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The Impact of Sleep Apnea on Postoperative Utilization of Resources and Adverse Outcomes

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Abstract

Background—Despite the concern that sleep apnea (SA) is associated with increased risk for postoperative complications, a paucity of information is available regarding the effect of this disease on postoperative complications and resource utilization in the orthopedic population. With an increasing number of surgical patients suffering from SA, this information is of high importance to physicians, patients, policymakers and administrators alike.

Methods—We analyzed hospital discharge data of patients who underwent total hip or knee arthroplasty (THA, TKA) in approximately 400 United States hospitals between 2006 and 2010. Patient, procedure, and healthcare-system related demographics and outcomes such as mortality, complications, and resource utilization were compared amongst groups. Multivariable logistic regression models were fit to assess the association between SA and various outcomes.

Results—We identified 530,089 entries for patients undergoing THA and TKA. Of those, 8.4% had a diagnosis code for SA. In the multivariate analysis, the diagnosis of SA emerged as

independent risk factor for major postoperative complications (OR 1.47 (95% CI 1.39;1.55)). Pulmonary complications were 1.86 (95% CI 1.65; 2.09) times more likely and cardiac complications 1.59 (95% CI 1.48; 1.71) times more likely to occur in patients with SA. In addition, SA patients were more likely to require ventilatory support, utilize more intensive care, step-down and telemetry services, consume more economic resources, and require increased lengths of hospitalization.

Conclusions—The presence of SA represents a major clinical and economic challenge in the postoperative period. More research is needed to identify SA patients at risk for complications and develop evidence-based practices in order to aid in the allocation of clinical and economic resources.

Introduction

The presence of sleep apnea (SA) represents a major challenge in the postoperative period. As many as one fourth of patients undergoing elective surgery may be affected [1]. The prevalence among orthopedic patients undergoing joint arthroplasty may be especially high, given that obesity is a wide-spread comorbidity in this patient population [2]. Despite the increasing amount of concern that SA is associated with increased risk for postoperative complications [2-7], there remains a paucity of population based information available in the literature regarding postoperative outcomes. Most available data represent results from relatively small samples and academic institutions, thus limiting external validity and applicability. Large-scale observational studies, using secondary administrative databases, are increasingly being performed, as they provide more robust information on the impact of specific diseases in a more representative care setting.

Given the combination of high prevalence of SA among orthopedic surgery patients [2] and the projection that by 2030 more than 4 million hip and knee arthroplasties will be performed in the United States alone [8], the joint replacement population represents an especially important group of patients in need of further investigation.

Despite some data suggesting increased risk for postoperative pulmonary complications associated with SA among orthopedic patients [2], more detailed analysis of other important outcomes such as utilization of economic resources remains largely unexplored. Such information is of high importance in order to assess and gain better insights into the clinical and economic impact of SA in patients undergoing surgery.

Therefore, we analyzed data on over 500,000 patients from approximately 400 institutions. We hypothesized that hip and knee arthroplasty patients with SA were at greater risk for experiencing postoperative complications and consumed greater hospital resources, as represented by increased risk for a longer length of hospital stay and greater use of economic resources.

Materials and Methods

Database and Study Design

For this study, data from Premier Perspective, Inc.'s (Charlotte, North Carolina) collected between 2006 and 2010 were used. This retrospective administrative database contains discharge information from approximately 400 hospitals [9,10] and is compliant with the Health Insurance Portability and Accountability Act. Because data are de-identified, the study was exempt from review by the Hospital for Special Surgery Institutional Review Board. Before distribution, rigorous quality assurance and data validation procedures are employed by the provider to assure the accuracy of entries. This database has previously been used for other studies by our group [11,12].

Study Population

The study population consisted of all patients in the Premier Perspective database undergoing primary hip and knee arthroplasty (THA, TKA), as identified by International Classification of Diseases-9th revision-Clinical Modification codes (ICD-9-CM) 81.51 and 81.54, respectively.

Study Variables

The presence of SA was determined by the presence of respective ICD-9 codes Appendix 1 lists specific diagnosis codes included and their individual prevalence.

Patient, procedure, and healthcare related characteristics analyzed were age, sex, race (White, Black, Hispanic, other), admission type (emergent, elective, other), hospital size (<300, 300-499, ≥ 500 beds), hospital location (urban, rural), hospital teaching status, anesthesia type (general, neuraxial, neuraxial-general, unknown), indication for surgery (osteoarthritis, rheumatoid arthritis, other), type of surgery (THA, TKA), year of surgery, and comorbidity prevalence (myocardial infarction (MI), cerebrovascular disease, peripheral vascular disease, renal disease, chronic obstructive pulmonary disease (COPD), uncomplicated and complicated diabetes mellitus, uncomplicated and complicated systemic hypertension, ("complicated" as defined by the absence or presence of disease related end organ complications), cancer, obesity, and pulmonary hypertension). Overall comorbidity burden was assessed with the Deyo adaptation of the Charlson comorbidity index method for use with administrative data for surgical outcomes [13]. In brief, the Deyo Index is comprised of the presence of a number of comorbidities. Each comorbidity is assigned a severity weight and its presence contributes to an overall score. A higher score correlates with increased risk of adverse outcomes.

Individual major postoperative complications studied were pulmonary embolism, deep venous thrombosis, cerebrovascular event, pulmonary complications, sepsis, cardiac complications (excluding MI), MI, pneumonia (including ventilator-associated pneumonia and aspiration pneumonitis), infectious complications, acute renal failure, gastrointestinal complications, and mortality. In order to evaluate these major complications, a combined outcome variable ("combined complications") was created to indicate having at least one of the complications listed above. A case with "pulmonary complications" had at least one

indication of pulmonary compromise, pneumonia, or pulmonary embolism. For "cardiac complications," cases had an indication of cardiac complications (except MI) or MI.

