A Matched Cohort Study of Postoperative Outcomes in Obstructive Sleep Apnea

Could Preoperative Diagnosis and Treatment Prevent Complications?

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This article has been selected for the Anesthesiology CME Program. Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue.

ABSTRACT

Background: Obstructive sleep apnea (OSA) is associated with increased risk of postoperative complications. The authors investigated whether preoperative diagnosis and prescription of continuous positive airway pressure therapy reduces these risks.

Methods: Matched cohort analysis of polysomnography data and Manitoban health administrative data (1987 to 2008). Postoperative outcomes in adult OSA patients up to 5 yr before (undiagnosed OSA, n = 1,571), and any time after (diagnosed OSA, n = 2,640) polysomnography and prescription of continuous positive airway pressure therapy for a new diagnosis of OSA, were compared with controls at low risk of having sleep apnea (n = 16,277). Controls were matched by exact procedure, indication, and approximate date of surgery. Procedures used to treat sleep apnea were excluded. Follow-up was at least 7 postoperative days. Results were reported as odds ratio (95% CI) for OSA or subgroup *versus* controls.

Results: In multivariate analyses, the risk of respiratory complications (2.08 [1.35 to 3.19], $P < 0.001$) was similarly increased for both undiagnosed and diagnosed OSA. The risk of cardiovascular complications, primarily cardiac arrest and shock, was significantly different ($P = 0.009$) between undiagnosed OSA (2.20 [1.16 to 4.17], $P = 0.02$) and diagnosed OSA patients (0.75 [0.43 to 1.28], $P = 0.29$). For both outcomes, OSA severity, type of surgery, age, and other comorbidities were also important risk modifiers.

Conclusions: Diagnosis of OSA and prescription of continuous positive airway pressure therapy were associated with a reduction in postoperative cardiovascular complications. Despite limitations in the data, these results could be used to justify and inform large efficacy trials of perioperative continuous positive airway pressure therapy in OSA patients.
(Anesthesiology 2014; 121:707-18)

OBSTRUCTIVE sleep apnea (OSA) is prevalent among preoperative patients and has been associated with increased risk of postoperative complications.[1,2] Strikingly, as many as 90% of those afflicted by OSA are not yet diagnosed, and therefore not treated.[2–4] These undiagnosed OSA (UOSA) patients are hypothesized to be at higher postoperative risk than patients with diagnosed OSA (DOSA) that is effectively treated with a continuous positive airway pressure (CPAP) device. Consequently, current practice guidelines advocate diligent preoperative screening for UOSA, preoperative initiation of CPAP therapy when feasible, and routine intensive monitoring of UOSA and DOSA patients after many types of surgery.[5–7]

Recently completed studies of large administrative databases[8–10] have demonstrated significantly increased risk of

What We Already Know about This Topic

- Continuous positive airway pressure is thought to reduce the risk of postoperative respiratory and cardiovascular complications
- The investigators tested this hypothesis in a cohort of patients with obstructive sleep apnea, diagnosed by polysomnography before or after surgery, who were matched to controls without sleep apnea

What This Article Tells Us That Is New

- Respiratory complications were twice as likely in obstructive sleep apnea patients, whether diagnosed before or after surgery, compared with controls
- Patients with a preoperative diagnosis of obstructive sleep apnea and prescription for continuous positive airway pressure were less than half as likely to experience cardiovascular complications as those diagnosed after surgery

This article is featured in "This Month in Anesthesiology," page 1A. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). This work was presented as an abstract at the Society for Anesthesia and Sleep Medicine 3rd annual meeting, October 10–11, 2013, San Francisco, California.

Submitted for publication December 16, 2013. Accepted for publication July 14, 2014. From the Department of Anesthesia (T.C.M.), Manitoba Centre for Health Policy, Department of Community Health Sciences (D.C.), Departments of Community Health Sciences and Pediatrics and Child Health (M.M.), Departments of Medicine and Community Health Sciences (C.R.), and Department of Community Health Sciences (L.L.R.), University of Manitoba, Winnipeg, Manitoba, Canada; and Yale University School of Medicine, Section of Pulmonary, Critical Care and Sleep Medicine, VA Connecticut Healthcare System, West Haven, Connecticut (M.K.).

 Anesthesiology 2014; 121:707-18

respiratory failure, mechanical ventilation, emergency intubation, aspiration pneumonia, acute respiratory distress syndrome, and atrial fibrillation in patients assigned a diagnosis of OSA in hospital discharge abstracts. A meta-analysis[11] of patients diagnosed with UOSA or DOSA by questionnaire or polysomnography also found an increased risk of postoperative respiratory failure and "any cardiac events." Risk estimates in these studies have varied significantly by outcome and surgical population, but have generally ranged from 1.5 to 3. Despite this valuable work, no study of OSA patients diagnosed by polysomnography, the reference standard, has been large enough to determine the effect of OSA severity on postoperative outcomes while simultaneously adjusting for surgical and patient-related covariates. Most importantly, no large studies exist that have compared outcomes between UOSA and DOSA patients or studied the efficacy of perioperative CPAP in OSA patients. These deficiencies in the evidence behind the guideline recommendations, and the significant cost of guideline implementation, have created a clinical and policy dilemma with potentially enormous effects on postoperative morbidity and healthcare resource allocation.[12] The increasing prevalence of OSA[13] only further magnifies the need for better evidence.

Accordingly, this study examined historical postoperative outcomes, predating the formal implementation of current practice guidelines, in a rarely available, large cohort of patients who were newly diagnosed with OSA and prescribed CPAP. By including surgery that occurred both before and after polysomnography, we sought to determine the effect of definitive diagnosis and prescription of CPAP on the incidence of clinically important postoperative respiratory and cardiovascular complications. We also examined the relative importance of OSA severity, other comorbidities, and the type of surgery in predicting these same outcomes. Consistent with published guidelines, we hypothesized that DOSA patients, and especially UOSA patients, would have increased risk of both types of complications compared with controls. We suspected increasing OSA severity would be associated with increased risk but that the type of surgery and patient comorbidities would also be important risk factors.

