JAMA Otolaryngology–Head & Neck Surgery | Original Investigation

Association of Systemic Diseases With Surgical Treatment for Obstructive Sleep Apnea Compared With Continuous Positive Airway Pressure

Badr Ibrahim, MD; Maria Isabel de Freitas Mendonca, MD; Saurabh Gombar, MD; Alison Callahan, PhD; Kenneth Jung, PhD; Robson Capasso, MD

IMPORTANCE The efficacy of surgical treatments for obstructive sleep apnea (OSA) is variable when considering only the Apnea Hypopnea Index as the treatment end point. However, only a few studies have shown an association between these procedures and improved clinically relevant outcomes, such as cardiovascular, endocrine, and neurological sequelae of OSA.

OBJECTIVE To evaluate the association of surgery for OSA with clinically relevant outcomes.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study used the Truven MarketScan Database from January 1, 2007, to December 31, 2015, to identify all patients diagnosed with OSA who received a prescription of continuous positive airway pressure (CPAP), were 40 to 89 years of age, and had at least 3 years of data on file. Data were analyzed September 19, 2019.

INTERVENTIONS Soft tissue and skeletal surgical procedures for the treatment of OSA.

MAIN OUTCOMES AND MEASURES The occurrence of cardiovascular, neurological, and endocrine complications was compared in patients who received CPAP alone and those who received surgery. High-dimensionality propensity score matching was used to adjust the models for confounders. Kaplan-Meier survival analysis with a log-rank test was used to compare differences in survival curves.

FINDINGS A total of 54 224 patients were identified (33 405 men [61.6%]; mean [SD] age, 55.1 [9.2] years), including a cohort of 49 823 patients who received CPAP prescription alone (mean [SD] age, 55.5 [9.4] years) and 4269 patients who underwent soft tissue surgery (mean [SD] age, 50.3 [7.0] years). The median follow-up time was 4.47 (interquartile range, 3-8) years after the index CPAP prescription. In the unadjusted model, soft tissue surgery was associated with decreased cardiovascular (hazard ratio [HR], 0.92; 95% CI, 0.86-0.98), neurological (HR, 0.49; 95% CI, 0.39-0.61), and endocrine (HR, 0.80; 95% CI, 0.74-0.86) events. This finding was maintained in the adjusted model (HR for cardiovascular events, 0.91 [95% CI, 0.83-1.00]; HR for neurological events, 0.67 [95% CI, 0.51-0.89]; HR for endocrine events, 0.82 [95% CI, 0.74-0.91]). Skeletal surgery (n = 114) and concomitant skeletal and soft tissue surgery (n = 18) did not demonstrate significant differences in rates of development of systemic complications.

CONCLUSIONS AND RELEVANCE In this cohort study, soft tissue surgery for OSA was associated with lower rates of development of cardiovascular, neurological, and endocrine systemic complications compared with CPAP prescription in a large convenience sample of the working insured US adult population. These findings suggest that surgery should be part of the early treatment algorithm in patients at high risk of CPAP failure or nonadherence.

JAMA Otolaryngol Head Neck Surg. doi:10.1001/jamaoto.2020.5179
Published online January 21, 2021.

Author Affiliations: Division of Sleep Surgery, Department of Otolaryngology–Head and Neck Surgery, Stanford University School of Medicine, Stanford Hospital and Clinics, Stanford, California (Ibrahim, de Freitas Mendonca, Capasso); Green Button, Stanford Center for Biomedical Informatics Research, Stanford, California (Gombar, Callahan, Jung).

Corresponding Author: Badr Ibrahim, MD, Division of Sleep Surgery, Department of Otolaryngology–Head and Neck Surgery, Stanford University School of Medicine, Stanford Hospital and Clinics, 450 Broadway St, Pavilion B, 2nd Floor, Redwood City, CA 94063 (ibra.badr@gmail.com).

Obstructive sleep apnea (OSA) is associated with neurocognitive, psychiatric, metabolic, and cardiovascular comorbidities as well as overall decreased survival. In addition, the annual economic costs of OSA are estimated to be $65 to $165 billion in the US alone, mostly owing to OSA comorbidities and health-related accidents.[1] Therefore, adequate treatment has evolved to become a medical and societal issue of high importance.

Although the criterion standard treatment for OSA is continuous positive airway pressure (CPAP), it is notoriously recognized for its limited tolerability and therefore less than optimal long-term adherence rates.[2,3] Oral appliance therapy for mild to moderate OSA is a recognized alternative, but it is also limited by patient's toleration and possible long-term adverse effects. Therefore, surgical alternatives addressing the nasal cavity, oropharynx, hypopharynx, and the facial skeleton have been devised to treat OSA by remodeling the airway and thereby improving airflow and decreasing collapsibility.