In addition, utilization of critical care, step down and telemetry services (each defined by specific billing records for these services representing distinctly different levels of care), blood transfusions, postoperative mechanical ventilation, and non-invasive ventilation were studied. Utilization of economic resources in US dollars and length of hospitalization were compared as continuous variables. Due to their skewed distributions, they were also dichotomized such that entries exceeding the 75th percentile were defined as increased length of hospitalization or increased use of economic resources, respectively. This approach was used by our group in various other publications [11,12]. Further, using this cutoff was not influenced by the length of hospitalization or patient costs of SA patients. To account for potential bias in choosing a cutoff for dichotomization, sensitivity analyses using cutoffs ranging from 50% to 90% were performed in the univariable analysis, and similar results were found. ICD-9 CM codes and billing data provided by the Premier database were used to define the presence of comorbidities, complications, and other outcomes and are listed in Appendix 2.

Statistical analysis

The primary goal of our analysis was to compare different outcomes between patients with and without SA. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

Patient- and Healthcare Related Characteristics by Presence of SA—Groups with and without SA diagnosis were compared with regard to patient and healthcare related characteristics in the univariable analysis. Means (standard deviation (SD)) and percentages were described for continuous and categorical variables, respectively. Length of stay and economic resource utilization exhibited a skewed distribution and were presented using median and interquartile ranges (IQR). Due to the large sample size, a significant difference of p-values (<0.05) for differences between two groups using traditional t-tests, Wilcoxon Ranked Sum tests, or Chi-Square tests were very likely to be detected, but may not be clinically meaningful. Therefore, standardized difference (STD) was calculated to measure group balance [14]. A standardized difference less than 0.1 for a continuous and 10% for a categorical variable indicated a negligible difference in the mean or proportion of a variable between groups [15]. Due to the large sample size, the standard errors of STDs were very small; therefore, and to support clarity of presentation they were not shown. Percentage of missing data was reported for all study variables, stratified by presence of a SA diagnosis.

Logistic Regression Analyses—Univariable and multivariable logistic regression analyses were performed to evaluate the association between patients with and without SA. Separate models were fitted for the binary outcomes: combined complications, pulmonary complications, cardiac complications, mortality, mechanical ventilation, non-invasive ventilation, use of blood product transfusion, intensive care utilization, stepdown/telemetry service utilization, increased length of hospitalization and increased economic resource utilization. Covariates included for controlling purposes comprised age, gender, race,

admission type, hospital size, hospital teaching status, hospital location, anesthesia type, indication for surgery, type of surgery, year of surgery, and individual comorbidities. The association between each covariate and outcome variable was performed by univariable analysis. Almost all associations had p-values < 0.05 and were entered into the multivariable model. Few covariates (e.g. gender and hospital characteristic) had p > 0.05 for the outcomes of mortality, and cardiac complication, but were included in the model due to the consensus that they were of clinical importance [16].

In addition to main effects described above, we evaluated the interaction terms of SA with age, gender, year, COPD, diabetes, obesity, hypertension and complicated hypertension for each of the outcomes. These interaction terms were selected based on (1) clinical relevance; (2) STD>10% between SA vs. non-SA status; and (3) sufficient frequency (>5% prevalence of comorbidities in SA) in order to achieve adequate power and obtain valid estimates. All interaction effects were included in each model, and a backward approach was used for testing the significance of interaction effects while keeping all main effects in the model. The significance of interaction effects was measured using a p-value of 0.004 (Bonferroni-corrected p-value=0.05/11 outcomes [17]) to adjust for multiple outcomes. If an interaction effect had a p-value < 0.004, but the corresponding coefficient was very small (e.g. <0.001), we considered it quantitatively unimportant and removed it from the model. For models with significant interaction terms, the interpretation of SA effect would be conditioned on the terms interacted with.

Missing data was excluded from analyses, but since 27.6% of cases had “unknown” anesthesia, it was treated as a separate category and modeled as a sensitivity analysis.

Crude and adjusted odds ratios (OR), Bonferroni-corrected 95% confidence intervals (CI) and p-values were reported due to multiple comparisons. Two-sided p-value<0.05 (conventional threshold of significance) was used to determine significance of variables. 95% CIs of estimates were reported to enable readers to interpret the significance of the findings; this was done to alleviate the potentially undue effect a very large sample size might have on the p-values.

Diagnostic of Models—In order to evaluate independence of individual predictor variables, the Value Inflation Factor (VIF) was calculated for each predictor variable to determine whether multicolinearity was present. The final models were validated using the Hosmer-Lemeshow (H-L) test [18]. It evaluated adequate calibration of a logistic regression model, so that the probability predictions from the model reflected the true occurrence of events in the data. The area under the receiver-operating characteristic curve [19] (c-statistic) was utilized to measure the level of model discrimination between observed data at different levels of the outcome. Discrimination was classified as perfect, excellent, very good, good, moderate, and poor if the AUCs, were 1.0, 0.9 to 0.99, 0.8 to 0.89, 0.7 to 0.79, 0.6 to 0.69, or <0.6, respectively [20]. Statistical analyses were performed using SAS software version 9.3 (SAS Institute, Cary, NC).

Sensitivity Analysis Based on Propensity Score Matching—The odds ratio from a matched sample using the propensity score method was performed as a sensitivity of the

results to different statistical approaches. All covariates used in the primary analysis above were included in the multivariable logistic regression with the outcome variable of SA versus non-SA to calculate propensity scores. One SA patient (case) was matched with three non-SA patients (controls) for statistical efficiency [21]. The matched pairs were generated by comparing the predicted propensity scores between cases and controls using the SAS macro % one to many match with 8 to 1 digit match without replacement [22]. Based on the matched sample, the effect of SA on outcomes was tested for significance using the Cochran-Mantel-Haenszel (CMH) test. To account for matching samples, common odds ratio (COR), an overall odds ratio across pairs of matching samples, and Bonferroni corrected 95% confidence intervals were estimated. For comparison purposes, multivariable models with main effects only were performed and reported.

