EDITORIAL

Unrecognized Obstructive Sleep Apnea and Postoperative Cardiovascular Complications
A Wake-up Call

Dennis Auckley, MD; Stavros Memtsoudis, MD, PhD, MBA

In the United States, obstructive sleep apnea (OSA) affects 14% of adult men and 5% of adult women, with higher rates among obese individuals and older adults.[1] The majority of individuals with OSA remain undiagnosed.[2,3] Although OSA has repeatedly been associated with unfavorable long-term cardiovascular outcomes,[4] it is increasingly recognized that patients with OSA are at risk for adverse events in the postoperative setting.[5,6] Perioperative clinicians have traditionally equated the presence of OSA with complications affecting the respiratory system, but based on a small number of mostly retrospective studies, it is unclear whether patients with unrecognized OSA are at higher risk of postoperative cardiovascular events. In addition, because most patients with OSA will be undiagnosed at the time of surgery, questions remain regarding the importance of identifying this population preoperatively, as well as of risk-stratifying individuals for clinically relevant adverse outcomes. Quality data are needed to address this issue, because the results could significantly influence clinical care pathways for patients undergoing surgery.

Related article page 1788

The study by Chan and colleagues[7] in this issue of *JAMA* provides new information about some of these important issues. The Postoperative Vascular Complications in Unrecognized OSA (POSA) study was a large, multicenter, prospective observational cohort study designed to evaluate the association between the results of preoperative sleep testing for OSA and 30-day postoperative cardiovascular outcomes among patients undergoing noncardiac surgery. The primary outcome was a composite of myocardial injury, heart failure, thromboembolism, atrial fibrillation, stroke, and cardiac death. Among the study population of 1218 patients, the authors identified high rates of undiagnosed OSA; 37.1% of patients had mild OSA, 19.3% moderate OSA, and 11.2% severe OSA. Postoperative cardiovascular events occurred in 235 patients (19.3%). Multivariable analysis, controlling for perioperative factors known to adversely affect outcomes, revealed that severe OSA was significantly associated with a higher rate of postoperative cardiovascular events (adjusted hazard ratio [HR], 2.23 [95% CI, 1.49-3.34]; $P = .001$). However, this association was not seen among patients with mild OSA (adjusted HR, 1.36 [95% CI, 0.97-1.91]; $P = .08$) or moderate OSA (adjusted HR, 1.47 [95% CI, 0.98-2.09]; $P = .07$). Overnight oximetry monitoring was performed on the first 3 postoperative nights and found that higher risk for postoperative cardiovascular events was associated with longer duration of postoperative oxygen desaturation less than 80% ($P < .001$). No significant interaction was observed between the type of anesthesia, use of postoperative opioids, and supplemental oxygen therapy with perioperative outcomes.

This study has several strengths that distinguish it from previous work in the field: the study is large, prospective, and well-organized; has predefined outcomes; and uses rigorous methodology and follow-up. A few of these strengths are worth discussing, as they suggest a causal relationship between OSA and postoperative cardiovascular complications.

First, the study used standardized objective sleep testing (also known as home sleep apnea testing [HSAT]) using a portable type 3 sleep testing device in the 30 days before the operation to determine the presence and severity of OSA. Arguments can be made that this type of testing, because of an inability to measure sleep, may underestimate the severity of OSA and should not be used for population screening.[2] However, the accuracy of HSAT is greater than the accuracy of questionnaire screening and is viewed as a reasonable alternative to expensive and resource-intensive polysomnography, particularly when time constraints exist (ie, preoperatively) and when quality oversight is ensured.[2] HSAT is already widely used in clinical practice, although its feasibility for preoperative testing is institution-dependent, largely because of the infrastructure (eg, personnel) needed to support testing in the context of a comprehensive preoperative program. HSAT might best be used as a second risk-stratification step in patients identified as high risk for OSA by questionnaire screening. Regardless, the use of objective data to define OSA in the POSA study confirms that the rate of undiagnosed and unrecognized OSA in the surgical population remains high (67.6% in this study). Of interest, the majority of patients in this study were Asian and had a lower body mass index (mean, 26.8) than that seen in the population of the United States. Even though Asian patients have been shown to have similar rates of OSA at lower body mass index compared with white patients,[8] many if not most of these patients would be missed by routine preoperative screening.[9]

Second, the study used predetermined clinically relevant outcomes, including a composite outcome as a primary outcome, which may initially be cause for criticism. However, when the data were analyzed independently for each indi-

vidual outcome making up the composite, statistically significant associations were found between severe OSA and myocardial injury (and myocardial infarction in post hoc analysis), congestive heart failure, new-onset atrial fibrillation, and cardiac death. Each of these outcomes has been associated with severe OSA in the long term[4]; thus, the outcomes are biologically plausible from a pathophysiologic standpoint. As a result, the findings from this study should bring attention to the association of OSA with cardiovascular events in the acute care setting.

Importantly, the authors avoided the pitfall often seen in the perioperative literature of assigning postoperative oxygen desaturation as an outcome; rather, they focused on clinically significant and measurable events. Oxygen desaturation is typically a clinical manifestation of OSA and is thus expected to be seen postoperatively in patients with OSA. However, the depth and duration of sleep-related hypoxemia is considered an important mediator for the development of more serious clinical complications.[10] In this context, the POSA study confirmed an association between severe and prolonged nocturnal hypoxemia and postoperative cardiovascular events. The findings of an association between moderate-to-severe OSA and unplanned readmission to the intensive care unit as well as postoperative reintubation have also been recognized in previous studies.[5,6]

Third, follow-up was excellent, and the data set was nearly 100% complete; thus, imputation to account for missing data was not needed. This is a testimony to the stringent quality oversight of the study and adds to the robustness of the findings.

Fourth, the authors were able to control for the majority of relevant confounders associated with poor outcomes in perioperative medicine. However, an important factor not addressed in the study was the dose of opioids used and how this may influence the relationship between OSA, its severity, and perioperative cardiovascular outcomes. Having a diagnosis of OSA, regardless of severity, as well as exposure to higher doses of opioids, have both been associated with postoperative opioid-induced respiratory depression,[11] although the potential effects of this association on cardiovascular outcomes is unclear.

