Serious postoperative cardiovascular and respiratory complications in obstructive sleep apnea patients: Matched cohort analysis of clinical and administrative data.

by

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A Thesis submitted to the Faculty of Graduate Studies of
The University of Manitoba
in partial fulfillment of the requirements of the degree of:

Master of Science

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Abstract

Problem: The risk of serious postoperative cardiovascular and respiratory complications (SPCRCs) in patients with obstructive sleep apnea (OSA) is poorly defined.

Methods: In this cohort study (n = 21221), patients with clinically diagnosed OSA were matched to controls without OSA to compare the risk of postoperative death and SPCRCs in an administrative database.

Results: Compared to non-OSA controls, OSA patients were at increased risk of postoperative respiratory failure both before and after diagnosis with OSA. Prior to diagnosis, OSA patients, particularly those with severe OSA, were also at increased risk of cardiac arrest and SPCRCs . After diagnosis with OSA, except for postoperative respiratory failure, the risk of SPCRC's was not different from controls. Also, the risk of postoperative death among OSA patients after diagnosis was not different from controls. Other important predictors of SPCRCs and death included admission in an intensive care unit at the time of surgery, a history of congestive heart failure, a higher Charlson comorbidity index score and the type of surgery.

Conclusions: OSA was associated with an increased risk of SPCRCs, especially prior to diagnosis and in severe disease. This suggests that screening for and treating OSA in preoperative patients would reduce the risk of SPCRCs. However, the significant influences of the type of surgery and the presence of medical comorbidities on the risks of SPCRCs and death, regardless of the presence of OSA, must be considered in planning efficient and equitable interventions to reduce these risks.

Acknowledgements

Dr. Leslie Roos, for his leadership and guidance as thesis advisor

Dr. Meir Kryger, Dr. Michael Moffat and Dr. Clare Ramsey, for their guidance as members of the thesis advisory committee

Dr. Meir Kryger, for his vision in creating the Saint Boniface General Hospital Sleep Disorder Centre Research and Teaching database

Charles Burchill, Heather Prior and Shelley Derksen, for their assistance in preparing the data for analysis

Dr. Dan Chateau, for his assistance with statistical analysis

Theresa Kennedy, for her assistance in navigating the policies and procedures of the Faculty of Graduate Studies and the Department of Community Health Sciences

My family, for their sacrifices and support

My colleagues in the Department of Anesthesia, for accommodating my scheduling requirements over the last five years

The Department of Anesthesia and the Faculty of Medicine at the University of Manitoba, for their financial support through the Donalda Huggins scholarship and an Anesthesia Oversight Committee research grant

The Department of Community Health Sciences at the University of Manitoba and Dr. Evelyn Shapiro, for their financial support through the Evelyn Shapiro award.

The Manitoba Centre for Health Policy for use of data contained in the Population Health Research Data Repository under project #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 and were derived from data provided by *Manitoba Health*.

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Introduction and Literature review

The frequency of serious postoperative cardiovascular and respiratory complications experienced by patients with obstructive sleep apnea (OSA) are defined primarily by small studies with narrow scope and considerable methodological limitations. Despite the existence of clinical guidelines, significant questions remain regarding the optimal perioperative management of these patients. The high incidence of sleep apnea in the general population, and its expected increase in parallel with the incidence of obesity, magnify the importance of answering these questions (Lee et al. 2008). This introduction reviews the epidemiology of OSA, the current postoperative management of OSA patients and the association of OSA with serious postoperative adverse outcomes in the literature. It then concludes by outlining the goals of the present study.

Epidemiology of obstructive sleep apnea

Obstructive sleep apnea (OSA) is a serious disorder whose prevalence may be as high as 10% (Chung, Yuan, and Chung 2008). OSA is characterized by repetitive upper airway collapse and obstruction during sleep (Pashayan, Passannante, and Rock 2005; Patil et al. 2007). Patients experience characteristic nocturnal symptoms such as loud snoring, choking, repetitive periods of apnea (not breathing) and frequent awakenings from sleep, leading to excessive daytime sleepiness (EDS). While EDS interferes with quality of life, repetitive apneic episodes stress the cardiovascular and respiratory systems, leading to long-term morbidity and mortality (Collop 2007; Pashayan, Passannante, and Rock

2005). As obesity and age are important risk factors for developing OSA (Lee et al. 2008), the prevalence of OSA would be expected to increase as the population ages and becomes more obese (Banno, Walld, and Kryger 2005).

Once diagnosed, the preferred treatment for OSA is a continuous positive airway pressure machine (CPAP) (Fleetham et al. 2006; Kushida et al. 2006). CPAP consists of an air pressure generator attached to a facemask that is worn during sleep. Pressurized air holds open the patient's pharynx (throat) to prevent airway collapse and obstruction. CPAP use in OSA patients is associated with reductions in apneic episodes, decreased EDS and reductions in cardiovascular morbidity and mortality (Campos-Rodriguez et al. 2005; Collop 2007; Gay et al. 2006). Other therapies for OSA include oral appliances and surgery (Fleetham et al. 2006; Woodson 2010; Fleisher and Krieger 2007), but these are primarily second and third line treatment options. Surgical interventions for OSA remove excessive airway tissue at various sites including the nose, pharynx, palate or tongue (Fleisher and Krieger 2007; Woodson 2010).

Unfortunately, OSA cannot be diagnosed by symptoms alone, and therefore sleep testing, with either an in-lab polysomnogram (PSG) or a home sleep test (HST), is required (Lee et al. 2008; Fleetham et al. 2006). During the in-lab PSG at least 12 channels of physiologic monitoring assess the patient's breathing, oxygen levels and other physiologic parameters to detect apnea and arousal from sleep. With a HST, typically only 4 channels are monitored. The apnea/ hypopnea index (AHI) is a measure of the number of apneas per hour and is used to assess the severity of the disease. An AHI less

than 5 is considered normal while AHI's between 5 and 15, between 15 and 30 and greater than 30 define mild, moderate and severe OSA respectively (Lee et al. 2008).

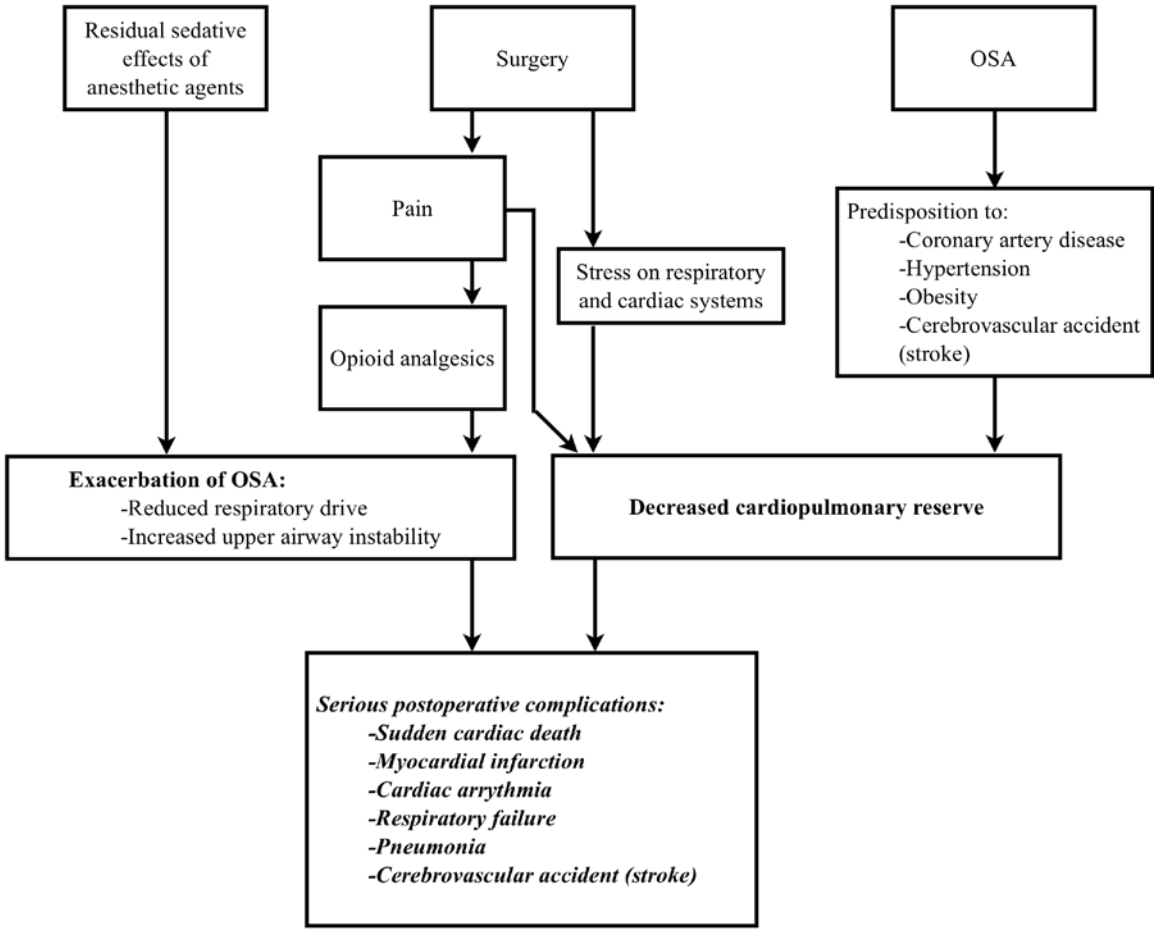
A historical lack of awareness of the symptoms and significance of OSA among patients and the medical community, along with the lack of an expedient diagnostic test, has resulted in a large burden of undiagnosed OSA (UOSA) patients (Lee et al. 2008). In fact, the prevalence of UOSA may exceed that of OSA (Lee et al. 2008; Chung, Yuan, and Chung 2008).

Current postoperative management of obstructive sleep apnea patients

In recent years, concern has arisen among the medical community that the postoperative period could predispose patients with OSA/UOSA to an increased risk of serious cardiovascular and respiratory complications, including death (Chung, Yuan, and Chung 2008; Gross et al. 2006; Kaw et al. 2006b). Two complementary root causes for this increased risk have been proposed: reduced physiologic reserve and exacerbation of airway obstruction (Figure 1). The magnitude of the risk, the relative importance of the two mechanisms and the possible existence of any interaction between them has not yet been elucidated (Chung, Yuan, and Chung 2008). However, based on the available literature and opinion, in November 2005, the American Society of Anesthesiologists (ASA) recommended that many patients with OSA receive extended, intensive, postoperative monitoring in a high dependency unit to prevent serious complications (Gross et al. 2006). This recommendation was part of a larger guideline endorsed by the

American Academy of Sleep Medicine, the American Academy of Otolaryngology- Head and Neck Surgery and the American Academy of Pediatrics. Due to the limited understanding of the mechanisms of postoperative complications in OSA patients, the selection of OSA patients for postoperative monitoring was based on an empirically derived risk stratification tool. This tool considers the severity of the OSA and the type of surgery, anesthetic and postoperative analgesic (pain) medication.

Figure 1. Possible mechanisms of increased postoperative risk in OSA patients



In June 2008, the Winnipeg Regional Health Authority adapted the ASA guideline's recommendations for local use, including the requirement for intensive postoperative monitoring. Compared to standard care, an additional cost is incurred with monitoring because almost all of these patients would otherwise recover in a surgical ward bed or be discharged on the day of surgery with less use of dedicated equipment and nursing resources. No studies have evaluated the efficacy and/or efficiency of intensive postoperative monitoring in preventing severe postoperative adverse outcomes in OSA patients.

Literature review: OSA and severe postoperative adverse outcomes

In this paper, the outcomes of interest were postoperative death and serious postoperative cardiovascular and respiratory complications (SPCRC), defined as cardiac arrest, respiratory failure, cerebrovascular accident (stroke), atrial fibrillation, myocardial infarction or pneumonia. Other severe complications, like hemorrhage or wound infection, can occur after surgery. However, it was the perceived risk of death and SPCRC's that resulted in the recommendation to intensively monitor OSA patients in the postoperative period. Considering the seriousness of the complications hypothesized and the high prevalence of OSA in the general population, clinical studies addressing severe postoperative adverse outcomes associated with OSA are surprisingly few in number, small in size, narrow in scope, and methodologically limited. The largest body of work examined patients undergoing surgical treatment for OSA but a growing body of work has begun to examine other common types of surgery. The findings of these studies and their limitations are reviewed in turn.

Severe adverse outcomes after surgery to treat OSA

Franklin et al. (2009) performed a systematic review of the efficacy and adverse effects of surgery to treat OSA. 45 studies evaluated adverse outcomes. Almost all had less than 200 patients and the reported rate of complications including death, respiratory failure and hemorrhage, was between 0 and 16%, with a trend toward reduced complications in more recent studies.

The largest study in this review included 3,130 patients (Kezirian et al. 2006; Kezirian et al. 2004). In this study 0.2% of patients died within 30 days of surgery and 1.6% experienced at least one of 15 life threatening complications. These complications included cardiovascular and respiratory complications but also hemorrhage and infection. A subsequent nested case control chart review was performed for the 43 patients who experienced complications and 212 matched controls. It was found that increasing body mass index (BMI), apnea/hypopnea index (AHI) and the presence of comorbidities were predictive of adverse outcomes in univariate models. However, these effects were no longer significant in a multivariate model, suggesting a lack of independence between these three variables or a lack of statistical power in the model.

In 2011, Franklin et al. (2011) subsequently published a review of 4876 health records of patients undergoing surgery for OSA in Sweden. No patients died within 30 days of surgery and the rate of severe complications was 2.9%. Complications were more

common in uvulopalatopharyngoplasty than in nasal surgery or uvulopalatoplasty. Most complications were hemorrhage or infection.

Due to two significant limitations in these studies, their results can not help define the role of postoperative monitoring in preventing serious cardiovascular and respiratory complications in other surgical populations. First, the additional risk attributable to the presence of OSA can not be determined because only patients with OSA undergo these surgeries. Second, even the largest studies have not separately measured complication rates for those complications that could potentially benefit from postoperative monitoring. Instead infection and hemorrhage have been combined with SPCRC's.

Severe adverse outcomes after other types of surgery

These studies differ in the types of surgeries considered, the criteria used to diagnose OSA and the outcomes measured. All but two studies had less than 1,000 patients. Many studies only considered specific types of surgery such as total joint replacement (Gupta et al. 2001; Memtsoudis et al. 2011; Parikh et al. 2002), cardiac surgery (Kaw et al. 2006a), bariatric surgery (Weingarten et al. 2011), ambulatory surgery (Gill et al. 2011; Sabers et al. 2003; Stierer et al. 2010), or inpatient surgery (Blake et al. 2008; Chung et al. 2008; Gali et al. 2007; Gali et al. 2009; Memtsoudis et al. 2011). Only 2 studies examined all types of surgery (Bolden et al. 2007; Liao et al. 2009). Generalizing results from one type of surgery to another is of questionable validity given the significant differences in risk posed by various types of surgery (Fleisher 2005).

Several studies (Blake et al. 2008; Bolden et al. 2007; Chung et al. 2008; Gali et al. 2007; Stierer et al. 2010) used clinical scoring systems to presume a diagnosis of OSA. The sensitivity and specificity of these scoring systems are limited (Ramachandran and Josephs 2009), so non-differential misclassification bias can be expected. Two studies (Liao et al. 2009; Memtsoudis et al. 2011) relied on coding of sleep apnea diagnosis in hospital discharge abstracts. No studies have validated the sensitivity and specificity of such an approach nor confirmed whether such coding is representative of the distribution of OSA severity in the population. Seven studies used PSG results to diagnose patients with OSA (Bolden et al. 2007; Gill et al. 2011; Gupta et al. 2001; Kaw et al. 2006a; Parikh et al. 2002; Sabers et al. 2003; Weingarten et al. 2011). Study methods varied with regard to ensuring control groups did not contain patients with OSA, undiagnosed OSA or other types of sleep apnea.

Many studies used surrogates for serious postoperative cardiac and respiratory complications (SPCRCs). Four studies used oxygen desaturation index (ODI) as the outcome of interest and found that patients with OSA experience desaturations more frequently than those without OSA (Blake et al. 2008; Chung et al. 2008; Gali et al. 2007), and that the use of opioids increases the ODI (Bolden et al. 2007). Unfortunately, the relationship between postoperative ODI and severe postoperative adverse outcomes has not been studied. Two other studies (Hwang et al. 2008; Liao et al. 2009) measured other surrogate outcomes such as atelectasis and oxygen desaturations, whose relationship with severe postoperative adverse outcomes is also not clear.

Among the studies that did measure SPCRCs, low event rates and small sample sizes precluded meaningful analysis in all but 3 cases. Increased rates of respiratory events were noted in patients with a high clinical likelihood of having OSA versus those with a lower clinical likelihood (Gali et al. 2009). Gupta et al. (2001) also noted increased postoperative cardiovascular and respiratory complications (defined as requiring transfer to an intensive care unit) in joint replacement patients with PSG proven OSA compared to controls. This study is also notable for being the only study to consider patients with UOSA. It found trends towards increased complications in patients having surgery prior to diagnosis compared to afterward.

One final study is notable for its large size and results (Memtsoudis et al. 2011). This administrative database study examined the hospital discharge abstracts of 234,152 patients. Rates of aspiration pneumonia, acute respiratory distress syndrome (a cause of respiratory failure) and intubation/ mechanical ventilation (a treatment of respiratory failure) were higher in patients with a discharge abstract diagnosis of OSA compared to those without, even after adjustment for age and comorbidities. Unfortunately, death and serious cardiac complications were not measured. Also, only two types of surgery were considered, lower extremity joint replacement and open abdominal surgery.

In summary, no large study has compared SPCRC's for a wide range of surgeries between patients with PSG proven OSA/ UOSA and a group of controls known to be free

of UOSA. The results from the available studies suggest that patients with OSA are at increased risk of respiratory and cardiac events in the postoperative period and that patients with UOSA may be at increased risk compared to patients with OSA. However, these studies often did not use patients with PSG proven OSA, rarely studied patients with UOSA and did not take steps to ensure control patients did not have UOSA. Patients with UOSA are thought to be at particularly high postoperative risk (Chung, Yuan, and Chung 2008; Gross et al. 2006), so their presence in a non-OSA control group could falsely increase control group risk.

Goals of the present study

To improve clinical management and equitably allocate resources, both clinicians and administrators need a better understanding of OSA patients' risk of severe postoperative adverse outcomes. Using a clinical database of OSA patients diagnosed with in-lab comprehensive PSG and an extensive population database registry, this study has avoided many of the limitations of previous studies and determined the effect of OSA relative to other surgical and patient related factors in causing SPCRC's. Specifically, the following research questions have been addressed:

Among patients with OSA and UOSA, how often do severe postoperative adverse outcomes attributable to OSA occur compared to patients without OSA or UOSA?

What is the relationship between the severity of OSA/ UOSA as measured by AHI and the risk of SPCRC's?

What role do patient comorbidities and the type of surgery play in determining the risk of SPCRC's in patients with OSA/UOSA compared to those without?

Methods

Data sources, Study design and Ethical considerations

This population based cohort study used previously collected data to compare serious postoperative complications between a cohort of patients with OSA diagnosed by comprehensive in-lab PSG and a matched sample from the general population, screened to be free of OSA. Outcomes were examined for surgeries occurring both before and after the diagnosis of OSA. Two data sources that have been previously linked for clinical research (Albarrak et al. 2005; Banno et al. 2009; Ronald et al. 1999) were used: the Saint Boniface General Hospital Sleep Disorder Centre Research and Teaching database (SBGH database), and health administrative data from the population health research data repository housed at the Manitoba Centre for Health Policy (MCHP data repository) (Manitoba Centre for Health Policy 2009b). The study was carried out with the approval of the University of Manitoba's Bannatyne Campus Health Research Ethics Board, the Government of Manitoba's Health Information Privacy Committee (HIPC) and the MCHP. Data were handled using procedures designed by MCHP and approved by HIPC to protect the privacy of Manitobans (Manitoba Centre for Health Policy 2012). HIPC's approval to use the data is not intended to, nor should it be inferred to represent official Government of Manitoba endorsement of the results and conclusions of the authors.

The SBGH database is a clinical research database that contains prospectively collected demographic, sleep diagnosis and PSG data for more than 4000 patients referred for sleep medicine assessment and in-lab PSG from 1990 to 2006. The St. Boniface General Hospital sleep laboratory was one of only three government funded sleep laboratories in the province of Manitoba during this time. The database includes only those patients referred to this laboratory that had a PSG and gave informed consent for participation in the database. For this study, only patients who had a sleep diagnosis of OSA were of interest.

The MCHP data repository contains health administrative data collected by Manitoba Health, the provincial agency wholly responsible for funding and administering Manitoba's universal health care insurance program. Under this provincial health insurance program, almost all of Manitoba's 1.1 million inhabitants have access to free physician visits, hospitalization, diagnostic tests and procedures. Only a small number of federal citizens, including members of the Canadian Armed Forces, inmates in federal penitentiaries and the Royal Canadian Mounted Police, do not participate in the provincial health insurance program. Prior to transfer of administrative data to MCHP, Manitoba Health removes identifying data. However, a scrambled personal health identification number (PHIN) is retained as an anonymised unique identifier for each citizen across individual databases.

Three databases from within the MCHP data repository were used in this study. The registry database was used to identify the date of termination of coverage due to death. The medical services database provided physician tariffs used to identify anesthetics provided for surgical and diagnostic procedures. Additionally, 3-digit International Classification of Diseases (ICD) diagnoses (version ICD9-CM), submitted with each physician visit were used to identify patient comorbidities and the indication for surgery. Finally, the hospital discharge abstract database was used to identify preexisting comorbidities, medical complications of surgical procedures and admissions to intensive care units. Diagnoses and procedure codes in this database are in ICD9-CM until March 31, 2004. After this date they are coded in ICD10-CA. All digits/ fields are used in coding the hospital discharge abstracts. In order to include surgeries for up to 5 years before the earliest SBGH database entries, administrative data were obtained for the period from April 1, 1985, to March 31, 2008 (the study period). At the time the data were obtained, these were the most recent data available from MCHP.