Results

Characterization by Presence of SA

We identified 530,089 entries for patients undergoing THA and TKA between 2006 and 2010. Overall, 8.4% had a diagnosis code for SA. The prevalence of SA increased from 6.1% in 2006 to 10.3% in 2010 (Fig 1). Compared to non-SA patients, individuals with SA were on average younger (SA: 63.4±9.6 years vs. non-SA: 66.2±11.3 years, STD=26.7%), more frequently male (53.9% vs. 37.3%, STD=33.63%), carried a higher overall Deyo comorbidity burden (1.00±1.12 vs. 0.59±0.92, STD=40.1%) and had a higher prevalence of most individual comorbidities (Table 1, Table 2). Amongst SA patients, 42.3% carried a diagnosis of obesity and 29.3% that of diabetes (complicated and uncomplicated), compared to only 15.6% and 16.4%, respectively, in the group with no diagnosis of SA (STD=61.7% for obesity; STD=31.3% for diabetes). Missing data were limited to the categories of anesthesia type, race, admission type and payor type (28.7%, 19.4%, 0.3%, 2.8% respectively).

SA patients exhibited a higher incidence of major postoperative complications including pulmonary, cardiac (non-MI), and renal outcomes. Analysis of the various subtypes of pneumonia yielded a higher incidence of post-procedural aspiration pneumonia and/or Mendelson's syndrome (as defined by ICD9 code 997.39) in the SA group, compared to the no SA-group (0.9% vs. 0.6%, $p<0.0001$). Among patients in the SA group and accounting for overlap, 14.5% required advanced services (critical care (6.0%), telemetry (5.2%) or stepdown unit (5.5%) services) as compared to 8.1% (2.8%, 3.8%, and 2.7%, respectively) in non-SA patients. Table 3 lists complication rates and other outcomes. Postoperative mechanical ventilation and non-invasive ventilatory support was used more frequently among SA patients (4.9% vs. 0.3%, STD=29.0% and 3.8% vs. 0.1%, STD=27.1%). However, postoperative blood transfusions were less frequently used in SA patients (14.5% vs. 19.3%, STD=13.1%). Appendix 3 details the incidence of individual cardiac complications. The data suggests that the higher incidence of atrial fibrillation among SA patients was responsible for the increased rates in this complication category. Moreover, median length of hospitalization was similar among groups (3 [IQR: 3 to 4] days vs. 3 [IQR: 3 to 4] days), STD=5.5%). Economic resource utilization was also similar among SA patients $15,514 [IQR:12,760 to 19,336] vs. $15,005 [IQR:12,314 to 18,677], STD=6.5%).

Logistic Regression Analyses

Tables 4 details the results of the univariable and multivariable logistic regression analysis. Table 5 details the effect of SA for the models with significant interaction modifications.

Complication Outcomes

No significant interaction terms were found for the models analyzing outcomes of combined complications, pulmonary complications, cardiac complications, and mortality. A diagnosis of SA emerged as an independent risk factor for the outcome of combined complications, as well as pulmonary and cardiac complications separately, but not for mortality.

Utilization Outcomes

Significant interaction terms were detected for the models assessing outcome of mechanical ventilation (e.g. complicated hypertension, COPD), non-invasive ventilation (e.g. complicated hypertension, COPD), utilization of critical care (e.g. gender, year), stepdown/ telemetry services (e.g. year, complicated hypertension, obesity) and prolonged length stay (e.g. obesity). None were found for the outcomes of the need for blood transfusion and increased economic resource. The details of odds ratios conditioned on the modifications are shown in Table 5, and the SA effect on outcomes will have to be interpreted in the context of these modifications. When taking interaction terms into account, SA was associated with increased odds for mechanical ventilation, non-invasive ventilatory support, utilization of ICU, stepdown and telemetry services as well as prolonged length of stay and increased economic resources.

In the sensitivity analysis including “unknown” anesthesia as a separate category, the results were similar.

Diagnostic of Model

The value inflation factors were all <10, indicating that no multicollinearity was present. The ranges of C-statistics were 0.7 to 0.9 except for the model evaluating increasing economic resource utilization (c=0.6), indicating good to very good discrimination for most outcomes.

Sensitivity Analysis Based on Propensity Score Matching

Out of 32,789 SA patients in the sample, 28,177 were successfully matched to non-SA patients. The propensity score matched samples were well balanced (STD <10%) between groups in terms of demographic variables and comorbidities (Appendices 4, 5). The common odds ratios were similar to the odds ratios found in the analysis with main effects only.

Discussion

In this study, we were able to show that SA was associated with higher rates and odds of postoperative complications, utilization of resources and length of stay.

We observed that SA was associated with a 47% increased risk for the combined outcome of postoperative major morbidity. An increased risk for adverse outcomes among SA patients has previously been described [2-7], but information on a wide range of outcomes beyond pulmonary complications in the setting of orthopedic surgery remains rare. While the exact mechanisms by which SA confers increased risk for complications remains unknown, a number of abnormalities have been described among SA patients that may lower the clinically relevant injury threshold for various organ systems to exhibit signs of dysfunction. For example, SA is associated with higher baseline levels of systemic and pulmonary inflammation [23], decreased pharyngeal sphincter function [24], and increased sensitivity to the respiratory depressant effects of opioids [25]. These and other pathologic states may contribute to the increased susceptibility of SA patients to perioperative insults, such as transfusion and ventilator related lung injury, and aspiration. However, it must be noted that not all our findings corroborate with available literature. For example, we did not find differences in the rates of cerebrovascular disease and complications between the two groups. Previous research has suggested that the presence of SA may indeed increase the risk for stroke [26], without allowing for inferences to be made in the postoperative setting. A factor to be considered when interpreting our findings is the fact that only patients with a known diagnosis of SA are included in our cohort and that use of positive airway pressure therapy, which may reverse some of the pathophysiology predisposing to long term adverse outcomes, may be more likely utilized in this population.

In addition, we identified lower rates of blood transfusions among SA patients in our study. Feasible explanations for this finding are not obvious, but warrant further inquiry. One possibility includes higher starting hematocrit levels frequently found in SA patients [27].

Recent literature has further suggested a lack of evidence for increased mortality among SA patients [28]. While speculative, an increase in vigilance among clinicians may indeed lead to better detection of complication in this patient group perceived to be at risk, thus allowing for interventions to avoid this extreme outcome despite higher complication rates.