Some important limitations of the study should be considered when interpreting the data. Some of these have already been mentioned and include the use of HSAT for diagnosing OSA (which may underestimate OSA severity and thus affect the associations seen), the lack of information about opioid dosing (likely important when considering adverse outcomes), and the high proportion of Asian patients in the study population (which may limit generalizability in the United States). An additional concern is that postoperative care was not standardized; thus, variability in patient care could have had some influence on the associations and outcomes reported.

The POSA study should raise awareness about the association between unrecognized OSA in the presurgical population and adverse postoperative cardiovascular outcomes. The study results provide further evidence to support preoperative screening for OSA, yet they also raise many important questions. Among these is how best to manage the care of patients identified as being at high risk for OSA or who have a preoperative diagnosis made by objective sleep testing. The avoidance of complications in the postoperative period has been the target of several suggested approaches that mechanistically could reduce airway obstruction and resultant hypoxemia. Currently, recommended perioperative interventions are largely consensus-based or have low-quality evidence.[12,13] Although the effectiveness of these interventions is poorly studied, some suggested strategies may include enhanced monitoring (oximetry, CO_2 monitoring), conservative measures (elevating the head of the bed, avoiding supine sleep position, minimizing opioids), and specific OSA therapies such as the perioperative use of positive airway pressure.

However, these interventions are intuitively designed to address respiratory concerns, and their relationship with preventing acute cardiovascular complications in the postoperative period is uncertain. With the insights provided by the POSA study, that cardiovascular complications represent a major concern after surgery in patients with undiagnosed OSA, a new or extended approach that focuses on detecting occult cardiovascular disease commonly associated with OSA, such as pulmonary hypertension as well as coronary disease and cerebral artery disease,[4] may be warranted. Until additional evidence is available to refine perioperative management pathways in patients with known or suspected OSA, clinicians should consider unrecognized OSA in their perioperative assessments.

It is time that OSA and its associated disease processes are widely recognized as major perioperative risk factors. Although more research is needed to further detail the mechanisms and clinical management strategies, OSA as a disease complex should receive the same attention as other comorbidities, such as diabetes, for which optimization has improved perioperative morbidity and mortality over recent decades.

ARTICLE INFORMATION

Author Affiliations: Division of Pulmonary, Critical Care and Sleep Medicine, MetroHealth Medical Center, Case Western Reserve University, Cleveland, Ohio (Auckley); Society of Anesthesia and Sleep Medicine, Milwaukee, Wisconsin (Auckley, Memtsoudis); Anesthesia and Health Policy and Research, Weill Cornell Medical College, New York, New York (Memtsoudis); Department of Anesthesiology, Hospital for Special Surgery, New York, New York (Memtsoudis).

Corresponding Author: Dennis Auckley, MD, Division of Pulmonary, Critical Care and Sleep Medicine, MetroHealth Medical Center, Case Western Reserve University, 2500 MetroHealth Dr, Cleveland, OH 44109 (dauckley@metrohealth.org).

Conflict of Interest Disclosures: Drs Auckley and Memtsoudis reported serving on the board of directors and as vice president and president, respectively, of the Society of Anesthesia and Sleep Medicine.

Funding/Support: Dr Auckley reported receiving research funding from Medtronic. Dr Memtsoudis reported receiving personal fees from Teikoku and Sandoz.

REFERENCES

1. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol*. 2013;177(9):1006-1014. doi:10.1093/aje/kws342

2. Kapur VK, Auckley DH, Chowdhuri S, et al. Clinical practice guideline for diagnostic testing for

adult obstructive sleep apnea: an American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med*. 2017;13(3):479-504. doi:10.5664/jcsm.6506

3. Redline S, Sotres-Alvarez D, Loredo J, et al. Sleep-disordered breathing in Hispanic/Latino individuals of diverse backgrounds: the Hispanic Community Health Study/Study of Latinos. *Am J Respir Crit Care Med*. 2014;189(3):335-344. doi:10.1164/rccm.201309-1735OC

4. Sarkar P, Mukherjee S, Chai-Coetzer CL, McEvoy RD. The epidemiology of obstructive sleep apnoea and cardiovascular disease. *J Thorac Dis*. 2018;10(suppl 34):S4189-S4200. doi:10.21037/jtd.2018.12.56

5. Kaw R, Chung F, Pasupuleti V, Mehta J, Gay PC, Hernandez AV. Meta-analysis of the association between obstructive sleep apnoea and postoperative outcome. *Br J Anaesth*. 2012;109(6):897-906. doi:10.1093/bja/aes308

6. Opperer M, Cozowicz C, Bugada D, et al. Does obstructive sleep apnea influence perioperative outcome? a qualitative systematic review for the Society of Anesthesia and Sleep Medicine Task Force on Preoperative Preparation of Patients With Sleep-Disordered Breathing. *Anesth Analg*. 2016;122(5):1321-1334. doi:10.1213/ANE.0000000000001178

7. Chan MTV, Wang CY, Seet E, et al; Postoperative Vascular Complications in Unrecognized Obstructive Sleep Apnea (POSA) Study Investigators. Association of unrecognized obstructive sleep apnea with postoperative cardiovascular events in patients undergoing major noncardiac surgery [published May 14, 2019]. *JAMA*. doi:10.1001/jama.2019.4783

8. Dudley KA, Patel SR. Disparities and genetic risk factors in obstructive sleep apnea. *Sleep Med*. 2016;18:96-102. doi:10.1016/j.sleep.2015.01.015

9. Singh M, Liao P, Kobah S, Wijeysundera DN, Shapiro C, Chung F. Proportion of surgical patients with undiagnosed obstructive sleep apnoea. *Br J Anaesth*. 2013;110(4):629-636. doi:10.1093/bja/aes465

10. Chung F, Zhou L, Liao P. Parameters from preoperative overnight oximetry predict postoperative adverse events. *Minerva Anestesiol*. 2014;80(10):1084-1095.