Identification of surgical procedures within administrative data using anesthesia tariffs

Key to the use of administrative data in studying postoperative outcomes is a reliable method for the identification of a surgical procedure. Several methods have previously been described at MCHP (De Coster et al. 2007; Roos, Sharp, and Wajda 1989; Roos et al. 1997) and elsewhere (Franklin et al. 2011; Kezirian et al. 2004). These methods have used either surgical tariffs submitted for billing purposes or procedure codes recorded on hospital discharge abstracts. In all instances they were applied to only a few specific types of surgery that were of interest. As described in the following paragraphs, the

broad cross section of surgical procedures of interest in the current study made these established methods less desirable than the use of anesthesia tariffs.

The Manitoba fee schedule of surgical tariffs includes instances where multiple tariffs are submitted for different aspects of the same operation (Manitoba Health and Healthy Living 2009). For example, a surgeon may submit tariffs for both a diagnostic laparoscopy and the lysis of adhesions in the abdomen, even though both procedures were part of the same operation. This creates a problem of multiplicity where the event of interest (the operation) is represented more than once in the data. Unfortunately, there is no simple, systematic way to sort these tariffs by relevance so that only the most relevant part of the procedure is represented as the operation. This makes surgical tariffs undesirable for use when a large number of surgeries are of interest. Hospital discharge abstract procedure codes also suffer from the same problem of multiplicity and also cannot be easily sorted by relevance. Additionally, these procedure codes document relatively minor procedures that are not of interest in this study (i.e. nasogastric tube insertion, intravenous therapy).

Conversely, the use of anesthesia tariffs resolves the issues of multiplicity and relevance with few limitations compared to the other methods. In Manitoba, anesthesia is principally remunerated by submission of a tariff for the operation performed. Even when more than one surgical tariff is submitted, the anesthesiologist can only submit one tariff. As remuneration is scaled to case complexity, the anesthesiologist would be expected to submit the tariff for the most complex aspect of the operation. For the

purposes of this study on postoperative outcomes, the most complex aspect of the surgery is the most relevant for controlling and comparing risk between surgeries. Throughout the study period, remuneration for adult anesthesia in Manitoba was fee for service based. Thus, anesthesia tariffs would be expected to be an almost complete record of surgical procedures undergone by the population because remuneration was dependent on complete and accurate submission of claims. They would also include not only surgical procedures but also those diagnostic procedures that require significant anesthesia and the presence of an anesthesiologist.

The use of anesthesia tariffs to define the occurrence of an anesthetic for a surgical or diagnostic procedure does present several limitations. First is the exclusion of procedures where anesthetics are used but anesthesiologists are not present. In Manitoba this would only be some minor surgical procedures including most therapeutic abortions and endoscopy procedures. Second, anesthesia tariffs (like surgical tariffs) do not include the same detail regarding procedural techniques as do hospital discharge abstract procedure codes. Most notably it is not possible to distinguish laparoscopic and arthroscopic techniques from open procedures. The matching strategy in this study attempted to control for differences in surgical techniques over time and due to diagnosis. However, it is possible that some variation in surgical technique associated with significant differences in postoperative risk is related to whether or not a patient has OSA. Consider laparoscopic cholecystectomy (gall bladder removal), which would be expected to be technically difficult in obese patients. As OSA patients tend to be obese, they may be more likely to have open incision cholecystectomies, which are higher risk than

laparoscopic cholecystectomies. However, the anesthesia tariff would only note cholecystectomy and not the technique. Finally, anesthetic tariffs cannot capture surgery performed in another province or cosmetic surgeries not covered under the provincial health care plan. (None of the methods described could capture the latter.) However, it was felt that these exposures were neither significantly numerous nor different enough from the captured surgeries/ procedures to bias the results.

Definition of exposed population: Obstructive sleep apnea group

Up to four sleep disorder diagnoses were assigned to each patient in the SBGH database by the respirologist interpreting the PSG. Patients diagnosed with OSA or upper airway resistance syndrome were considered to have OSA. Patients with OSA and central sleep apnea, Cheyne Stokes respiration or sleep hypoventilation were considered to have a co-diagnosis of central sleep apnea (CSA). Patients with OSA and obesity hypoventilation syndrome (OHS) were considered to have a co-diagnosis of OHS.

Both the period before and after the PSG was examined because of the high prevalence of UOSA and the keen interest in postoperative outcomes for these patients (Gross et al. 2006). After the patient's PSG, all surgeries were considered for analysis regardless of the length of time from the PSG. Before the PSG, it was assumed that OSA patients had UOSA for a period of 5 years prior to their PSG and all surgeries in this period were considered for analysis. This 5 year interval is within the range used by others for similar work (Banno et al. 2009; Gupta et al. 2001; Ronald et al. 1999). OSA patients also had to

be at least 18 years of age at the time of surgery for a surgery to be considered in the analysis.

For surgeries occurring in patients prior to their PSG, the outcome of death could not be studied because the definition of the exposure (OSA) by PSG was contingent on survival after the event of interest (surgery). With the other outcomes, the serious postoperative cardiovascular and respiratory complications (SPCRCs), there was also potential for 2 competing types of selection bias. First, patients with SPCRC outcomes may have been more likely to be referred for PSG than those patients with UOSA who did not have SPCRCs (Figure 2). This would be due to closer postoperative observation and lead to inflated estimates of risk in UOSA patients. Second, patients with UOSA who experienced postoperative complications of interest and died could not be part of the cohort and the analysis (Figure 3). This would lead to underestimation of risk in UOSA patients.

Figure 2. Undiagnosed OSA patients experiencing serious postoperative cardiovascular and respiratory complications may have been more likely to eventually enter the cohort.
(U)OSA = (undiagnosed) obstructive sleep apnea. SPCRC = serious postoperative cardiovascular or respiratory complication. PSG = polysomnogram (sleep study).

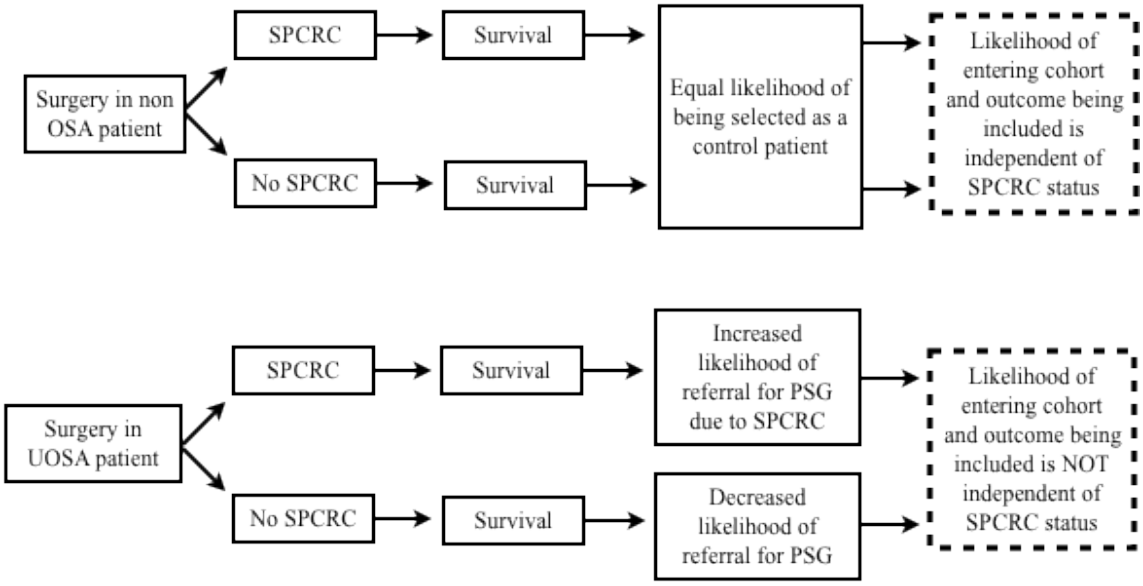
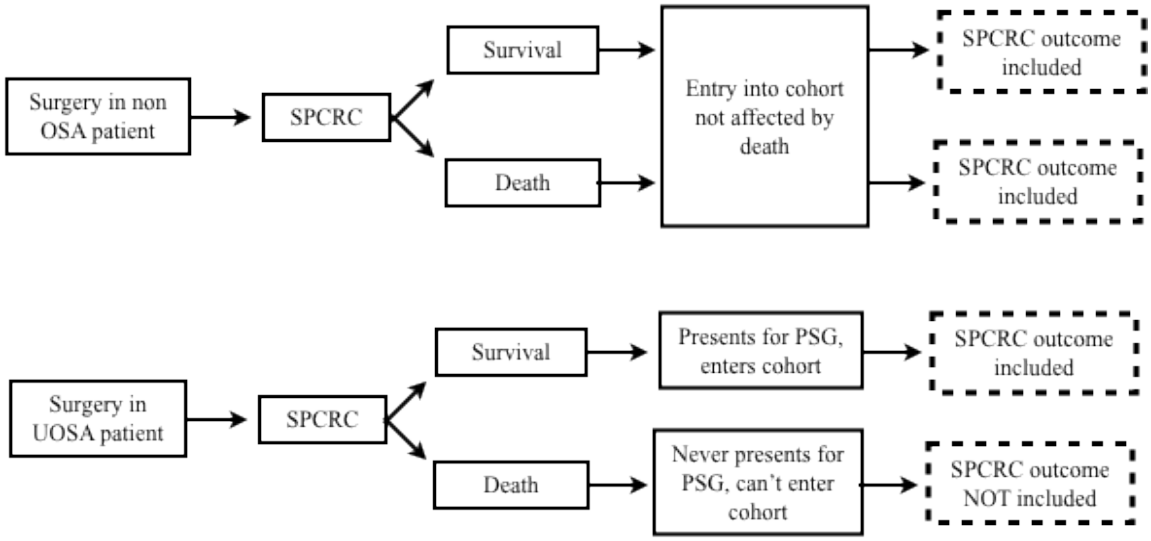


Figure 3. Serious postoperative cardiovascular and respiratory complications resulting in death would not be included as outcomes in undiagnosed OSA patients.
(U)OSA = (undiagnosed) obstructive sleep apnea. SPCRC = serious postoperative cardiovascular or respiratory complication. PSG = polysomnogram (sleep study).



Definition of Unexposed population: Matched control group

Surgeries for patients from the general population without evidence of OSA were matched to the OSA patient surgeries. Potential control patients were identified within the medical services database from all anesthetic tariffs submitted for surgical procedures performed within the study period (1 April 1985 to 31 March 2006). Potential controls had to be Manitoba residents and at least 18 years of age at the time of surgery. All surgeries for a given control patient within the years of available data were considered for matching but each control patient was only used once to maximize the independence between observations in the control group. As detailed in the paragraphs below, patients with OSA or at high risk of having sleep apnea were excluded from the pool of potential matches. Then up to 4 non OSA control patient surgeries for each OSA patient surgery were matched by surgical tariff, diagnosis and approximate date of surgery.

Exclusion of patients with OSA or at high risk of undiagnosed obstructive sleep apnea

Epidemiologic studies have asserted that there is a high prevalence of UOSA in the general population (Lee et al. 2008). In the perioperative literature, these patients are thought to be at increased risk of postoperative complications, perhaps even more so than patients with diagnosed and treated OSA (Gross et al. 2006). Thus, to minimize a differential misclassification bias when attempting to compare patients with OSA to a non-OSA control group, contamination of the control group with patients who have UOSA had to be minimized.

In this study four methods were used to avoid selecting patients at high risk for UOSA, OSA or other types of sleep apnea as potential controls. First, those surgeries that are used to treat OSA or to relieve symptoms associated with OSA (Fleisher and Krieger 2007; Woodson 2010) (Table 1), were excluded from matching and analysis. In addition, potential controls were excluded from matching if they were in the SBGH database or had ever had a tariff submitted for sleep study interpretation in the medical services database (Table 2). Finally, potential controls that had been given a diagnosis of sleep apnea in the available hospital discharge abstract data were also excluded (Table 3). Only hospital discharge abstract database diagnoses could be used, as the medical service database diagnoses were not specific enough because they are limited to 3 digits.

The occurrence of any of these tariffs or diagnoses at least once at any time in the study period eliminated that patient from the list of potential controls for the entire study period. This method does not exclude patients with UOSA who never seek treatment. However, given the long period of observation for which data were available, these patients would be expected to have short lived or mild chronic disease to have never presented for diagnosis and treatment. This method also fails to capture those patients who chose to pay privately for diagnosis and treatment of their OSA and for whom a diagnosis of sleep apnea was not recorded in the hospital discharge abstract.

Table 1. OSA patient surgeries excluded from matching to non-OSA controls.

Tariff	Description
583	Lefort II maxillary osteotomy and advancement
616	Mandibular osteoplasty
1928	Nasal septoplasty
1929	Nasal septoplasty with repair of septal perforation
1935	Turbinectomy
1949	Rhinoplasty with septoplasty
1966	Nasal turbinate cautery
2021	Septoplasty and ethmoidectomy, unilateral
2022	Septoplasty and ethmoidectomy bilateral
2023	Septoplasty and polypectomy, unilateral
2024	Septoplasty and polypectomy, bilateral
2026	Septoplasty and polypectomy and ethmoidectomy, bilateral
2028	Septoplasty, polypectomy, ethmoidectomy, antrostomy, bilateral
2883	Uvulopalatopharyngoplasty
2885	Palate lesion resection
2887	Uvulectomy
2898	Pharyngoplasty
2899	Palate resection unlisted or unusually complicated
2992	Tonsillectomy, < 13y.o.
2993	Tonsillectomy, adult
2994	Hemorrhage post-tonsillectomy
2996	Adenoidectomy without tonsillectomy
3011	Pharyngoplasty

Table 2. Medical service tariffs used to exclude members of the general population at high risk of sleep apnea from the pool of potential matches.
(Manitoba Health and Healthy Living 2009)

Tariff	Description
77921	Neurophysiology screening sleep disorder study: interpretation
77922	Neurophysiology screening sleep disorder: technical
8872	Diagnostic polysomnography
8873	Therapeutic polysomnography
8874	Multiple sleep latency testing

Table 3. ICD codes used to exclude patients at high risk of sleep apnea from the pool of potential matches
(Canadian Institute for Health Information 2009; ICD9.chrisendres.com)

Code	Description
ICD9-CM	
327.2	Organic sleep apnea
327.2	Organic sleep apnea, unspecified
327.21	Primary central sleep apnea
327.22	High altitude periodic breathing
327.23	Obstructive sleep apnea (adult) (pediatric)
327.24	Idiopathic sleep related nonobstructive alveolar hypoventilation
327.25	Congenital central alveolar hypoventilation syndrome
327.26	Sleep related hypoventilation/ hypoxemia in conditions classifiable elsewhere
327.27	Central sleep apnea in conditions classified elsewhere
327.29	Other organic sleep apnea
780.51	Insomnia with sleep apnea, unspecified
780.53	Hypersomnia, unspecified
780.57	Unspecified sleep apnea
786.04	Cheyne-Stokes respiration
ICD10-CA	
G47.3	Sleep apnoea
G47.30	Sleep apnoea, obstructed
G47.31	Sleep apnoea, central
G47.38	Other sleep apnoea
E66.2	Extreme obesity with alveolar hypoventilation
R06.3	Periodic breathing

Matching strategy

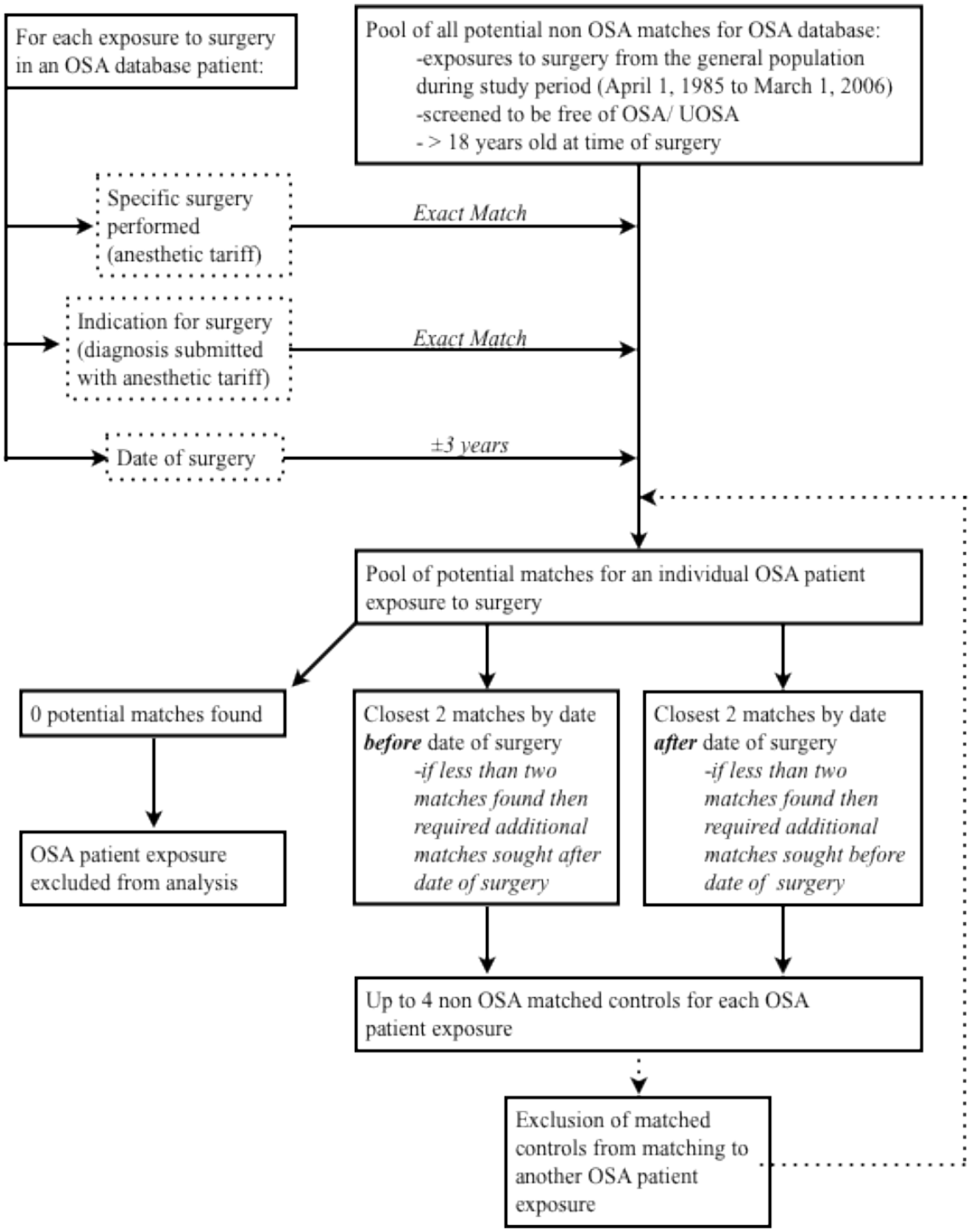
After applying the exclusions in Tables 1, 2 and 3, the remaining potential control patient surgeries were matched to OSA patient surgeries with the same anesthetic tariff and diagnosis submitted with that tariff, within +/- 3 years of the OSA patient's date of surgery. This effectively matched OSA patient surgeries with control surgeries by type of surgery, indication for surgery and approximate date. The latter was necessary for two reasons:

(1) an anticipated skewed distribution of OSA patient surgery dates over the years of available data and

(2) the potential for changes in techniques or indications for specific surgeries that might result in significant changes in outcomes over the course of the study.

It was anticipated that surgeries in OSA patients would be more common in the later years of the available data due to the growth of the SBGH database with time and the aging of the patients in it. Thus, random sampling of matching surgeries from all the years of available data would lead to more surgeries in non-OSA patients being selected from earlier years of available data. Further, as these changes would be difficult to anticipate and model at the analysis stage, they were best managed by matching (Rothman, Greenland, and Lash 2008b). When more than 4 potential matches existed for one surgery, only 4 potential matches were chosen and differences in the date of surgery between the OSA patient and the matches were minimized. The matching process is summarized schematically in Figure 4.

Figure 4. The procedure for matching OSA patient exposures to surgery to non-OSA control exposures to surgery from the general population.



Matching by anesthetic tariff, representing the specific surgery performed, was also done to account for variation that would otherwise be difficult to model in the analysis. Severe

postoperative complications would be expected to vary widely by type and incidence across different types of surgery. The specific types of surgery experienced by OSA patients was anticipated to differ from the general population due to the comorbidities associated with SA, particularly the sequelae of obesity that lead to surgery: cardiovascular disease and arthritis. Again, matching controlled for this anticipated imbalance between OSA and non-OSA patients that would otherwise be difficult to model at the analysis stage (Rothman, Greenland, and Lash 2008b).

The final matched variable was the 3-digit ICD9-CM diagnosis submitted with the anesthesia tariff for the particular surgery, effectively the indication for the surgery. Outcomes from surgical procedures vary by their indication. For example, a small bowel resection for intestinal ischemia (lack of blood supply) would be expected to have worse outcomes than a small bowel resection due to adhesions (scarring of the bowel). The significance of the effect of diagnosis for specific surgeries was unknown. However, the use of this third matching variable was justified by the difficulty in modeling such effects in an analysis. As noted in the previous section (Identification of surgical procedures within administrative data using anesthesia tariffs), matching by diagnosis was also expected to partially compensate for the inability of anesthesia tariffs to distinguish between laparoscopic and open procedures. Thus, where the diagnosis (cholecystitis, gall bladder infection vs. cholelithiasis, uninfected gall bladder with stones) would influence whether an open or laparoscopic procedure was done, matching on the submitted tariff would partially account for these differences. In preliminary work with this matching

strategy on this his data we found that 37% of OSA patient exposures matched to non-OSA exposures within 2 weeks of surgery and 96% matched within 1 year.

Data processing

To assemble a matched cohort of surgeries for OSA patients and non-OSA controls the data were processed in two phases. In the first phase records of surgeries for OSA patients were developed. In the second phase, matched controls were obtained and their records developed.

