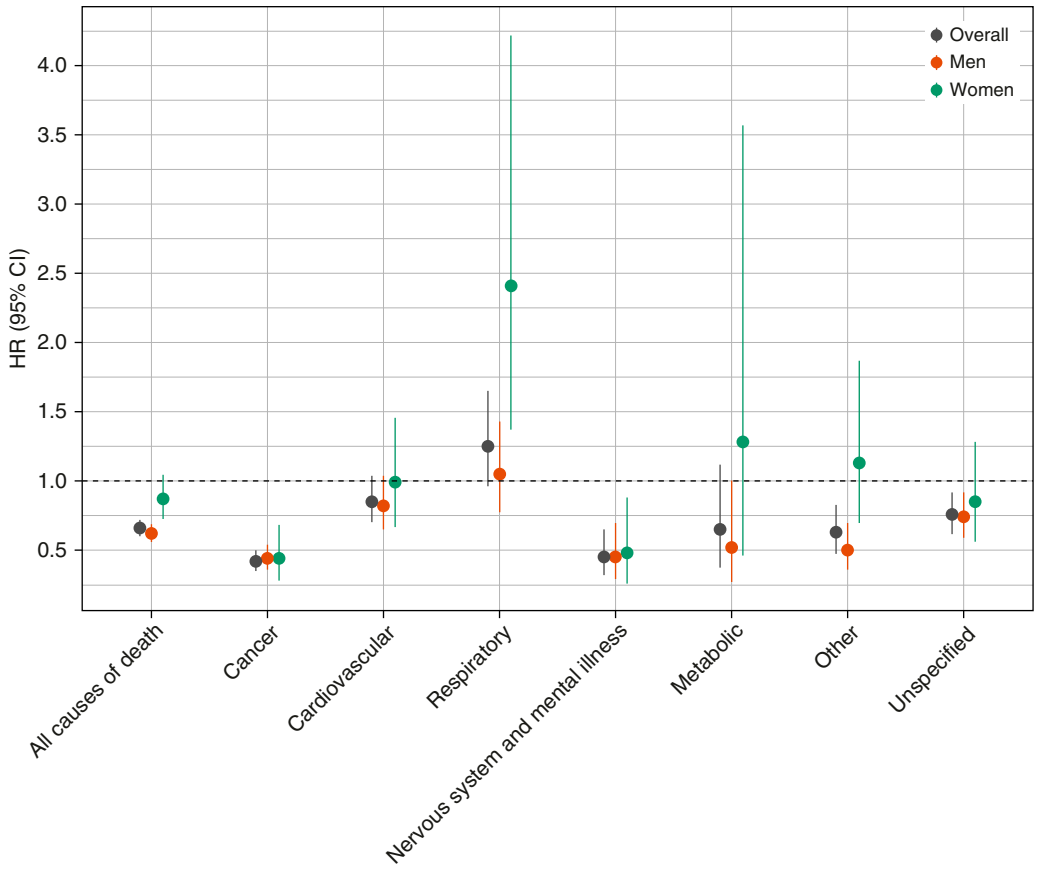

Figure 2. Cox proportional hazards regression models assessing the association between continuous positive airway pressure treatment and overall mortality, grouped by the causes of death and stratified by sex. All models were adjusted by the 5-year age group and adjusted morbidity group. CI = confidence interval; HR = hazard ratio.

Interestingly, a cluster analysis showed that the largest number of women (53%) was found in the asthma-driven cluster (23), and asthma is one of the main drivers of respiratory mortality, together with chronic obstructive pulmonary disease, bronchitis, and emphysema, accounting for 30% of deaths. Previous research has suggested the existence of an OSA–asthma overlap syndrome that would be more prevalent in women than men (24, 25). However, the fact that CPAP treatment could potentially be detrimental in this scenario is novel and deserves further studying. These findings suggest a need for research involving precision medicine (26), especially research that considers the role of sex; initiatives attempting to tailor CPAP treatment prescription and adjustments on the basis of sex should be fostered (27).