11. Gupta K, Nagappa M, Prasad A, et al. Risk factors for opioid-induced respiratory depression in surgical patients: a systematic review and meta-analyses. *BMJ Open*. 2018;8(12):e024086. doi:10.1136/bmjopen-2018-024086

12. American Society of Anesthesiologists Task Force on Perioperative Management of Patients With Obstructive Sleep Apnea. Practice guidelines for the perioperative management of patients with obstructive sleep apnea: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Management of Patients With Obstructive Sleep Apnea. *Anesthesiology*. 2014;120(2):268-286. doi:10.1097/ALN.0000000000000053

13. Chung F, Memtsoudis SG, Ramachandran SK, et al. Society of Anesthesia and Sleep Medicine guidelines on preoperative screening and assessment of adult patients with obstructive sleep apnea. *Anesth Analg*. 2016;123(2):452-473. doi:10.1213/ANE.0000000000001416

JAMA | Original Investigation

Association of Unrecognized Obstructive Sleep Apnea With Postoperative Cardiovascular Events in Patients Undergoing Major Noncardiac Surgery

Matthew T. V. Chan, MBBS, PhD; Chew Yin Wang, MBChB; Edwin Seet, MBBS, MMed; Stanley Tam, MD; Hou Yee Lai, MBBS; Eleanor F. F. Chew, MBBS; William K. K. Wu, PhD; Benny C. P. Cheng, MBBS; Carmen K. M. Lam, MBBS; Timothy G. Short, MD; David S. C. Hui, MD; Frances Chung, MBBS; for the Postoperative Vascular Complications in Unrecognized Obstructive Sleep Apnea (POSA) Study Investigators

IMPORTANCE Unrecognized obstructive sleep apnea increases cardiovascular risks in the general population, but whether obstructive sleep apnea poses a similar risk in the perioperative period remains uncertain.

OBJECTIVES To determine the association between obstructive sleep apnea and 30-day risk of cardiovascular complications after major noncardiac surgery.

DESIGN, SETTING, AND PARTICIPANTS Prospective cohort study involving adult at-risk patients without prior diagnosis of sleep apnea and undergoing major noncardiac surgery from 8 hospitals in 5 countries between January 2012 and July 2017, with follow-up until August 2017. Postoperative monitoring included nocturnal pulse oximetry and measurement of cardiac troponin concentrations.

EXPOSURES Obstructive sleep apnea was classified as mild (respiratory event index [REI] 5-14.9 events/h), moderate (REI 15-30), and severe (REI >30), based on preoperative portable sleep monitoring.

MAIN OUTCOMES AND MEASURES The primary outcome was a composite of myocardial injury, cardiac death, heart failure, thromboembolism, atrial fibrillation, and stroke within 30 days of surgery. Proportional-hazards analysis was used to determine the association between obstructive sleep apnea and postoperative cardiovascular complications.

RESULTS Among a total of 1364 patients recruited for the study, 1218 patients (mean age, 67 [SD, 9] years; 40.2% women) were included in the analyses. At 30 days after surgery, rates of the primary outcome were 30.1% (41/136) for patients with severe OSA, 22.1% (52/235) for patients with moderate OSA, 19.0% (86/452) for patients with mild OSA, and 14.2% (56/395) for patients with no OSA. OSA was associated with higher risk for the primary outcome (adjusted hazard ratio [HR], 1.49 [95% CI, 1.19-2.01]; $P = .01$); however, the association was significant only among patients with severe OSA (adjusted HR, 2.23 [95% CI, 1.49-3.34]; $P = .001$) and not among those with moderate OSA (adjusted HR, 1.47 [95% CI, 0.98-2.09]; $P = .07$) or mild OSA (adjusted HR, 1.36 [95% CI, 0.97-1.91]; $P = .08$) ($P = .01$ for interaction). The mean cumulative duration of oxyhemoglobin desaturation less than 80% during the first 3 postoperative nights in patients with cardiovascular complications (23.1 [95% CI, 15.5-27.7] minutes) was longer than in those without (10.2 [95% CI, 7.8-10.9] minutes) ($P < .001$). No significant interaction effects on perioperative outcomes were observed with type of anesthesia, use of postoperative opioids, and supplemental oxygen therapy.

CONCLUSIONS AND RELEVANCE Among at-risk adults undergoing major noncardiac surgery, unrecognized severe obstructive sleep apnea was significantly associated with increased risk of 30-day postoperative cardiovascular complications. Further research would be needed to assess whether interventions can modify this risk.

JAMA. 2019;321(18):1788-1798. doi:10.1001/jama.2019.4783

Editorial page 1774

Video and Supplemental content

CME Quiz at jamanetwork.com/learning and CME Questions page 1824

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: Members of the Postoperative Vascular Complications in Unrecognized Obstructive Sleep Apnea (POSA) Study Investigators appear at the end of the article.

Corresponding Author: Matthew T. V. Chan, MBBS, PhD, 4/F Main Clinical Block and Trauma Centre, Department of Anaesthesia and Intensive Care, Chinese University of Hong Kong, Prince of Wales Hospital, 30-32 Ngan Shing St, Shatin, Hong Kong Special Administrative Region, China (mtvchan@cuhk.edu.hk).

Obstructive sleep apnea (OSA) is the most common type of sleep-disordered breathing and is characterized by cyclical alterations between pharyngeal collapse and arousals during sleep.[1] Consequently, there are recurrent episodes of nocturnal hypoxemia, hypercapnia, endothelial dysfunction, hypercoagulability, and sympathetic overactivity.[2] In the general population, OSA is associated with higher risk of cardiovascular complications[3] such as hypertension,[4] myocardial ischemia, heart failure,[5] arrhythmias, stroke,[6] and sudden cardiac death.[7]

General anesthetics, sedatives, and postoperative analgesics are potent respiratory depressants that relax the upper airway dilator muscles and impair ventilatory response to hypoxemia and hypercapnia.[1] Each of these events exacerbates OSA and may predispose patients to postoperative cardiovascular complications. In this respect, perioperative mismanagement of OSA has led to serious medicolegal consequences.[8] However, recent analyses of large database repositories showed conflicting results. Depending on the selected end points, OSA was associated with worse,[9-14] equivocal,[10,12,15] or better outcome[10,11] after surgery. Uncertainty remains whether unrecognized OSA adversely affects postoperative outcomes.

Based on preoperative overnight sleep studies, the Postoperative Vascular Complications in Unrecognized OSA (POSA) study was designed to determine the association between OSA and a composite of cardiac death, myocardial injury, heart failure, thromboembolism, atrial fibrillation, and stroke within 30 days of noncardiac surgery.

Key Points

Question What is the relationship between unrecognized obstructive sleep apnea (OSA) and 30-day cardiovascular complications after major noncardiac surgery?

Findings In this prospective cohort study that included 1218 at-risk patients undergoing major noncardiac surgery, the rate of a composite outcome of postoperative cardiovascular events (myocardial injury, cardiac death, congestive heart failure, thromboembolism, atrial fibrillation, and stroke) among those with OSA vs no OSA was 21.7% vs 14.2%, a difference that was statistically significant. However, the difference was significant only for the subgroup with severe OSA.