First phase

Patients with a diagnosis of OSA from the SBGH database were linked to the administrative databases and all anesthetics for surgical or diagnostic procedures that each linked patient underwent in the period 5 years before their PSG until March 31 2008 were identified. To do this, all anesthesia tariffs submitted during the study period for the linked patients were obtained. Those associated with modifiers or anesthetic procedures were removed and only those associated with the specific surgical or diagnostic procedure performed were retained. Duplicate records due to a change in the anesthesiologist providing care, usually during a longer surgery, were removed. When patients had more than one operation in one calendar day the second operation was removed from the data and the first operation flagged to indicate it was associated with a second operation on the same calendar day. Such reoperations were usually performed for postoperative bleeding, wound dehiscence or critical illness. This list of anesthesia

tariffs formed the backbone around which a detailed record of information about each surgery and its outcome were assembled with information from other databases.

Separately, other databases were prepared to supply information about predictors and outcomes for each surgery. Death dates were taken from the registry database while the sleep lab database provided information about the patient's sleep diagnoses and in-lab PSG. The medical service database provided information about comorbidities while the hospital discharge abstract database provided further information about comorbidities and outcomes other than death. Duplicate hospital discharge abstracts were removed.

Ultimately, each database was merged to the anesthetic tariffs by the anonymised identifier or, in the case of the hospital discharge abstract database by the anonymised identifier and date of surgical procedure. In the latter case, merges were attempted for all procedure dates and for the dates of up to the first 31 days during the admission. Less than 10 percent of all anesthetic tariffs for OSA patients remained unmerged at this point and these were treated differently based on the type of surgery. Unmerged major surgeries (surgeries where overnight hospital admission would be expected regardless of whether the patient had OSA or not) were not considered for further analysis. These were the minority of unmatched tariffs. Unmerged minor surgeries (surgeries where same day discharge is feasible in a patient without OSA) were the majority of unmatched tariffs. These were presumed to represent surgery performed at day surgery centers that provide only ambulatory care and surgical services where same day discharge is expected. Their discharge abstracts do not appear in the available data but the medical

services provided by anesthesiologists in these facilities are available. Despite the absence of discharge abstracts from these facilities in the available data, information about preexisting comorbidities and postoperative complications was available by examining medical services claims and hospital discharge abstracts prior and subsequent to the minor surgery in question (see following section on follow up). As these centers can not admit patients overnight, the occurrence of serious complications immediately after surgery would require transfer and admission to a hospital, which would result in completion of a hospital discharge abstract.

Rarely, an anesthesia tariff would merge to two hospital discharge abstracts, usually due to sequential admissions to two hospitals due to an initial assessment and urgent transfer to another facility for emergency surgery. In these cases the hospital discharge abstract with the procedure code for the surgery was kept as the appropriate record. Occasionally, both hospital discharge abstracts contained the procedure code, usually due to a single day visit to another facility for a procedure in the middle of a longer admission at the primary facility. In these cases, the longer admission was kept as the most informative admission. The resulting final list of anesthesia tariffs successfully merged to a hospital discharge abstract or assigned as minor surgery performed at a day surgery centre formed the basis for matching non-OSA controls in the second phase of data processing.

Second phase

From the final list of anesthesia tariffs representing OSA patient surgeries, matched non-OSA controls were sought from the general population. This was carried out as described in the previous section: Definition of unexposed population: matched control group. The matched control patient database of anesthesia tariffs contained the same information as the anesthesia tariffs for the OSA patients' surgeries but it also contained the OSA patient's anonymised unique identifier and the date of service. This allowed the control patient's surgery to continue to be linked to the matching OSA patient's surgery during the analysis. The non-OSA patient data were then processed identically to the OSA patient data, except that there were no data from the sleep lab database to merge. The frequency with which matched control patients had minor surgeries at day surgery centers was slightly higher than the number of OSA patients (6% vs 5%). In a final step, the OSA patient and non-OSA patient surgeries were combined to provide a complete matched cohort.

Predictor variables

The predictor variables that could be operationalized within the available data were selected from those that have been previously hypothesized or demonstrated to predict respiratory and/ or cardiovascular morbidity and mortality after surgery. Predictor variables included common medical comorbidities, comorbidity indices, type of surgery, OSA severity and other factors.

Medical comorbidities

Six medical comorbidities were operationalized from International Classification of Diseases (ICD) codes in hospital discharge abstracts and medical services diagnosis coding. The six comorbidities were ischemic heart disease (IHD), cerebrovascular accident (CVA), chronic renal failure (CRF), diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD) and congestive heart failure (CHF). These comorbidities were chosen because they are common, they have been associated with serious postoperative cardiovascular and respiratory complications in other studies (Arozullah et al. 2000; Lee et al. 1999) and have been operationalized from administrative data previously.

The ICD codes used to define individual comorbidities in this study are shown in Table 4. International Classification of Diseases version 9-CM and 10-CA codes used in assigning comorbidities.. When choosing administrative data definitions for comorbidities in this study, ICD code groupings developed and validated at MCHP or elsewhere for general populations were reviewed. These were then adapted to better represent the perioperative population and the clinical risk factors of interest as defined in the perioperative literature (Arozullah et al. 2000; Lee et al. 1999). When literature sources for ICD10 codes could not be found, ICD9-CM codes were cross-referenced similar to what has been done elsewhere (Quan et al. 2005).

Table 4. International Classification of Diseases version 9-CM and 10-CA codes used in assigning comorbidities.
The designation .x or .xx indicates that the three-digit root and all valid four or five digit combinations were included.

Comorbidity and Subcategories	*Coding Reference(s)*	*Codes*
Ischemic heart disease	(Boersma et al. 2005; Lix et al. 2006)	410.xx, 411.xx, 412.xx, 413.xx, 414.xx, I20.xx, I21.xx, I22.xx, I24.xx, I25.xx
Cerebrovascular accident	(Lix et al. 2006; Quan et al. 2005)	
Intracranial hemorrhage		430, 431, 432.x, I60.x, I61.x, I62.x
Cerebral Infarction		433.x1, 434.x1, 997.02, I63.x, I64
Transient or chronic cerebral ischemia		435.x, 437.1, V12.54, 997.01, I67.8
Late effects of cerebrovascular disease		438.x, I69.x
Renal disease	(Kern et al. 2006; So, Evans, and Quan 2006; van Walraven et al. 2010)	
Hypertensive renal disease		403.x, 404.x, I12
Diabetes mellitus with renal disease		249.4, 250.4, E10.2x, E11.2x, E13.2x, E14.2x
Nephritis, nephrotic syndrome, nephrosis		580.x, 581.x, 582.x, 583.x, 585.x, 586.x, 587.x, N00.x, N01.x, N03.x, N04.x, N05.x, N07.x, N08.x, N14.x, N16.x, N18.x, N19
Diabetes mellitus	(Lix et al. 2006; Quan et al. 2005)	249.xx, 250.xx, E10.xx, E11.xx, E13.xx, E14.xx
Chronic obstructive pulmonary disease	(Cooke et al. 2011; Lacasse et al. 2005)	
Chronic bronchitis		491.xx, J41.x, J42
Emphysema		492.x, J43.x
Asthma, other chronic airway obstruction		493.xx, 496, J44.x, J45.xx
Congestive heart failure	(Quach, Blais, and Quan 2010)	
Heart failure		428.xx, I50.x
With hypertensive heart disease		402.01, 402.11, 402.91
With hypertensive heart and kidney disease		404.01, 404.11, 404.91, 404.03, 404.13, 404.93

All codes within the comorbidity and its subcategories were considered as equally valid.

The first occurrence of any relevant code in either a medical service claim or hospital

discharge abstract was assigned as the date of first diagnosis of that comorbidity. This inclusive approach has been shown to improve sensitivity with minimal impact on specificity (Lix et al. 2006). On the date of diagnosis, the patient's status was permanently changed to having the comorbidity. When the diagnosis arose from a medical services claim the date of diagnosis was assigned as the date the service was provided. When the diagnosis arose within a hospital admission the date of diagnosis was assigned based on the diagnosis type assigned. If the diagnosis type was a complication, the diagnosis date was assigned to the discharge date. If the diagnosis type represented a transfer diagnosis, the diagnosis date was assigned to transfer of service date. If the diagnosis type represented a preexisting condition, the diagnosis date was assigned to the day before admission. As most surgery occurs on the date of admission, this assignment ensured that patients' preexisting comorbidities were correctly assigned as such and not as complications occurring on the day of surgery/ admission.

In general, administrative data coding of chronic comorbid disease is recognized to have variable sensitivity and consistently high specificity (Lix et al. 2006; Quan et al. 2008). To our knowledge, no studies have examined whether the presence of OSA or postoperative complications affects the coding of other comorbid diseases. Thus, we consider the misclassification of comorbid illness in administrative data to be nondifferential and bias towards a nil effect of the comorbid disease on the outcome (Rothman, Greenland, and Lash 2008c).

Comorbidity indices

Two comorbidity indices were operationalized from ICD codes in hospital discharge abstracts and medical services diagnosis coding: the Charlson Comorbidity index (CCI) (Charlson et al. 1987) and the revised cardiac risk index (RCRI) (Lee et al. 1999). The CCI has been used extensively to measure comorbidity in administrative data and has been adapted to use with ICD10 (Quan et al. 2005; Quan et al. 2008). It was operationalized using a programming macro developed for use with MCHP data that is applicable to ICD9-CM or ICD10-CA(Manitoba Centre for Health Policy 2009a) and based on the work of Quan et al (2005). The RCRI was originally developed from a clinical database (Lee et al. 1999) as a predictor of serious postoperative cardiac complications and death. It has been used widely in clinical practice (Fleisher et al. 2007) and applied to administrative data previously (Boersma et al. 2005). The index assigns one point for the presence of each of six risk factors: IHD, CHF, CVA, DM, CRF and high-risk surgery. (In this study high-risk surgery was approximated with the definition for major surgery, as defined below.) Increasing point scores are associated with increased risk of postoperative complications in non-cardiac surgery. When patients with 1, 2 or more than 2 risk factors were compared to those with no risk factors in an administrative data study (Boersma et al. 2005), the odds ratios of cardiovascular death were significantly increased to 2.0, 5.1 and 11.0 respectively.

The two comorbidity indices were operationalized within the available data in different ways. The RCRI could be derived for every patient and was based on the patient comorbidities from the available longitudinal data and the type of surgery. However, the

macro for the CCI could only be applied to an individual hospital discharge abstract and thus disregarded diagnoses assigned in medical services claims or previous hospital admissions. Application of the CCI also produced missing values for those surgeries that occurred at day surgery centres and were not associated with a hospital discharge abstract. The CCI values for these patients, representing 5.4% of all surgeries, were excluded in all analyses that included the CCI.

Type of surgery

The nature of the surgery is known to have a significant effect on the occurrence of serious postoperative cardiovascular and respiratory complications (Arozullah et al. 2000; Gross et al. 2006; Lee et al. 1999). For this study, each surgery was classified in five dimensions with binary predictor variables based on the perioperative literature: cardiac surgery, emergency surgery, surgery to treat OSA, major surgery and surgery associated with a high risk of respiratory failure. All but the emergency surgery predictor variable was defined by the procedure listed on the anesthetic tariff. For example, all open-heart surgeries were considered to be cardiac surgery. In contrast, the emergency surgery predictor was operationalized from the admission status of the hospital discharge abstract. Surgery was considered an emergency for all surgeries within a non-elective admission and the second and any subsequent surgery within an elective admission. The first surgery within an elective admission was considered elective surgery, as were those surgeries that were not matched to a hospital discharge abstract and were presumed to have occurred at a day surgery center.

Surgeries to treat OSA were previously listed in Table 1 and included surgeries that seek to treat OSA or relieve symptoms associated with OSA (Fleisher and Krieger 2007; Woodson 2010). This variable was used to exclude these surgeries from matching because of the high likelihood of matched controls for these surgeries having undiagnosed OSA.

The major surgery predictor variable was derived from a clinical guideline(Fleisher et al. 2007). We considered as major surgery those surgeries classified by Fleisher et al. as being at intermediate or high risk of cardiac complications. Although this classification was designed for non-cardiac surgery, we also considered open-heart surgery as major surgery. We defined minor surgery according to the low risk category of Fleisher et al., breast surgery, superficial procedures and those procedures typically done on an ambulatory basis including endoscopic procedures and cataract surgery. Thus, in this study major surgery included intrathoracic (including cardiac), vascular, intraperitoneal, intracranial, head and neck, orthopedic, plastic and prostate surgery. However, procedures in these surgical domains that are typically done on an outpatient basis would be considered minor surgery (i.e. knee arthroscopy is a minor surgery while knee replacement is a major surgery).

The surgery associated with a high risk of respiratory failure (RF surgery) predictor variable was derived from Arozullah et al. (2000). As in that study, RF surgery in this study included cardiac, thoracic, upper abdominal, intracranial and vascular surgery.

Non-RF surgery was defined by not meeting the criteria for RF surgery. Table 5 compares the major surgery variable with the RF surgery variable.

Table 5. Comparison of major surgery and surgery associated with a high risk of respiratory failure (RF) predictor variables.

Surgery type	*RF*	*non-RF*
Major	Vascular, Cardiac, Thoracic, Intracranial, Intestinal and Hepatic	Orthopedic, Gynecologic intraperitoneal procedures, Kidney and Prostate surgery
Minor	Cholecystectomy, Diagnostic laparoscopy, Bronchoscopy, Mediastinoscopy, Umbilical hernia repair, Implantation of cardiac pacemakers and defibrillators	Most other Ambulatory, Superficial or Endoscopic procedures in any of the listed surgical domains, including cataract surgery.

OSA severity

More severe forms of OSA are thought to increase postoperative risk. The apnea hypopnea index (AHI) is used to grade the severity of OSA. An AHI between 5 and 15 events per hour is considered mild, between 15 and 30 events per hour is moderate OSA and greater than 30 is severe OSA. Control patients were assigned to a baseline category when using this categorization as a multinomial ordinal predictor variable. The AHI was not applied directly as a continiuous predictor variable because the AHI was not known for the control patients, and could not plausibly be assigned to zero for all control patients (Lee et al. 2008). However, as a multinomial ordinal predictor variable, patients with mild, moderate and severe OSA were compared to controls without OSA. Additionally, co-diagnoses of central sleep apnea or obesity hypoventilation syndrome were tested as separate binary predictor variables.

Other factors

Several other predictor variables were considered in this study. The patient's age at the time of surgery (in years) was modeled as a continuous predictor variable. When patients had a second operation in the same day as the index operation, usually for postoperative bleeding or wound dehiscence, the occurrence of this reoperation was flagged. We also noted when patients were in an intensive care unit at the time of surgery (indicating a complicated preoperative course). A count of the number of surgeries within an admission was kept and second and subsequent surgeries were compared to first surgeries. We anticipated significant increased risk for second and subsequent surgeries as they would largely indicate a complicated postoperative course. Finally, we considered sex as a predictor variable, anticipating a higher number of OSA patients to be male compared to controls.

Outcomes

Censorship and Postoperative follow up period

For both death outcomes and non-fatal serious postoperative cardiovascular and respiratory complications (SPCRCs) censorship could occur if a patient ceased coverage with Manitoba Health in the period after surgery. This could be due to enrolling in a health insurance program with the federal government (by becoming a federal citizen) or another province or country (by taking up residence in that province or country). It would censor the outcome by preventing data capture by Manitoba Health. Such an occurrence would lead to SPCRC's or death not being captured in the available data.

This censorship was not measured but is considered negligible given the postoperative period of interest is relatively short and associated with convalescence from surgery.

For the non-fatal SPCRCs, which were operationalized from hospital discharge abstract coding, a potential source of differential censorship also existed. Differences between the groups in the rate of admission to hospital, length of stay in hospital or transfer between hospitals due to the presence of OSA or other medical comorbidities could have led to different periods of postoperative observation between groups and lack of comparability of information for these complications (Rothman, Greenland, and Lash 2008a). To minimize this bias, the next three hospital discharge abstracts following the procedure of interest were retained for every surgery in both groups. The goal, as explained in the section on SPCRCs below, was to provide at least one week of administrative data follow up for SPCRCs after every surgery. This censorship issue was not relevant to death outcomes because these were captured independent of the patient being in or out of hospital.

Death

Three outcomes were considered, death within 3, 7 and 28 calendar days of surgery. The former was to probe for increased death rates in OSA patients in the period immediately after surgery when postoperative physiologic changes, pain and narcotic requirements are greatest. It is also the period in which intensive postoperative monitoring of OSA patients would occur. The 7 and 28 day outcomes are similar to what has been used

elsewhere in postoperative patients (Fleisher 2005). The date of death as listed in the registry database was the source for all death outcomes. Death outcomes were only measured for OSA patient surgeries (and their matches) occurring after the OSA patient's PSG. Because the UOSA group was defined retrospectively by their later presentation for a PSG, the patients by definition survived all operations prior to their PSG and analysis of death outcomes was not possible.

Some OSA patients had multiple surgeries during the last days of their lives. When more than one surgery for an OSA patient occurred within the time period of interest for a given death outcome (i.e. 3, 7 or 28 days), then the death outcome was assigned to the last surgery and any other surgeries occurring in the time period of interest and their matches were excluded from the analysis. The statistical management of multiple presentations for surgery in some OSA patients (i.e. clustering) is described in the *Statistical analyses* section below. As each control patient only contributed one surgery to the analysis, there was no possibility of assigning one death to more than one control patient surgery.

Serious postoperative cardiovascular and respiratory complications (SPCRCs)

Six SPCRCs were considered: atrial fibrillation, myocardial infarction (MI), pneumonia, cerebrovascular accident (CVA), respiratory failure and cardiac arrest. These complications have been previously studied in postoperative OSA patients (Gali et al. 2009; Gupta et al. 2001; Kezirian et al. 2004; Kezirian et al. 2006; Memtsoudis et al.

2011), and were amenable to operationalization in administrative data. We also defined a composite outcome of *any postoperative complication* as the occurrence of any one or more of the above 6 SPCRCs in the postoperative follow up period. These variables were operationalized from the hospital discharge abstracts using the diagnostic codes and were adapted from other administrative data studies examining similar outcomes (Table 6).

Table 6. ICD9-CM and ICD10-CA codes used in defining serious postoperative cardiac and respiratory complications.
The designation .x or .xx indicates that the three-digit root and all valid four or five digit combinations were included.

Complication and Subcategories	***Coding Reference***	***Codes***
Cardiac arrest	(Chung et al. 2010; Hennessy et al. 2010)	
Ventricular flutter/ fibrillation		427.1; 427.41; 427.42; I47.2; I49.0x
Cardiac arrest		427.5, 668.1x; 798.x; 997.1; O29.1xx; O74.2xx; O89.1xx; R96.x; R98
Myocardial Infarction (MI)	(Varas-Lorenzo et al. 2008)	
Unstable angina		411.1; 411.89; I20.0
Acute or subsequent MI		410.xx; I21.x; I22.x
Atrial fibrillation	(Birman-Deych et al. 2005)	427.31; 427.32; I48.0; I48.1
Cerebrovascular accident	(Lix et al. 2006; Quan et al. 2005)	
Intracranial hemorrhage		430, 431, 432.x, I60.x, I61.x, I62.x
Cerebral Infarction		433.x1, 434.x1, 997.02, I63.x, I64
Transient or chronic cerebral ischemia		435.x, 437.1, V12.54, 997.01, I67.8
Late effects of cerebrovascular disease		438.x, I69.x
Acute respiratory failure	(Pickard et al. 2009; Riley et al. 1993; Wu et al. 2006)	518.5; 518.81; 518.82; 518.84; 786.09; 799.1; J80; J95.1; J95.2; J96.0; J96.9; R09.2
Pneumonia	(Pickard et al. 2009; Riley et al. 1993; Wu et al. 2006)	
Bacterial		481; 482.x; 483.x; 485; 486; J13; J14; J15.x; J16.8; J18.x; J85.x;
Aspiration and ventilator associated		507.0; 668.0x; 997.3x; J69.0; J69.8; O29.0x; O74.0x; O89.0x

For a complication to be assigned to a surgery, the date of diagnosis for the complication had to be on or after the day of surgery. Thus, for the hospital admission associated with the surgery, only diagnoses assigned a diagnosis type of complication (assigned to the discharge date) or a transfer to a different service (assigned to the transfer date) were considered as complications. Diagnoses assigned a diagnosis type for a preexisting condition were assigned to the day prior to the admission. In addition to the hospital admission associated with the surgery, up to three subsequent hospital discharge abstracts were examined for the occurrence of SPCRC's, provided the admission occurred within 7 calendar days of surgery. All diagnoses for these admissions were considered to fall after the surgery and thus the main reason for admission could be a SPCRC. For example, a patient discharged same day after minor surgery who presented to hospital with an acute MI 3 days later would be assigned as having had an MI as a postoperative complication, even though MI was the main diagnosis and not assigned a diagnosis type of complication in the follow up admission.

Three other exclusions were necessary to maximize accuracy and minimize bias in the analysis of SPCRCs. Surgeries occurring prior to April 1, 1987 were excluded from these analyses because prior to this date, diagnosis types were not coded so distinguishing between complications and comorbidities was not possible. Second, when multiple surgeries occurred within one admission, it was not possible to accurately determine which surgery should be assigned as having caused the complication. This is because the date of the complication was not truly known and only inferred from the diagnosis type. It was decided to assign all complications to the first surgery within an admission, as any

subsequent surgeries would likely be a complication of the first and thus an indirect consequence of the first surgery. Thus, for OSA patients, when there was a second or subsequent surgery within the admission, they were excluded from analysis as were those surgeries' matches. Consequent to this, it was also necessary to exclude from analysis matched control surgeries that were a second or subsequent surgery within an admission. This is because second or subsequent surgeries within an admission were strong predictors of complications. Finally, for each SPCRC outcome it was necessary to *a priori* exclude certain surgical procedures where the indication for the surgery was the SPCRC, or the SPCRC was a very common (and thus not unexpected) complication of that surgery (Table 7). The statistical management of multiple presentations for surgery in some OSA patients (i.e. clustering) in different admissions is described in the *Statistical analyses* section below.

Table 7. Excluded surgeries and corresponding Manitoba Physician's manual tariffs for each serious postoperative cardiac and respiratory complication.
Reasons for exclusion are given in the text. Other tariffs that relate to the excluded surgery may exist but were not included because they did not occur among the OSA patients.