The variable efficacy of various surgical procedures to improve the Apnea Hypopnea Index (AHI), snoring, and sleepiness has been well demonstrated in prior studies.[4] However, only a few studies to date[5-9] have focused on the relevance of surgical procedures for mortality and health-related outcomes, including fatal and nonfatal cardiovascular events and neurocognitive and endocrine ailments. Therefore, we sought to study the effect of surgical treatment options on clinical outcomes related to OSA at a population level using a large health care insurance database.

Key Points

Question Is surgery associated with clinically relevant systemic complications of obstructive sleep apnea (OSA)?

Findings In this cohort study of 54 224 patients with OSA, cardiovascular, neurological, and endocrine comorbidities of OSA were associated with lower rates of occurrence after soft tissue surgery of the oropharynx in the unadjusted and adjusted models compared with continuous positive airway pressure (CPAP) prescription alone.

Meaning These findings suggest that in patients at high risk of CPAP nonadherence or for whom CPAP failed, surgery should be considered early in the treatment algorithm, because its use was associated with a reduction in the development of systemic complications of OSA.

Methods

Study Design

We performed a retrospective cohort analysis of adults aged 40 to 90 years diagnosed with OSA who were prescribed CPAP using a portion of the Truven MarketScan Database (TMD) that spanned from January 1, 2007, to December 31, 2015, and aimed to evaluate the development of cardiovascular, neurological, and metabolic complications in surgically and nonsurgically treated patients. The TMD is a commercially available database with fully deidentified data, and institutional review board oversight is not needed for its use. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Data Source

The TMD is a large convenience sample of the US adult working insured population containing medical, drug, and dental records on as many as 250 million patients.[10] It integrates deidentified patient-level health data, productivity, health risk assessments, hospital discharges, and electronic medical records into data sets available for health care research.[10] We accessed a portion of the TMD spanning the years 2007 to 2015. The total sample size available in this portion of the TMD was 124 257 670 million US insured working adults for a total of 3 052 587 721 recorded encounters.

Study Population

Patients with an OSA diagnosis were identified based on code 327.23 from the *International Classification of Diseases, Ninth Revision* (*ICD-9*). Only patients with a record of CPAP use after or 1 month or less before OSA diagnosis were included. The use of CPAP was identified by the Healthcare Common Procedure Coding System code E0601. Moreover, patients were only included if they had at least 3 years of follow-up data from the time of their first CPAP record. Patients were then divided based on having had surgery for OSA or not. Three subgroups of OSA surgery were analyzed: (1) soft tissue procedures, including palatopharyngoplasty (*Current Procedural Terminology* [*CPT*] code 42145) and tonsillectomy (*CPT* code 42826); (2) skeletal procedures, including Le Fort I osteotomy (*CPT* code 21141), reconstruction of the midface with Le Fort I osteotomy (*CPT* code 21145), and mandibular reconstruction/mandibular sagittal split (*CPT* code 21196); and (3) any combination of both types of procedures. Given the large sample size in the no-surgery group, a sample of 50 000 randomly selected patients was later used for downstream analysis and propensity score matching. The sample was restricted to 50 000 patients to be sufficiently large to capture any confounders while still being small enough to prevent multiple weeklong times for a high-dimensionality propensity score match (HDPSM) to resolve. After exclusion of patients 90 years or older, 49 823 records were included in the no-surgery group for comparison with the surgical groups.

Variables Analyzed

Demographic information relative to age, sex, number of medical encounters, year of entry into the cohort, and record length were recorded. Medical encounters included the number of hospitalizations and visits to the emergency department and clinic. To evaluate our primary outcome, specific *ICD-9* codes for cardiovascular, neurological, and metabolic comorbidities (**Table 1**) were used to identify the first occurrence of systemic complications after the index CPAP prescription in the surgical and nonsurgical cohorts.

Statistical Analysis

Data were analyzed September 19, 2019. Cohorts were compared after HDPSM to control for all observable confounders in the data set.[11-13] The high-dimensionality propensity scores were assigned based on age, sex, year of entry into the cohort, record length, and diagnoses and medications preceding CPAP. High-dimensionality propensity score matching is a statistical method that allows the reduction of a large vector of covariates estimating an outcome into a single score. This composite score allows us to match patients based on complex constructs, such as health status, by including in its calculation all observable data in multiple dimensions (age, sex, record length, *ICD-9* codes, and medications) for each patient. The time of first CPAP record was used as the index time. Adjusted cohorts were then analyzed to time of first event using a Kaplan-Meier estimator.[14] Events were considered by category (cardiovascular, neurological, and endocrine), and differences in the survival curves were analyzed using the log-rank test. To ensure that the trends we observed were not solely statistical artifacts related to the large sample sizes that the TMD provided us, we used E values to estimate the risk of unmeasured confounding. This extra measure of statistical validity is a modern statistical tool that allows for the estimation of the effect size that an unmeasured confounder would need to have to nullify the measured association.[15] The higher the value, the bigger the effect size of the unmeasured confounder would have to be. Therefore, the more unlikely it is that an unmeasured confounder would have been unaccounted for.