Materials and Methods

Study Design, Data Sources, Setting, and Participants

This matched cohort study was restricted to patients at least 18-yr old at the time of surgery and was conducted with the ethical approval of the University of Manitoba (H2010:203; Winnipeg, Manitoba, Canada) and the government of Manitoba's Health Information Privacy Committee (#2010/2011–16; Winnipeg). It linked a clinical database of polysomnography data for patients newly diagnosed with OSA to a large, Canadian, health administrative database repository[14] to compare postoperative outcomes in OSA patients, before and after diagnosis, with matched controls from the general population who were at low risk of having OSA. The repository data are collected by the province of Manitoba for the administration of a free and universal health insurance system and thus provide a complete, longitudinal record of hospital and physician service use, in addition to a vital statistics registry, for almost all 1.25 million citizens.[14] The clinical database contained over 3,500 patients prescribed CPAP for a new diagnosis of OSA, between 1990 and 2006 at a university affiliated, tertiary hospital sleep laboratory.[15–17] Sleep apnea diagnoses within the clinical database were made according to widely accepted criteria,[18] after in-lab polysomnography and sleep medicine evaluation. Databases were linked at the level of the individual between all sources.

Surgeries attended by an anesthesiologist that were performed on OSA patients from the clinical database were identified in the repository between April 1, 1987 (the first date in-hospital complications could be distinguished from preexisting comorbidities on hospital discharge abstracts) and March 31, 2008 (the last fiscal year of data before routine postoperative monitoring for OSA patients was widely adopted in Manitoba). Surgeries used to treat OSA or its symptoms were excluded (see table, Supplemental Digital Content 1, http://links.lww.com/ALN/B74, for a list of these procedures). Otherwise, all surgeries occurring at any time after polysomnography (DOSA subgroup), and up to 5 yr before (UOSA subgroup), were considered for analysis. This UOSA subgroup definition assumed patients had OSA up to 5 yr before their diagnosis, based on previous work with the clinical database,[15,16] and analogous to another study.[19] For each UOSA and DOSA patient surgery, we matched up to four unique controls from the general population of Manitoba who had undergone the same surgery for the same indication within 3 yr of the OSA patient's procedure date. This matching strategy adjusted *a priori* for variables otherwise difficult to control for at analysis: different surgical procedures and indications for surgery between OSA and control patients, changes in procedures and indications for procedures over time, and changes in the coding of comorbidities and complications over time. Controls were considered to be at low risk of having UOSA or DOSA because members of the general population were excluded from matching if, anywhere in the over 20 yr of available repository data, they had a physician service claim for interpretation of a sleep study, or a diagnosis of sleep disordered breathing (see table, Supplemental Digital Content 2, http://links.lww.com/ALN/B75, for a list of the International Classification of Diseases [ICD] codes used). See the text, Supplemental Digital Content 3, http://links.lww.com/ALN/B76, for additional information on the study design and data sources.

Predictor Variables

Relevant comorbidities,[20,21] including chronic obstructive pulmonary disease, ischemic heart disease, congestive heart failure, cerebrovascular accident, renal disease, and diabetes

mellitus, were assigned to patients by applying previously published ICD code definitions (see table, Supplemental Digital Content 4, http://links.lww.com/ALN/B77, for a list of these codes). The patient's comorbidity status was permanently changed on the date of the first occurrence of a relevant code in either a hospital discharge abstract or a physician service claim. The patient's sex and whether the patient was in an intensive care unit at the time of surgery were also recorded. Age at the time of surgery was modeled as a continuous linear predictor variable. Previously described ordinal variables were developed for Charlson comorbidity index scores,[22,23] the modified revised cardiac risk index,[21,24] and OSA severity. See the text, Supplemental Digital Content 3, http://links.lww.com/ALN/B76, for additional information regarding these predictor variables. Control patients were the reference group for OSA severity, with apnea hypopnea indices in OSA patients of 5 to 15, 15 to 30, and greater than 30 events per hour corresponding to mild, moderate, and severe OSA, respectively.[18] Concomitant clinical diagnoses of central sleep apnea and obesity hypoventilation syndrome, based on polysomnography data, were also noted in OSA patients. Each surgery was characterized as being cardiac (open heart) or noncardiac, elective or emergency, high or low risk for respiratory failure[20], and major or minor,[25] where major included cardiac surgery. Body mass index at the time of surgery, the type of anesthesia, postoperative analgesia, caregiver awareness of the OSA diagnosis, use of intensive postoperative monitoring, and adherence to CPAP therapy before and after surgery were unknown.

Outcomes

Selected outcomes were previously studied,[8–11,19,26,27] clinically significant postoperative complications that could plausibly be prevented by improvement of hypoxemia and airway obstruction with CPAP and intensive monitoring. Using previously published ICD code definitions (see tables, Supplemental Digital Content 5, http://links.lww.com/ALN/B78, for lists of the ICD codes used), we included cardiac arrest, acute coronary syndrome, cerebrovascular accident, and atrial fibrillation/flutter as cardiovascular complications and adult respiratory distress syndrome (ARDS), respiratory failure, and pneumonia as respiratory complications. In the hospital discharge abstract associated with the surgery, new complications were distinguished from preexisting comorbidities with the diagnosis type field.[28] Any outcomes occurring during readmission to hospital within 7 days of surgery were also included, to ensure comparability of follow-up. Censorship from follow-up in the repository data (due to termination of insurance coverage) was considered negligible, because the period of observation after each surgery was short. Patients who died during the follow-up period were included in the analysis but were not considered to have had a cardiovascular or respiratory complication unless they also had one of the relevant ICD codes recorded. Before analysis, specific surgeries were excluded where the indication for the surgery would commonly be the complication being studied (*i.e.*, tracheostomy and respiratory complications) or where the complication was a relatively common outcome after the specific surgery and would cause a regression toward a nil effect (*i.e.*, cerebrovascular accident after intracranial surgery).

Statistical Analysis

All data were analyzed using SAS® software version 9.2 and 9.3 (SAS Institute Inc., Cary, NC). To account for the matched study design and provide robust empirical standard error measurements, all analyses used generalized estimating equations with an exchangeable correlation matrix.[29] The occurrence of multiple surgeries in the same OSA patient before and/or after diagnosis was a separate potential source of clustering. For each outcome, this clustering was quantified by calculating the intraclass correlation coefficient from the empirical model covariance in a generalized estimating equation null model of all OSA patient surgeries, with the patient as the repeating variable.[30]

The sample size was fixed by the number of events in the available data. Univariate predictor variables with P values less than 0.01 were considered for inclusion in multivariate models that were created using stepwise backward regression. Consistent with the study objectives, OSA status was included in every multivariate model, regardless of significance. Values of P less than 0.05 were considered statistically significant for main effects, interactions, and contrasts. To compare differences in risk between UOSA and DOSA groups while adjusting for differences in overall surgical risk between the UOSA and DOSA groups, it was necessary to assign a binary "timing of surgery" variable (pre- *vs.* post-OSA patient diagnosis) to each OSA patient surgery and its matched controls. A significant statistical interaction between "timing of surgery" and OSA status (OSA *vs.* control) indicated that UOSA and DOSA were associated with significantly different postoperative risk. Data are reported as the odds ratio (95% CI) or mean (SD).