Complication	***Excluded surgeries***	***Tariffs corresponding to excluded surgeries***
Atrial fibrillation (AF)	Cardioversion, Insertion or revision of pacemaker or defibrillator	2312, 2328, 2329, 2309, 2367, 2363, 2365
Myocardial infarction (MI)	As for AF, plus all cardiac surgery	As for AF, plus 2378, 2407, 2409-2415, 2417, 2462
Cardiac arrest	As for MI	As for MI
Respiratory failure	Tracheostomy	2101
Pneumonia	Tracheostomy	2101
Cerebrovascular accident	Intracranial surgery	5009, 5015, 5031, 5087, 5089, 5092, 5095, 5103, 5107, 5215, 5399

Statistical analyses

All data processing, programming and statistical analyses were conducted using SAS® software version 9.2 of the SAS System for Unix, Copyright © 2008 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institue Inc., Cary, NC, USA. As a standard condition of approval by the Health Information Privacy Committee, patient counts greater than zero but less than 6 cannot be reported due to privacy concerns. The method of generalized estimating equations (GEE) estimation was used in all models. GEE estimation accounted efficiently for two types of clustering in the study and provided robust empirical standard error estimates (Allison 1999). Given the hypothesis generating nature of the work, p-values less than 0.05 were considered statistically significant in all models. For the descriptive statistics used in comparing OSA patient comorbidities with those of non-OSA controls, clustering was ignored and the Chi-Square test or t-test used as appropriate.

The first type of clustering in the study was due to the possibility of each OSA patient having more than one exposure to surgery and the possibility of recurrence of each serious postoperative cardiac and respiratory complication (SPCRC) outcome. To determine if the intraclass (within patient) correlation coefficient (ICC) was significant for each SPCRC, a GEE null model with an exchangeable correlation matrix and the patient as the repeating variable was constructed from all the OSA patient exposures to surgery. The empirical model covariance from each model was used to calculate the ICC for each SPCRC: ICC = $[\text{covariance}]^2 / [(\text{covariance})^2 + (\pi^2/3)]$ (Clarke 2008). This type

of clustering was not possible in the non-OSA control patients as each patient was restricted to only one exposure to surgery in the data. When the ICC approached or exceeded 0.1 for a given SPCRC, the subsequent analyses comparing OSA patients with non-OSA control patients were interpreted with caution, recognizing an increased risk of type 1 error due to an underestimation of the coefficient standard errors (Clarke 2008). An ICC significantly less than 0.1 was interpreted as a negligible clustering effect. It was ignored in subsequent comparative analyses between OSA and non-OSA patients.

In all analyses comparing OSA patients with non-OSA controls it was also necessary to account for clustering effects due to matching. In these analyses, GEE was again employed with an exchangeable correlation and the repeating variable set as the matched group, defined as the OSA patient's exposure and its non-OSA matches. For these analyses multivariate modeling was carried out by stepwise forward regression, using the Z-score from the univariate model as a measure of a variable's explanatory power. However, OSA status was included in every multivariate model, regardless of statistical significance because the primary focus of this study was to compare outcomes between OSA and non-OSA patients, not to study predictors of postoperative risk in general. For the same reason first order statistical interactions were tested between OSA status and other model variables, but not between other model variables. The number of variables included in the multivariate models was limited by the number of outcomes: approximately 1 explanatory variable per 10 outcomes was modeled when there were less than 30 outcomes and approximately 1 one variable for every 5 outcomes when there were 30 or more outcomes (Chateau 2011). In keeping with the primary focus of the

study, and because most outcomes were rare, it was necessary in most multivariate analyses to model the ordinal comorbidity index scores as simpler variables. This allowed for modeling of other important predictor variables. Unless stated otherwise, in multivariate analyses the revised cardiac risk index score was modeled as a linear variable and the Charlson comorbidity index was modeled as a binary variable (0 vs. ≥1).

Results

Derivation and Description of base cohort

99% of SBGH database patients could be linked to administrative data. Among patients with a diagnosis of OSA, 4754 exposures to surgery/ anesthesia were identified. Figure 5 shows the derivation of the base cohort from these patients. At least seven days of postoperative follow up were available for over 99.9% of the base cohort.

The 4322 exposures in OSA patients in the base cohort occurred in 1926 individuals with a range of 1 to 14 exposures per patient (Figure 6). 2722 (63%) of these exposures occurred after the patient was diagnosed with OSA, and these were concentrated in the later years of the study data (Figure 7). 46.2% of all OSA patient exposures were in patients with severe OSA (median AHI = 60), 22.4% were in moderate OSA patients and 31.4% were in mild OSA patients. Major surgery, cardiac surgery and surgery associated with a high risk of respiratory failure respectively accounted for 30.4%, 3.3% and 20.1% of all surgeries. When OSA was stratified by severity there were no statistically significant differences in the frequencies of these types of surgery.

Figure 5. Derivation of the base cohort consisting of exposures to surgery for OSA patients and non-OSA matched controls.

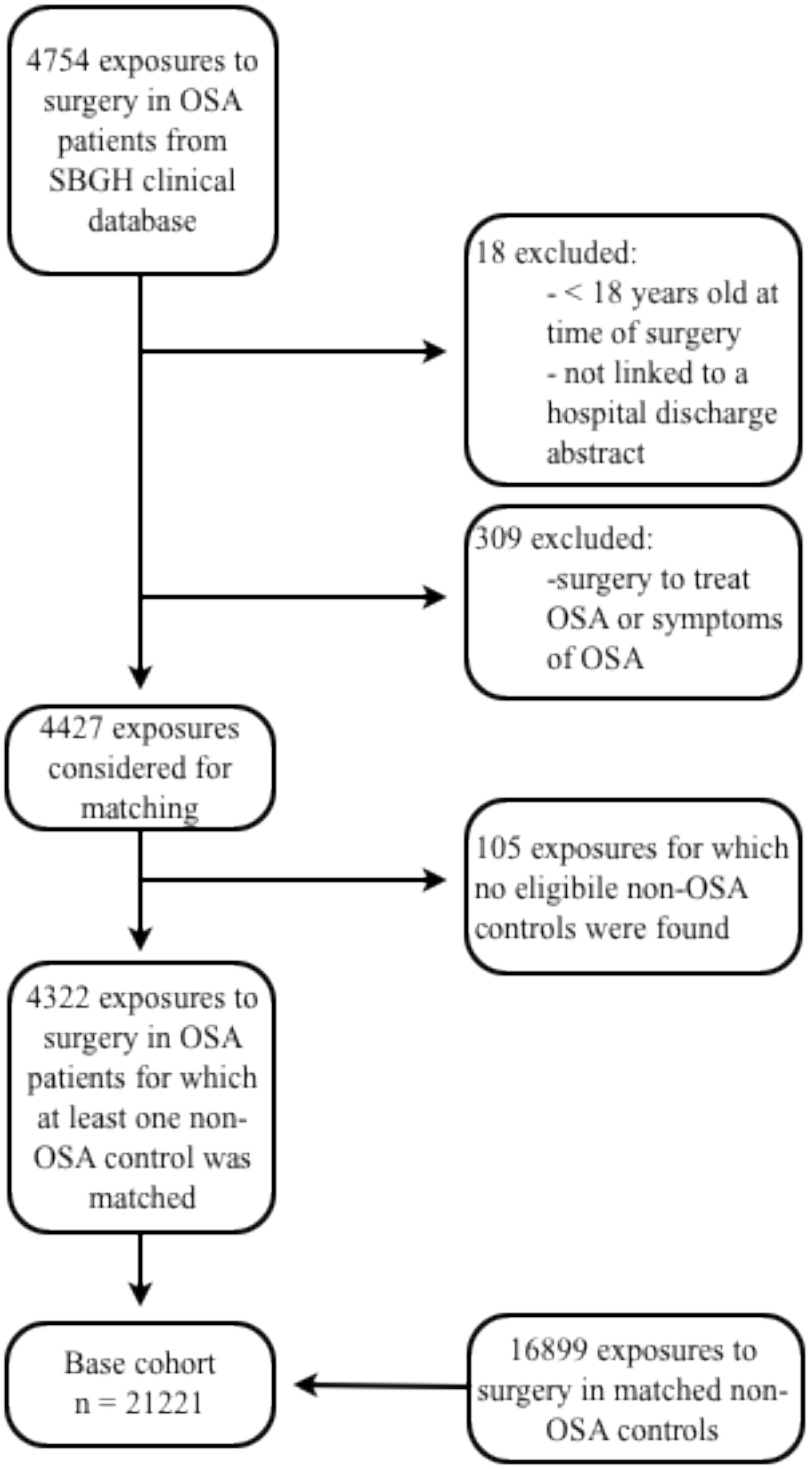


Figure 6. Number of surgeries per OSA patient.

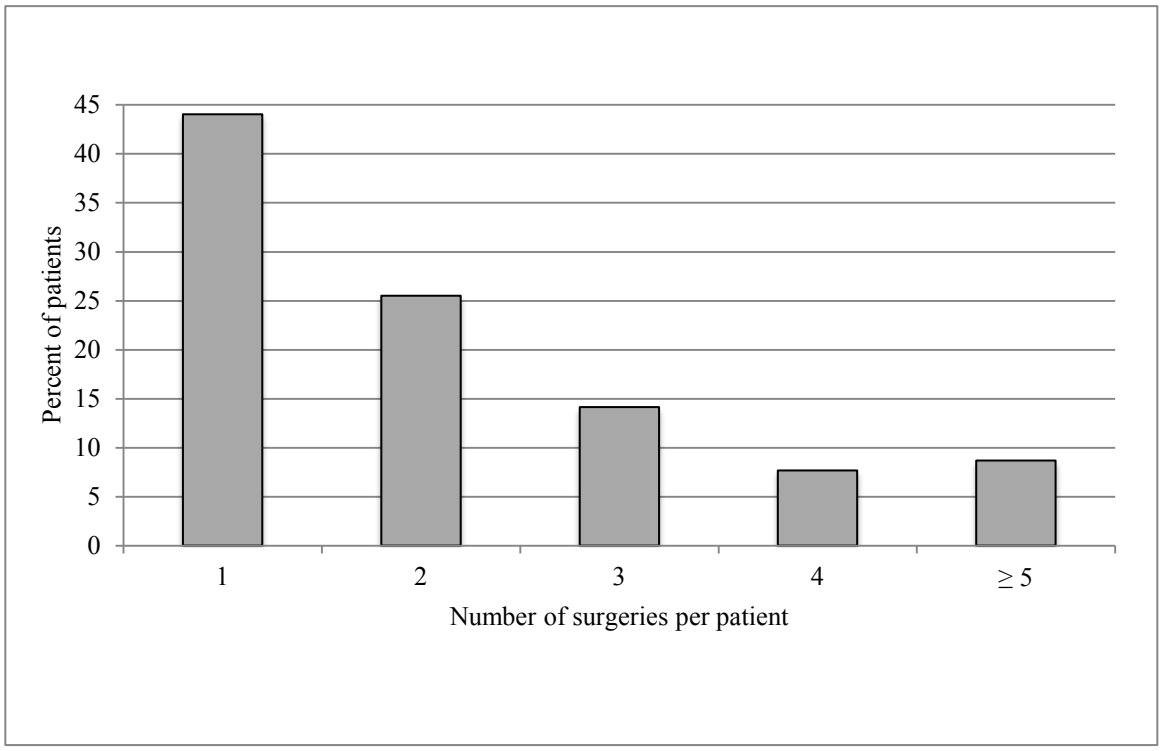
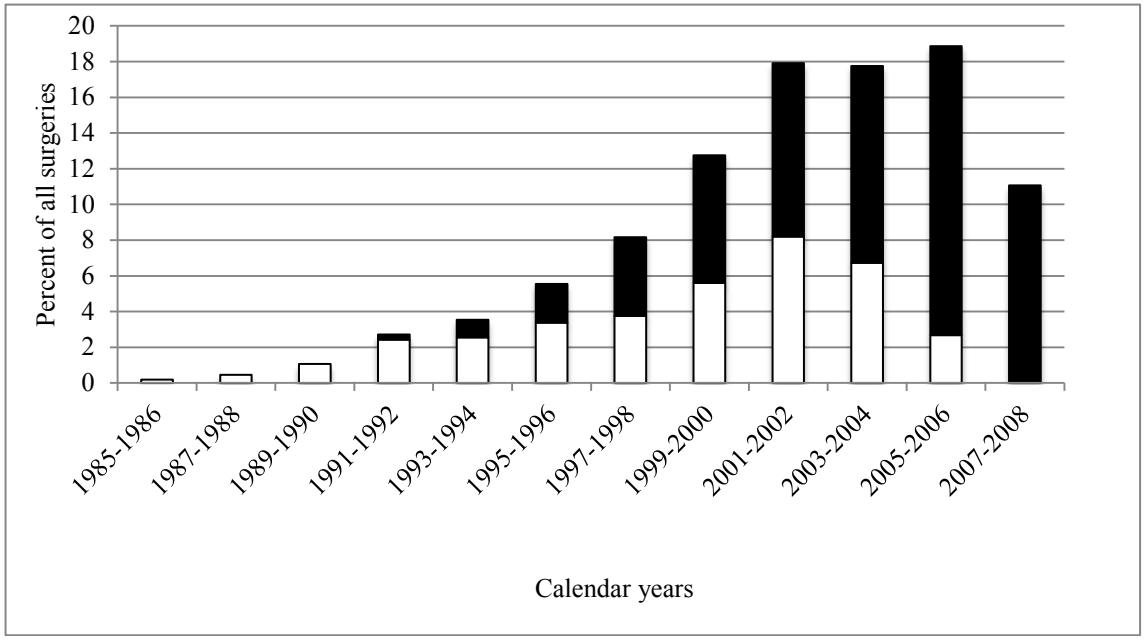


Figure 7. Distribution of OSA patient surgeries over the period of study, stratified by pre and post diagnosis of OSA.
Prediagnosis = white. Postdiagnosis = black. Only the first quarter of 2008 calendar year data was available for the study.



2.2% of exposures occurred in patients with a co-diagnosis of obesity hypoventilation syndrome (OHS), 2.7% occurred in patients with a co-diagnosis of central sleep apnea (CSA) and the remainder of exposures occurred in patients with OSA only. The CSA and OHS co-diagnosis variables were not included in analyses because most of the outcomes were rare and the groups were small.

94.9% of OSA patient exposures matched to 4 non-OSA controls, 2.7% to 3 controls and 2.4% to 1 or 2 controls. Compared to matched controls, at the time of surgery OSA patients were slightly younger, more likely to be male, more likely to have comorbid illness and have higher scores on comorbidity indices (Table 8). They also were slightly more likely to be in an intensive care unit (ICU) at the time of surgery, be having a second or subsequent surgery during a given hospital admission and were slightly less likely to have a reoperation on the same day compared to the non-OSA controls. However, these last three events were uncommon in both groups. When OSA patient exposures were stratified by OSA severity (mild, moderate, severe) and compared to their respective controls, the same differences were observed with the exception of the characteristics listed in Table 9.

Table 8. Comparison of age, sex, comorbidities and surgical characteristics between OSA and non-OSA controls in the base cohort (n = 21221).

Data are presented as mean (standard deviation) or as percent. RCRI = Revised cardiac risk index score. CCI = Charlson comorbidity index score. ICU = intensive care unit. S = data suppressed for privacy concerns.

Characteristic	***OSA (n = 4322)***	***non-OSA (n = 16899)***	***p***
Age at time of surgery (years)	55.7 (12.4)	57.4 (18.0)	< 0.0001
Male sex	66.2	46.9	< 0.0001
Ischemic heart disease	31.4	25.7	< 0.0001
Congestive heart failure	15.4	11.2	< 0.0001
Diabetes mellitus	34.7	20.5	< 0.0001
Cerebrovascular accident	8.9	8.1	0.09
Renal disease	7.9	5.6	< 0.0001
Chronic obstructive pulmonary disease	41.9	28.8	< 0.0001
RCRI ≥ 1	67.3	56.9	< 0.0001
CCI ≥ 1	27.4	21.8	< 0.0001
Emergency surgery	16.1	15.8	0.84
In an ICU at the time of surgery	1.4	1.0	0.007
Reoperation on same day	S	0.3	0.02
Not first surgery during hospital admission	2.2	1.8	0.04

Table 9. Patient characteristics where differences between OSA and non-OSA controls were dependent on OSA severity.

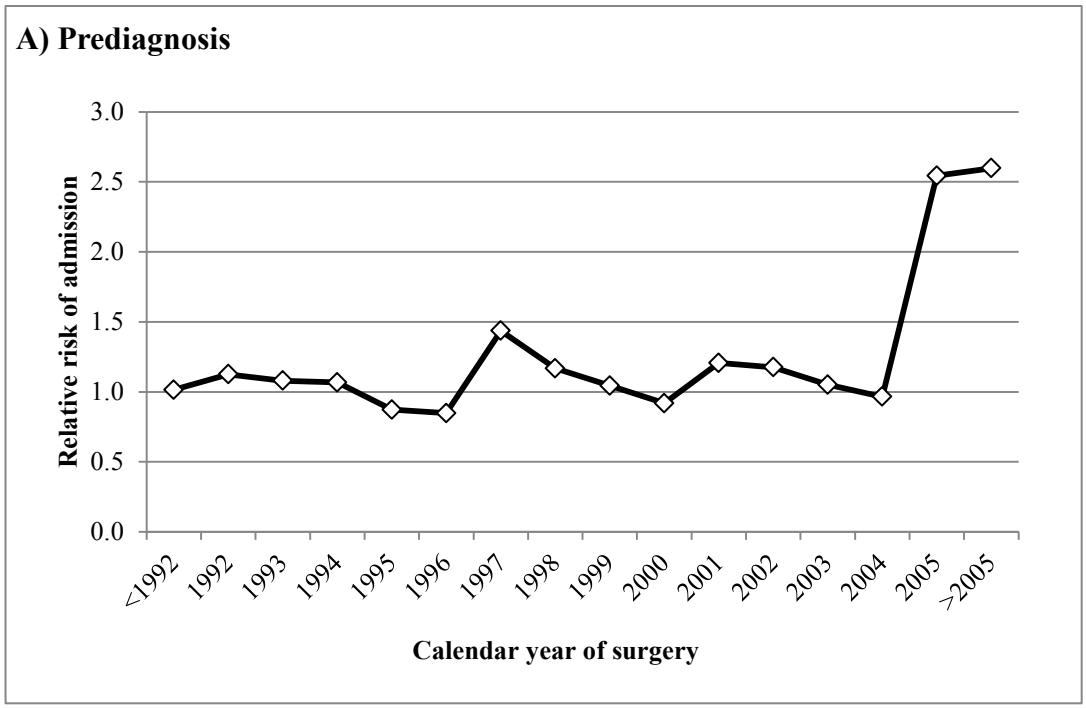
Counts (n) of OSA patient and matched non-OSA control exposures stratified by OSA severity are provided at the bottom of the table. Data are from the base cohort (n = 21221). Patient characteristic data are presented as percent. CCI = Charlson comorbidity index score.

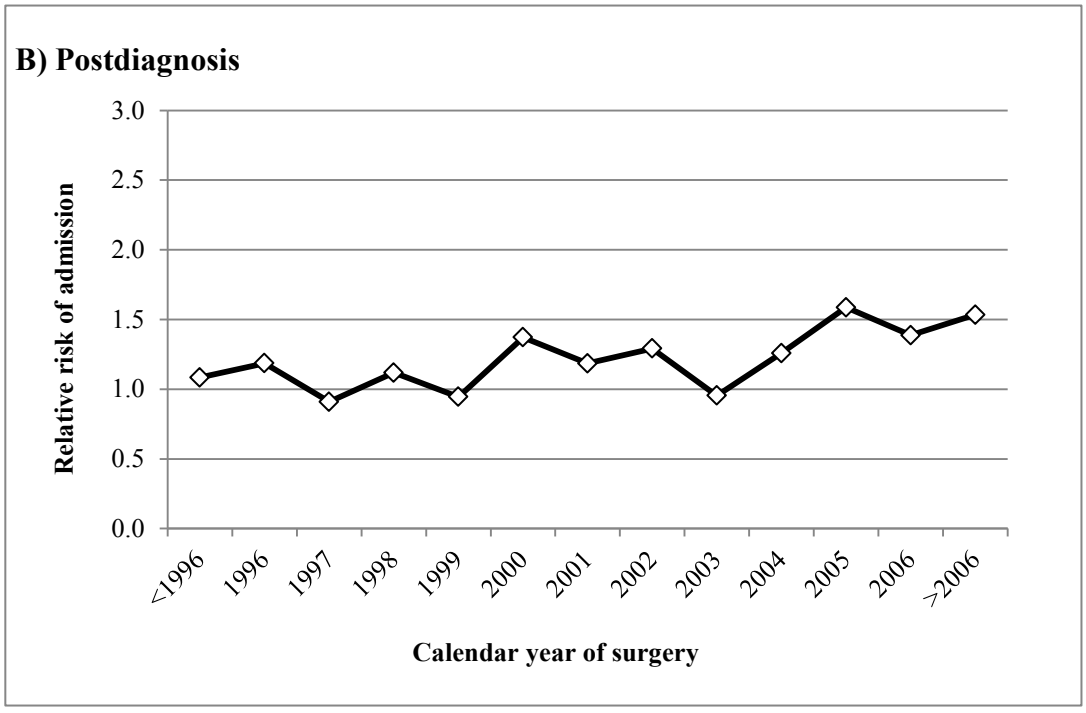
Characteristic	***OSA severity***	***OSA***	***non-OSA***	***p***
Congestive heart failure	Mild	11.1	10.3	0.24
	Moderate	13.3	11.0	0.05
	Severe	19.3	12.0	< 0.0001
Cerebrovascular accident	Mild	9.6	7.5	0.01
	Moderate	8.8	8.6	0.81
	Severe	8.5	8.3	0.80
Renal disease	Mild	4.4	4.0	0.31
	Moderate	7.8	5.0	0.003
	Severe	10.4	7.0	< 0.0001
CCI ≥ 1	Mild	22.8	20.7	0.10
	Moderate	28.9	21.2	< 0.0001
	Severe	29.9	22.9	< 0.0001
n	Mild	1356	5302	
	Moderate	969	3802	
	Severe	1997	7795	

We suspected that patterns of care for postoperative OSA patients were likely to have changed in the later years of data studied, around the publication of the ASA guidelines in 2006. Changes would have included increased screening of preoperative patients for a diagnosis or symptoms of OSA, changes in anesthetic techniques, prolonged recovery room stays, postoperative admission to monitored settings and reduced day surgery discharge rates. The available data only allowed measurement of the latter. We compared the relative risk of overnight admission after minor surgery between OSA patients and their controls (matched to the same type of surgery and indication for surgery) over time (Figure 8). By 2005, a trend toward increased overnight admission rates in OSA patients was evident, most dramatically in pre OSA diagnosis period. Multivariate models accounting for clustering and testing for differences in discharge rates investigated this graphical trend by searching for a significant interaction between OSA status and date of surgery (pre vs. post January 1, 2005). Statistically significant interactions were confirmed in both the pre ($p < 0.01$) and post OSA diagnosis ($p < 0.001$) populations. These models included age at surgery, year of surgery, and all comorbidities or the comorbidity indices. They suggest that these and potentially other changes in care were occurring by 2005 that may have obscured the increased risk of OSA on postoperative outcomes from when the base cohort was examined as a whole. To investigate the sensitivity of our results to these potential changes in care, we tested for a statistical interaction (product term) between OSA status and date of surgery (pre vs. post January 1, 2005) for all outcomes where multivariate analysis was feasible.