In addition to the increased risk for adverse medical outcomes, we were able to show an effect of the presence of SA on increased resource utilization. The argument can be made that at least some of the increased utilization of services is not an indication of higher morbidity but reflects planned use of monitored settings and perioperative positive airway pressure equipment in an attempt to reduce complications. However, despite the recommendation by the American Society of Anesthesiologists task force on perioperative care of patients with obstructive sleep apnea that patient with SA be observed in a monitored setting postoperatively and treated with positive pressure ventilation in certain cases [29], little data is available on the use of resources such as telemetry, step-down and intensive care units. If the utilization of these resources would have to be interpreted in this context, the conclusion to be drawn would point towards a surprisingly low use of perioperative monitoring and use of ventilatory assistance. Indeed, there remains a paucity of data regarding the adoption of guidelines for the perioperative care in current practice. Interestingly, a single published inquiry into the existence of perioperative policies amongst anesthesia departments in Canada concluded that only 28% had such provisions [30]. While lack of proof that these interventions lead to improved outcomes among SA patients may be

one reason, the additional use of economic resources associated with implementation of these practices on a wider level certainly represents a contributing factor. It is therefore not surprising that in our study SA was associated with higher odds for this outcome.

Our study is subject to a number of limitations. As a consequence of retrospective database analysis, clinically important covariates are not obtainable. However, a very large sample size provides access to outcomes as seen in actual practice. A further limitation is the reliance on ICD-9 coding for the diagnosis of SA. Thus it is not possible to correlate the diagnosis with the severity of SA. This also applies to the severity of various other comorbidities. It is also almost certain that the true incidence of SA is higher than that reported here, as only patients with a pre-operative diagnosis code for SA would have been entered. This potential misclassification may have lead to an underestimation of the effects of SA on outcomes. As mentioned previously, we were unable to determine if the utilization of higher levels of care as well as that of non-invasive ventilation was the result of a complication and thus represented treatment or if it was used in a prophylactic manner. The inability to determine causal relationships makes it impossible to study if these interventions are capable of modifying outcomes in our sample. Thus, the value of this data lies in the estimation of the magnitude of utilization of these resources. Further, because cause and effect or mechanisms of adverse events cannot be established from this data we are unable to conclusively explain some of the findings. Finally, all comorbidities and complications are based on the ICD-9-CM coding system or billing codes (see Appendix 1). Although rigorous quality checks are being performed by the vendor before release, coding errors or inconsistencies remain a possibility. However, there is no indication that this potential bias would affect one of the groups more than the other.

In conclusion, SA is associated with higher rates and odds ratios of postoperative complications, utilization of resources and length of stay among hip and knee arthroplasty recipients. Interestingly, despite a higher rate of advanced monitoring among SA patients, the overall use of these modalities was still less than 17%, at least partially putting into question the adoption of guidelines and perioperative protocols for the treatment of SA. The subject of outcomes among SA patients requires further study in order to identify patients at risk and determine ways to prevent complications using evidence-based and accountable approaches.

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Appendix

Appendix 1

Diagnosis codes, prevalence, and percent of total for sleep apnea cohort

Sleep apnea diagnosis codes		
Diagnosis code	**Description**	**% of SA diagnoses [a]**
327.23	Obstructive sleep apnea (adult) (pediatric)	59.43
780.57	Unspecified sleep apnea	39.00
786.03	Apnea	0.60
780.51	Insomnia with sleep apnea, unspecified	0.35
780.53	Hypersomnia with sleep apnea, unspecified	0.24
327.24	Idiopathic sleep related nonobstructive alveolar hypoventilation	0.17
327.26	Sleep related hypoventilation/hypoxemia in conditions classifiable elsewhere	0.11
327.27	Central sleep apnea in conditions classified elsewhere	0.07
327.20	Organic sleep apnea, unspecified	0.02
327.21	Primary central sleep apnea	0.02

*a)*Please note that percentages add up to more than 100% as a small fraction of patients carried more than one sleep apnea diagnosis

Appendix 2

International Classification of Diseases-9th revision-Clinical Modification (ICD-9-CM) diagnosis codes for major complications and comorbidities.

Complications	
Event	**ICD-9-CM diagnosis codes**
Pulmonary Embolism	415.1
Deep Vein Thrombosis	451.1, 451.2, 451.8, 451.9, 453.2, 453.4, 453.8, 453.9
Cerebrovascular Event	433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 997.02
Pulmonary Compromise	514, 518.4, 518.5, 518.81, 518.82
Sepsis	038, 038.0, 038.1x, 038.2, 038.3, 038.40, 038.41, 038.42, 038.43, 038.44, 038.49, 038.8, 038.9, 790.
Cardiac (Non-myocardial Infarction)	426.0, 427.41, 427.42, 429.4, 997.1, 427.4, 427.3, 427.31, 427.32
Acute Myocardial Infarction	410.XX
Pneumonia	481, 482.00- 482.99, 483, 485, 486, 507.0, 997.31, 997.39
All Infections	590.1, 590.10, 590.11, 590.8, 590.81, 590.2, 590.9, 595.0, 595.9, 599.0, 567.0 480, 480.0, 480.1, 480.2, 480.8, 480.9, 481, 482.0, 482.1, 482.2, 482.3, 482.30, 482.31, 482.32, 482.39, 482.4, 482.40, 482.41, 482.42, 482.49, 482.5, 482.8, 482.81, 482.82, 482.83, 482.84, 482.89, 482.9, 483, 483.0, 483.1, 483.8, 485, 486, 487, 997.31, 038, 038.0, 038.1, 038.10, 038.11, 038.12, 038.19, 038.2, 038.3, 038.4, 038.40, 038.41, 038.42, 038.43, 038.44, 038.49, 038.8, 038.9, 790.7,