We avoided the propensity-based methods used in other studies[8,10,27] for several reasons. First, propensity methods for multicategory variables (*i.e.*, UOSA *vs.* DOSA *vs.* control, with or without stratification by OSA severity) are not well established. In this study, these stratifications were of primary importance. Second, the control group in this study was defined by absence of ICD code diagnosis of OSA, not absence of OSA on polysomnography, as in another study using propensity analysis.[27] If we used propensity methods based on the available covariates (*i.e.*, age and comorbidities), we would have selected general population control patients that have comorbidities associated with OSA, and consequently, are at high risk of having UOSA. Third, propensity methods would make it difficult to preserve the match on type of surgery and approximate date of surgery, which in this study are also very important covariates.

Sensitivity analyses probed for a healthy user effect in DOSA patients and investigated whether changes in patient management over time were an unrecognized confounder. Complication rates in excluded surgeries were measured, and the sensitivity of the results to the removal of OSA patients with concomitant diagnoses of central sleep apnea or obesity hypoventilation syndrome was tested. As the Charlson comorbidity index was missing for some patients, we also modeled each outcome without using this variable. As forcing OSA status into every model, regardless of statistical significance, might have obscured the important effects of the comorbidities associated with OSA, we also created models where OSA status was added to the model only after all other variables were considered for statistical significance. Finally, to validate the outcomes as clinically important events, we used registry data to measure mortality within 28 days of included surgeries among control patients who experienced each outcome. Mortality was not measured in OSA patients because they could have more than one included surgery.

Results

Cohort Description

Ninety-nine percent of clinical database patients were linked to the data repository, and ultimately 4,211 UOSA and DOSA patient surgeries, in 1,922 individual patients (range of 1 to 13 surgeries per OSA patient), were matched to 16,277 non-OSA control surgeries. From this base cohort, subcohorts for the analysis of both complications were derived (fig. 1). Twenty-two percent and 43% of DOSA patient surgeries *versus* 24 and 51% of UOSA patient surgeries occurred in patients with moderate and severe OSA, respectively (see the figure, Supplemental Digital Content 6, http://links.lww.com/ALN/B79, for the distribution of surgeries by calendar year).

UOSA patients, and especially DOSA patients, were more likely than non-OSA controls to have comorbidities at the time of surgery (table 1). UOSA patients were also significantly younger than non-OSA patients. Cardiac surgery, major surgery, and surgery associated with a high risk of respiratory failure were similarly distributed between UOSA and DOSA patients, comprising 3.4, 29.5, and 19.8% of all OSA patient surgeries, respectively. See the text, Supplemental Digital Content 7, http://links.lww.com/ALN/B80, for lists of specific surgeries stratified by type of surgery. The Charlson comorbidity index could not be calculated for 1,128 surgeries; these were the only missing study data.

Respiratory and Cardiovascular Complications

Respiratory complications occurred in 33 (0.79%) UOSA and DOSA patient surgeries and 69 (0.42%) matched controls. Cardiovascular complications occurred in 35 (0.88%) OSA patient surgeries and 130 (0.84%) matched controls. Clustering of outcomes in individual OSA patients who presented for more than one surgery was considered negligible, as the intraclass correlation coefficient was less than 0.01 for both outcomes. Mortality rates within 28 days of surgery among control patients who experienced respiratory and cardiovascular complications were 26.1 and 17.7%, respectively.

OSA overall (UOSA and DOSA subgroups combined) was a significant univariate predictor of respiratory complications and patients with severe disease were at highest risk (table 2). Comparatively, rates of cardiovascular complications were only significantly increased in patients with severe UOSA. Interestingly, many surgical factors and medical comorbidities were stronger predictors of complications than OSA. However, a concomitant diagnosis of central sleep apnea or obesity hypoventilation syndrome was not significant, likely due to the small number of affected patients. Surgeries with missing Charlson comorbidity index scores were excluded from univariate and multivariate models that included this variable. These were all minor surgeries at freestanding ambulatory surgery centers. They were associated with no respiratory complications and five or less cardiovascular complications.

In multivariate analyses, OSA overall remained a significant predictor of respiratory complications (2.08 [1.35 to 2.19], $P = 0.0008$), but DOSA was not associated with a significant reduction in risk (0.68 [0.27 to 1.71], $P = 0.41$), compared with UOSA. Comparatively, DOSA patients had significantly reduced risk of cardiovascular complications compared with UOSA patients (0.34 [0.15 to 0.77], $P = 0.009$). Compared with matched controls, DOSA patients had comparable risk (0.75 [0.43 to 1.28], $P = 0.29$), whereas UOSA patients had increased risk (2.20 [1.16 to 4.17], $P = 0.02$) of cardiovascular complications.

In multivariate models stratified by disease severity (table 3), significant trends to increased risk with increasing OSA severity were present for respiratory complications in OSA overall ($P = 0.01$) and cardiovascular complications in UOSA patient surgeries only ($P = 0.03$). In these models, only patients with severe OSA or UOSA had significantly increased risk of respiratory and cardiovascular complications, respectively, although CIs were wide for patients with less severe disease. For both outcomes, medical comorbidities and the type of surgery were also important predictors of risk. Increased respiratory complications in OSA patients were primarily due to increased risk of ARDS and acute respiratory failure, whereas increased cardiovascular complications in UOSA patients were primarily due to increased risk of shock and cardiac arrest (table 4).