Figure 8. Relative risk of overnight admission after minor surgery for OSA patients vs. non-OSA controls.

Different years of data are combined in each figure to produce adequate sample sizes.





Interpretation

This study is the largest by far to consider serious postoperative outcomes in OSA patients following a broad spectrum of surgeries and using a gold standard clinical definition of OSA. To identify exposures to surgery, we used anesthesia tariffs from the MCHP data repository. Although this method has not been previously described, the rules of application that guide how anesthesiologists are remunerated in Manitoba provided criterion validity (Manitoba Health and Healthy Living 2009). Our success in matching anesthesia tariffs to hospital admissions also suggests this was a valid construct. This method allowed us to efficiently study a broad spectrum of surgeries and incorporate surgical factors into our models of postoperative risk.

We recognized a limitation in this method was an inability to distinguish between traditional open surgical techniques and minimally invasive techniques for those surgeries where such techniques exist. By matching on indication and approximate date of surgery we attempted to minimize the impact of this limitation on our results. In addition, even though surgeries did not occur in an even distribution over the years of study, by matching on approximate date of surgery we minimized bias due to changes in surgical techniques, coding practices or postoperative outcomes over time. However, persistent residual differences in surgical techniques between OSA and non-OSA patients may still bias the results. It is difficult to predict the overall direction of this bias, but in most surgeries, it would be expected that high levels of obesity in OSA patients would make minimally invasive techniques more difficult. This would lead to higher rates of classical open approaches to surgery in OSA patients, potentially more adverse outcomes, and an overestimation of the risk due to OSA.

We achieved our follow up goal of 1 week postoperatively for essentially the entire cohort (>99.9%). Thus, missed outcomes due to differences in admission rates or hospital stay between OSA and non-OSA patients should not have occurred.

We found OSA patients to have significantly more comorbid disease than matched non-OSA controls at the time of surgery. Our administrative data definitions of these comorbidities were obtained from coding definitions accepted in the literature. We recognized these definitions typically have a lower sensitivity despite a high specificity, meaning as a nondifferential misclassification bias they would tend to underestimate the effect of the comorbid disease on the outcome(Rothman, Greenland, and Lash 2008c). However, if OSA patients are more frequently assigned comorbidities in administrative data because they more frequently contact the health system, the direction of this differential misclassification would be more difficult to predict (Rothman, Greenland, and Lash 2008c). It should be emphasized that the Charlson comorbidity index score was calculated only from the hospital discharge abstract associated with the surgery. Differential coding of hospital discharge abstracts due to the presence of OSA would seem unlikely, thus differential misclassification of this measure of comorbidity is unlikely.

Several variables of interest in predicting postoperative risk could not be included in the analysis. Although the body mass index (BMI) of SBGH database patients at the time of their sleep study was available, we did not have this information available for controls.

We considered administrative data definitions of obesity but in preliminary work with the SBGH patients we found them to be too unreliably coded. We also could not determine if patients were compliant with CPAP use preoperatively or if CPAP was used in the postoperative period. Thus, our estimates of the risk of OSA are not independent of any effects of BMI or CPAP use on the outcomes. We also were unable to consider the effect of a co-diagnosis of central sleep apnea or obesity hypoventilation syndrome because of the low frequency of these diagnoses in the cohort.

Other variables related to the anesthetic technique and postoperative care also could not be operationalized. Elements of the anesthetic technique of potential interest would include the type of anesthesia and the type of postoperative analgesia. However, it is the minority of surgical procedures where choice exists in significant aspects of the anesthetic and where more than one technique is used frequently. Unfortunately, in most of these cases, the type of technique used is often confounded by the patient's comorbidities, so an estimate of the independent effect of the anesthetic or analgesic technique is difficult without a randomized study. We also were unable to determine if intensive postoperative monitoring was used other than to note if the patient was admitted to a step down unit or an intensive care unit. We chose not to use these as outcomes as it was not possible to determine if patients were admitted to such units to prevent postoperative complications or to treat them.

We also tested for changing patterns in the care of OSA patients in the later years of the data and found evidence for change after January 1, 2005, based on admission rates after

minor surgery. Without doubt, changes in this and other aspects of postoperative care for OSA patients changed asynchronously and over time. Our inability to reflect the timing and effect of all of these changes would result in an underestimation of the true effect of OSA on postoperative risk. Guided by the admission after minor surgery results, we hoped this sensitivity analysis would identify dramatic differences in outcomes that may have significantly biased our results.

Postoperative death outcomes

The cohort for death outcomes consisted of OSA patient exposures occurring after the diagnosis of OSA and the non-OSA matches to these patients. Because the cohort was assembled from OSA patients who presented for a sleep study, by definition all OSA patients had survived surgeries prior to their sleep study. For those OSA patients having more than one surgery within the last 3, 7 or 28 days of their lives, only the final surgery and its matches were included in the analysis. The other OSA patient's surgeries within the time period and their matches were excluded. This ensured each OSA patient could only have one death outcome. When the number of outcomes was sufficient, OSA was stratified by severity as a multinomial ordinal variable.

Death within 3 days of surgery

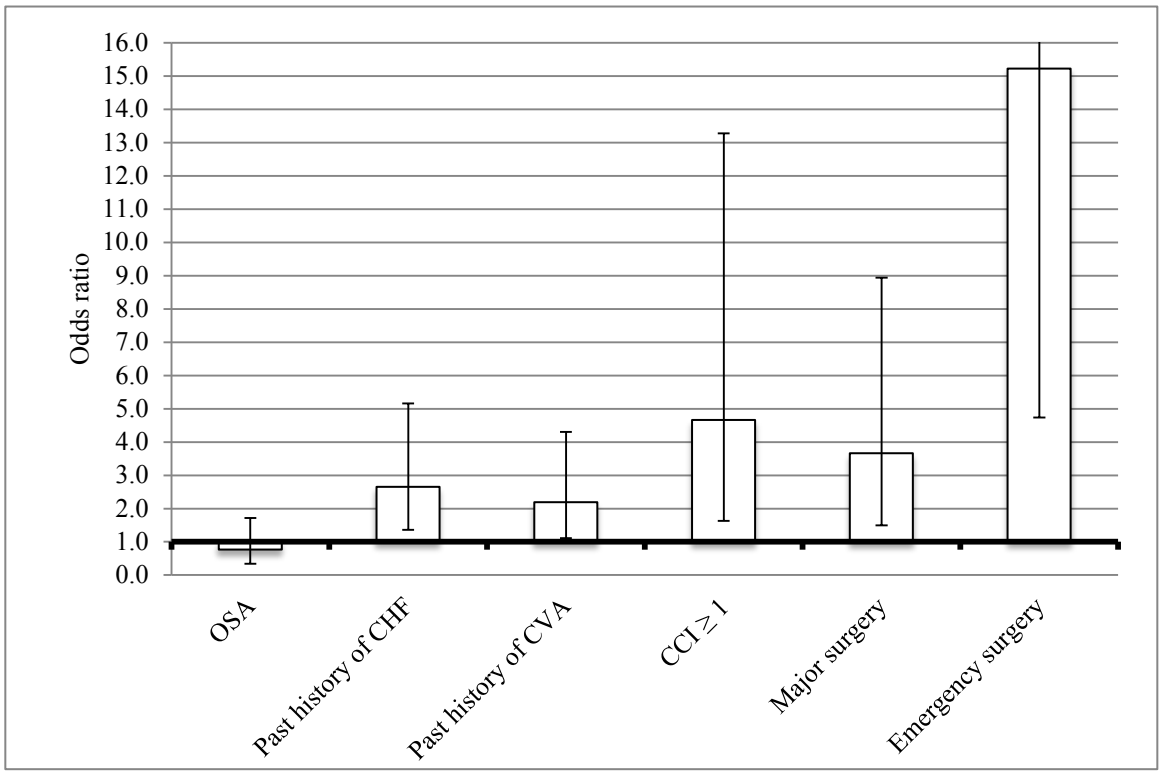
There were 39 deaths within three days of surgery and the unadjusted risks of death were 0.29% in both groups. In univariate analyses (Table 10), OSA of any severity, and

overall, was not a significant predictor of death within three days of surgery, despite these patients' comorbidity burden. Conversely, many surgical and patient related factors were strong predictors. In the multivariate analysis, OSA remained insignificant and its estimated odds ratio was much smaller than other parameters in the model (Figure 9). No other variables other than those presented were significant in this model. There was also no significant interaction between OSA and date of surgery (pre vs. post January 1, 2005), with or without adjusting for age.

Table 10. Univariate analyses for death within 3 days of surgery (n = 13350).
Resp fail = Surgery associated with increased risk of respiratory failure. Not first surgery during admission = The surgery was a 2nd or subsequent surgery during the same hospital admission, or was the first surgery and was associated with a 2nd operation on the same day. ICU = Intensive care unit. RCRI = Revised cardiac risk index. CCI = Charlson comorbidity index.

Predictor variable	Odds ratio	95% confidence limits		p
OSA				
All post diagnosis	**1.00**	0.46	2.21	0.99
Mild post diagnosis	**0.35**	0.04	2.73	0.31
Moderate post diagnosis	**1.16**	0.27	4.91	0.84
Severe post diagnosis	**1.46**	0.57	3.76	0.43
Surgery				
Major	**12.12**	5.05	29.10	<0.0001
Cardiac	**6.84**	3.05	15.36	<0.0001
Resp fail	**8.31**	4.21	16.39	<0.0001
Emergency	**46.39**	16.43	130.95	<0.0001
Not first surgery during admission	**14.32**	6.41	31.98	<0.0001
Age, sex and comorbidities				
Age at surgery (1 year increase)	**1.06**	1.03	1.08	<0.0001
Male	**4.96**	1.87	13.17	0.001
Ischemic heart disease	**5.18**	2.50	10.72	<0.0001
Congestive heart failure	**8.94**	4.85	16.49	<0.0001
Cerebrovascular accident	**5.33**	2.74	10.38	<0.0001
Diabetes mellitus	**1.53**	0.78	3.02	0.22
Renal disease	**4.39**	2.00	9.64	0.0002
Chronic obstructive pulmonary disease	**1.69**	0.91	3.16	0.10
In an ICU at time of surgery	**19.16**	9.18	39.98	<0.0001
RCRI score (vs. score of 0)				
1	**9.46**	1.35	66.14	0.02
2	**33.23**	4.87	226.51	0.0003
≥ 3	**75.47**	11.50	495.47	<0.0001
CCI score (vs. score of 0)				
1-2	**17.50**	6.62	46.29	<0.0001
3-4	**37.96**	12.31	117.06	<0.0001
≥ 5	**22.04**	5.88	82.70	<0.0001

Figure 9. Adjusted odds ratios of death within 3 days of surgery.
Columns = estimate. Bars = 95% confidence limits. CHF = congestive heart failure. CVA = cerebrovascular accident. CCI = Charlson comorbidity index score. The upper confidence limit for emergency surgery is 48.9.



Death within 7 days of surgery

There were 59 deaths with unadjusted risks of death of 0.48% in the OSA group and 0.43% in the non-OSA group. In univariate analyses (Table 11), OSA of any severity, and overall, was not a significant predictor of death within 7 days of surgery. Many surgical and patient related factors were strong predictors. In the multivariate analyses, OSA stratified by severity (Figure 10), or combined into one group (not shown), remained insignificant. Consistent with the univariate analyses there was a pattern of increased risk with increasing severity of OSA. Even amongst those with severe OSA, the estimated adjusted odds ratio for death at 7 days was smaller than some of the other,

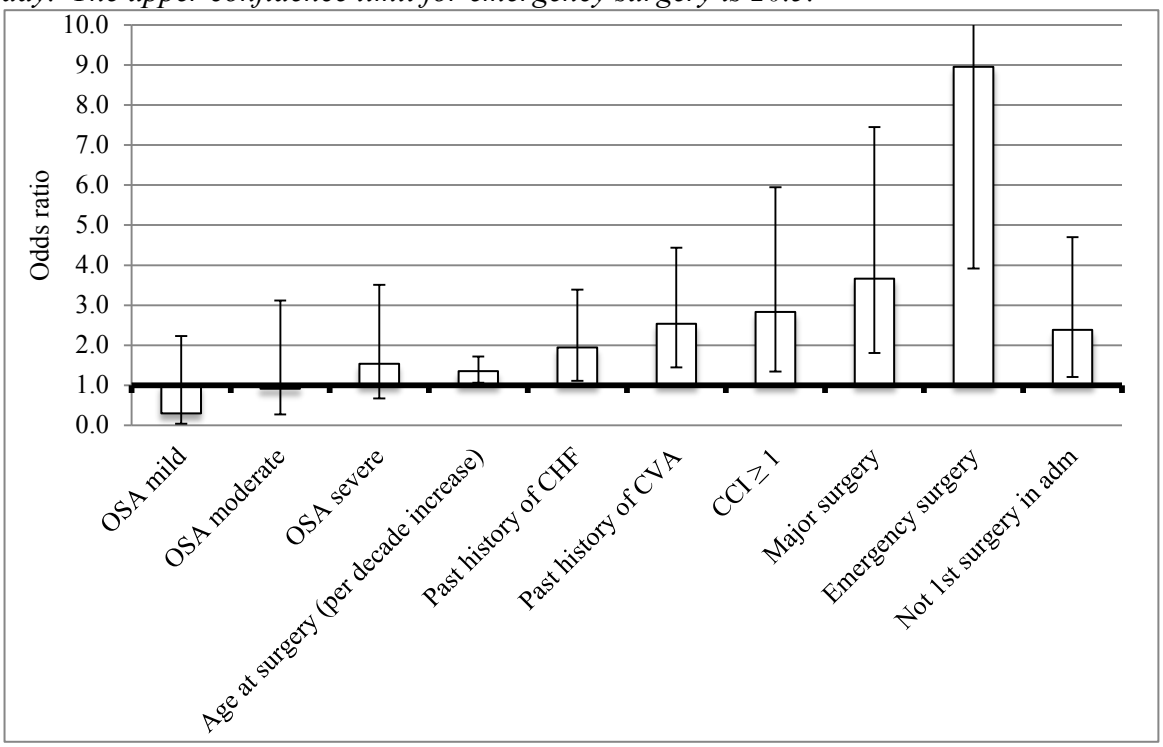
more significant, predictor variables in the model. There was no significant interaction between OSA and timing of surgery (pre vs. post January 1, 2005), with or without adjustment for age.

Table 11. Univariate analyses for death within 7 days of surgery (n = 13350).
Resp fail = Surgery associated with increased risk of respiratory failure. Not first surgery during admission = The surgery was a 2nd or subsequent surgery during the same hospital admission, or was the first surgery and was associated with a 2nd operation on the same day. ICU = Intensive care unit. RCRI = Revised cardiac risk index. CCI = Charlson comorbidity index.

Predictor variable	Odds ratio	95% confidence limits		*p*
OSA				
All post diagnosis	**1.10**	0.60	2.01	0.76
Mild post diagnosis	**0.24**	0.03	1.74	0.16
Moderate post diagnosis	**1.15**	0.36	3.70	0.81
Severe post diagnosis	**1.76**	0.87	3.57	0.12
Surgery				
Major	**10.84**	5.45	21.54	<0.0001
Cardiac	**4.21**	1.93	9.15	0.0003
Resp fail	**6.52**	3.80	11.21	<0.0001
Emergency	**29.08**	14.38	58.82	<0.0001
Not first surgery during admission	**13.46**	6.90	26.24	<0.0001
Age, sex and comorbidities				
Age at surgery (1 year increase)	**1.06**	1.04	1.08	<0.0001
Male	**2.83**	1.51	5.28	<0.0001
Ischemic heart disease	**3.62**	2.02	6.19	<0.0001
Congestive heart failure	**8.41**	5.16	13.69	<0.0001
Cerebrovascular accident	**6.59**	3.86	11.24	<0.0001
Diabetes mellitus	**1.50**	0.87	2.58	0.14
Renal disease	**5.11**	2.81	9.29	<0.0001
Chronic obstructive pulmonary disease	**1.55**	0.93	2.58	0.09
In an ICU at time of surgery	**9.86**	4.32	22.50	<0.0001
RCRI score (vs. score of 0)				
1	**9.48**	1.34	67.00	0.02
2	**33.42**	4.88	228.61	0.0003
≥ 3	**80.87**	12.30	531.55	<0.0001
CCI score (vs. score of 0)				
1-2	**11.99**	5.86	24.53	<0.0001
3-4	**26.31**	11.14	62.17	<0.0001
≥ 5	**22.33**	8.76	56.91	<0.0001

Figure 10. Adjusted odds ratios of death within 7 days of surgery.

Columns = estimate. Bars = 95% confidence limits. CHF = congestive heart failure. CVA = cerebrovascular accident. CCI = Charlson comorbidity index score. Not 1st surgery in adm = The surgery was a 2nd or subsequent surgery during the same hospital admission, or was the first surgery and was associated with a 2nd operation on the same day. The upper confidence limit for emergency surgery is 20.5.



Death within 28 days of surgery

There were 135 deaths, with the unadjusted risks of death 0.81% in the OSA group and 1.07% in the non-OSA group. In univariate analyses (Table 12), OSA of any severity, and overall, was not a significant predictor of death within 28 days of surgery. Similar to the previous death outcomes, a trend toward increased risk in patients with increasing severity of OSA is evident. However, for death within 28 days of surgery the coefficients are smaller than for death within 3 or 7 days of surgery.

In multivariate analyses, larger numbers of outcomes allowed treatment of the RCRI score and the CCI score as multinomial ordinal variables. In these multivariate analyses, OSA stratified by severity (Figure 11), or combined into one group (not shown), remained insignificant. Consistent with the death within 7 days outcome, there was a pattern of increased risk with increasing severity of OSA but all odds ratio estimates were less than 1. A past history of renal disease was a significant predictor of death at 28 days but a past history of cerebrovascular accident or congestive heart failure, both significant at 3 and 7 days, were not significant. There was no significant interaction between OSA and timing of surgery (pre vs. post January 1, 2005), with or without adjusting for age.

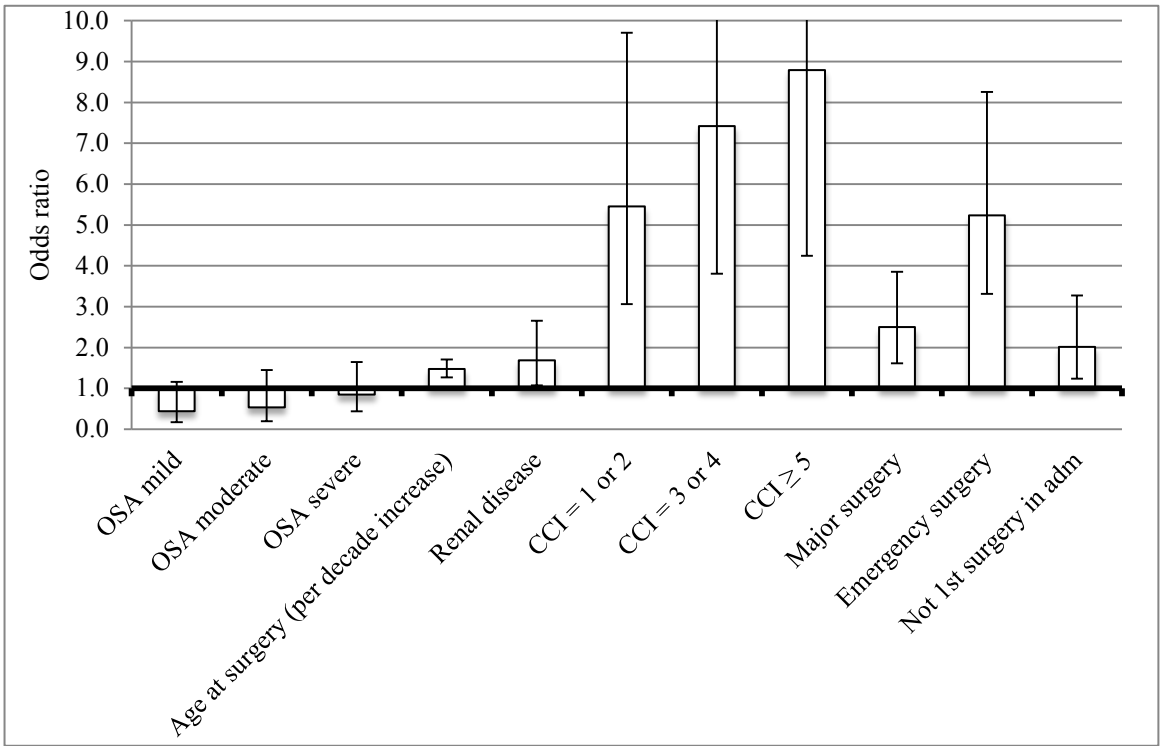
Interpretation

We did not find evidence for a significantly increased postoperative mortality rate in patients with OSA at 3, 7 or 28 days postoperatively. The analyses at three or seven days were hampered by relatively sparse outcomes so a significant effect cannot be ruled out. However, at 28 days there was no evidence for residual increased mortality. In fact, at 28 days patients with OSA were trending towards reduced mortality rates compared to non-OSA controls. Our postoperative death rates at 28 days (approximately 1%) were higher than two other smaller studies of OSA patients, where rates of 0.4% were found (Liao et al. 2009; Weingarten et al. 2011). However, these studies did not consider emergency surgeries. Large studies of postoperative mortality (Fleisher 2005) have found rates of death and predictors of death similar to the ones identified in the present study.