Meaning Among patients undergoing major noncardiac surgery, severe OSA was significantly associated with 30-day cardiovascular complications.

Methods

Study Design and Participants

This was a multicenter, prospective cohort study of patients undergoing major noncardiac surgery. Ethics approval was obtained for all participating centers, and all patients provided written informed consent. We reported the trial objectives, design, and methods previously.[16]

We recruited patients who were 45 years or older and undergoing major noncardiac surgery (intraperitoneal, major orthopedic, or vascular). Patients were eligible for the study if they had 1 or more risk factors for postoperative cardiovascular events (ie, history of coronary artery disease, heart failure, stroke or transient ischemic attack, diabetes requiring treatment, and renal impairment with preoperative plasma creatinine concentration >1.98 mg/dL [175 µmol/L]). We excluded patients with prior diagnosis of obstructive sleep apnea or undergoing corrective surgery for OSA (eg, tonsillectomy, uvulopalatopharyngoplasty, tracheostomy), or anticipated to require prolonged (>2 days) mechanical lung ventilation after surgery.

Procedures

Patients underwent a preoperative overnight sleep study using a type 3 portable sleep monitoring device (ApneaLink Plus; ResMed).[17] Sleep studies were performed either at home within the preceding month (34.1%) or in the surgical ward on the night before surgery (65.9%). In addition, we used a high-resolution pulse oximeter wristwatch (PULSOX-300i; Konica Minolta Sensing Inc) to monitor oxyhemoglobin saturation. Monitors were applied to the patients by experienced research staff at bedtime and were collected the following morning. Recordings were transferred to the coordinating center for subsequent analysis. We scored the sleep-associated apnea and hypopnea events according to American Academy of Sleep Medicine criteria (eAppendix 1 in the Supplement).[18] Respiratory event index (REI) was calculated as the number of these events per hour of recording. Mild OSA was diagnosed when REI was 5 to 14.9, moderate OSA when REI was 15 to 30, and severe OSA when REI was greater than 30.[18,19] Based on the pulse oximetry signals obtained from the wristwatch, we also calculated the oxygen desaturation index (ODI) as the number of events (duration >10 seconds) per hour when there was a decrease in oxyhemoglobin saturation of 4% or more from baseline.[20]

Before surgery, research staff interviewed all patients to record their baseline characteristics and risk factors for postoperative cardiovascular complications. Patients also indicated their race and ethnicity from a list of fixed categories, so that differences in OSA by race or ethnicity could be determined. In addition, we assessed patients' risk for OSA using the STOP-Bang (Snoring, Tiredness, Observed Apnea, High Blood Pressure, Body Mass Index, Age, Neck Circumference, and Gender) screening tool (scores range from 0-8, with a score of 0-2 indicating low risk; 3-4, moderate risk; and 5-8, high risk).[21]

Patients, the attending surgical team, and research staff who collected the outcome data were blinded to the results of the sleep study, STOP-Bang questionnaire scores, and oximetry recordings until 30 days after surgery. After this time, we referred patients with abnormal sleep study findings to their local sleep clinic for further management of care.

Follow-up

All types of anesthetic techniques were permitted, and surgery was performed according to routine standard of care at each site. After surgery, electrocardiograms and venous blood samples (for measuring plasma cardiac troponin concentrations) were collected at 6 to 12 hours and then daily during the

first 3 days after surgery. Additional echocardiograms and lung scans were performed, if clinically indicated, to ascertain the diagnosis of cardiac complications. During the first 3 postoperative nights, we recorded oxyhemoglobin saturation using the PULSOX-300i device. All patients were followed up regularly up to 30 days after surgery. Patients discharged home were contacted by telephone. The interview was conducted in a structured fashion. If patients or their relatives indicated that an event had occurred, we contacted the attending physicians or hospitals to obtain documentation.

Outcomes

The primary outcome was a composite of myocardial injury, cardiac death, congestive heart failure, thromboembolism, new atrial fibrillation, and stroke within 30 days of surgery. The prespecified secondary outcomes were unplanned tracheal intubation or postoperative lung ventilation, readmission to the intensive care unit (ICU), and infections. Details regarding the outcome definitions are listed in eAppendix 2 in the Supplement. All outcome events were evaluated by adjudicators blinded to the results of the sleep study.

Statistical Analysis

We estimated that a sample size of 1200 patients was required to ensure a stable regression model with an anticipated primary event rate of 4%.[16] Crude comparisons among patients with varying severity of OSA was performed using analysis of variance, Kruskal-Wallis test, or χ^2 test, as appropriate. We used Cox proportional-hazards models to determine the association between outcome events and OSA, except for unplanned tracheal intubation or postoperative lung ventilation and readmission to the ICU, for which we used logistic-regression analysis. The independent variables consisted of severity of OSA (severe, moderate, mild, or no disease) and factors previously shown to adversely affect outcomes.[22,23] These included age, history of coronary artery disease, congestive heart failure, stroke or transient ischemic attack, diabetes mellitus, chronic renal impairment, peripheral vascular disease, chronic obstructive pulmonary disease, abdominal or vascular surgery, and surgery for cancer. In addition, we included baseline variables that were unbalanced in patients with different severity of OSA—ethnicity, history of hypertension, and preoperative use of β-blockers. The proportionality assumption was evaluated by Schoenfeld residuals test. Collinearity was assessed by variance inflation factor, with a cutoff threshold of 10.[24] We also undertook a random-effects (frailty) Cox model to account for possible site-clustering effect.[25] The adjusted hazard ratios (HRs) for different severity of OSA were compared among groups using χ^2 test.

We used a general linear model to determine the association between nocturnal hypoxia and the primary outcome. In this model, severity of postoperative hypoxia was expressed as ODI. Other covariates included in the model were risk factors for the primary outcome as described above. We repeated the analysis to determine the association between the primary outcome and other measures of nocturnal hypoxia, including the lowest oxyhemoglobin saturation and the duration of oxyhemoglobin desaturation less than 80% and less than 90% recorded.