In sensitivity analyses, neither there was evidence for a significant healthy user effect, nor was there evidence for a significant effect on outcomes from potential changes in patient care in the later years of data. Results for OSA patients and their subgroups were not significantly altered by using individual comorbidities in the models instead of the Charlson comorbidity index (these models include patients with missing Charlson comorbidity index scores), by excluding from the models OSA patients who also had

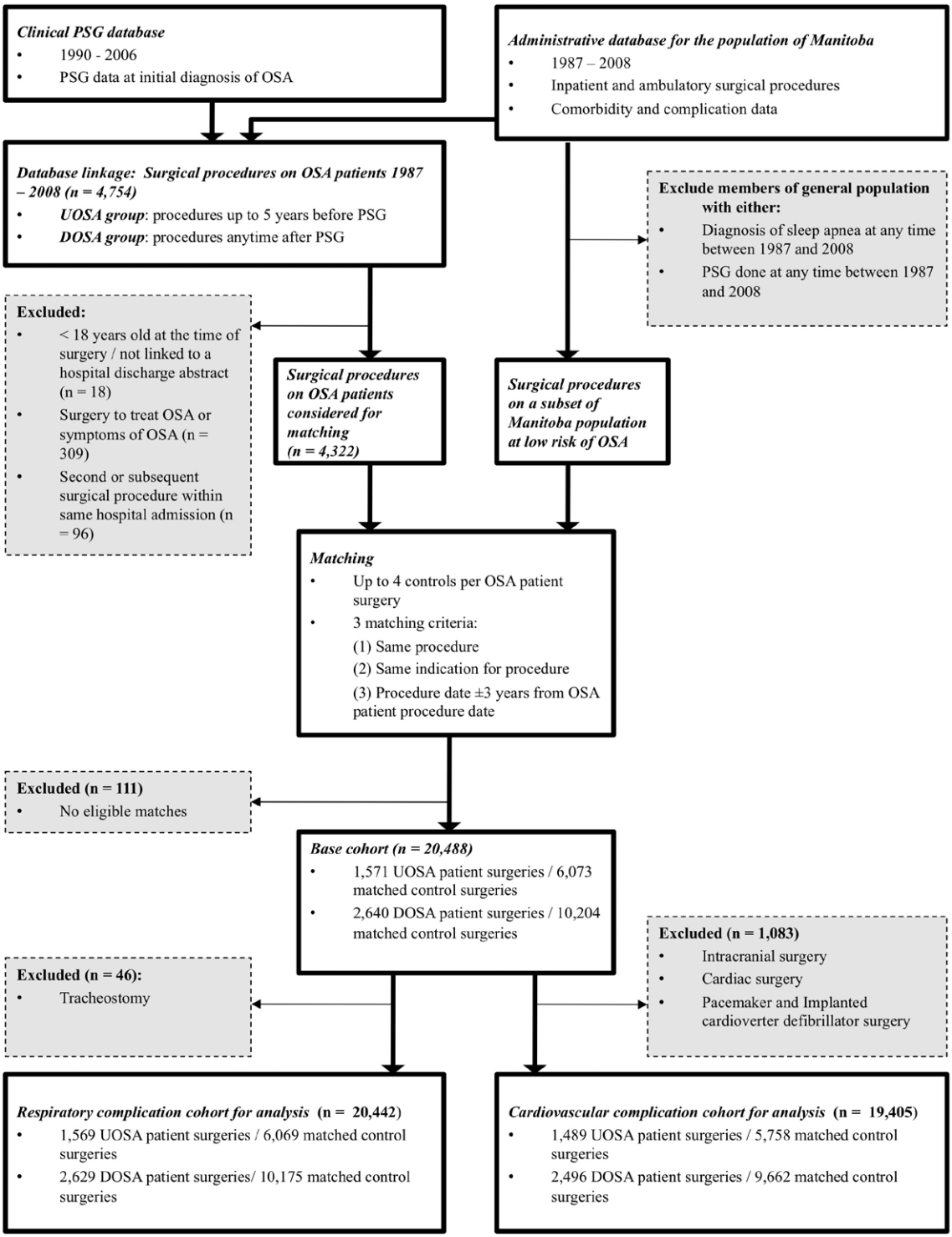

Fig. 1. Study flow diagram summarizing derivation of the respiratory and cardiovascular complication cohorts. DOSA = diagnosed obstructive sleep apnea; OSA = obstructive sleep apnea; PSG = in-lab polysomnography; UOSA = undiagnosed obstructive sleep apnea.

other sleep diagnoses, or by not adding OSA status until the end of modeling, instead of automatically including it at the beginning of modeling. See the text, Supplemental Digital Content 8, http://links.lww.com/ALN/B81, for a detailed report of the sensitivity analyses.

Discussion

This cohort study is the largest published comparison of postoperative outcomes in UOSA and DOSA patients. We found that the risk of cardiovascular complications, primarily cardiac arrest and shock, was increased in UOSA but not DOSA.

Table 1. Baseline Characteristics of the Base Cohort, Stratified into Undiagnosed and Diagnosed Obstructive Sleep Apnea Subgroups

	Undiagnosed Obstructive Sleep Apnea			Diagnosed Obstructive Sleep Apnea		
Variable*	Obstructive Sleep Apnea Patients (n = 1,571)	Matched Controls (n = 6,073)	*P* Value	Obstructive Sleep Apnea Patients (n = 2,640)	Matched Controls (n = 10,204)	*P* Value
Age at time of surgery (yr)	51.6 (12.2)	55.1 (18.4)	<0.001	58.1 (11.8)	58.6 (17.7)	0.09
Male sex	938 (59.7)	2,673 (44.0)	<0.001	1,831 (69.4)	4,906 (48.1)	<0.001
Emergency surgery	221 (14.1)	844 (13.9)	0.69	373 (14.1)	1,376 (13.5)	0.78
Ischemic heart disease	381 (24.3)	1,368 (22.5)	0.12	915 (34.7)	2,753 (27.0)	<0.001
Congestive heart failure	140 (8.9)	569 (9.4)	0.52	480 (18.2)	1,163 (11.4)	<0.001
Previous cerebrovascular accident	99 (6.3)	392 (6.5)	0.81	265 (10.0)	897 (8.8)	0.05
Diabetes mellitus	418 (26.6)	1,043 (17.2)	<0.001	1,019 (38.6)	2,219 (21.8)	<0.001
Renal disease	74 (4.7)	254 (4.2)	0.38	237 (9.0)	583 (5.7)	<0.001
Chronic obstructive pulmonary disease	583 (37.1)	1,576 (26.0)	<0.001	1,178 (44.6)	3,075 (30.1)	<0.001
In an intensive care unit at time of surgery	7 (0.4)	23 (0.4)	0.72	29 (1.1)	69 (0.7)	0.02
Revised cardiac risk index score†						
0	628 (40.0)	2,911 (47.9)		774 (29.3)	4,263 (41.8)	
1	539 (34.3)	1,822 (30.0)	<0.001	798 (30.2)	3,074 (30.1)	<0.001
2	248 (15.8)	779 (12.8)		574 (21.7)	1,574 (15.4)	
3	156 (9.9)	561 (9.2)		494 (18.7)	1,293 (12.7)	
Charlson comorbidity index score‡						
0	1,190 (75.7)	4,715 (77.6)		1,786 (67.7)	7,490 (73.4)	
1–2	280 (17.8)	841 (13.8)	0.005	601 (22.8)	1,592 (15.6)	<0.001
3–4	22 (1.4)	105 (1.7)		83 (3.1)	261 (2.6)	
≥5	15 (1.0)	104 (1.7)		54 (2.0)	221 (2.2)	
Charlson comorbidity index score missing	64 (4.1)	308 (5.1)	0.09	116 (4.4)	640 (6.3)	<0.001
Central sleep apnea§	54 (3.4)			57 (2.2)		0.02
Obesity hypoventilation syndrome§	47 (3.0)			45 (1.7)		0.009