Table 12. Univariate analyses for death within 28 days of surgery (n = 13284).
Resp fail = Surgery associated with increased risk of respiratory failure. Not first surgery during admission = The surgery was a 2nd or subsequent surgery during the same hospital admission, or was the first surgery and was associated with a 2nd operation on the same day. ICU = Intensive care unit. RCRI = Revised cardiac risk index. CCI = Charlson comorbidity index.

Predictor variable	Odds ratio	95% confidence limits		*p*
OSA and subgroups				
All post diagnosis	**0.75**	0.49	1.15	0.19
Mild post diagnosis	**0.42**	0.18	0.97	0.04
Moderate post diagnosis	**0.75**	0.29	1.95	0.81
Severe post diagnosis	**1.01**	0.57	1.77	0.12
Surgery				
Major	**7.60**	4.97	11.61	<0.0001
Cardiac	**2.47**	1.31	4.65	0.01
Resp fail	**4.87**	3.26	7.27	<0.0001
Emergency	**18.40**	12.16	27.85	<0.0001
Not first surgery during admission	**10.87**	6.39	18.48	<0.0001
Age, sex and comorbidities				
Age at surgery (1 year increase)	**1.06**	1.04	1.07	<0.0001
Male	**1.62**	1.11	2.36	0.01
Ischemic heart disease	**2.64**	1.88	3.71	<0.0001
Congestive heart failure	**4.19**	3.01	5.83	<0.0001
Cerebrovascular accident	**3.48**	2.29	5.30	<0.0001
Diabetes mellitus	**1.87**	1.32	2.67	0.0005
Renal disease	**4.89**	3.20	7.49	<0.0001
Chronic obstructive pulmonary disease	**1.48**	1.06	2.05	0.02
In an ICU at time of surgery	**15.53**	8.60	28.03	<0.0001
RCRI score (vs. score of 0)				
1	**7.38**	3.11	17.50	<0.0001
2	**14.20**	5.86	34.44	<0.0001
≥ 3	**36.54**	15.61	85.51	<0.0001
CCI score (vs. score of 0)				
1-2	**14.74**	8.70	24.97	<0.0001
3-4	**34.24**	18.27	64.16	<0.0001
≥ 5	**42.67**	22.65	80.36	<0.0001

Figure 11. Adjusted odds ratios of death within 28 days of surgery.
Columns = estimate. Bars = 95% confidence limit. CCI = Charlson comorbidity index score. Not 1st surgery in adm = The surgery was a 2nd or subsequent surgery during the same hospital admission, or was the first surgery and was associated with a 2nd operation on the same day. The upper confidence limit for CCI = 3 or 4 is 14.5 and for CCI ≥ 5 it is 18.2.



We consistently noted an empiric trend of increased mortality with increasing severity of OSA, emphasizing the importance of considering the severity of OSA. This has been done only infrequently in other studies. We also noted other surgical factors and medical comorbidities were consistently more important predictors of postoperative mortality than OSA, emphasizing the importance of studying a broad spectrum of surgeries and considering patient comorbidities beyond OSA. It would appear that overall postoperative mortality is significantly affected by surgical factors and preexisting health

but that the role of OSA is relatively small. This suggests that postoperative care decisions aimed at reducing postoperative mortality in OSA and non-OSA patients should include consideration of the type of surgery and the patient's medical comorbidities, not just whether or not the patient has OSA. These other factors are not adequately incorporated into current guidelines. It must be emphasized that these results are based only on patients having surgery after a diagnosis of OSA has been established. They should not be extrapolated to patients with undiagnosed OSA, based on the results of the serious postoperative cardiovascular and respiratory complication outcomes in the section below.

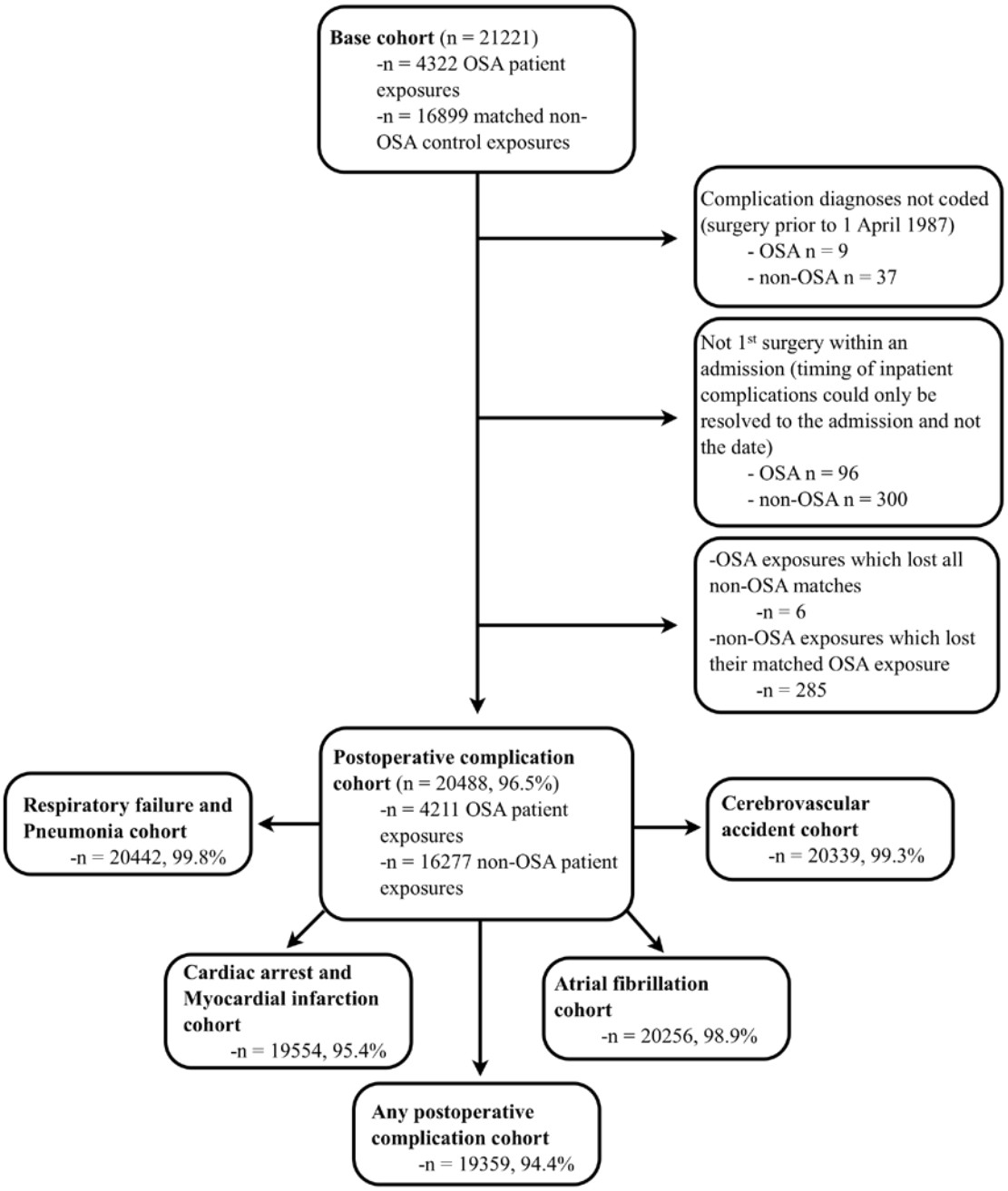
Serious postoperative cardiovascular and respiratory complications

Derivation and characteristics of postoperative complication cohorts

After elimination of those exposures where complication data were unavailable or unusable, the postoperative complication cohort contained over 96% of the base cohort (Figure 12). Once those surgeries that could be a treatment of a complication were eliminated (i.e. tracheostomy for respiratory failure and pneumonia), the cohort for each medical complication contained between 94.4% and 99.8% of the postoperative complication cohort. Unlike the death outcomes, which contained only exposures after the diagnosis of OSA, the postoperative complication cohort contained exposures in OSA patients from both before and after their diagnosis of OSA. To investigate differences in outcomes pre and post diagnosis we stratified OSA patients and their matches by the timing of surgery relative to the PSG in univariate analyses. We also sought statistical interactions between timing of surgery (pre vs. post diagnosis) and OSA status in

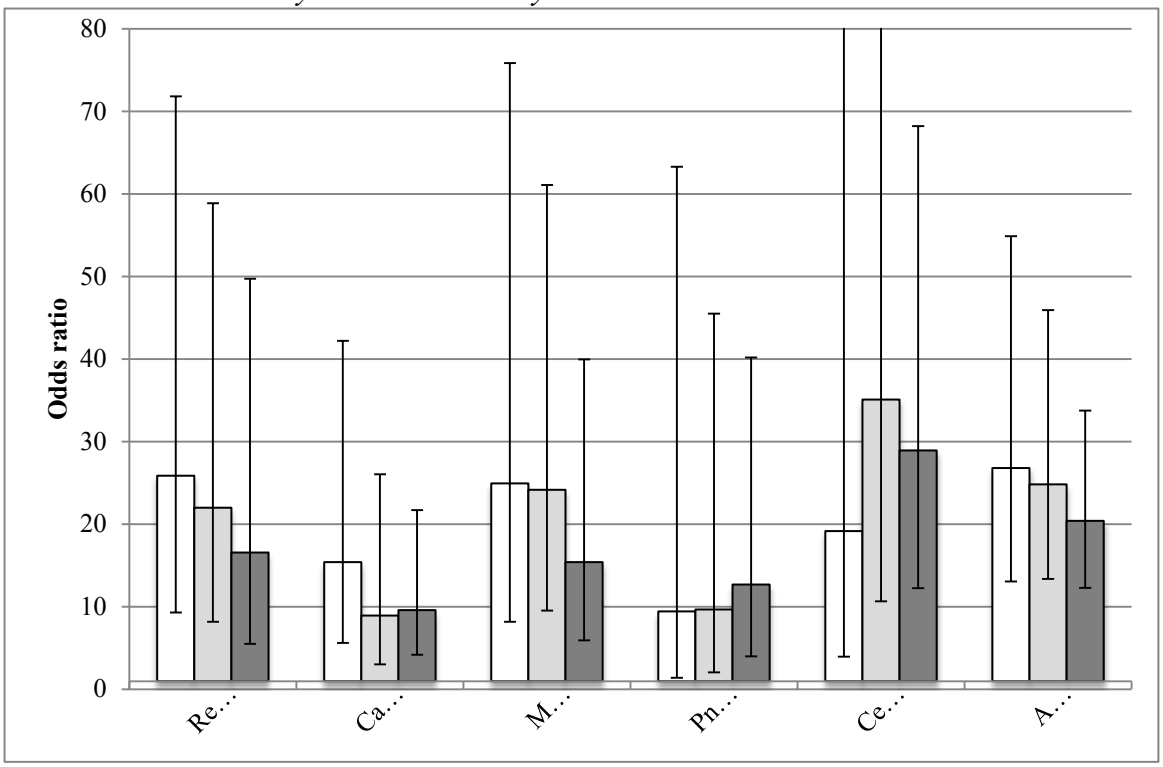
multivariate analyses. When the number of outcomes was sufficient, OSA was stratified by severity as a multinomial variable.

Figure 12. Derivation of the postoperative complication cohorts from the base cohort. *Any postoperative complication is a composite outcome of any of the other 6 postoperative complications.*



We also tested the validity of the assumption that the postoperative complications, derived from administrative data, represented serious postoperative cardiac and respiratory events. Univariate analyses were carried out on the death cohort using the postoperative complications as predictor variables for each death outcome. Data were too sparse for modeling atrial fibrillation. Despite being uncommon events, all other complications were very strong predictors ($p < 0.0001$) of death within 3, 7 and 28 days of surgery, except for pneumonia at 3 and 7 days ($p = 0.02$ and 0.004 respectively) (Figure 13). However, because of their rarity, confidence intervals were wide.

Figure 13. Odds ratio of postoperative death in surgeries associated with a postoperative complication vs. those without.
Columns = estimate. Bars = 95% confidence limits. Death within 3 days = white, 7 days = light grey, 28 days = dark grey. The upper confidence limits for cerebrovascular accident are 92 at 3 days and 115 at 7 days.



Respiratory failure

The intra-cluster correlation coefficient for respiratory failure among OSA patients in the respiratory failure and pneumonia cohort was 0.011. This coefficient was considered negligible and this clustering effect disregarded in the analyses. 64 exposures were complicated by respiratory failure, 27 (0.64%) in OSA patients and 37 (0.23%) in non-OSA matched controls. Prior to OSA diagnosis the respiratory failure rate was 0.64% (10/1569) in OSA patients and 0.31% in controls whereas after diagnosis of OSA it was 0.65% in OSA patients and 0.18% in controls. In univariate analyses, severe OSA and all OSA severities combined were significant predictors of respiratory failure (Table 13). Pre diagnosis, OSA trended to increased risk while post diagnosis OSA was a significant predictor of increased risk.

The overall mortality rate from respiratory failure among OSA patients post diagnosis and control patients pre and post diagnosis was 22%. There were no differences in mortality between these groups. If this death rate is applied to the prediagnosis OSA group, an additional 3 outcomes would be expected for an adjusted raw rate of 0.83% (13/1572). Assuming no deaths in any matched controls for these additional outcomes, the raw odds ratio of respiratory failure in pre diagnosis OSA patients versus matched controls would be 2.6.

Table 13. Univariate analyses for respiratory failure (n = 20442).
Resp fail = Surgery associated with increased risk of respiratory failure. Reoperation = The surgery of interest was associated with another operation on the same day for an immediate complication. ICU = Intensive care unit. RCRI = Revised cardiac risk index. CCI = Charlson comorbidity index.

Predictor variable	Odds ratio	95% confidence limits		*p*
OSA and subgroups				
All	**2.82**	1.70	4.69	<0.0001
Mild	**2.28**	0.99	5.27	0.05
Moderate	**2.22**	0.85	5.84	0.11
Severe	**3.51**	1.93	6.37	<0.0001
All OSA pre diagnosis	**2.04**	0.94	4.43	0.07
All OSA post diagnosis	**3.65**	1.85	7.19	0.0002
Surgery				
Major	**17.32**	8.22	36.52	<0.0001
Cardiac	**13.09**	7.40	23.17	<0.0001
Resp fail	**13.48**	7.50	24.24	<0.0001
Emergency	**7.07**	4.25	11.74	<0.0001
Reoperation	**14.22**	2.61	77.39	0.002
Age, sex and comorbidities				
Age at surgery (1 year increase)	**1.03**	1.01	1.04	0.0003
Male	**1.31**	0.77	2.20	0.32
Ischemic heart disease	**4.27**	2.54	7.17	<0.0001
Congestive heart failure	**6.13**	3.65	10.29	<0.0001
Cerebrovascular accident	**3.14**	1.75	5.65	0.0001
Diabetes mellitus	**2.55**	1.55	4.21	0.0002
Renal disease	**3.34**	1.67	6.70	0.0007
Chronic obstructive pulmonary disease	**3.26**	1.96	5.43	<0.0001
In an ICU at time of surgery	**30.05**	13.58	66.47	<0.0001
RCRI score (vs. score of 0)				
1	**4.73**	1.01	22.11	0.05
2	**28.00**	6.77	115.77	<0.0001
≥ 3	**57.68**	14.19	234.44	<0.0001
CCI score (vs. score of 0)				
1-2	**7.45**	4.03	13.80	<0.0001
3-4	**27.94**	13.14	59.43	<0.0001
≥ 5	**17.11**	7.03	41.66	<0.0001

In the multivariate analysis OSA status remained a very significant predictor of the risk of respiratory failure ($p = 0.0001$), and there was a significant product term (statistical interaction) between OSA status and surgery associated with a high risk of respiratory failure (odds ratio 0.06, 95% confidence limits (0.01, 0.52) (Figure 14). The effect of this

interaction on the risk of postoperative respiratory failure among patients with and without OSA having various types of surgery is illustrated in Figure 15. The risk of respiratory failure in OSA patients was dramatically increased in patients having major surgery, not typically associated with respiratory failure. The episodes of respiratory failure in OSA patients having these surgeries were distributed evenly amongst the common surgeries in this category: total joint replacement, other orthopedic surgeries and genitourinary tract surgeries.

Figure 14. Adjusted odds ratios of postoperative respiratory failure.
*Columns = estimate. Bars = 95% confidence limits. COPD = chronic obstructive pulmonary disease. CCI = Charlson comorbidity index score. Resp fail surgery = Surgery associated with a high risk of respiratory failure. OSA * Resp fail surgery = product term (statistical interaction). The upper confidence limits for OSA and respfail surgery are both 89.5.*

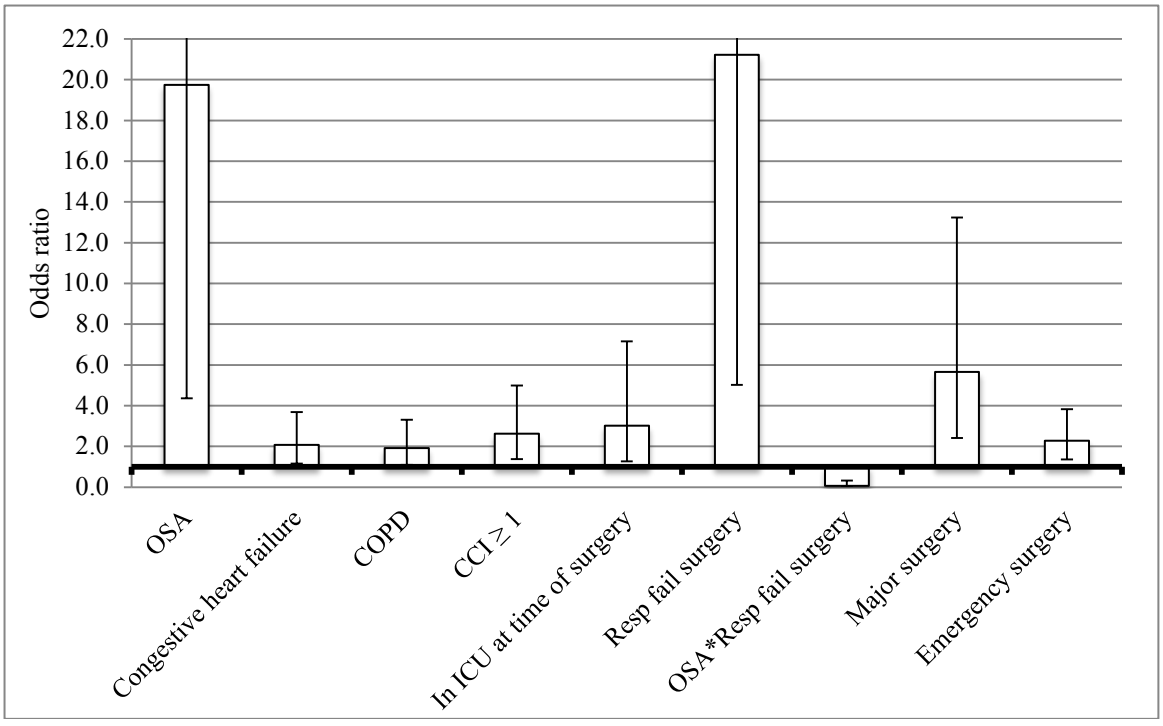
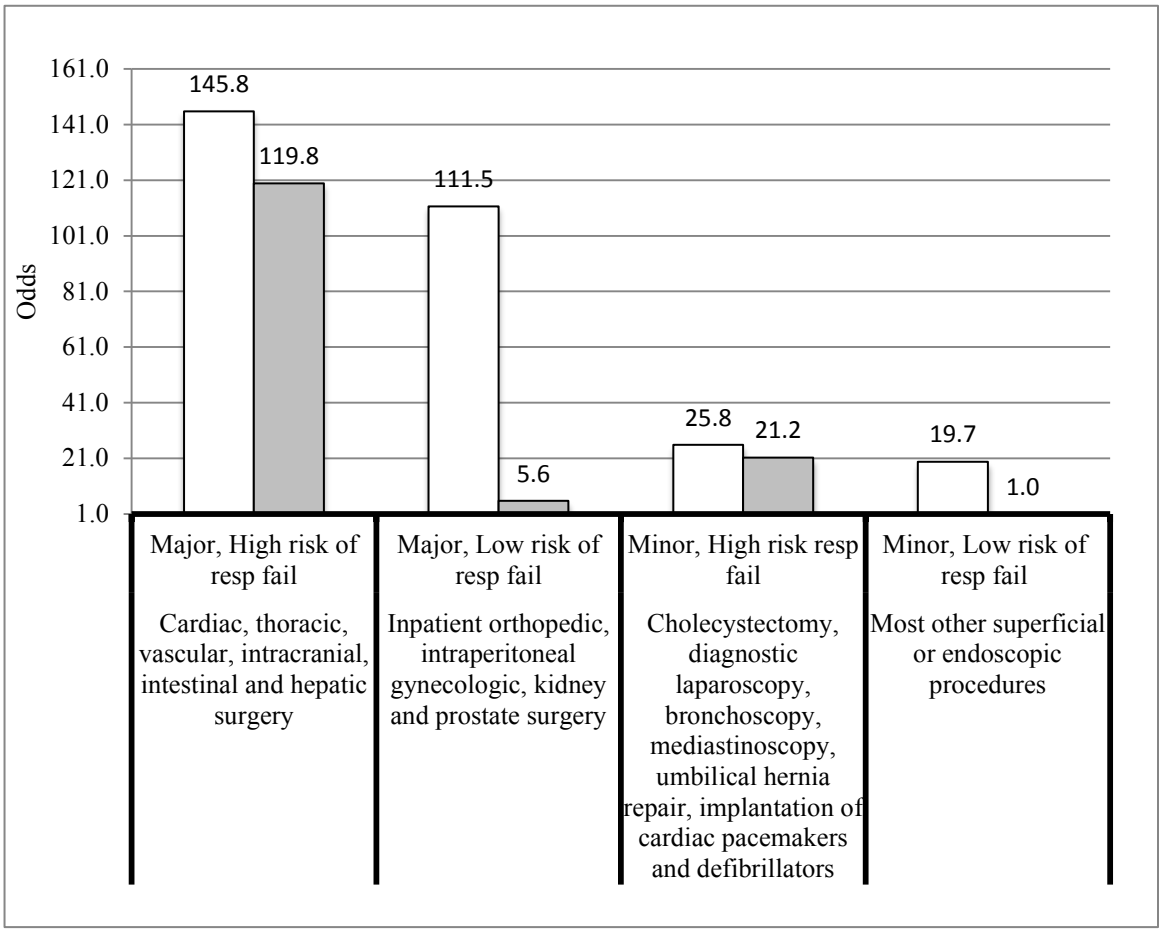


Figure 15. Odds of postoperative respiratory failure by type of surgery, for patients with and without OSA, after adjustment for comorbidities.
The baseline odds for each comparison is the patient without OSA undergoing minor surgery that is not associated with a high risk of respiratory failure. White columns = OSA, shaded columns = non-OSA, major/minor = major/ minor surgery, high/ low risk of resp fail = surgery associated with a high/ low risk of respiratory failure.