Complications	
Event	**ICD-9-CM diagnosis codes**
	998.0, 958.4, 998.5, 998.59, 998.89, 785, 785.50, 785.52, 785.59, 999.39, 999.31, 999.3
Acute Renal Failure	584, 584.5, 584.9
Gastrointestinal Complication	997.4, 560.1, 560.81, 560.9, 536.2, 537.3
Mechanical Ventilation	93.90, 96.7, 96.70, 96.71, 96.72, (CPT Code) 94002, 94656, 94003, 94657
Blood Transfusion	99.0, 99.01, 99.02, 99.03, 99.04, 99.05, 99.06, 99.07, 99.08, 99.09, (HCPCS codes) P9010, P9011, P9012, P9016, P9017, P9019, P9020, P9021, P9022, P9023, P9031, P9032, P9033, P9034, P9035, P9036, P9037, P9038, P9039, P9040
Non-invasive ventilation	93.90, 93.91
Comorbidities	
Event	**ICD-9-CM diagnosis codes**
Myocardial Infarction	412.XX
Peripheral Vascular Disease	441.X, 785.4, V43.4, 38.48
Cerebrovascular disease	430.X-438.X
Dementia	290.XX
COPD	490, 491.X, 492.X, 493.X, 495.X, 500-505, 506.4
Rheumatic Disease	710.0, 710.1, 710.4, 714.0, 714.1, 714.2, 714.81, 725
Peptic ulcer disease	531-534
Mild Liver Disease	571.2, 571.4X, not 571.42, 571.5, 571.6
Diabetes	250.0, 250.1, 250.2, 250.3, 250.7
Diabetes with Complications	250.4, 250.6
Hemiplegia or Paraplegia	344.1, 342.X
Renal Disease	582.X, 583.X, 585, 586, 588
Malignancy	140-239.99
Moderate or Severe Liver Disease	456.0-456.29, 572.2 - 572.8
AIDS	042
Hypertension	401.1, 401.9, 642.0X
Complicated Hypertension	401.0, 402.X-405.X, 642.1, 642.2, 642.7, 642.9

Complications	
Event	**ICD-9-CM diagnosis codes**
Pulmonary Hypertension	416.X
Obesity	278.0, 278.00, 278.01, 649.1, V85.3, V85.4, V85.54, 792.91
Sleep Apnea	786.03, 780.51, 780.53, 780.57, 327.20-327.27, 327.29

Appendix 3

The incidence of individual cardiac outcomes for patients without and with diagnosis of sleep apnea

Incidence of Selected Cardiac Complications/Outcomes					
	No SA diagnosis		**SA Diagnosis**		
Event	**N**	**%**	**N**	**%**	**STD(%)**
Conduction disorders	10,433	2.15	1,155	2.61	3.04
Atrial fibrillation and flutter	27,357	5.63	3,854	8.71	11.94
Ventricular fibrillation and flutter	80	0.02	10	0.02	0.50
Cardiac arrest	269	0.06	57	0.13	2.44
Functional disturbances following cardiac surgery	5	0.001	0	0	0.45
Cardiogenic shock	96	0.02	13	0.03	0.58
Cardiac complications not elsewhere classified	3,849	0.79	419	0.95	1.67

(STD = standardized difference)

Appendix 4

Patient and Healthcare System Related Characteristics Based on the Propensity Scoring Matched Samples

Patient and Healthcare System Related Demographics (based on propensity matching)					
	No SA diagnosis		**SA Diagnosis**		
	N	**%**	**N**	**%**	**STD (%)**
Total	**84,531**	**75**	**28,177**	**25**	
Average Age (Year) (SD)	63.63 (10.56)		63.70 (9.56)		0.63
Gender					
Female	13,203	15.6	4,071	14.5	2.16
Male	71,328	84.4	24,106	85.6	
Race					
White	68,623	81.2	22,331	79.3	4.84
Black	5,834	6.9	2,250	8.00	4.13
Hispanic	1,321	1.6	498	1.8	1.60
Other	8,753	10.4	3,098	11.00	2.07
Average Deyo Index [a] (SD)	0.82 (1.04)		0.87 (1.05)		4.36

Patient and Healthcare System Related Demographics (based on propensity matching)					
	No SA diagnosis		SA Diagnosis		
	N	%	N	%	STD (%)
Deyo Index Category					
0	45,444	53.8	14,452	51.3	4.95
1	16,042	19.00	5,659	20.1	2.79
2	16,588	19.6	5,708	20.3	1.59
≥ 3	6,457	7.6	2,358	8.4	2.69
Type of Procedure					
THA	71,328	84.4	24,106	85.6	2.46
TKA	13,203	15.6	4,071	14.5	
Type of Anesthesia					
N	8,342	9.9	2,874	10.2	1.10
G	64,747	76.6	21,397	75.9	1.55
N+G	11,442	13.5	3,906	13.9	0.95
Year of Procedure					
2006	11,886	14.1	4,064	14.4	1.04
2007	15,122	17.9	5,103	18.1	0.58
2008	17,690	20.9	5,913	21.00	0.14
2009	22,472	26.6	7,341	26.1	1.21
2010	17,361	20.5	5,756	20.4	0.27
Admission Type					
Emergent	1,867	2.2	694	2.5	1.68
Urgent	3,095	3.7	1,175	4.2	2.62
Elective	79,321	93.8	26,253	93.2	2.70
Other	248	0.3	55	0.2	1.99
Indication					
RA	2,151	2.5	829	2.9	2.43
OA	80,487	95.2	26,588	94.4	3.85
Other	1,893	2.2	760	2.7	2.95
Hospital Size (Beds)					
< 299	25,619	30.3	8,610	30.6	0.54
300-499	34,874	41.3	11,602	41.2	0.16
≥ 500	24,038	28.4	7,965	28.3	0.38
Hospital Location					
Rural	71,328	84.4	24,106	85.6	2.48
Urban	13,203	15.7	4,071	14.5	
Hospital Teaching Status					
Non-Teaching	71,328	84.4	24,106	85.6	1.25
Teaching	13,203	15.6	4,071	14.5	

[a]The Deyo Index was validated for the outcomes of complications, mortality, blood transfusion, use of hospital resources, and other adverse events on a cohort of surgical patients [13].