* Variables are expressed as number (percent) except for age at time of surgery, which is expressed as mean (SD). † The revised cardiac risk index score assigns one point each for the presence of diabetes mellitus, ischemic heart disease, congestive heart failure, history of cerebrovascular disease, parenchymal renal disease, and high-risk surgery (in this study defined as major surgery). Increasing scores are associated with increased risk of cardiac complications including myocardial infarction, pulmonary edema, ventricular fibrillation, cardiac arrest, and complete heart block. ‡ The Charlson comorbidity index predicts 1-yr mortality from hospital discharge abstracts by assigning scores for the presence of comorbidities, with higher scores predicting higher mortality. One point each is assigned for the presence of myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, and diabetes mellitus. Two points each are assigned for renal disease, diabetes with end-organ damage, and the presence of any tumor. Three points are assigned for moderate or severe liver disease and six points each for the presence of a metastatic solid tumor or the acquired immune deficiency syndrome. § As diagnosed concurrently with obstructive sleep apnea in the clinical database at the time of polysomnography, *P* values for these rows are for the comparison of the undiagnosed obstructive sleep apnea patients with the diagnosed obstructive sleep apnea patients, not with respective matched controls as in the other rows.

However, the risk of respiratory complications, primarily ARDS and acute respiratory failure, was increased in both groups, without significant difference in risk between them. For both complications, increasing severity of OSA, age, comorbid disease, and the type of surgery were also important risk predictors. These results were robust in multiple sensitivity analyses that addressed the limitations in the data.

Compared with previous work with administrative data on this topic,[8–10] the strengths of this study were the reliable coding of complications separate from comorbidities, the availability of polysomnography data to definitively diagnose OSA and quantify its severity, and longitudinal data for the definition of comorbidities and the identification of complications occurring after hospital discharge. However, some limitations in the data remain, including the definition of the UOSA group, potential contamination of the control group with UOSA patients, the use of ICD codes to define clinical comorbidities and complications, and the inability to measure all relevant variables.

The ideal study design for UOSA postoperative outcome research is elusive, despite its clinical importance.[12] As in another study,[19] the UOSA group in this study was defined by subsequent presentation for definitive diagnosis by polysomnography. This approach introduces two potential biases that both result in *underestimation* of UOSA patient risk. First, patients with UOSA who do not survive postoperative complications will not later present for polysomnography and have the outcome recorded in the study. Second, as the

Table 2. Univariate Analyses of Respiratory and Cardiovascular Complications

Potential Risk Factor	Respiratory Complications		Cardiovascular Complications	
	Odds Ratio (95% Confidence Limits)	*P* Value	Odds Ratio (95% Confidence Limits)	*P* Value
Obstructive sleep apnea				
Overall	1.85 (1.22–2.80)	0.004	1.03 (0.71–1.49)	0.87
Mild	1.42 (0.67–2.98)	0.36	0.71 (0.35–1.42)	0.23
Moderate	1.47 (0.63–3.42)	0.38	0.90 (0.42–1.94)	0.78
Severe	2.34 (1.42–3.87)	<0.001	1.30 (0.81–2.09)	0.55
Undiagnosed	1.79 (0.90–3.56)	0.10	1.56 (0.89–2.74)	0.12
Mild	0.54 (0.06–4.73)	0.58	0.82 (0.22–3.03)	0.77
Moderate	1.21 (0.29–5.07)	0.80	1.21 (0.39–3.74)	0.74
Severe	2.73 (1.28–5.81)	0.01	2.05 (1.06–3.98)	0.03
Diagnosed	1.89 (1.12–3.18)	0.02	0.78 (0.48–1.27)	0.32
Mild	1.81 (0.82–4.01)	0.14	0.66 (0.29–1.48)	0.31
Moderate	1.64 (0.57–4.69)	0.36	0.75 (0.26–2.14)	0.59
Severe	2.07 (1.05–4.09)	0.04	0.89 (0.44–1.79)	0.75
Comorbidities at the time of surgery				
Age (yr)	1.04 (1.03–1.06)	<0.001	1.06 (1.05–1.07)	<0.001
Male sex	1.77 (1.17–2.68)	0.007	1.32 (0.97–1.80)	0.08
Central sleep apnea*			2.56 (0.59–11.10)	0.21
Obesity hypoventilation syndrome*	2.21 (0.30–16.28)	0.44	1.05 (0.09–12.79)	0.97
Ischemic heart disease	3.49 (2.34–5.20)	<0.001	3.86 (2.79–5.33)	<0.001
Congestive heart failure	5.11 (3.39–7.72)	<0.001	5.94 (4.37–8.08)	<0.001
Chronic obstructive pulmonary disease	2.70 (1.81–4.01)	<0.001	1.72 (1.27–2.33)	<0.001
Previous cerebrovascular accident	3.09 (1.92–4.97)	<0.001	3.82 (2.61–5.59)	<0.001
Diabetes mellitus	2.05 (1.36–3.09)	<0.001	2.17 (1.57–2.98)	<0.001
Chronic renal disease	4.34 (2.65–7.10)	<0.001	3.34 (2.17–5.13)	<0.001
In an intensive care unit	19.93 (9.26–42.90)	<0.001	24.70 (11.72–52.06)	<0.001
Charlson comorbidity index score†				
0	1 (Reference)		1 (Reference)	
1–2	5.41 (3.35–8.74)	<0.001	7.95 (5.49–11.53)	<0.001
3–4	21.38 (11.94–38.28)	<0.001	31.12 (19.58–49.44)	<0.001
≥5	17.94 (9.48–33.95)	<0.001	10.77 (5.60–20.71)	<0.001
Revised cardiac risk index score‡				
0	1 (Reference)		1 (Reference)	
1	2.23 (0.93–5.36)	0.07	13.27 (4.92–35.78)	<0.001
2	11.91 (5.54–25.60)	<0.001	29.66 (10.95–80.37)	<0.001
≥3	20.02 (9.42–42.55)	<0.001	84.87 (32.02–224.98)	<0.001
Type of surgery				
Emergency surgery	7.68 (5.14–11.48)	<0.001	5.06 (3.62–7.08)	<0.001
Major surgery	8.53 (5.34–13.62)	<0.001	7.61 (5.30–10.92)	<0.001
Cardiac surgery§	7.46 (4.44–12.55)	<0.001		
Respiratory failure surgery‖	6.97 (4.61–10.54)	<0.001	3.72 (2.65–5.22)	<0.001