Results

Overall Cohort Overview

In total, 462 570 records of patients diagnosed with OSA and having had CPAP prescribed from 2007 to 2015 were identified. Of those, 458 169 did not undergo surgery for OSA, and 4401 went on to have a surgical intervention. Including a convenience sample of patients in the no-surgery group, 54 224 were included in the analysis (33 405 men [61.6%] and 20 819 women [38.4%]; mean [SD] age, 55.1 [9.2]). In the surgery group, 4269 patients had isolated soft tissue surgery, 114 had isolated skeletal surgery, and 18 had both types of surgery (**Figure**). Demographic information of the cohorts is summarized in **Table 2**. Follow-up after CPAP prescription ranged from 3 to 8 years for all patients included in this study, with a median follow-up time of 4.47 (range, 3-8) years from after the index CPAP prescription.

Unadjusted Model

In this model, we observed clinically meaningful reductions in neurological (hazard ratio [HR], 0.49; 95% CI, 0.39-0.61) and endocrine (HR, 0.80; 95% CI, 0.74-0.86) complications (**Table 3**) for soft tissue surgery. Soft tissue surgery was also associated with decreased cardiovascular events (HR, 0.92; 95% CI, 0.86-0.98). Associations with meaningful differences on outcomes of interest were found for skeletal surgery (HR for cardiovascular events, 1.07 [95% CI, 0.74-1.57]; HR for neurological events, 0.22 [95% CI, 0.03-1.57]; HR for endocrine events, 0.76 [95% CI, 0.47-1.22]) and combined skeletal and soft tissue surgery (HR for cardiovascular events, 3.18 [95% CI, 0.33-30.62]; HR for endocrine events, 0.59 [95% CI, 0.15-2.34]) cases, but the width of the 95% CIs prevented definitive conclusions (**Table 4**).

Table 1. *ICD-9* Diagnostic Codes Used to Identify Systemic Complications

ICD-9 code	Diagnosis
Cardiovascular event	
410.x	Myocardial infarction
414.x	Coronary artery disease
413.9	Angina pectoris
401.1, 401.9, 402.x	Hypertension
	Chronic ischemic heart disease
277.7	Metabolic syndrome
427.x	Arrhythmia
Neurological event	
434.91	CVA/stroke
331.0	Alzheimer
Endocrine event	
790.2	Impaired fasting glucose level, impaired glucose tolerance test result, or other abnormal glucose finding

Abbreviations: CVA, cerebrovascular accident; *ICD-9*, *International Classification of Diseases, Ninth Revision*.

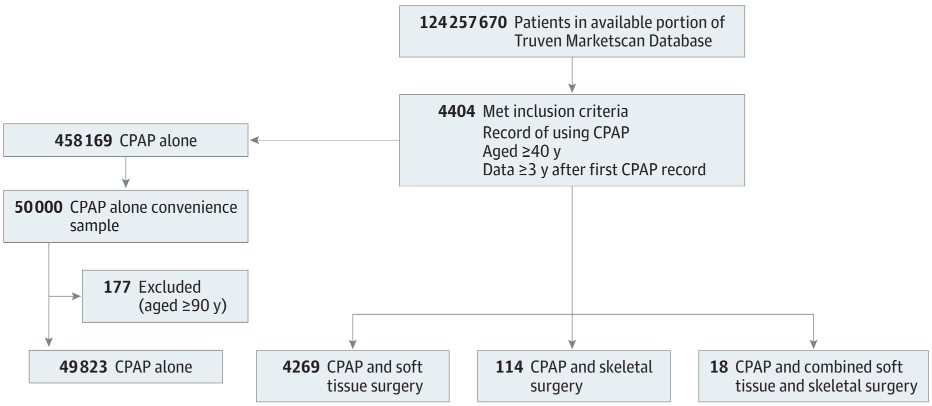
HDPSM-Adjusted Model

Given the low number of cases available in the skeletal and combined soft tissue and skeletal surgery groups, adequate HDPSM analysis was not possible in these groups. The soft tissue surgery group was large enough to perform HDPSM analysis. Matched cohorts of 4269 patients were generated in the no-surgery and soft tissue surgery groups, and the likelihood of developing cardiovascular, neurological, and endocrine outcomes of interest was compared. The finding of decreased events was maintained in the adjusted model (HR for cardiovascular events, 0.91 [95% CI, 0.83-1.00]; HR for neurological events, 0.67 [95% CI, 0.51-0.89]; HR for endocrine events, 0.82 [95% CI, 0.74-0.91]). Further details of this analysis are summarized in Table 3.