We also analyzed the primary outcome in prespecified subgroups of patients with the following characteristics: general or regional anesthesia, volatile-based anesthesia or propofol infusion, the number of postoperative nights with supplemental oxygen therapy, receiving (or not receiving) opioids after surgery, using (or not using) patient-controlled analgesia, and whether the surgery was considered minimally invasive. Subgroup analyses were performed using Cox models with the addition of corresponding interaction terms.

To better understand the basis of adverse outcomes, we performed post hoc analyses by repeating the Cox models using individual components of the primary outcome as the dependent variable. In addition, we conducted a sensitivity analysis to determine the validity of myocardial injury as an outcome measure. In this analysis, myocardial injury in the composite primary outcome was replaced by myocardial infarction according to the universal definition.[26] A post hoc comparison of the length of hospital stay in patients with different severity of OSA was also performed using log-rank test. In-hospital deaths were assigned with the longest length of stay.

For the association between outcomes and preoperative risk assessment for OSA based on the STOP-Bang screening tool, we repeated the primary analysis by stratifying patients as low-, intermediate-, and high-risk. We planned to conduct multiple imputations if there were more than 5% missing data on the outcomes or baseline variables included in the regression models. There was no adjustment for multiple comparisons; therefore, the results of the secondary analyses, subgroup analyses, and other analyses should be interpreted as exploratory.

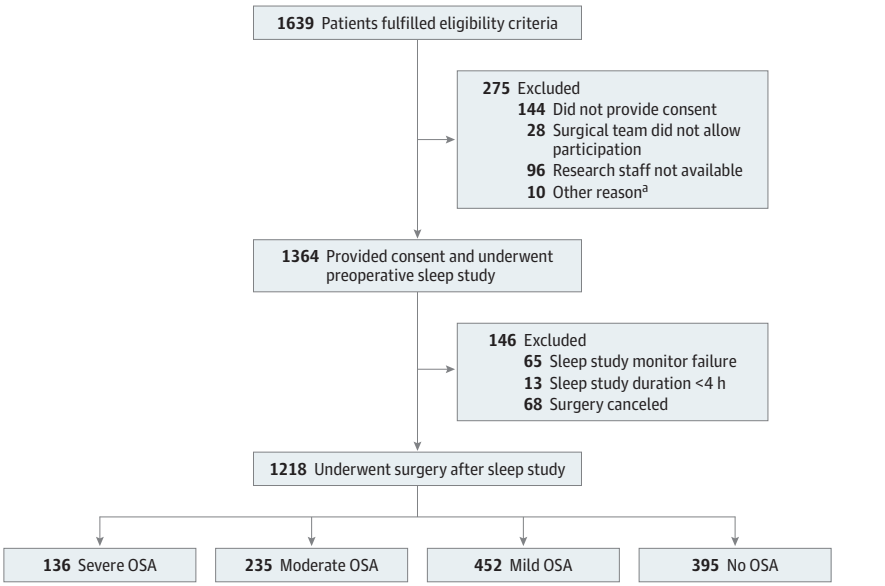
All tests were 2-sided, and $P<.05$ was designated as statistically significant. Analyses were performed using Stata Release 13 (StataCorp) and R version 3.5.2 (R Project for Statistical Computing).

Results

A total of 1364 patients were recruited from 8 hospitals in 5 countries between January 2012 and July 2017. We excluded 78 patients because sleep recordings (<4 hours) were unsatisfactory for analysis. Another 68 patients were excluded because surgery was canceled and could not be rescheduled within the subsequent month. Overall, 1218 patients who completed a preoperative sleep study and had undergone major noncardiac surgery were included in the current analyses (**Figure 1**). Among these patients, 67.6% had unrecognized OSA (REI ≥5), 30.5% had at least moderate OSA (REI ≥15), and 11.2% had severe OSA (REI >30). Details of preoperative sleep studies are reported in eTable 1 in the Supplement. All patients completed 30 days follow-up; no imputation of data was performed.

Table 1 summarizes patient characteristics, type of surgery, preoperative medications, and results of preoperative sleep studies. A total of 59.8% patients had at least 2 risk factors for cardiac disease. The most commonly performed surgical

Figure 1. Screening, Enrollment, and Assessment of Study Participants



OSA indicates obstructive sleep apnea.

[a] Include family refusal (n = 4) and enrollment in another study (n = 6).

procedures were intraperitoneal (35.0%) or major orthopedic (29.9%), 42.1% of procedures were performed for cancer, and 28.3% were performed using a minimally invasive approach. Patients with OSA had a higher mean age and higher mean body mass index, and 63.7% were men. These patients had a higher rate of hypertension (85.9%), and 37.3% were taking β-blockers before surgery. The details of anesthetic administration and use of postoperative analgesia are presented in eTable 2 and eTable 3, respectively, in the Supplement. Perioperative anesthetic management was not different between groups. At least 1 postoperative measurement of cardiac troponin concentration was obtained for 95.8% of patients (eTable 4 in the Supplement).

Outcomes

The primary outcome occurred in 235 patients (19.3%) within 30 days of surgery. Among these patients, 17 (1.4%) died of cardiac cause; 205 (16.8%) had myocardial injury; 21 (1.7%) had congestive heart failure; 30 (2.5%) had atrial fibrillation; 10 (0.8%) had thromboembolism; and 5 (0.4%) had stroke. In patients with myocardial injury, 67 (5.5%) had ischemic symptoms, changes in electrocardiogram or cardiac imaging, and fulfilled the diagnosis of myocardial infarction.[26] Age, renal impairment, peripheral vascular disease, and OSA were independent risk factors for postoperative cardiovascular events (eTable 5 in the Supplement). There was no collinearity between variables. The Cox models showed no interaction between severity of OSA and age (P = .06 for interaction), preexisting renal impairment (P = .07 for interaction), and history of peripheral vascular disease (P = .56 for interaction).

At 30 days after surgery, rates of the primary outcome were 30.1% (41/136) for patients with severe OSA, 22.1% (52/235) for patients with moderate OSA, 19.0% (86/452) for patients with mild OSA, and 14.2% (56/395) for patients with no OSA (**Figure 2**). Compared with the reference group (patients without OSA), OSA was associated with higher risk for the primary outcome (adjusted HR, 1.49 [95% CI, 1.19-2.01]; P = .01). However, the association was only significant among patients with severe OSA (adjusted HR, 2.23 [95% CI, 1.49-3.34]; P = .001) and not among those with moderate OSA (adjusted HR, 1.47 [95% CI, 0.98-2.09]; P = .07) or mild OSA (adjusted HR, 1.36 [95% CI, 0.97-1.91]; P = .08) (P = .01 for interaction). There was no evidence for nonproportionality of hazards (P = .22) or site clustering (eTable 6 in the Supplement).