* As diagnosed concurrently with obstructive sleep apnea at the time of polysomnogaphy in the clinical database, there were no respiratory complications in patients with central sleep apnea. † The Charlson comorbidity index predicts 1-yr mortality from hospital discharge abstracts by assigning scores for the presence of comorbidities, with higher scores predicting higher mortality. One point each is assigned for the presence of myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, and diabetes mellitus. Two points each are assigned for renal disease, diabetes with end-organ damage and the presence of any tumor. Three points are assigned for moderate or severe liver disease and six points each for the presence of a metastatic solid tumor or the acquired immune deficiency syndrome. ‡ The revised cardiac risk index score assigns one point each for the presence of diabetes mellitus, ischemic heart disease, congestive heart failure, history of cerebrovascular disease, parenchymal renal disease, and high-risk surgery (in this study defined as major surgery). Increasing scores are associated with increased risk of cardiac complications including myocardial infarction, pulmonary edema, ventricular fibrillation, cardiac arrest, and complete heart block. § Cardiac surgery was excluded from the cardiovascular complication outcome. ‖ Surgery associated with a high risk of respiratory failure, as defined by Arozullah *et al.*[20]

natural history of UOSA is likely variable, at the time of some surgeries, UOSA group patients may actually have not had UOSA or it may have been less severe than was subsequently diagnosed. Other studies have instead used validated clinical questionnaires to define UOSA groups,[11,31] but this approach prevents quantification of OSA severity and, due to the limited specificity of these instruments, also leads to misclassification of patients without OSA to a UOSA group.

Identification of controls without OSA despite the high population prevalence of UOSA is another methodological

Table 3. Multivariate Models of Postoperative Respiratory and Cardiovascular Complications

Variable*	Respiratory Complications		Cardiovascular Complications†	
	Odds Ratio (95% Confidence Limits)	*P* Value	Odds Ratio (95% Confidence Limits)	*P* Value
OSA‡				
Overall				
Mild	1.66 (0.76–3.64)	0.21	—	—
Moderate	1.49 (0.63–3.51)	0.36	—	—
Severe	2.69 (1.58–4.57)	<0.001	—	—
Undiagnosed				
Mild	—	—	1.27 (0.28–5.83)	0.76
Moderate	—	—	1.78 (0.53–5.95)	0.35
Severe	—	—	2.70 (1.31–5.53)	0.007
Diagnosed				
Mild	—	—	0.76 (0.29–2.00)	0.58
Moderate	—	—	0.64 (0.22–1.88)	0.42
Severe	—	—	0.79 (0.38–1.65)	0.54
Comorbidities at the time of surgery				
Age (yr)	1.04 (1.02–1.06)	<0.001	1.04 (1.02–1.05)	<0.001
Chronic obstructive pulmonary disease	1.75 (1.15–2.66)	0.009	—	
Diabetes mellitus§	—		0.60 (0.40–0.89)	0.01
In an intensive care unit	2.33 (1.07–5.07)	0.03	5.10 (2.36–11.01)	<0.001
Charlson comorbidity index score‖				
0	1 (Reference)		1 (Reference)	
1–2	1.83 (1.08–3.11)	0.02	3.19 (2.06–4.92)	<0.001
3–4	4.71 (2.35–9.41)	<0.001	8.75 (5.03–15.20)	<0.001
≥5	4.32 (2.12–8.79)	<0.001	3.56 (1.78–7.13)	<0.001
Revised cardiac risk index score#				
0	—		1 (Reference)	
1	—		4.56 (1.52–13.70)	0.007
2	—		6.90 (2.15–22.17)	0.001
≥3	—		11.60 (3.52–38.28)	<0.001
Type of surgery				
Emergency surgery	2.99 (1.92–4.65)	<0.001	1.84 (1.25–2.71)	0.002
Major surgery	3.06 (1.79–5.23)	<0.001	2.09 (1.34–3.26)	0.001
Respiratory failure surgery**	2.36 (1.48–3.76)	<0.001	1.73 (1.18–2.54)	0.005