The current study was designed to determine the effect of CPAP treatment on mortality at the population level (real-world patients) in an attempt to avoid the limitations of controlled settings such as the strict inclusion and exclusion criteria or the ethical implications of not treating patients in the control group with CPAP. To do so, we proposed the use of a large public dataset and conceived a novel approach consisting in the choice of a nonconventional comparator group (patients without OSA from the same dataset). This setting was based on two premises. First, if CPAP was an effective treatment capable of mitigating OSA consequences, the mortality rates in CPAP-treated patients and patients without OSA at a similar risk of decease would be similar. Second, provided that OSA has a high prevalence in the adult population and a remarkable level of underdiagnosis, comparisons against patients without OSA at a similar risk of dying would indeed include an unneglectable proportion of patients with nondiagnosed OSA potentially requiring CPAP treatment (estimated by the authors to be ≈7% on the basis of Spanish OSA prevalence data [28] and the population pyramid of Catalonia in 2011). In this scenario, the amount of underdiagnosed patients with OSA in the control group could potentially be sufficient to tip the scales toward a reduced risk of mortality by OSA-related causes among CPAP-treated patients. This setting and premises are key for the interpretation of the current manuscript and sustain its conclusions.

This study has several potential limitations that should be noted. First, the current study design, comparing CPAP-treated patients to matched subjects who were in contact with the Catalan Health System for non–OSA-related causes, implies difficulties in disentangling the effect of CPAP treatment from the effects of being a patient with OSA. Second, the data used in this study did not include information about CPAP adherence. Therefore, our results constitute an intention-to-treat analysis in which data on CPAP compliance (hours/night) were not available. However, it must be stated that, according to AQuAS, the overall CPAP compliance in Catalonia is high (>80% of treated patients with >3 h/night), which is in line with 80% of patients having a compliance above 4 hours in the Health Region of Barcelona (29). Third, it was not possible to control for undiagnosed OSA in control subjects. Fourth, the observational design could not rule out potential residual confounding by known or unknown factors, such as socioeconomic status, the level of health literacy and self-care, or the level of delivered health care. Fifth, subjects prescribed with CPAP therapy in private medical centers were not included in the studied database. However, in Catalonia, up to 90% of complex treatments such as CPAP therapy, are prescribed through the public health system. Sixth, the matching of CPAP users and control subjects was limited to sex, age, and health region, as this is the standard method of AQuAS for supplying matched control subjects, and thus it was beyond the research team's decisions. Seventh, the study database did not include the main cause of contact with the health system that caused each of the patients to be in the database; this variable, if included in adjusted models, could have contributed to reducing potential selection bias. Finally, it could be argued that OSA diagnosis could be a marker of a better access to public healthcare providers; in this regard, it must be noticed that the Catalan Health System provides public, universal, freely available health coverage to all citizens of Catalonia and ensures a common standard of services and quality across all the territory, and, moreover, matching by healthcare region should attenuate this potential bias. On the other hand, this study has several strengths. First, the inclusion of all patients prescribed CPAP therapy through the Catalan Health System in 2011 allowed an accurate picture of real life in Catalonia as well as provided sufficient statistical power to perform sex-stratified analyses and to consider different causes of mortality. Moreover, this population-based approach granted adequate generalizability of the results to western populations. Second, the 5-year follow-up allowed the measurement of the short-term and midterm effects of CPAP prescription and is a significant improvement over previous cross-sectional results of the group (9). Finally, the use of the AMG variable, which combines data on comorbidities and the past use of health resources, allowed us to adjust the results in terms of the risk of dying of each cause.

In conclusion, the analysis of all patients with OSA prescribed CPAP treatment in Catalonia during 2011 showed that CPAP-treated patients had a lower mortality rate than matched control subjects after a 5-year follow-up. However, this relationship was not related to cardiovascular diseases but rather to cancer and, to a lesser extent, nervous system and mental illnesses; furthermore, the relationship was not as clear in women as in men. Overall, these results suggest that there is a need to embrace precision medicine when considering treatment for individual patients with OSA, especially for women, and should foster a debate on the relationship between OSA and cardiovascular outcomes. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank the Catalan Health Quality and Assessment Agency and its Public Data Analytical Program for Health Research and Innovation for kindly providing all required data at the request of the Master Plan for Respiratory Diseases (Ministry of Health, Catalonia).

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