Data were too sparse to allow a complete model when OSA status was considered by severity, as a multinomial variable. In an incomplete model that excluded major surgery and emergency surgery but included the statistically significant comorbidities, severe OSA and mild OSA both remained significant predictors ($p < 0.005$) of respiratory failure, and had significant product terms with surgery associated with respiratory failure ($p < 0.05$). Moderate OSA was not a significant predictor and did not have a significant

product term ($p < 0.3$). In any multivariate model, there were no significant interactions between OSA status and timing of surgery pre or post diagnosis of OSA or with OSA status and date of surgery (pre vs. post January 1, 2005).

Interpretation

In univariate analyses, we found consistent estimates of increased risk of postoperative respiratory failure among OSA patients and subgroups. These reached statistical significance for patients with severe OSA, OSA patients post diagnosis and overall. In multivariate analyses it became evident that the risk of postoperative respiratory failure was primarily driven by the presence of OSA and the type of surgery, particularly whether the surgery was minor or major and whether it was associated with an increased risk of respiratory failure as per the study by Arrozullah et al (2000). Medical comorbidities as measured in this study, and emergency surgery were less important statistically significant predictors of postoperative respiratory failure. However, we can't rule out that patients with very high Charlson comorbidity scores or severe COPD would have higher risk than what is attributed by our model.

An important finding of our multivariate model was a significant negative statistical interaction between OSA and surgery typically associated with an increased risk of respiratory failure. The consequences of this interaction were:

- a dramatically increased risk of respiratory failure in OSA patients for surgeries not associated with a high risk of respiratory failure, mainly lower limb total joint

replacement, other orthopedic surgeries, major genitourinary surgeries and minor procedures.

- a modestly increased risk compared to a non-OSA patient in surgeries that are associated with a high risk of respiratory failure, mainly operations on the heart lungs, brain, abdominal organs and major blood vessels.

The clinical significance of these differences in risk is dependent on the baseline risk of respiratory failure for a given type of surgery. For minor surgeries not associated with a high risk of respiratory failure, the baseline risk is probably too low to make the increased odds in OSA patients (19.7) a significant absolute risk increase (Sabers et al. 2003; Stierer et al. 2010). Comparatively, in major surgeries not typically associated with respiratory failure (major orthopedic and genitourinary surgery), the risk of respiratory failure approaches that of patients having much more risky surgeries. It is worth emphasizing that this risk (odds 111.5) does not exceed the calculated risk for non-OSA patients having surgery associated with respiratory failure (odds 119.8). Thus, our model suggests decisions regarding the allocation of resources to prevent postoperative respiratory failure should consider not only whether the patient has OSA but also what type of surgery the patient is having and what comorbidities they possess.

When comparing the risk of respiratory failure between different severities of OSA, we found in the multivariate analyses that unlike severe and mild OSA, moderate OSA was not associated with a statistically significant increased risk of respiratory failure. This finding was incongruous with the trend toward increasing risk with increasing severity of OSA that was consistently observed with the death outcomes. We attribute this aberrant

finding to random error and the smaller sample size of moderate OSA patients (22% of all OSA patient surgeries).

In our multivariate analysis we also did not find a statistically significant difference in respiratory failure rates before and after the diagnosis of OSA, despite slightly lower risk in OSA patients prediagnosis in the univariate analyses. It may be that this is due to a lack of statistical power and a difference in risk does exist. This would be a surprising finding, as it would be expected that knowledge of the diagnosis of OSA and treatment with CPAP would reduce the risk of respiratory failure. It could be that variable compliance with CPAP(Park, Ramar, and Olson 2011) and the only recent emphasis on its use in the postoperative period(Chung, Yuan, and Chung 2008; Gross et al. 2006) prevented us from seeing improved outcomes in patients after their diagnosis.

However, this could also be due to an inherent bias in considering complications with significant mortality rates in patients prior to entrance into the cohort. That is, some patients in the population with undiagnosed OSA would have had respiratory failure and died and thus could not join the cohort at a later date by undergoing a sleep study. This would bias estimates of increased risk in undiagnosed OSA patients downward in proportion to the mortality rate from the complication under study. We attempted an approximate correction for this by measuring the mortality rate from postoperative respiratory failure in the other study groups and, once confirming it was similar between groups, applied this rate to the undiagnosed OSA group. This gave us an increased estimate of the raw odds of death due to respiratory failure closer to the odds observed in

OSA patients after diagnosis. The similarity in death rates from respiratory failure between OSA and non-OSA controls also provides reassurance that respiratory failure was not being coded excessively and capriciously in OSA patients.

Our multivariate model has several variables in common with the multivariable model derived by Arrozullah et al. (2000), including emergency surgery, chronic obstructive pulmonary disease (COPD) and surgeries typically associated with a high risk of respiratory failure. Arrozullah et al.'s estimates of the risk for emergency surgery and COPD are comparable to ours while our high risk surgery variable is much larger, due to the interaction with OSA, which was not studied by Arrozullah et al. Both models include several variables that were not studied in the other study.

Several other studies have reported significant numbers of serious postoperative respiratory complications, including respiratory failure, in OSA patients (Table 14). Only one study reported a large number of outcomes (Memtsoudis et al. 2011). This study propensity matched comorbidities for OSA and non-OSA patients undergoing two types of major surgery based on the classification of Arrozullah et al. One was associated with respiratory failure (abdominal surgery) and the other not (total joint replacement). Mirroring the results of our study, the OSA patients had a much higher likelihood of intubation (a consequence of respiratory failure) in total joint replacement than in abdominal surgery. Also similar to the results of our study, Memtsoudis et al. found that the incidence of intubation for OSA patients in surgery not associated with respiratory failure (3.99%) was lower than the non-OSA patient in surgery associated with

respiratory failure (5.94%). These differences by type of surgery were not as dramatic as the differences that we observed. However, Memtsoudis et al. used an administrative data definition of OSA and did not take any steps to exclude patients with undiagnosed OSA from the control group that could have resulted in an underestimation of the differences between OSA and non-OSA patients. Interestingly, this study did not find as dramatic a difference in the risk of adult respiratory distress syndrome (ARDS) for OSA and non-OSA patients between the two surgeries. The code for ARDS was one of 6 ICD9-CM codes used to define respiratory failure in this study.

Table 14. Odds ratios of serious postoperative respiratory complications in OSA patients versus non-OSA patients derived from the literature.
TJR = total lower extremity joint replacement. PC = prospective cohort. CR = chart review. AD = administrative data. OR = odds ratio. 95% CL = 95% confidence limit. N = total outcomes.

Reference	Surgical population	Data source	OR (95% CL)	N	Outcome
(Gali et al. 2009)	Major	PC	3.5	33	Respiratory events, primarily ICU admission, additional therapies
(Gupta et al. 2001)	TJR	CR	4.8	11	Acute hypercapnia and reintubation
(Memtsoudis et al. 2011)	TJR	AD	5.20 (5.05-5.37)	1399	Intubation/ mechanical ventilation
(Memtsoudis et al. 2011)	abdominal	AD	1.95 (1.91-1.98)	3812	Intubation/ mechanical ventilation
(Weingarten et al. 2011)	abdominal	CR	2.1	13	Respiratory arrest, reintubation, extended ventilatory support

There is no clear underlying mechanism to explain why the risk of respiratory failure in OSA patients would be conditional on the type of major surgery. It has been recognized that OSA patients are susceptible to the sedative effects of analgesic medication (Chung, Yuan, and Chung 2008), but these medications would be used in both types of surgery. It is possible that postoperative care cultures on wards contribute to outcomes. Where

respiratory failure is more common, staff may recognize early signs and prevent episodes. However, on wards where patients recover from surgeries typically not associated with respiratory failure, routine care may be less effective at preventing this complication because of less familiarity with it.

Cardiac arrest

The intracluster correlation coefficient for cardiac arrest among OSA patients in the cardiac arrest and myocardial infarction cohort was 0.006. This coefficient was considered negligible and this clustering effect disregarded in the analyses. 79 exposures were complicated by cardiac arrest, 23 (0.57%) in OSA patients and 56 (0.36%) in non-OSA matched controls. Prior to diagnosis of OSA the cardiac arrest rate was 0.94% (14/1496) in OSA patients and 0.38% in controls whereas after diagnosis of OSA it was 0.36% in OSA patients and 0.35% in controls. In univariate analyses, only severe OSA and OSA prior to diagnosis were significant predictors of cardiac arrest (Table 15).

The overall mortality rate from cardiac arrest among OSA patients post diagnosis and control patients pre and post diagnosis was 13%. There were no differences in mortality between these groups. If this death rate is applied to the undiagnosed OSA group, an additional 2 outcomes would be expected for an adjusted raw rate of 1.07% (16/1498). Assuming no deaths in any matched controls for these additional outcomes, the adjusted raw odds ratio of cardiac arrest in undiagnosed OSA patients versus matched controls would be 2.8.

Table 15. Univariate analyses for cardiac arrest (n = 19554).
Resp fail = Surgery associated with increased risk of respiratory failure. ICU = Intensive care unit. RCRI = Revised cardiac risk index. CCI = Charlson comorbidity index.

Predictor variable	Odds ratio	95% confidence limits		*p*
OSA and subgroups				
All	**1.59**	1.00	2.52	0.05
Mild	**0.91**	0.36	2.34	0.85
Moderate	**1.19**	0.43	3.30	0.73
Severe	**2.23**	1.26	3.94	0.01
All OSA pre diagnosis	**2.47**	1.28	4.77	0.007
All OSA post diagnosis	**1.02**	0.51	2.02	0.96
Surgery				
Major	**8.09**	4.84	13.52	<0.0001
Resp fail	**4.09**	2.58	6.50	<0.0001
Emergency	**4.05**	2.55	6.42	<0.0001
Age, sex and comorbidities				
Age at surgery (1 year increase)	**1.05**	1.04	1.07	<0.0001
Male	**1.10**	0.71	1.70	0.68
Ischemic heart disease	**3.11**	1.99	4.88	<0.0001
Congestive heart failure	**6.70**	4.31	10.42	<0.0001
Cerebrovascular accident	**4.46**	2.73	7.30	<0.0001
Diabetes mellitus	**1.99**	1.24	3.19	0.004
Renal disease	**3.74**	2.08	6.72	<0.0001
Chronic obstructive pulmonary disease	**1.86**	1.21	2.87	0.01
In an ICU at time of surgery	**9.38**	1.99	44.25	0.005
RCRI score (vs. score of 0)				
1	**7.80**	2.31	26.28	0.01
2	**21.69**	6.50	72.34	<0.0001
≥ 3	**52.54**	16.29	169.51	<0.0001
CCI score (vs. score of 0)				
1-2	**7.45**	4.40	12.60	<0.0001
3-4	**22.85**	11.36	45.97	<0.0001
≥ 5	**9.87**	4.01	24.32	<0.0001

In a multivariate model incorporating all severities of OSA in one variable, there was a significant product term (statistical interaction) between the timing of surgery (before vs. after diagnosis) and OSA status. The main effects of OSA and timing of surgery were not significant ($p = 0.8$, 0.2 respectively), but the product term was ($p = 0.01$), such that OSA patients having surgery prior to diagnosis had a significantly increased risk of

postoperative cardiac arrest compared to those having surgery after diagnosis, and to non-OSA controls. When OSA was modeled as a multinomial ordinal variable by severity, the same interaction was found to be driven by increased risk in patients with severe OSA ($p = 0.01$) (Figure 16). The effect of this interaction on the risk of postoperative cardiac arrest among patients with and without OSA having surgery before and after their diagnosis is illustrated in Figure 17. The odds of cardiac arrest in the non-OSA patients were increased in the prediagnosis period compared to the postdiagnosis period (odds 1.45), but not significantly ($p = 0.2$). This represents either random variation or an unrecognized confounder in the data not controlled for in the multivariate model. Regardless, in the prediagnosis period, patients with moderate and severe OSA show an increased risk of cardiac arrest out of proportion to the increase in control patients, although only severe OSA was statistically significant ($p = 0.01$). In the postdiagnosis period OSA patients had odds very close to 1 of having a postoperative cardiac arrest, compared to a control patient. There were no significant interactions between OSA status and date of surgery (pre vs. post January 1, 2005).

Figure 16. Adjusted odds ratios of postoperative cardiac arrest.
*Columns = estimate. Bars = 95% confidence limits. COPD = chronic obstructive pulmonary disease. CCI = Charlson comorbidity index score. Resp fail surgery = Surgery associated with a high risk of respiratory failure. Severe OSA * Surgery prior to diagnosis = product term (statistical interaction). The upper confidence limits for mild, moderate and severe OSA product terms are 10.8, 18.3 and 18.7 respectively.*

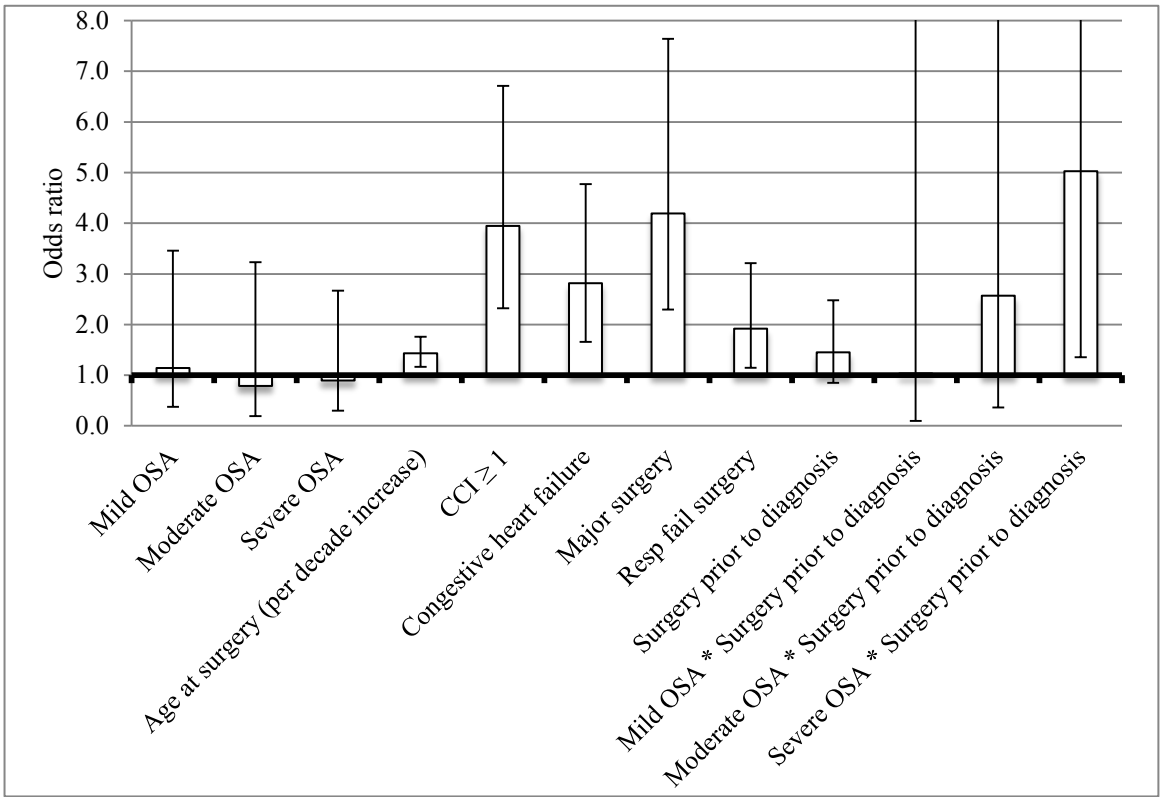
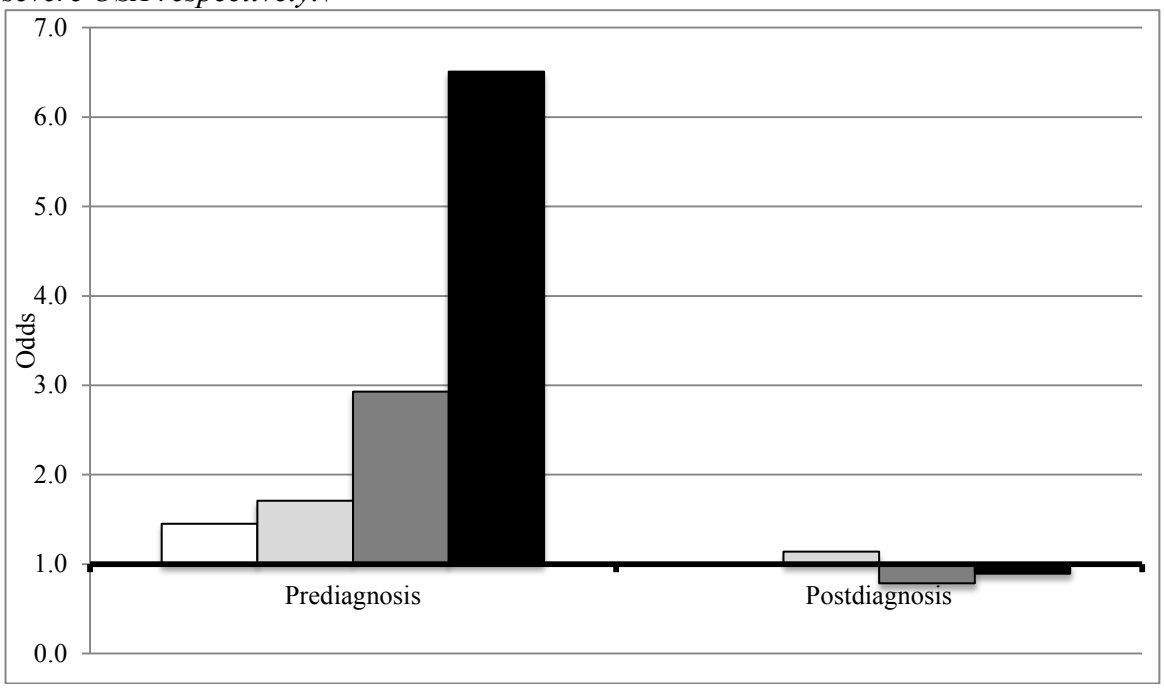


Figure 17. Odds of postoperative cardiac arrest by timing of surgery relative to diagnosis of OSA, after adjustment for age, comorbidities and type of surgery.
The baseline odds for each comparison is the non-OSA patient in the postdiagnosis period. White columns = non-OSA. Light grey, dark grey, black = mild, moderate, severe OSA respectively.



Interpretation

In univariate analyses, we found patients with severe OSA and patients with undiagnosed OSA had significantly increased risk of postoperative cardiac arrest. Multivariate analyses suggested that postdiagnosis OSA patients have similar risk to non-OSA patients when controlling for age, the type of surgery and comorbidities. However, large confidence limits mean we can not exclude that OSA may significantly increase or decrease the risk of cardiac arrest after diagnosis of OSA. Among OSA patients prior to their diagnosis, we found a trend for increasing risk with increasing severity of OSA. Confidence limits were again wide but mild OSA demonstrated a marginal increase in risk, moderate OSA a larger increase and severe OSA a statistically significant increase. These risks would be modestly elevated by patients who would have become part of the

cohort but died due to postoperative cardiac arrest. Based on the rest of the cohort, the death rate after postoperative cardiac arrest was 13%. Conversely, we can not exclude that patients who experienced a cardiac arrest postoperatively would have been more likely to be referred for sleep study than other patients with undiagnosed OSA who did not have postoperative cardiac arrest. We were unable to estimate the magnitude of this bias.

Age, medical comorbidities as measured in this study, and the type of surgery were also important predictors. Similar to the postoperative respiratory failure model, the postoperative cardiac arrest model suggests that in making decisions about postoperative care it is important to consider not just whether the patient has OSA but also their comorbidities and the type of surgery. For example, after controlling for age and type of surgery, a patient with a past history of congestive heart failure and any one of the comorbidities in the Charlson comorbidity index would have a higher risk of postoperative cardiac arrest than a patient with undiagnosed severe OSA. These other factors should be incorporated into guidelines.

Only three other studies have examined serious postoperative cardiac complications in OSA patients (Gali et al. 2009; Gupta et al. 2001; Liao et al. 2009). Arrhythmias and cardiac arrest events were sparse, even in the only study that examined OSA patients both before and after diagnosis (Gupta et al. 2001).

The mechanism by which undiagnosed severe OSA would lead to increased complications is likely related to the pathophysiology of OSA. Prior to diagnosis, OSA patients don't have access to the beneficial effects of CPAP and caregivers may be unaware of the symptoms and consequences of OSA. As defined in this study, the cardiac arrest outcome consisted of cardiac arrest, cardiorespiratory failure and life threatening arrhythmias. Prolonged hypoxemia could also induce life threatening arrhythmias and cardiorespiratory arrest. Increasing severity of OSA likely reduces physiologic reserve in the cardiac and respiratory systems, making postoperative stressors most harmful in patients with severe disease.