* Cells with dashes indicate the variable was not included in the multivariate model for that complication. † The reference group for undiagnosed OSA patient surgeries is matched *undiagnosed* OSA controls and the reference group for diagnosed OSA patient surgeries is matched *diagnosed* OSA controls. The estimated reduction in risk for mild DOSA compared with mild UOSA was 0.60 (0.10–3.64), $P = 0.58$. The estimated reduction in risk for moderate DOSA compared with moderate UOSA was 0.36 (0.07–1.78), $P = 0.21$. The estimated reduction in risk for severe DOSA compared with severe UOSA was 0.29 (0.11–0.81), $P = 0.02$. ‡ There was no significant difference in outcomes between UOSA and DOSA patients for respiratory complications. There was a significant difference for cardiovascular complications. See the text for estimates, CIs, and *P* values for these interaction terms. § Diabetes mellitus appears to reduce risk in the cardiovascular complication model but because it is also a factor in both the Charlson comorbidity index and the Revised cardiac risk index, its net effect is to increase risk. ‖ The Charlson comorbidity index predicts 1-yr mortality from hospital discharge abstracts by assigning scores for the presence of comorbidities, with higher scores predicting higher mortality. One point each is assigned for the presence of myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, and diabetes mellitus. Two points each are assigned for renal disease, diabetes with end-organ damage, and the presence of any tumor. Three points are assigned for moderate or severe liver disease and six points each for the presence of a metastatic solid tumor or the acquired immune deficiency syndrome. # The revised cardiac risk index score assigns one point each for the presence of diabetes mellitus, ischemic heart disease, congestive heart failure, history of cerebrovascular disease, parenchymal renal disease, and high-risk surgery (in this study defined as major surgery). Increasing scores are associated with increased risk of cardiac complications including myocardial infarction, pulmonary edema, ventricular fibrillation, cardiac arrest, and complete heart block. ** Surgery associated with a high risk of respiratory failure, as defined by Arozullah *et al*.[20]

DOSA = diagnosed obstructive sleep apnea; OSA = obstructive sleep apnea; UOSA = undiagnosed obstructive sleep apnea.

challenge. Other administrative data studies[8–10] defined controls only by the absence of a sleep apnea diagnosis in the hospital discharge abstract associated with the surgery. To reduce misclassification of UOSA patients as controls, this study excluded controls with either a diagnosis of sleep apnea in a hospital discharge abstract, or a physician claim for polysomnography interpretation, in all 21 yr of available data. Based on the increased risk observed for UOSA patients in this study, any residual misclassification of UOSA patients as controls would result in underestimation of the risks associated with UOSA and DOSA, proportionate to the prevalence of UOSA in the control group. Unfortunately, this prevalence, and consequently, the effectiveness of these measures, cannot be determined in the available data. The use of contemporaneous polysomnography to definitively rule out UOSA in control patients is an alternative

Table 4. Risk of Specific Respiratory and Cardiovascular Complications in Obstructive Sleep Apnea Patients *vs.* Matched Controls

Specific Complications (n)*	Odds Ratio (95% Confidence Limits)	*P* Value
Respiratory complications		
All obstructive sleep apnea *vs.* all matched controls		
Adult respiratory distress syndrome (n = 40)	3.17 (1.68–5.98)	<0.001
Respiratory failure (n = 27)	2.28 (1.04–4.99)	0.04
Bacterial pneumonia (n = 34)	0.66 (0.26–1.67)	0.39
Aspiration pneumonia (n = 14)	1.55 (0.49–4.94)	0.46
Cardiovascular complications		
Undiagnosed obstructive sleep apnea *vs.* matched controls		
Cardiac arrest and shock (n = 34)	2.40 (1.22–4.72)	0.01
Acute coronary syndrome (n = 10)	0.97 (0.20–4.74)	0.97
Atrial fibrillation and flutter (n = S†)	0.97 (0.11–8.67)	0.98
Cerebral vascular accident (n = 12)	0.35 (0.05–2.70)	0.31
Diagnosed obstructive sleep apnea *vs.* matched controls		
Cardiac arrest and shock (n = 40)	0.82 (0.38–1.78)	0.61
Acute coronary syndrome (n = 37)	0.60 (0.24–1.50)	0.27
Atrial fibrillation and flutter (n = 11)	0.86 (0.19–3.99)	0.85
Cerebral vascular accident (n = 19)	0.21 (0.03–1.61)	0.13

* See tables, Supplemental Digital Content 5, http://links.lww.com/ALN/B78, for specific International Classification of Diseases version 9-CM and 10-CA codes used in defining complications. Counts (n) are the total number of all obstructive sleep apnea, undiagnosed obstructive sleep apnea, or diagnosed obstructive sleep apnea patients, and their respective matched controls. Some patients experienced more than one specific complication after a given surgery, so the sum of specific respiratory or cardiovascular complications exceeds the total number of respiratory or cardiovascular complications as reported in the text of the results. † Cell counts ≤5 are suppressed as a privacy requirement of using the administrative database.

method used in only a few small studies.[27,32] However, these controls represent a referral population that may not be representative of the typical surgical patient.

In this study, both comorbidities and complications were defined from ICD codes in administrative data. Compared with clinical data, this method is associated with variable construct validity.[33] To improve construct validity, for both comorbidities and complications, we used code definitions based on work previously validated against hospital chart review, when available. The differences between the cardiovascular and respiratory complication models and the performance of the comorbidities and comorbidity indices in our analyses suggest their construct validity was adequate. Also, the high-mortality rates associated with both complications suggested they were significant clinical events.

Propensity-based analytic methods were inappropriate in this study (see Materials and Methods: Statistical Analysis). As propensity methods can be effective in adjusting for confounding from imbalances in covariates when outcomes are sparse, we cannot exclude that in the models presented, some residual confounding of the effect of OSA from an excess of relevant comorbidities exists. However, in sensitivity analyses where models were built without adding OSA status until the end of modeling, OSA remained a statistically significant predictor of the outcomes, suggesting its effect is primarily independent from the effects of excess comorbidities.

One final important limitation of this study was the inability to account for all important risk modifiers. Although all DOSA patients were prescribed CPAP at diagnosis, it is unknown whether it was used in the perioperative period. Conversely, UOSA patients by definition did not have access to CPAP. In addition, for both UOSA and DOSA patients, caregiver awareness of the UOSA or DOSA diagnosis and the type of anesthetic and analgesic care were unknown. Although we also cannot determine whether intensive postoperative monitoring was used, we analyzed data that predated the local implementation of routine intensive postoperative monitoring,[7] to minimize confounding due to differential use of monitoring between patient groups. Our sensitivity analysis suggests this was accomplished. Finally, body mass index could not be measured and may have contributed to the observed increased risk in OSA patients due to the close association between these two variables.[34] However, it is difficult to assemble a large enough cohort of obese patients without OSA on polysomnography to address this association with adequate adjustment for other potential confounders.[27] For all these reasons, the multivariate analyses presented here cannot be directly translated and applied to clinical practice.