Discussion

Continuous positive airway pressure is the criterion standard treatment for the correction of the physiological abnormalities in sleep disordered breathing. Its tolerability and adherence rate make it a challenging solution at a populational level. Indeed, adherence rate estimates at 5 years range from 40% to 80%.[2,16] A recent body of literature examining the effect of CPAP treatment as a primary and secondary prevention method for cardiovascular and neurological morbidity in adult patients with OSA has consistently demonstrated null results in 3 distinct systematic reviews of randomized clinical trials.[17-19] However, subgroup analysis of these trials demonstrated a benefit of CPAP for cardiovascular events in patients with more than 4 hours of CPAP treatment per night. To this day, this is the highest level of evidence suggesting a clinically meaning-

Figure. Flow Diagram of Patient Inclusion



CPAP indicates continuous positive airway pressure.

Table 2. Demographic Characteristics

Characteristic	CPAP alone (n = 49 823)	CPAP plus soft tissue surgery (n = 4269)	CPAP plus skeletal surgery (n = 114)	CPAP plus skeletal and soft tissue surgery (n = 18)
Age, mean (SD), y	55.5 (9.4)	50.3 (7.0)	50.8 (7.0)	49.5 (5.4)
Female, %	38.9	32.3	47.4	22.2
Events, No. (%)				
Cardiovascular	10 771 (21.6)	913 (21.4)	27 (23.7)	3 (16.7)
Neurological	1826 (3.7)	84 (2.0)	1 (0.9)	0
Endocrine	9092 (18.2)	673 (15.8)	17 (14.9)	2 (11.1)
Length of record, median (IQR), y	7.0 (5.1-8.0)	7.0 (5.2-8.0)	7.0 (5.5-8.0)	7.1 (6.3-7.5)

Abbreviations: CPAP, continuous positive airway pressure; IQR, interquartile range.

Table 3. HRs for Occurrence of Cardiovascular, Neurological, and Endocrine Outcomes After Soft Tissue Surgery Compared With CPAP Prescription Alone

Outcome	Unadjusted model[a]		Propensity score–matched model[b,c]	
	HR (95% CI)	E value (95% CI)	HR (95% CI)	E value (95% CI)
Cardiovascular event	0.92 (0.86-0.98)	1.31 (1.46-1.12)	0.91 (0.83-1.00)	1.34 (1.53-1.05)
Neurological event	0.49 (0.39-0.61)	3.53 (4.55-2.69)	0.67 (0.51-0.89)	2.33 (3.34-1.49)
Endocrine event	0.80 (0.74-0.86)	1.61 (1.77-1.45)	0.82 (0.74-0.91)	1.56 (1.77-1.34)

Abbreviations: CPAP, continuous positive airway pressure; HR, hazard ratio.

[a] Includes 4269 patients undergoing soft tissue surgery and 49 823 prescribed CPAP alone.

[b] Includes 4269 patients undergoing soft tissue surgery and 4269 prescribed CPAP alone.

[c] Matched by age, sex, year of entry into the cohort, record length, diagnoses preceding CPAP, and medications preceding CPAP.

ful objective systemic benefit of OSA treatment. These results emphasize the need for a minimum use time of CPAP and, more importantly, its lack of benefit when a minimal treatment time is not achieved. Because surgical modifications of the upper airway exercise their effect all night, the adherence issue is removed from the equation.

The present study is one of the few studies available to examine such clinically relevant systemic outcomes for surgical treatments of OSA. It complements the existing literature by introducing a very large US cohort of matched patients undergoing surgical and nonsurgical treatment and followed up longitudinally for as long as 8 years and by using a database that represents a real-life setting rather than a controlled trial environment.

Several smaller cohorts have previously evaluated the effect of various surgical procedures on cardiovascular morbidity in OSA.[5] Larger cohorts with designs similar to the one presented in this study have also demonstrated outcomes similar to ours.[9,20] Notably, a study spanning 192 316 patients with OSA in South Korea[9] has recently been published with similar findings. Lee et al[9] used a government-run national insurer database to identify cohorts of patients with OSA treated with uvulopalatopharyngoplasty (UPPP) and compared them with a cohort of patients with OSA not undergoing surgery from 2007 to 2014. They found that UPPP decreased the incidence of congestive heart failure and atrial fibrillation in unadjusted models and significantly decreased the incidence of congestive heart failure alone (HR, 0.757; 95% CI, 0.596-0.960) when ad-

Table 4. HRs for Occurrence of Cardiovascular, Neurological, and Endocrine Outcomes After Skeletal Surgery and Combined Skeletal and Soft Tissue Surgery Cases Compared With CPAP Prescription Alone

	Unadjusted model			
	Skeletal surgery alone[a]		Combined skeletal and soft tissue surgery[b]	
Outcome	HR (95% CI)	E value (95% CI)	HR (95% CI)	E value (95% CI)
Cardiovascular event	1.07 (0.74-1.57)	1.28 (1.77-2.07)	3.18 (0.33-30.62)	5.82 (60.73-5.49)
Neurological event	0.22 (0.03-1.57)	8.53 (2.51-63.89)	0 (0-∞)[c]	325 703 (∞-∞)[c]
Endocrine event	0.76 (0.47-1.22)	1.72 (1.56-2.75)	0.59 (0.15-2.34)	2.25 (2.99-6.64)

Abbreviation: CPAP, continuous positive airway pressure; HR, hazard ratio.