In the post hoc analyses, severe OSA was also associated with cardiac death (adjusted HR, 13.66 [95% CI, 1.63-114.19]), myocardial injury (adjusted HR, 1.80 [95% CI, 1.17-2.77]), congestive heart failure (adjusted HR, 6.55 [95% CI, 1.71-25.06]), and atrial fibrillation (adjusted HR, 3.96 [95% CI, 1.24-12.60]) (**Table 2**). In a sensitivity analysis that replaced myocardial injury with myocardial infarction in the primary outcome, severe OSA remained independently associated with postoperative cardiovascular complications (eTable 7 and eFigure 1 in the Supplement). OSA was also associated with infective outcomes, unplanned tracheal intubation, or postoperative lung ventilation and readmission to the ICU (Table 2). The association between OSA and postoperative cardiovascular events was similar across all subgroups of patients (P > .14 for interaction) (**Figure 3**). The associations in subgroup analysis were unchanged with varying severity of OSA (eFigures 2-4 in the Supplement). The median length of hospital stay in all patients was 5 days (interquartile range, 4-8) and was similar between different severities of OSA (P = .08 by log-rank test) (eFigure 5 in the Supplement).

STOP-Bang Score and Outcomes

Based on the preoperative STOP-Bang risk score questionnaire, 317 patients (26.3%) were rated as at high risk for OSA,

Table 1. Characteristics: Patients, Surgery, Preoperative Medications, and Preoperative Sleep Study Findings

Characteristic	No. (%)				*P* Value[a]
	Severe OSA	Moderate OSA	Mild OSA	No OSA	
No. of patients	136 (11.2)	235 (19.3)	452 (37.1)	395 (32.4)	
Age, mean (SD), y	68 (9)	68 (9)	68 (9)	66 (9)	
45-64	39 (28.7)	73 (31.1)	159 (35.2)	162 (41.0)	.004
65-74	61 (44.9)	110 (46.8)	181 (40.0)	161 (40.8)	
≥75	36 (26.5)	52 (22.1)	112 (24.8)	72 (18.2)	
Sex					
Men	107 (78.7)	155 (66.0)	262 (58.0)	204 (51.6)	<.001
Women	29 (21.3)	80 (34.0)	190 (42.0)	191 (48.4)	
Race/ethnicity					
Chinese	68 (50.0)	108 (46.0)	254 (56.2)	236 (59.7)	.002
Malay	27 (19.9)	55 (23.4)	51 (11.3)	62 (15.7)	
White	23 (16.9)	40 (17.0)	74 (16.4)	46 (11.6)	
Indian	17 (12.5)	29 (12.3)	70 (15.5)	45 (11.4)	
Other[b]	1 (0.7)	3 (1.3)	3 (0.7)	6 (1.5)	
Risk factors for postoperative cardiovascular event					
Hypertension	128 (94.1)	210 (89.4)	369 (81.6)	330 (83.5)	.001
Coronary artery disease	44 (32.4)	74 (31.5)	124 (27.4)	89 (22.5)	.04
Diabetes receiving insulin treatment	22 (16.2)	36 (15.3)	66 (14.6)	73 (18.5)	.84
Stroke or transient ischemic attack	23 (16.9)	38 (16.2)	62 (13.7)	54 (13.7)	.66
Current smoker	23 (16.9)	23 (9.8)	45 (10.0)	46 (11.6)	.14
Peripheral vascular disease	18 (13.2)	30 (12.8)	44 (9.7)	35 (8.9)	.29
Preoperative creatinine concentration >1.98 mg/dL (175 µmol/L)	11 (8.1)	16 (6.8)	19 (4.2)	25 (6.3)	.26
Congestive heart failure	6 (4.4)	15 (6.4)	15 (3.3)	24 (6.1)	.19
COPD	9 (6.6)	15 (6.4)	17 (3.8)	19 (4.8)	.36
Anthropometric measures, mean (SD)					
Body mass index[e]	31.0 (20.1)	27.5 (5.8)	26.5 (4.8)	25.2 (4.9)	<.001
Neck circumference, cm	41 (3)	39 (4)	39 (3)	37 (3)	<.001
Waist circumference, cm	99 (12)	93 (15	92 (11)	90 (12)	<.001
Surgery					
Major noncardiac					
Intraperitoneal	34 (25.0)	70 (29.8)	157 (34.7)	166 (42.0)	.41
Orthopedic	45 (33.1)	70 (29.8)	148 (32.7)	101 (25.6)	
Vascular	25 (18.4)	49 (20.9)	51 (11.3)	42 (10.6)	
Other[c]	32 (23.5)	46 (19.6)	96 (21.2)	86 (21.8)	
Cancer	52 (38.2)	81 (34.6)	187 (41.4)	192 (48.6)	.004
Minimally invasive[d]	37 (27.2)	47 (20.0)	140 (31.0)	121 (30.6)	.01
Preoperative Medications					
Statin	106 (77.9)	164 (69.8)	320 (452)	264 (66.8)	.11
ACE inhibitor or ARB	74 (54.4)	132 (56.2)	237 (52.4)	202 (51.1)	.65
β-Blocker	57 (41.9)	101 (43.0)	149 (33.0)	108 (27.3)	<.001
Aspirin	31 (22.8)	69 (29.4)	110 (24.3)	99 (25.1)	.46
Clopidogrel	7 (5.1)	6 (2.6)	28 (6.2)	14 (3.5)	.11
Preoperative Sleep Studies					
Site of measurement					
Home	47 (34.6)	82 (34.9)	167 (36.9)	119 (30.1)	.21
Hospital	89 (65.4)	153 (65.1)	285 (63.1)	276 (69.9)	
Results, median (IQR)					
Respiratory event index, events/h[f]	40 (35-52)	20 (17-24)	8 (6-10)	2 (1-3)	<.001
Oxygen desaturation index, events/h[g]	37 (30-44)	20 (16-25)	9 (7-12)	3 (2-5)	<.001
STOP-Bang score[h]	5 (4-6)	4 (3-5)	3 (3-4)	3 (2-4)	<.001

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; OSA, obstructive sleep apnea; STOP-Bang, Snoring, Tiredness, Observed Apnea, High Blood Pressure, Body Mass Index, Age, Neck Circumference, Gender.