Appendix 5

Comorbidity Incidence Based Propensity Scoring Matched Samples

Incidence of Comorbid Disease (based on propensity matching)					
	No SA diagnosis		SA Diagnosis		
Comorbidity	N	%	N	%	STD(%)
MI	3,611	4.3	1,386	4.9	3.09
Cerebrovascular Disease	186	0.2	68	0.2	0.44
Peripherovascular Disease	1,580	1.9	595	2.1	1.74
Dememtia	57	0.1	21	0.1	0.27
Renal Disease	35	<0.1	15	0.1	0.54
COPD	17,087	20.2	5,983	21.2	2.52
Diabetes	20,608	24.4	7,140	25.3	2.22
Complicated Diabetes	1,366	1.6	490	1.7	0.96
Cancer	1,354	1.6	500	1.8	1.34
Hypertension	58,936	69.7	19,330	68.6	2.42
Complicated Hypertension	4,181	5.0	1,498	5.3	1.68
Pulmonary Hypertension	695	0.8	243	0.9	0.44
Obesity	27,886	33.0	9,561	33.9	2.00

(SA = sleep apnea; STD = standardized difference; COPD = chronic obstructive pulmonary disease)

Appendix 6

Results comparisons between the propensity score method-based sensitivity analysis and multivariable logistic regressions with main effects only Based on the matched sample, the effect of SA on outcomes was tested for significance using the Cochran-Mantel-Haenszel test. Common odds ratio (COR) Bonferroni corrected 95% confidence intervals and p-values are reported.

	Propensity Score Matched Samples	Multivariable logistic regression with main effects only
Outcome	Common Odds Ratio (Corrected 95% CI) [a,b]	Adjusted Odds Ratio (Corrected 95% CI) [a,b]
Combined Complications	1.45 (1.37, 1.53)	1.47 (1.40, 1.54)
Pulmonary Complications	1.90 (1.68, 2.15)	1.86 (1.68, 2.06)
Cardiac Complications	1.54 (1.43, 1.66)	1.59 (1.49, 1.69)
Mortality	1.20 (0.69, 2.07)	1.27 (0.80, 2.04)
Mechanical Ventilation	10.84 (8.97, 13.09)	10.26 (9.01, 11.69)
Non-Invasive Ventilation	27.78 (20.02, 38.56)	29.04 (23.55, 35.80)
Blood Product Transfusion	0.91 (0.86, 0.96)	0.88 (0.83, 0.92)
ICU Utilization	1.85 (1.69, 2.03)	1.85 (1.71, 2.00)
Telemetry / Stepdown Unit Utilization	1.69 (1.57, 1.82)	1.64 (1.55, 1.75)
Length of Stay > 75th percentile	1.18 (1.13, 1.23)	1.16 (1.12, 1.20)

	Propensity Score Matched Samples	Multivariable logistic regression with main effects only
Outcome	**Common Odds Ratio (Corrected 95% CI) [a,b]**	**Adjusted Odds Ratio (Corrected 95% CI) [a,b]**
Utilization of economic resources > 75th percentile	1.13 (1.11, 1.22)	1.13 (1.09, 1.18)

[a] All 95% CIs and the associated p-values were both Bonferroni corrected for multiple comparisons

[b] All corrected p-values were <0.0001 except for mortality (p>0.99).

[c] All corrected p-values were <0.0001 except for mortality (p=0.43).

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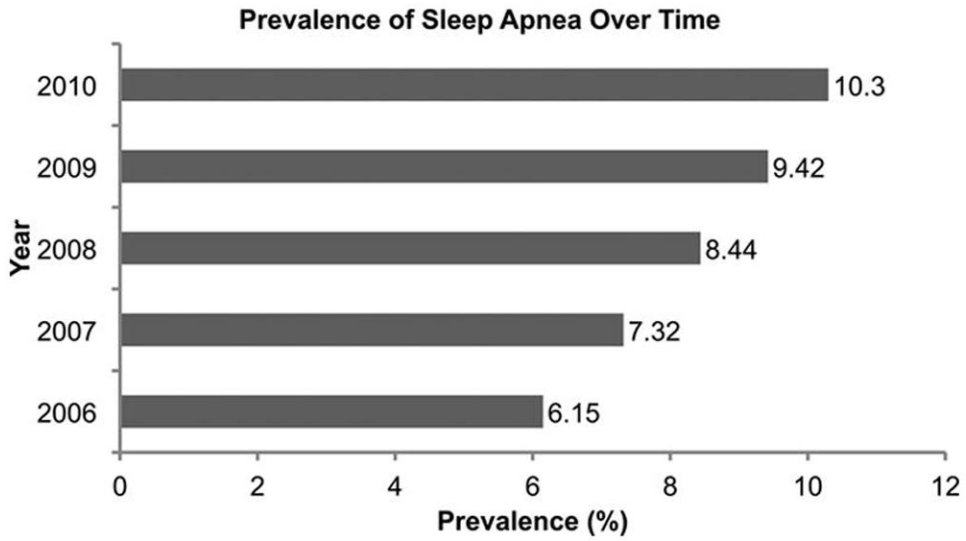

Figure 1.
Figure 1 displays the prevalence of sleep apnea over time.

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Table 1

Patient and Healthcare System Related Characteristics

Patient and healthcare system related variables for patients without and with diagnosis of sleep apnea.