[a] Includes 114 patients undergoing skeletal surgery and 49 823 prescribed CPAP alone.

[b] Includes 18 patients undergoing skeletal plus soft tissue surgery and 49 823 prescribed CPAP alone.

[c] No neurological events were observed in the subset of patients with combined surgery, yielding a degenerate HR estimate.

justing for income level, age, sex, hypertension, dyslipidemia, and diabetes. Of note, however, although the present study's results with regard to cardiovascular morbidity support the result of Lee et al,[9] our result shows some vulnerability in the strength of association and to confounding as assessed by the 95% CIs of the HRs and E values. We hypothesize that 2 mechanisms can explain this vulnerability. First, contrary to the findings of Lee et al,[9] which have analyzed the effect of UPPP on each selected *ICD* code independently, we have chosen to consider all selected *ICD-9* codes for each domain as a single outcome to have a broad view on the association with surgery. This less granular analysis might have caused a dilution of the strength of association by incorporating *ICD-9* codes that are not individually associated with lower incidence of complications after UPPP. Moreover, the incorporation of multiple distinct diagnoses as a single outcome leads to exposure to more unobserved confounding. Still, the general trend is concordant with previously published data and confirms that surgery has a role as a therapeutic tool in the reduction of cardiovascular morbidity of OSA.

Chen et al[20] demonstrated a decrease in the 1-year incidence of cerebrovascular events in patients undergoing UPPP compared with those not undergoing surgery in a fully adjusted model (relative risk, 0.45; 95% CI, 0.33- 0.61) using the Taiwanese National Health Insurance Database. A previous study by Weaver et al[6] using the health care database of the Veterans Affairs hospital network demonstrated a benefit in survival of patients treated by UPPP compared with CPAP prescription alone with an adjusted HR of 1.31 (95% CI, 1.03-1.67) for mortality at 5 years for CPAP prescription alone. Weaver et al[6] provided one of the first evaluations of clinically relevant outcomes in surgical treatment of OSA independent of the AHI-related outcomes and an early demonstration of the benefit of treating patients surgically, even if to obtain an incomplete cure by polysomnographic standings.

The present study strengthens the findings of the previously cited reports by expanding the applicability of the results and using an exhaustive method for creating matched cohorts. Indeed, the analysis presented in this report expands the size of the cohorts of US patients treated surgically for OSA available in the literature and captures a different segment of the US population: insured working adults. Also, compared with the Korean and Taiwanese insurance databases, the US population represents a larger and more ethnically heterogenous patient pool. However, the findings are replicable. Moreover, previous studies have attempted to control for various confounders by stratifying based on a prespecified limited set of comorbidities[9] or using a composite marker for comorbidity, such as the Charlson comorbidity index in data available only in part of the database.[6] The analysis provided in this study relies on propensity score matching to create comparable cohorts while decreasing the risk of indication bias. All variables available in the database were used in the matching process (including every individual's recorded *ICD-9* codes), resulting in uniquely comparable cohorts. This significant methodological improvement allowed us, within the bounds of the available data, to control for the confounding to which this kind of observational insurance-based database studies is prone. Moreover, in the context of biomedical and social science research, it is generally accepted that unmeasured confounders with an E value of 2 to 3 are relatively uncommon.[15] Hence, our data do not seem to be significantly affected by unmeasured confounders.

As far as metabolic complications are concerned, prior studies demonstrated that patients with moderate or severe OSA have a higher frequency of type 2 diabetes and that treating OSA with CPAP lowers the prevalence of diabetes of any severity level.[21,22] Moreover, surgical treatment for OSA has been shown to affect various metabolic markers, notably decreasing postoperative leptin, triglyceride, and total cholesterol levels, independently of changes in body mass index.[23] However, no association was noted with hemoglobin A_{1c} levels. In contrast, the present study's findings show an association between soft tissue surgery and reduced rates of prediabetes and impaired glucose intolerance compared with CPAP prescription alone.