Despite these limitations, several novel results emerged in the analysis. First, a positive association was demonstrated between OSA severity and postoperative risk. Although, on the basis of pathophysiology, this relationship has been incorporated into practice guidelines,[5–7] this study is the first empiric demonstration of such a relationship. Statistical power was likely inadequate in previously published, small, negative studies.[27,32,35] The elucidation of this disease severity trend supports ongoing efforts to target patients with more severe UOSA in preoperative screening.[36,37] Second, the multivariate models of postoperative risk developed in this study are the first of their kind to include OSA. Previous large studies have used propensity analysis to adjust for covariates,[8,27,38] did not present full models,[9,10] or did not adjust for surgical risk.[31] Although

limitations in the data prevent generalization, our models suggest that patient age, comorbidities, and the type of surgery may be as important as the presence of OSA in estimating postoperative risk. Verification of these findings in a clinical study would greatly facilitate equitable allocation of intensive postoperative monitoring to both OSA and non-OSA patients.

Third, with regard to respiratory complications, UOSA patients were not found to be at significantly increased risk compared with DOSA patients. We hypothesized UOSA patients would experience worse outcomes due to a lack of perioperative CPAP and less caregiver awareness of the diagnosis.[1,39] This finding may reflect poor compliance with perioperative CPAP use in our cohort, as has been reported elsewhere.[40,41] It could also reflect a lack of statistical power and underestimation of UOSA risk due to limitations of the data described above. Alternatively, it may represent the presence of an unmeasured confounder that is associated with UOSA and DOSA but not responsive to CPAP or other supportive care associated with DOSA. Increasing body mass index is a risk factor for the development of ARDS, possibly due to increased ventilatory pressures in intubated obese patients,[42] and the postoperative risk of both ARDS and mechanical ventilation was previously found to be increased in OSA patients.[8,10] Without data on perioperative CPAP use or body mass index, these hypotheses cannot be addressed by this study.

We did find that OSA patients overall (UOSA and DOSA) had an approximately two-fold increased risk of respiratory complications, similar to a meta-analysis examining postoperative outcomes in patients diagnosed with OSA by polysomnography or questionnaire.[11] Our results also mirror the risk estimates for respiratory failure, ARDS, and emergent intubation after abdominal and cardiovascular surgery (*i.e.*, major surgery[25] associated with a high risk of respiratory failure[20]) published in two large administrative data studies that defined OSA from ICD codes.[8,9] These studies also found orthopedic and prostate surgeries (*i.e.*, major surgery associated with a low risk of respiratory failure) in OSA patients were associated with much higher risks of a procedure code for emergent intubation. This finding was not replicated in our smaller database of OSA patients defined by polysomnography.

Most importantly, this study demonstrated increased risk of cardiovascular complications in UOSA patients compared with DOSA patients, who had risk comparable to controls. The increased risk was primarily due to shock and cardiac arrest. Unexpected cardiopulmonary arrests in postoperative patients with UOSA or DOSA were prominent in early case reports, and may be a consequence of acute hypoxemia.[1] A meta-analysis has demonstrated a two-fold increased risk of "any cardiac event" in a mix of UOSA and DOSA patients (diagnosed by polysomnography or questionnaire) *versus* controls,[11] but no comparison between UOSA and DOSA outcomes was attempted. Two large administrative database studies[9,10] also found OSA patients to be at increased risk of atrial fibrillation, but it is unclear whether this was a preexisting comorbidity or a postoperative complication. One of these studies[10] also found higher rates of cardiac arrest and cardiogenic shock in OSA patients compared with controls. These studies could not distinguish between UOSA and DOSA patients because OSA was defined by ICD codes. Also, in a nonsurgical setting, increasing apnea hypopnea index in OSA patients was independently associated with sudden cardiac death.[43]

The current study cannot determine whether the reduction in cardiovascular complications in DOSA patients was due to CPAP use or other unmeasured interventions because data on perioperative CPAP use was unavailable. Although it is likely that some DOSA patients did not use CPAP in the perioperative period, the dramatic elimination of risk in DOSA patients across the entire risk gradient of OSA severity suggests that CPAP, through reliable reversal of airway obstruction[34] and hypoxemia,[44] was likely more important than other supportive measures. Ultimately, definitive evaluation of the efficacy of CPAP and other interventions in reducing postoperative risk in UOSA and DOSA patients will require randomized trials that are much larger than those recently reported.[40,45]

In summary, this is the first large study to use polysomnography data in comparing important postoperative outcomes between UOSA and DOSA patients. Of several significant findings, the most important was that diagnosis of UOSA and prescription of CPAP, especially in severe UOSA, was associated with a reduction in postoperative cardiovascular complications, specifically cardiac arrest and shock. Despite the limitations of the data, including an inability to establish causality, these results could help to justify and inform large clinical trials that would definitively determine the efficacy of perioperative CPAP therapy and other interventions in OSA patients undergoing surgery.

Acknowledgments

Charles Burchill, M.Sc., Heather Prior, M.Sc., and Shelley Derksen, M.Sc. (all affiliated with the Manitoba Centre for Health Policy, Winnipeg, Manitoba, Canada), provided assistance with data acquisition. The Manitoba Centre for Health Policy allowed use of data contained in the Population Health Research Data Repository under project No. 2010–017 (HIPC#2010/2011–16). The results and conclusions are those of the authors and no official endorsement by the Manitoba Centre for Health Policy, Manitoba Health, or other data providers is intended or should be inferred. Data used in this study are from the Population Health Research Data Repository housed at the Manitoba Centre for Health Policy, University of Manitoba, Winnipeg, Manitoba, Canada, and were derived from data provided by Manitoba Health.

Continuation of the clinical database was supported in part by National Institutes of Health, Bethesda, Maryland, grant RO1 HL082672-01. The Department of Anesthesia and Department of Community Health Sciences at the University of Manitoba Winnipeg, Manitoba, Canada, funded this project.

Competing Interests

Drs. Mutter, Chateau, Moffatt, Ramsey, and Roos declare no real or potential conflicts of interest. Dr. Kryger is a volunteer board member with the National Sleep Foundation (Arlington, Virginia). He has received research grants from Respironics, Inc. (Murrysville, Pennsylvania), ResMed Corp. (San Diego, California), and Dymedix Diagnostics Inc. (Shoreview, Minnesota) that were not used to fund this research. Since this research has been completed, he has received consultancy fees from Inspire Medical Systems Inc. (Maple Grove, Minnesota), Ventus Medical Inc. (Belmont, California), Dymedix, Medtronic (Minneapolis, Minnesota), and Merck & Co., Inc. (Whitehouse Station, New Jersey).

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