[a] For tests to determine imbalance among groups; continuous variables were compared using analysis of variance, and categorical variables were compared using Pearson χ^2 test.

[b] Included black and Arab.

[c] Included major urologic surgery, major hernia repair, and spine surgery.

[d] Determined by attending surgeon.

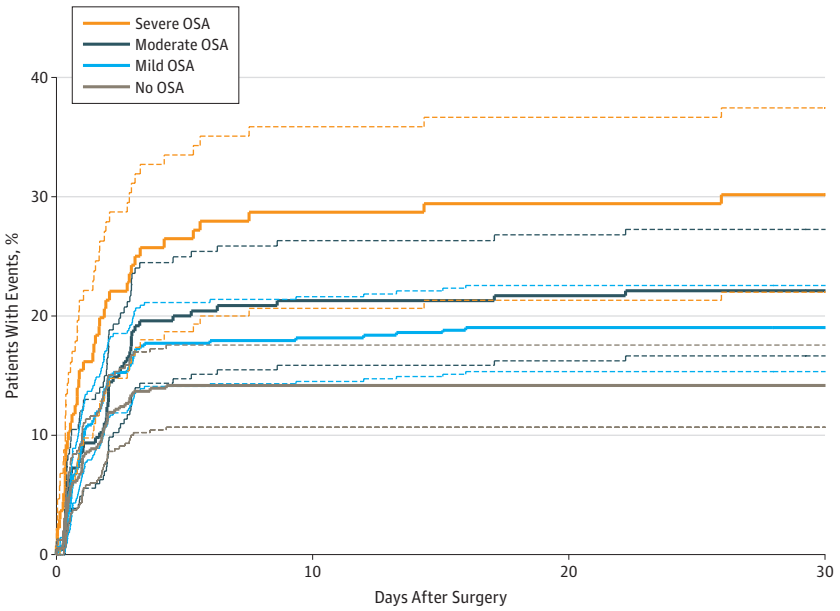
[e] Calculated as weight in kilograms divided by height in meters squared.

[f] Number of apnea and hypopnea events per hour of recording.

[g] Number of events per hour of oximetry recording in which oxyhemoglobin saturation decreased by 4% or more from baseline for 10 or more seconds.

[h] A risk score for OSA (range, 0 [low risk] to 8 [high risk]).

Figure 2. Kaplan-Meier Estimates of the Primary Composite Outcome (Death, Myocardial Injury, Congestive Heart Failure, Thromboembolism, New Atrial Fibrillation, and Stroke at 30 Days After Surgery)



No. at risk

Severe OSA	136	98	97	95
Moderate OSA	235	186	185	183
Mild OSA	452	371	367	366
No OSA	395	340	340	340

Dashed lines indicate 95% confidence intervals. Median follow-up time was 30 days (interquartile range [IQR], 30-32) for patients with severe obstructive sleep apnea (OSA), 30 days (IQR, 30-32) for those with moderate OSA; 30 days (IQR, 30-31) for those with mild OSA, and 30 days (IQR, 30-33) for those with no OSA.

648 (53.2%) at intermediate risk, and 253 (20.8%) at low risk (eTable 8 and eTable 9 in the Supplement). Being a high-risk patient was significantly associated with increased rate of primary outcome (adjusted HR, 1.68 [95% CI, 1.11-2.54]), myocardial injury, and ICU readmission (eTable 10 and eFigure 6 in the Supplement). Being an intermediate-risk patient was significantly associated with ICU readmission and wound infection.

Postoperative Nocturnal Oximetry Monitoring

A total of 1131 patients (92.9%) received nocturnal oximetry monitoring during the first night after surgery, 1076 (88.3%) during the second night, and 983 (80.7%) during the third night (eFigures 7-9 in the Supplement). In patients without OSA, there was a significant increase in ODI after surgery ($P < .001$ for general linear model). In contrast, ODI in patients with OSA was reduced during the first 2 nights and returned to baseline on the third night after surgery. These changes were associated with supplemental oxygen administration ($P = .009$ for general linear model) (eFigure 7 in the Supplement). There was no difference in ODI, lowest oxyhemoglobin saturation, and maximum heart rate in patients with and without postoperative cardiovascular events (eTable 12 in the Supplement). However, the mean cumulative duration of oxyhemoglobin desaturation less than 80% during the first 3 postoperative nights for patients with cardiovascular complications (23.1 [95% CI, 15.5-27.7] minutes) was longer than for patients with no cardiovascular complications (10.2 [95% CI, 7.8-10.9] minutes) ($P < .001$ for general linear model) (eTable 12 and eFigure 10 in the Supplement).

Discussion

In this study of adults undergoing major noncardiac surgery, unrecognized severe obstructive sleep apnea was significantly associated with increased risk of 30-day postoperative vascular complications.

Kaw et al[27] conducted a meta-analysis of 9 cohort and case-control studies (n = 2615 patients) that evaluated the association between OSA and postoperative cardiovascular complications. They reported an increased risk with OSA (odds ratio, 2.07 [95% CI, 1.23-3.50]), but there were few events (event rate, 2.6%), and the studies used less stringent criteria to diagnose OSA and postoperative cardiovascular complications. More recently, the Society of Anesthesia and Sleep Medicine reported a systematic review of 61 studies, including analyses of large-scale national databases,[9-15] to examine the association of OSA with perioperative outcomes.[28] Although a large number of patients were included (N = 8 969 583), there were substantial variations in outcome definitions and duration of follow-up, and the studies reported inconsistent results. In particular, it is unclear whether patients in the control groups of the 61 studies had unrecognized OSA, and those who had a preoperative diagnosis of OSA may have received extra treatment to modify perioperative outcomes. This heterogeneity precluded quantitative analysis of data.