Other emerging findings in clinically relevant outcomes research in OSA surgery have demonstrated that UPPP can reduce the risk of development of dementia in OSA.[7] However, no beneficial effect was demonstrated for Alzheimer disease. Moreover, UPPP has also been linked to a decreased risk of developing depression in a similar study design based on a long-term retrospective follow-up of patients from insurance databases.[8]

Uvulopalatopharyngoplasty is the surgical procedure most commonly performed for OSA. Historically, UPPP has been a controversial procedure owing to concerns about its efficacy, postoperative recovery, and long-term adverse effects. Indeed, highly variable surgical cure rates have been reported[24] based on various different definitions of *cure*. Importantly, all these definitions used the AHI as the main indicator of success. However, meeting specific AHI targets does not guarantee that the successful treatment will translate to meaningful clinical benefits to the patient. In fact, polysomnographic indices have been shown to correlate very poorly with patient's symptoms, quality of life, and reaction time.[25] Moreover, a decade-long historical cohort evaluating factors associated with cardiovascular morbidity failed to demonstrate an association of AHI in the final adjusted multivariate analysis.[26] Furthermore, AHI is highly affected by the subjectivity inherent to the interpretation of hypopnea. This makes the AHI a much less objectively quantifiable marker of disease over time. Hence, it seems sensible to evaluate the value of an intervention based on its capacity to yield meaningful health-related outcomes rather than purely based on polysomnographic outcomes. Therefore, it is highly relevant to reconsider the value of surgical interventions, even if they only partially resolve the polysomnographic findings but provide physiological improvements in breathing that translate into meaningful clinical outcomes.

The TMD did not allow us to identify sufficient cases to evaluate the value of skeletal surgery or combined soft tissue and skeletal surgery. However, these procedures have been reported to be highly effective in the treatment of OSA.[27,28]

Limitations

The present study presents some limitations in its design. Given the available data in the TMD, we could not match patients based on their body mass index. However, the confounding effect of this limiting factor was partially mitigated by the inclusion of every patient's individual list of *ICD-9* codes, including any obesity-related *ICD-9* code, in the propensity score matching process when generating the cohorts. Moreover, the TMD did not provide a measure of the severity of OSA of each patient or the rates of adherence to CPAP therapy per night or over time. Although not having AHI information can be a confounding factor, this is a limitation that does not invalidate the results of this study, because severity grouping by AHI has been proven to not correlate with the risk of developing cardiovascular disease,[26] and inclusion of other physiological criteria, such as the desaturation index, might prove to be more informative to estimate systemic complications for future studies.[29] Moreover, potential selection bias in the choice of surgery and surgical technique coded under the same *CPT* code, depending on each clinician's practice preferences and habits, can affect the outcome. Indeed, UPPP and its associated *CPT* code encompasses various techniques of palatal and oropharyngeal surgical procedures that share the common goal of widening the oropharyngeal airway. This limitation is inherent to retrospective insurance database–based studies and should be kept in mind when interpreting the data presented.

Also, this study is subject to the limitations of studies performed on large health care utilization databases. The validity of the data in these databases depends on the accuracy of the medical coding and billing information input. Specifically, at any given encounter for any patient, secondary *ICD-9* codes may not be accurately reported. Hence, the overall *ICD-9* code list for each patient may not reflect the patient's actual full list of comorbidities but the ones for which the patient sought medical care as captured by the payer or insurer. This loss of secondary and tertiary *ICD-9* codes may induce an uncontrolled confounding by inaccurately matching patients with dissimilar comorbidity profiles simply based on the observed *ICD-9* codes in the database.

Several features of our study design were used to control for this inherent feature of insurance database–based studies. First, all patients had to have a minimum of 3 years of follow-up on the database to be included. Hence, one can reasonably assume that any medical condition of significant importance for the patient's health would have required a service captured under that condition's specific *ICD-9* code during that period, and so it would be accounted for in the patient's list of comorbidities included in the HDPSM. Also, we have used E values to quantify the risk of uncontrolled confounding to better detect inaccuracies in our results owing to such risks. Furthermore, *ICD-9* codes do not reflect accurately the severity of a disease process. Therefore, even with appropriate matching based on the *ICD-9* codes, a degree of confounding by severity may be present and uncontrolled for. Moreover, information for each patient is only available for the duration of the patient's enrollment with particular insurers covered by the scope of the database. The TMD belongs to a family of health care databases that track individual patient information from multiple databases to improve the longitudinal follow-up and attenuate data loss with changes in work or insurers. Moreover, the TMD covers a large sample of the adult working population of the US covered by private insurers. It is not representative of a random sample of the US population. Also, only patients with sufficient coverage are likely to present to their specialist for care of a disease that is not directly life-threatening. This further affects the representativity of the sample.