Other postoperative complications

For each of the four other individual postoperative complications examined in this study, there were 9 or fewer outcomes among OSA patients. This sparse data precluded a multivariate analysis, but the univariate analysis for OSA vs. non-OSA is presented in Table 16. For atrial fibrillation and cerebrovascular accident, the intracluster correlation coefficient for the complication among OSA patients (who may present for surgery more than once) approached or exceeded 0.1. This is high enough to bias standard error and confidence limits downward and increase the risk of type I error (Clarke 2008).

Table 16. The risk of uncommon postoperative complications in OSA patients vs. non-OSA controls.
ICC = Intracluster correlation coefficient for the occurrence of the event among OSA patients. CVA = cerebrovascular accident.

Complication	ICC	Odds ratio	95% confidence limits		*p*	*n*
Myocardial infarction	0.04	0.67	0.30	1.48	0.32	19554
Pneumonia	0.03	0.96	0.43	2.16	0.93	20442
Atrial fibrillation	0.09	0.34	0.10	1.12	0.07	20256
CVA	0.23	0.22	0.05	0.91	0.04	20339

Any postoperative complication

Any postoperative complication (APC) was defined as experiencing any one or more of the 6 individual complications under study. The intracluster correlation coefficient for APC among OSA patients in the APC cohort was 0.006. This coefficient was considered negligible and this clustering effect disregarded in the analyses. 217 exposures to surgery were complicated by APC, 52 (1.31%) in OSA patients and 165 (1.07%) in non-OSA matched controls. Prior to diagnosis the complication rate was 1.55% (23/1487) in OSA patients and 0.96% in controls whereas after diagnosis of OSA it was 1.17% in OSA patients and 1.14% in controls. In univariate analyses, severe OSA and OSA prior to diagnosis were significant predictors of APC along with many surgical factors and comorbidities (Table 17).

The overall mortality rate from cardiac arrest among OSA patients post diagnosis and control patients pre and post diagnosis was 18%. There were no differences in mortality between these groups. If this death rate is applied to the undiagnosed OSA group, an additional 5 outcomes would be expected for an adjusted raw rate of 1.07% (28/1492).

Assuming no deaths in any matched controls for these additional outcomes, the adjusted raw odds ratio of cardiac arrest in undiagnosed OSA patients versus matched controls would be 2.0.

Table 17. Univariate analyses for any postoperative complication (n = 19359).
Resp fail = Surgery associated with increased risk of respiratory failure. Reoperation = The surgery of interest was associated with another operation on the same day for an immediate complication. ICU = Intensive care unit. RCRI = Revised cardiac risk index. CCI = Charlson comorbidity index.

Predictor variable	Odds ratio	95% confidence limits		*p*
OSA and subgroups				
All	**1.19**	0.88	1.61	0.60
Mild	**0.94**	0.54	1.63	0.82
Moderate	**0.81**	0.40	1.67	0.57
Severe	**1.58**	1.09	2.30	0.02
All OSA pre diagnosis	**1.62**	1.01	2.61	0.05
All OSA post diagnosis	**1.01**	0.68	1.48	0.97
Surgery				
Major	**7.47**	5.41	10.30	<0.0001
Resp fail	**4.25**	3.14	5.75	<0.0001
Emergency	**5.83**	4.30	7.91	<0.0001
Reoperation	**1.75**	0.04	73.56	0.77
Age, sex and comorbidities				
Age at surgery (1 year increase)	**1.06**	1.05	1.07	<0.0001
Male	**1.38**	1.05	1.80	0.02
Ischemic heart disease	**3.37**	2.54	4.47	<0.0001
Congestive heart failure	**5.80**	4.37	7.69	<0.0001
Cerebrovascular accident	**3.46**	2.47	4.85	<0.0001
Diabetes mellitus	**2.04**	1.52	2.73	<0.0001
Renal disease	**3.89**	2.70	5.60	<0.0001
Chronic obstructive pulmonary disease	**1.90**	1.45	2.48	<0.0001
In an ICU at time of surgery	**43.00**	15.83	116.79	<0.0001
RCRI score (vs. score of 0)				
1	**4.99**	2.69	9.24	<0.0001
2	**14.62**	7.98	26.83	<0.0001
≥ 3	**35.03**	19.62	62.57	<0.0001
CCI score (vs. score of 0)				
1-2	**6.58**	4.71	9.19	<0.0001
3-4	**28.32**	18.77	42.73	<0.0001
≥ 5	**13.40**	7.88	22.76	<0.0001

In a multivariate model incorporating all severities of OSA as one variable, there was a significant product term (statistical interaction) between the timing of surgery (before vs. after diagnosis) and OSA status. Similar to the cardiac arrest outcome, the main effects of OSA and timing of surgery were not significant (p = 0.8, 0.6 respectively), but the product term was (p = 0.007), such that OSA patients having surgery prior to diagnosis had a significantly increased risk of APC compared to those having surgery after diagnosis, and to non-OSA controls. When OSA was modeled as a multinomial ordinal variable by severity, the same interaction was shown to be primarily driven by increased risk in patients with severe OSA (p = 0.007) (Figure 15). The effect of this interaction on the risk of APC among patients with and without OSA having surgery before and after their diagnosis is illustrated in Figure 16. Only patients in the pre diagnosis period who went on to be diagnosed with severe OSA showed a significantly increased risk of APC. There were no significant interactions between OSA status and date of surgery (pre vs. post January 1, 2005).

Figure 18. Adjusted odds ratios of any postoperative complication.
*Columns = estimate. Bars = 95% confidence limits. COPD = chronic obstructive pulmonary disease. CCI = Charlson comorbidity index score. ICU = Intensive care unit. Resp fail surgery = Surgery associated with a high risk of respiratory failure. Severe OSA * Surgery prior to diagnosis = product term (statistical interaction). The upper confidence limit forin ICU at time of surgery is 27.6.*

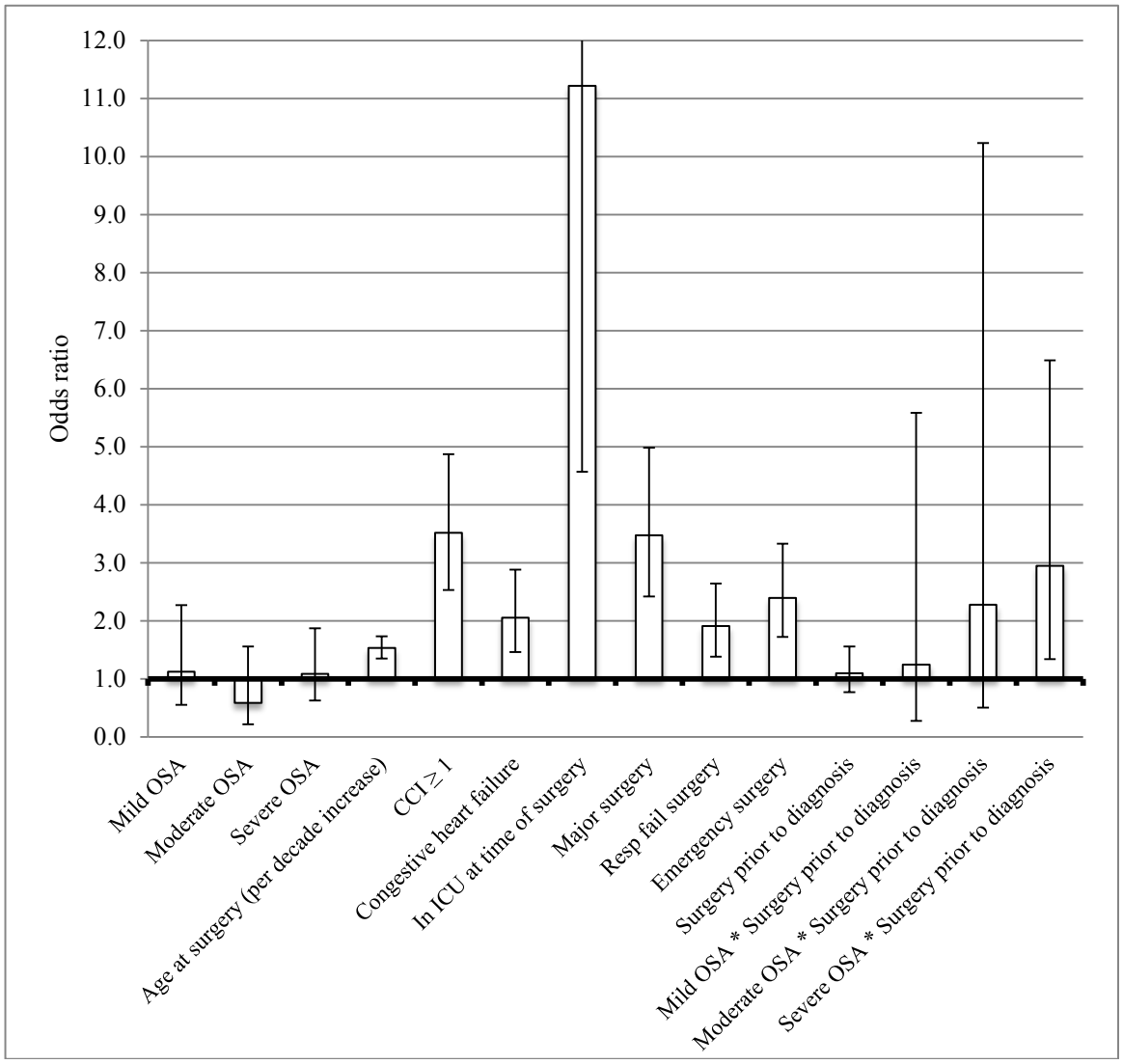
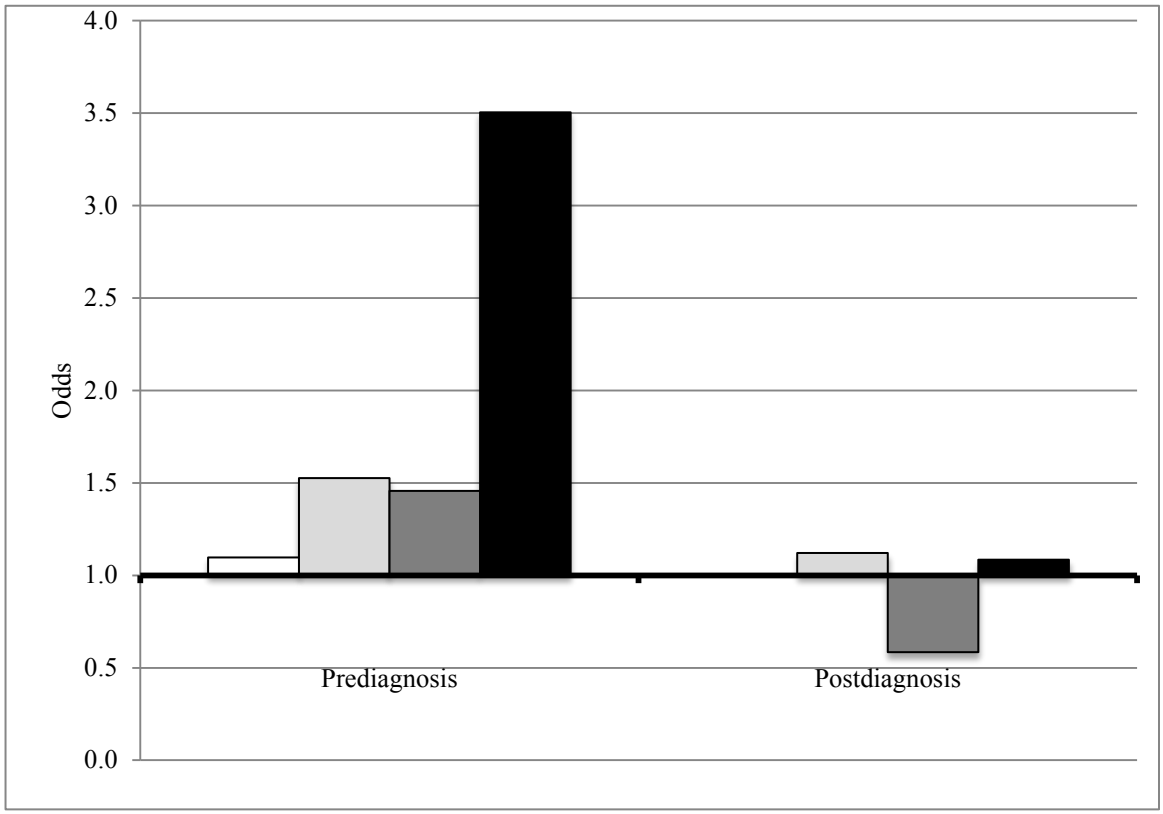


Figure 19. Odds of any postoperative complication by timing of surgery relative to diagnosis of OSA, after adjustment for age, comorbidities and type of surgery.
The baseline odds for each comparison is the non-OSA patient in the postdiagnosis period. White columns = non-OSA. Light grey, dark grey, black = mild, moderate, severe OSA respectively.



Interpretation

In univariate analyses, we found patients with severe OSA and OSA patients prior to diagnosis had significantly increased risk of APC. Multivariate analyses suggested that postdiagnosis OSA patients have similar risk to non-OSA patients when controlling for age, the type of surgery and comorbidities. Even when using upper 95% confidence limits, the maximum expected risk of OSA after diagnosis may be an odds ratio of about 2, smaller than many surgical and medical comorbidity predictors in the model. Among

OSA patients prior to their diagnosis, we found marginal increases in risk for patients with mild and moderate OSA but significant increase in risk for patients with severe OSA. These risks would be modestly elevated by patients who would have become part of the cohort but died due to a postoperative complication. Based on the rest of the cohort, the death rate after APC was 18%. Conversely, we can not exclude that patients who experienced a postoperative complication would have been more likely to be referred for sleep study than other patients with undiagnosed OSA who did not have a postoperative complication. We were unable to estimate the magnitude of this bias.

Age, medical comorbidities as measured in this study, and the type of surgery were also important predictors. Consistent with the other analyses, the APC multivariate model suggests that in making decisions about postoperative care it is important to consider not just whether the patient has OSA but also their comorbidities and the type of surgery. For example, after controlling for age and type of surgery, a non-OSA patient with a CCI ≥ 1 would have comparable risk of APC to a patient with severe OSA, prior to diagnosis. These other comorbidities, and the relative importance of the type of surgery should be incorporated into guidelines for the postoperative care of OSA patients.

Four other studies have examined composite outcomes similar to the APC outcome in this study. Gali et al. (2009) and Gupta et al. (2001) found increased risk of postoperative complications in patients with undiagnosed OSA. Using an administrative data definition of OSA, Liao et al. (2009) found increased risk of postoperative complications in OSA patients after diagnosis. This study included less serious

complications such as oxygen desaturation, which was the most commonly reported adverse outcome. Weingarten et al. (2011) found no increased risk of postoperative complications in patients diagnosed with OSA undergoing bariatric surgery, compared to patients without OSA undergoing bariatric surgery. The various cardiac and respiratory complications that make up the APC outcome likely share the same mechanism as was proposed for cardiac arrest. That is, reduced physiologic reserve in the face of postoperative stress being most severe in patients with more severe OSA.

Conclusions

In this study we found increased risk of serious postoperative cardiac and respiratory complications (SPCRCs) among OSA patients compared to non-OSA patients but that the risks differed by the type of complication. We found increased risk of cardiac arrest and the composite outcome of any postoperative complication in patients with undiagnosed OSA only, in particular those who were eventually diagnosed with severe OSA. We also found significantly increased risk of respiratory failure in OSA patients both before and after diagnosis, of any severity. This risk was dependent on the type of surgery, though. Compared to non-OSA patients, OSA patients had dramatically increased risk of respiratory failure in surgeries not typically associated with respiratory failure and modestly increased risk in surgeries typically associated with postoperative respiratory failure. For four other postoperative SPCRCs with sparse outcomes, pneumonia, cerebrovascular accident, atrial fibrillation and myocardial infarction, we did not find any evidence of increased risk due to OSA.

Despite the increased risk of some SPCRCs, and their strong association with postoperative mortality, we did not find a statistically significant increase in postoperative death due to OSA in univariate or multivariate analyses at 3, 7 or 28 days after surgery. However, we did observe consistent trends of increased risk with increasing severity of OSA among the three death outcomes. There are several possible explanations for the absence of significant differences in postoperative mortality. First, due to the infrequency of death as an outcome, our study was not powered to rule out a small statistically significant risk. This would be most likely for patients with severe OSA at 3 or 7 days after surgery. Regardless, other predictor variables describing the nature of the surgery and the patient's other comorbidities were consistently more important predictors of postoperative death. Second, the postoperative death analyses were restricted to patients who were already diagnosed with OSA at the time of their surgery. For patients already diagnosed with OSA, the risk of cardiac arrest or any postoperative complication was similar to those without OSA. The risk of respiratory failure was increased (odds ratio 3.65), but even though this complication had a 28 day death rate of 22%, the overall rates of this complication as measured in this study would not have resulted in enough death outcomes to produce a statistically significant difference in postoperative death. Third, postoperative death likely results from more than just the cardiac and respiratory complications measured in this study. Although not generally an indication for intensive postoperative monitoring, these causes of death could obscure differences in mortality attributable to SPCRCs. Finally, it should be noted that our sensitivity analysis suggested that the absence of significant differences in death rates is not due to changing patterns of care for OSA patients in the later years of

the data. We found no significant differences in any of the measured outcomes when comparing the periods before and after January 1 2005.

These important results are a corollary of the methodological advantages of the study design. The study used a clinical database of sleep apnea patients to define the presence of OSA and its severity, instead of using clinical scoring systems or administrative data definitions. These have limited sensitivity and specificity and can't stratify OSA by severity. The study was also relatively large and had essentially equal and complete follow-up for the first postoperative week to ensure comparability of information between OSA and non-OSA patients. The non-OSA controls were rigorously screened to be free of undiagnosed OSA and OSA, an important consideration given the increased risk attributed to undiagnosed OSA (Gross et al. 2006) and the high prevalence of undiagnosed OSA in the general population (Lee et al. 2008). Our matching strategy ensured the estimates of risk between OSA and non-OSA patients were not due to differences in the specific types of surgery that occurred, their indication or changes in their risk over time. We also measured and accounted for clustering within the study design when necessary. We did not measure surrogate outcomes like episodes of oxygen desaturation that may be markers of OSA rather than predictors of more serious outcomes. The outcomes chosen for this study were death and serious postoperative cardiac and respiratory complications (SPCRCs). The SPCRCs were strong predictors of death and along with death, are the outcomes that intensive postoperative monitoring of OSA patients would be expected to prevent.

Despite these strengths, three limitations of the study design may have influenced the results. First, we were unable to distinguish between minimally invasive and classical open approaches to the same surgery. For the small number of surgeries where this is a relevant concern, we have postulated that the risk due to OSA has been overestimated but could not estimate the magnitude of this effect. Second, we attempted to retrospectively study outcomes in patients prior to their diagnosis with OSA, due to the interest in undiagnosed OSA patients in the literature (Gross et al. 2006). This introduced two competing sources of bias: a referral bias in that OSA patients experiencing outcomes may have been more likely to be referred for sleep study and, the unintentional exclusion of pre diagnosis OSA patients who had died subsequent to postoperative complications and could not present later for sleep study to be included in the cohort. We attempted to estimate the effect of the latter and for all the postoperative complications it would have increased the magnitude of all estimates, strengthening the findings. We were unable to estimate the referral bias, which would have had the opposite effect of overestimating the effect of OSA on the outcomes. Short of prospectively collecting all data, there is no way to eliminate this bias. Finally, we were unable to study the effects of body mass index, the type of anesthetic and the type of postoperative care on outcomes. Because of the high correlation between obesity and OSA, even if body mass index data were available it would be difficult to separate these effects. For the other variables, where significant choice in anesthetic and analgesic technique exists, it is often influenced by patient comorbidities. Thus again, even if the data were available, it would be difficult to separate these effects. While changing patterns of postoperative care may have

influenced outcomes in the later years of the study, our sensitivity analysis did not find evidence for this.

Notwithstanding these limitations our results are generalizable to other surgical populations. We have included and analyzed outcomes after surgeries representing the entire surgical experience of a large cohort of OSA patients. This cohort had a wide spectrum of severity of OSA and a variety of comorbidities. Allowing for differences in study design, our results were within the range that has been reported elsewhere. We represented our measures of risk as odds ratios because of the recognized limitations in the specificity of administrative data constructs (Lix et al. 2006; Quan et al. 2008). Assuming nondifferential misclassification, these relative risks can be converted to absolute risk differences by obtaining accurate absolute rates from other sources.

Our results should inform future work in the following ways. First, patients with undiagnosed OSA should continue to be a focus of future study based on our finding of increased risk of SPCRCs in those with undiagnosed OSA compared to those already diagnosed with OSA and those without OSA. Second, our results consistently found surgical factors to be more important than allowed for in current guidelines on the care of OSA patients, and these guidelines should be updated to reflect these results. Finally, we frequently found that other medical comorbidities and comorbidity scores were at least as important as OSA in predicting SPCRCs and death. Assuming these outcomes are equally preventable in OSA and non-OSA patients, our results suggest current guidelines

may be inequitably directing resources to OSA patients at the expense of other high-risk patients without OSA.

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Appendix: List of abbreviations

AHI	apnea/ hypopnea index
APC	Any postoperative complication
ARDS	Acute respiratory distress syndrome
ASA	American Society of Anesthesiologists
BMI	Body mass index
CCI	Charlson comorbidity index
CHF	Congestive heart failure
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure machine
CRF	Chronic renal failure
CSA	Central sleep apnea
CVA	Cerebrovascular accident
DM	Diabetes mellitus
EDS	Excessive daytime sleepiness
GEE	Generalized estimating equations
HIPC	Health Information Privacy Committee of the Government of Manitoba
HST	Home sleep test
ICC	Intraclass correlation coefficient
ICD	International Classification of Diseases
ICU	Intensive care unit
IHD	Ischemic heart disease
MCHP	Manitoba Centre for Health Policy
OHS	Obesity hypoventilation syndrome
OSA	Obstructive sleep apnea
PSG	Polysomnogram (an in lab sleep study)
RCRI	Revised cardiac risk index
RF	Respiratory failure
RF surgery	Surgery associated with a high risk of respiratory failure
SBGH database	Saint Boniface General Hospital Sleep Disorder Centre Research and Teaching database
SPCRCs	Serious postoperative cardiovascular and respiratory complications
UOSA	Undiagnosed obstructive sleep apnea