	No SA Diagnosis		SA Diagnosis		
N	485,843		44246		
%	91.6%		8.4%		
Year of Procedure [b]					
	N	**%**	**N**	**%**	**STD (%)**
2006	91,731	18.9	6,007	13.6	14.42
2007	97,545	20.1	7,709	17.4	6.80
2008	102,177	21.0	9,419	21.3	0.63
2009	111,892	23.0	11,640	26.3	7.61
2010	82,498	17.0	9,471	21.4	11.25
Type of Procedure [b]					
THA	162,011	33.3	10,939	24.7	19.08
TKA	323,832	66.7	33,307	75.3	
Type of Anesthesia					
N	36,702	7.6	3,332	7.5	0.09
G	269,495	55.5	24,798	56.0	1.16
N+G	44,762	9.2	4,659	10.5	4.41
Unknown	134,884	27.8	11,457	25.9	4.22
Deyo Index Category [a,b]					
0	315,316	64.9	20,662	46.7	37.28

	No SA Diagnosis		SA Diagnosis		
1	80,419	16.6	8,894	20.1	9.18
2	68,275	14.1	9,531	21.5	19.67
> 3	21,833	4.5	5,159	11.7	26.53
Average Deyo Index [a,b] **(SD, range)**	0.59 (0.92, 0-10)		1.00 (1.12, 0-8)		40.11
Average Age (Year) [b] **(SD)**	66.16 (11.32)		63.36 (9.56)		26.72
Gender [b]					
Female	304,459	62.7	20,419	46.1	33.63
Male	181384	37.3	23,827	53.9	
Race					
White	360840	74.3	34,231	77.4	7.23
Black	32844	6.8	3,353	7.6	3.17
Hispanic	11191	2.3	741	1.7	4.50
Other	80968	16.7	5,921	13.4	9.20
Admission Type					
Emergent	11,430	2.4	978	2.2	0.95
Urgent	19,433	4.0	1,821	4.1	0.59
Elective	453,700	93.4	41,373	93.5	0.50
Other	1,280	0.3	74	0.2	2.08
Hospital Size (No of Beds)					
< 299	158,567	32.6	12,991	29.4	7.09
300-499	189,123	38.9	19,102	43.2	8.64
> 500	138,153	28.4	12,153	27.5	2.16

	No SA Diagnosis		SA Diagnosis		
Hospital Location					
Rural	49,240	10.1	4,203	9.5	2.14
Urban	436,603	89.9	40,043	90.5	
Hospital Teaching Status					
Non-Teaching	286,759	59.0	24,537	55.5	7.21
Teaching	199,084	41.0	19,709	44.5	
Indication					
RA	15,980	3.3	1,217	2.8	3.15
OA	451,184	92.9	41,984	94.9	8.44
Other	18,679	3.8	1,045	2.4	8.56

(SA = sleep apnea; STD = Standardized Difference; SD = Standard Deviation; THA = total hip arthroplasty; TKA = total knee arthroplasty; OA = osteoarthritis; RA = rheumatoid arthritis).

[a]The Deyo Index was validated for the outcomes of complications, mortality, blood transfusion, use of hospital resources, and other adverse events on a cohort of surgical patients [13]. (Deyo Index = 1 *Myocardial Infarction + 1 *Cerebrovascular Disease + 1 *Peripheral Vascular Disease + 2 *Renal Disease + 1 *COPD + 1 *Diabetes + 2*Complicated Diabetes + 1 *Dementia + 1*Rheumatoid Disease +1 * Mild Liver Disease + 1*Severe Liver Disease + 6 *AIDS + 1 *Plegia + 1 *Cancer)

[b]Variables met the standardized difference > 10% threshold

Table 2

Prevalence of Comorbidities

Prevalence of pre-existing comorbidities for patients without and with diagnosis of sleep apnea

	No SA Diagnosis		SA Diagnosis		
Comorbidity	**N**	**%**	**N**	**%**	**STD (%)**
Myocardial Infarction	17,069	3.5	2,433	5.5	9.58
Cerebrovascular Disease	1,136	0.2	98	0.2	0.26
Peripheral Vascular Disease	8,187	1.7	1,057	2.4	4.98
Renal Disease	243	0.1	23	0.1	0.09
COPD[a]	64,816	13.3	11,051	25.0	29.89
Diabetes[a]	79,444	16.4	12,980	29.3	31.30
Complicated Diabetes[a]	4,610	0.9	1,108	2.5	11.96
Cancer	8,556	1.8	782	1.8	0.05
Obesity[a]	75,644	15.6	18,708	42.3	61.65
Hypertension[a]	293,277	60.4	30,862	69.8	19.78
Complicated Hypertension[a]	17,576	3.6	2,764	6.2	12.16
Pulmonary Hypertension[a]	2,476	0.5	765	1.7	11.61

(SA = sleep apnea; STD = Standardized Difference; COPD = chronic obstructive pulmonary disease).

[a]Variables met the standardized difference > 10% threshold

Table 3

Incidence of Complications

The incidence of selected outcomes for patients without and with diagnosis of sleep apnea

	No SA diagnosis		SA Diagnosis			
Event	**N**	**%**	**N**	**%**	**STD(%)**	**p-value**
Pulmonary Embolism	1,908	0.4	267	0.6	2.99	<0.0001
Deep Venous Thrombosis	2,665	0.5	266	0.6	0.70	0.15
Cerebrovascular Accident	560	0.1	46	0.1	0.34	0.50
Pulmonary Complications	2,672	0.6	839	1.9	12.27	<0.0001
Sepsis	697	0.1	91	0.2	1.49	0.0011
Cardiac Complications (Non MI)	29,847	6.1	4,110	9.3	11.81	<0.0001
Pneumonia	3,987	0.8	591	1.3	4.99	<0.0001
All Infectious Complications	19,738	4.1	1,899	4.3	1.15	0.02
Acute Renal Failure	6,741	1.4	1,245	2.8	9.96	<0.0001
Gastrointestinal Complications	3,571	0.7	507	1.1	4.26	<0.0001
Acute MI	1,280	0.3	114	0.3	0.11	0.82
30 Day Mortality	716	0.1	85	0.2	0.79	<0.0001
ICU Utilization	14,647	3.0	2,713	6.1	14.96	<0.0001
Stepdown and Telemetry Use	26,847	5.5	4,108	9.3	14.39	<0.0001
Mechanical Ventilation	1,622	0.3	2,183	4.9	29.03	<0.0001
Non-invasive ventilation	400	0.1	1,665	3.8	27.05	<0.0001
Transfusion	93,958	19.3	6,394	14.5	13.07	<0.0001

(SA = sleep apnea; STD = Standardized Difference; MI = myocardial infarction)

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Table 4

Results from the logistic regression models – SA diagnosis vs. Non-SA diagnosis

Multivariable regression for various outcomes. Present diagnosis of sleep apnea is the effect variable (CI = confidence interval).