Furthermore, although HDPSM is an excellent tool to create a matched cohort for comparison in a retrospective setting, it remains mainly a statistical technique whereby patients are matched based on their propensity score rather than their true clinical state. Given the limitations of *ICD-9* coding presented earlier, it is conceivable that patients matched by HDPSM are not perfect clinical matches for one another but ideal statistical matches based on prespecified empirically selected criteria available in the database. Moreover, despite using a database designed for longitudinal follow-up of patients, the median follow-up of 4.47 years from the index CPAP prescription could limit our capacity to detect larger differences that may have arisen in time, because systemic comorbidities tend to develop over a long period.

Last, the choice of codes used for outcome selection could be expanded to include more stroke-related outcomes and encompass a broader variety of dementias. With regard to the endocrine outcomes, the *ICD-9* code chosen could be narrowed to target type 2 diabetes specifically in a future study. For all these reasons, we consider the design of the present study to allow for exploratory analysis of the comparative effects of CPAP prescription and soft tissue surgery for OSA on the rate of systemic complications in a real life setting and over time but do not claim to have established any link of causality within the present study design.

Conclusions

This cohort study presents observational evidence of reduced rates of occurrence of cardiovascular, neurological, and endocrine comorbidities of OSA after UPPP compared with CPAP prescription alone. It expands on the findings of an emerging body of literature evaluating clinically meaningful health-related outcomes. Further observational and experimental studies focusing on similar outcomes are needed to critically assess the value of surgical interventions in the treatment of OSA and establish causality.

ARTICLE INFORMATION

Accepted for Publication: November 16, 2020.

Published Online: January 21, 2021. doi:10.1001/jamaoto.2020.5179

Author Contributions: Dr Gombar had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Ibrahim, de Freitas Mendonca, Capasso.
Acquisition, analysis, or interpretation of data: Gombar, Callahan, Jung, Capasso.
Drafting of the manuscript: Ibrahim, de Freitas Mendonca.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Gombar, Callahan, Jung.
Administrative, technical, or material support: Callahan, Jung, Capasso.
Supervision: de Freitas Mendonca, Capasso.

Conflict of Interest Disclosures: None reported.

REFERENCES

1. Harvard Medical School Division of Sleep Medicine. The price of fatigue: the surprising economic costs of unmanaged sleep apnea. Harvard Medical School Division of Sleep Medicine. Published December 2010. Accessed July 5, 2020. https://sleep.hms.harvard.edu/sites/g/files/mcu911/files/assets/Images/The_Price_of_Fatigue.pdf

2. Kribbs NB, Pack AI, Kline LR, et al. Objective measurement of patterns of nasal CPAP use by patients with obstructive sleep apnea. *Am Rev Respir Dis*. 1993;147(4):887-895. doi:10.1164/ajrccm/147.4.887

3. Engleman HM, Martin SE, Douglas NJ. Compliance with CPAP therapy in patients with the sleep apnoea/hypopnoea syndrome. *Thorax*. 1994;49(3):263-266. doi:10.1136/thx.49.3.263

4. Holty JE, Guilleminault C. Surgical options for the treatment of obstructive sleep apnea. *Med Clin North Am*. 2010;94(3):479-515. doi:10.1016/j.mcna.2010.02.001

5. Halle TR, Oh MS, Collop NA, Quyyumi AA, Bliwise DL, Dedhia RC. Surgical treatment of OSA on cardiovascular outcomes: a systematic review. *Chest*. 2017;152(6):1214-1229. doi:10.1016/j.chest.2017.09.004

6. Weaver EM, Maynard C, Yueh B. Survival of veterans with sleep apnea: continuous positive airway pressure versus surgery. *Otolaryngol Head Neck Surg*. 2004;130(6):659-665. doi:10.1016/j.otohns.2003.12.012

7. Cho JH, Suh JD, Han KD, Jung JH, Lee HM. Uvulopalatopharyngoplasty may reduce the incidence of dementia caused by obstructive sleep apnea: national insurance service survey 2007-2014. *J Clin Sleep Med*. 2018;14(10):1749-1755. doi:10.5664/jcsm.7388

8. Cho JH, Suh JD, Han KD, Lee HM. Uvulopalatopharyngoplasty reduces the incidence of depression caused by obstructive sleep apnea. *Laryngoscope*. 2019;129(4):1005-1009. doi:10.1002/lary.27294

9. Lee HM, Kim HY, Suh JD, et al. Uvulopalatopharyngoplasty reduces the incidence of cardiovascular complications caused by obstructive sleep apnea: results from the national insurance service survey 2007-2014. *Sleep Med*. 2018;45:11-16. doi:10.1016/j.sleep.2017.12.019

10. IBM. White Paper: IBM MarketScan research databases for health services researchers. Volumes 1-15. Published 2019. Accessed July 5, 2020. https://www.ibm.com/downloads/cas/6KNYVVQ2

11. Linden A. Combining propensity score-based stratification and weighting to improve causal inference in the evaluation of health care interventions. *J Eval Clin Pract*. 2014;20(6):1065-1071. doi:10.1111/jep.12254

12. Jupiter DC. Propensity score matching: retrospective randomization? *J Foot Ankle Surg*. 2017;56(2):417-420. doi:10.1053/j.jfas.2017.01.013

13. Schuler A, Callahan A, Jung K, Shah NH. Performing an informatics consult: methods and challenges. *J Am Coll Radiol*. 2018;15(3 Pt B):563-568. doi:10.1016/j.jacr.2017.12.023

14. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53(282):457-481. doi:10.1080/01621459.1958.10501452

15. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. *Ann Intern Med*. 2017;167(4):268-274. doi:10.7326/M16-2607

16. Pépin JL, Krieger J, Rodenstein D, et al. Effective compliance during the first 3 months of continuous positive airway pressure. A European prospective study of 121 patients. *Am J Respir Crit Care Med*. 1999;160(4):1124-1129. doi:10.1164/ajrccm.160.4.9802027

17. da Silva Paulitsch F, Zhang L. Continuous positive airway pressure for adults with obstructive sleep apnea and cardiovascular disease: a meta-analysis of randomized trials. *Sleep Med*. 2019;54:28-34. doi:10.1016/j.sleep.2018.09.030

18. Abuzaid AS, Al Ashry HS, Elbadawi A, et al. Meta-analysis of cardiovascular outcomes with continuous positive airway pressure therapy in patients with obstructive sleep apnea. *Am J Cardiol*. 2017;120(4):693-699. doi:10.1016/j.amjcard.2017.05.042

19. Yu J, Zhou Z, McEvoy RD, et al. Association of positive airway pressure with cardiovascular events and death in adults with sleep apnea: a systematic review and meta-analysis. *JAMA*. 2017;318(2):156-166. doi:10.1001/jama.2017.7967

20. Chen S-Y, Cherng Y-G, Lee F-P, et al. Risk of cerebrovascular diseases after uvulopalatopharyngoplasty in patients with obstructive sleep apnea: a nationwide cohort study. *Medicine (Baltimore)*. 2015;94(41):e1791. doi:10.1097/MD.0000000000001791

21. Abud R, Salgueiro M, Drake L, Reyes T, Jorquera J, Labarca G. Efficacy of continuous positive airway pressure (CPAP) preventing type 2 diabetes mellitus in patients with obstructive sleep apnea hypopnea syndrome (OSAHS) and insulin resistance: a systematic review and meta-analysis. *Sleep Med*. 2019;62:14-21. doi:10.1016/j.sleep.2018.12.017

22. Xu PH, Hui CKM, Lui MMS, Lam DCL, Fong DYT, Ip MSM. Incident type 2 diabetes in OSA and effect of CPAP treatment: a retrospective clinic cohort study. *Chest*. 2019;156(4):743-753. doi:10.1016/j.chest.2019.04.130

23. Chin CH, Lin PW, Lin HC, Friedman M, Lin MC. Effects of OSA surgery on leptin and metabolic profiles. *Otolaryngol Head Neck Surg*. 2019;161(6):1048-1055. doi:10.1177/0194599819877647

24. Elshaug AG, Moss JR, Southcott AM, Hiller JE. Redefining success in airway surgery for obstructive sleep apnea: a meta analysis and synthesis of the evidence. *Sleep*. 2007;30(4):461-467. doi:10.1093/sleep/30.4.461

25. Weaver EM, Woodson BT, Steward DL. Polysomnography indexes are discordant with quality of life, symptoms, and reaction times in sleep apnea patients. *Otolaryngol Head Neck Surg*. 2005;132(2):255-262. doi:10.1016/j.otohns.2004.11.001

26. Kendzerska T, Gershon AS, Hawker G, Leung RS, Tomlinson G. Obstructive sleep apnea and risk of cardiovascular events and all-cause mortality: a decade-long historical cohort study. *PLoS Med*. 2014;11(2):e1001599. doi:10.1371/journal.pmed.1001599

27. Zaghi S, Holty JE, Certal V, et al. Maxillomandibular advancement for treatment of obstructive sleep apnea: a meta-analysis. *JAMA Otolaryngol Head Neck Surg*. 2016;142(1):58-66. doi:10.1001/jamaoto.2015.2678

28. Cillo JE Jr, Dattilo DJ. Maxillomandibular advancement for severe obstructive sleep apnea is a highly skeletally stable long-term procedure. *J Oral Maxillofac Surg*. 2019;77(6):1231-1236. doi:10.1016/j.joms.2019.01.009

29. Rashid NH, Zaghi S, Scapuccin M, Camacho M, Certal V, Capasso R. The value of oxygen desaturation index for diagnosing obstructive sleep apnea: a systematic review. *Laryngoscope*. 2020. doi:10.1002/lary.28663