Outcome	Crude Odds Ratio (Corrected 95% CI) [a,b,c]	Adjusted Odds Ratio (Corrected 95% CI) [a,c]	Significant interaction term with SA (p-value [d])	C-statistic
Combined Complications	1.53 (1.47, 1.60)	1.47 (1.39, 1.55)	None	0.69
Pulmonary Complications	2.19 (2.00, 2.40)	1.86 (1.65, 2.09)	None	0.69
Cardiac Complications	1.56 (1.48, 1.65)	1.59 (1.48, 1.71)	None	0.74
Mortality	1.27 (0.82, 1.98)	1.27 (0.74, 2.19)	None	0.74
Mechanical Ventilation	11.94 (10.64, 13.40)	See table 5	Complicated Hypertension (p<0.0001) COPD (p<0.0001)	0.83
Non-Invasive Ventilation	37.13 (30.64, 45.00)	See table 5	Complicated Hypertension (p<0.0001), COPD (p<0.0001)	0.88
Blood Product Transfusion	0.71 (0.68, 0.74)	0.88 (0.83, 0.93)	None	0.67
ICU Utilization	2.06 (1.92, 2.21)	See table 5	Gender (p=0.0002), Year (p=0.0007)	0.73
Telemetry / Stepdown Unit Utilization	1.76 (1.66, 1.86)	See table 5	Year (p=0.0008), Complicated Hypertension(p<0.0001), Obesity (p<0.0001)	0.68
Length of Stay > 75th percentile	1.09 (1.05, 1.13)	See table 5	Obesity (p=0.0006)	0.65
Utilization of economic resources > 75th percentile	1.22 (1.18, 1.26)	1.14 (1.09, 1.19)	None	0.60

Reference = no sleep apnea diagnosis.

[a] All 95% CIs and the associated p-values were both Bonferroni corrected for multiple comparisons

[b] All corrected p-values were <.0001 except for mortality (p>0.99).

[c] All corrected p-values were <.0001 except for mortality (p>0.99).

[d] P-values were raw p-values from multivariate regressions, and compared with threshold 0.05/11=0.004 to determine the statistical significance.

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Table 5

Effect of SA vs. Non-SA from Logistic Regression Models with Significant Interaction Terms of SA Diagnosis vs. Non-SA diagnosis

Multivariable regression for outcomes with significant interactions. Present diagnosis of sleep apnea is the effect variable.

Interaction Terms [c]			Adjusted OR (95% CI) [a]	Adjusted p-value [a]	c-statistic
Mechanical Ventilation					
Complicated Hypertension = No	COPD = No		13.80 (11.53, 16.52)	<0.0001	0.83
	COPD = Yes		8.01 (6.19, 10.36)	<0.0001	
Complicated Hypertension = Yes	COPD = No		5.30 (3.62, 7.74)	<0.0001	
	COPD = Yes		3.07 (2.04, 4.64)	<0.0001	
Non-Invasive Ventilation					
Complicated Hypertension = No	COPD = No		46.12 (33.88, 62.77)	<0.0001	0.88
	COPD = Yes		16.20 (10.95, 23.97)	<0.0001	
Complicated Hypertension = Yes	COPD = No		15.62 (8.53, 28.60)	<0.0001	
	COPD = Yes		5.49 (2.92, 10.30)	<0.0001	
ICU Utilization					
Male	2006		1.86 (1.49, 2.30)	<0.0001	0.73
	2007		1.82 (1.49, 2.23)	<0.0001	
	2008		2.05 (1.70, 2.48)	<0.0001	
	2009		1.37 (1.13, 1.67)	<0.0001	
	2010		1.37 (1.09, 1.72)	0.0005	
Female	2006		2.28 (1.82, 2.84)	<0.0001	
	2007		2.23 (1.82, 2.73)	<0.0001	
	2008		2.52(2.09, 3.04)	<0.0001	
	2009		1.69 (1.38, 2.05)	<0.0001	
	2010		1.68 (1.34, 2.11)	<0.0001	
Telemetry/Stepdown Unit Utilization					
Complicated Hypertension = No	**Obesity = No**	2006	1.81 (1.47, 2.23)	<0.0001	0.68
		2007	1.49 (1.24, 1.78)	<0.0001	
		2008	1.40 (1.19, 1.65)	0.0584	

Interaction Terms [c]			Adjusted OR (95% CI) [a]	Adjusted p-value [a]	c-statistic
		2009	1.73 (1.52, 1.96)	0.0213	
		2010	1.54 (1.33, 1.78)	0.0268	
	Obesity = Yes	2006	2.17 (1.73, 2.72)	<0.0001	
		2007	1.78 (1.47, 2.17)	<0.0001	
		2008	1.68 (1.41, 2.00)	0.0689	
		2009	2.07 (1.79, 2.39)	0.0262	
		2010	1.85 (1.58, 2.16)	0.0309	
Complicated Hypertension = Yes	**Obesity = No**	2006	1.25 (0.91, 1.73)	>0.99	
		2007	1.03 (0.76, 1.39)	>0.99	
		2008	0.97 (0.73, 1.29)	0.1853	
		2009	1.19 (0.91, 1.57)	0.17	
		2010	1.07 (0.80, 1.41)	0.1773	
	Obesity = Yes	2006	1.50 (1.08, 2.08)	0.0047	
		2007	1.23 (0.91, 1.67)	0.2089	
		2008	1.16 (0.87, 1.55)	0.1901	
		2009	1.43 (1.08, 1.89)	0.1731	
		2010	1.28 (0.96, 1.69)	0.1801	
Increased Length of Hospitalization					
Obesity = No			1.12 (1.06, 1.18)	<0.0001	0.65
Obesity = Yes			1.23 (1.15, 1.31)	<0.0001	

(Reference = no sleep apnea diagnosis).

[a] All 95% CIs and the associated p-values were both Bonferroni corrected for multiple comparisons

[b] All unadjusted models had p-values < 0.001

[c] All interaction terms had p-values < 0.001