In this study, a representative sample of patients undergoing major noncardiac surgery was included. Standardized preoperative sleep monitoring was performed to diagnose OSA, and patients were stratified according to disease severity. All patients

Table 2. Association Between Severity of Obstructive Sleep Apnea and Postoperative Cardiovascular Events

	Events/Total, No. (%)	Unadjusted HR (95%CI)	*P* Value	Adjusted HR (95%CI)	*P* Value
Primary Outcome (Cardiac Death, Myocardial Injury, Congestive Heart Failure, Thromboembolism, New Atrial Fibrillation, and Stroke)					
Severe OSA	41/136 (30.1)	2.33 (1.55-3.48)	<.001	2.23 (1.49-3.34)	.001
Moderate OSA	52/235 (22.1)	1.59 (1.09-2.32)	.02	1.47 (0.98-2.09)	.07
Mild OSA	86/452 (19.0)	1.37 (0.98-1.91)	.07	1.36 (0.97-1.91)	.08
No OSA	56/395 (14.2)	1 [Reference]		1 [Reference]	
Post Hoc Analysis of Components of Primary Outcome					
Cardiac death[a]					
Severe OSA	6/136 (4.4)	17.90 (2.16-148.69)	.008	13.56 (1.60-114.19)	.02
Moderate OSA	8/235 (3.4)	13.57 (1.70-108.53)	.01	10.56 (1.31-84.89)	.03
Mild OSA	2/452 (0.4)	1.75 (0.16-19.31)	.65	1.43 (0.93-15.93)	.77
No OSA	1/395 (0.3)	1 [Reference]		1 [Reference]	
Myocardial injury[b]					
Severe OSA	35/124 (28.2)	2.11 (1.37-3.24)	.001	1.80 (1.17-2.77)	.008
Moderate OSA	41/220 (18.6)	1.34 (0.89-2.02)	.16	1.20 (0.80-1.81)	.39
Mild OSA	77/416 (18.5)	1.32 (0.93-1.88)	.12	1.37 (0.93-1.89)	.12
No OSA	52/364 (14.3)	1 [Reference]		1 [Reference]	
Congestive heart failure[c]					
Severe OSA	8/136 (5.9)	7.86 (2.09-29.62)	.002	7.04 (1.86-26.66)	.004
Moderate OSA	6/235 (2.6)	3.39 (0.85-13.57)	.08	3.12 (0.78-12.50)	.10
Mild OSA	4/452 (0.9)	1.17 (0.26-5.20)	.84	1.10 (0.25-4.97)	.89
No OSA	3/395 (0.8)	1 [Reference]		1 [Reference]	
Thromboembolism[d]					
Severe OSA	1/136 (0.7)	2.91 (0.18-46.57)	.45	2.66 (0.17-42.86)	.49
Moderate OSA	4/235 (1.7)	6.78 (0.76-60.70)	.09	6.38 (0.71-57.34)	.10
Mild OSA	4/452 (0.9)	3.51 (0.39-31.41)	.26	3.42 (0.38-30.70)	.27
No OSA	1/395 (0.3)	1 [Reference]		1 [Reference]	
New-onset atrial fibrillation[e]					
Severe OSA	7/136 (5.1)	4.13 (1.31-13.02)	.02	3.75 (1.19-11.87)	.03
Moderate OSA	7/235 (3.0)	2.37 (0.75-7.45)	.14	2.18 (0.69-6.89)	.82
Mild OSA	11/452 (2.4)	1.75 (0.60-5.11)	.31	1.89 (0.66-5.46)	.24
No OSA	5/395 (1.3)	1 [Reference]		1 [Reference]	
Stroke[f]					
Severe OSA	1/136 (0.7)	1.45 (0.13-15.99)	.76	1.14 (0.10-12.67)	.92
Moderate OSA	1/235 (0.4)	0.84 (0.08-9.26)	.89	0.76 (0.07-8.33)	.82
Mild OSA	1/452 (0.2)	0.44 (0.04-4.80)	.50	0.38 (0.03-4.15)	.42
No OSA	2/395 (0.5)	1 [Reference]		1 [Reference]	
Secondary Outcomes					
Unplanned admission or readmission to ICU[g]					
Severe OSA	15/136 (11.0)	OR, 6.87 (2.74-17.24)	<.001	OR, 6.60 (2.61-16.70)	<.001
Moderate OSA	20/235 (8.5)	OR, 5.16 (2.15-12.39)	<.001	OR, 4.99 (2.06-12.06)	<.001
Mild OSA	26/452 (5.8)	OR, 3.38 (1.45-7.88)	.005	OR, 3.55 (1.52-8.31)	.005
No OSA	7/395 (1.8)	1 [Reference]		1 [Reference]	
Unplanned tracheal intubation or postoperative lung ventilation[h]					
Severe OSA	18/136 (13.2)	OR, 6.54 (2.86-14.95)	<.001	OR, 6.16 (2.51-15.16)	<.001
Moderate OSA	31/235 (13.2)	OR, 6.52 (3.04-13.95)	<.001	OR, 6.26 (2.85-13.75)	<.001
Mild OSA	23/452 (5.1)	OR, 2.29 (1.05-5.03)	.04	OR, 2.28 (1.04-5.03)	.04
No OSA	9/395 (2.3)	1 [Reference]		1 [Reference]	

(continued)

Table 2. Association Between Severity of Obstructive Sleep Apnea and Postoperative Cardiovascular Events (continued)

	Events/Total, No. (%)	Unadjusted HR (95%CI)	*P* Value	Adjusted HR (95%CI)	*P* Value
Pneumonia[i]					
Severe OSA	5/136 (3.7)	2.92 (0.85-10.09)	.09	3.03 (0.87-10.50)	.08
Moderate OSA	10/235 (4.3)	3.41 (1.17-9.97)	.03	3.47 (1.18-10.20)	.02
Mild OSA	16/452 (3.5)	2.84 (1.04-7.76)	.04	2.83 (1.04-7.78)	.04
No OSA	5/395 (1.3)	1 [Reference]		1 [Reference]	
Wound infection[j]					
Severe OSA	10/136 (7.4)	1.06 (0.51-2.20)	.87	1.07 (0.52-2.23)	.85
Moderate OSA	27/235 (11.5)	1.73 (1.01-2.95)	.04	1.73 (0.99-2.95)	.05
Mild OSA	34/452 (7.5)	1.08 (0.65-1.80)	.77	1.10 (0.67-1.85)	.69
No OSA	27/395 (6.8)	1 [Reference]		1 [Reference]	
Other infections[k]					
Severe OSA	11/136 (8.1)	2.50 (1.12-5.58)	.03	2.31 (1.03-5.18)	.04
Moderate OSA	21/235 (8.9)	2.79 (1.40-5.56)	.004	2.68 (1.34-5.36)	.005
Mild OSA	25/452 (5.5)	1.70 (0.87-3.32)	.12	1.67 (0.85-3.27)	.14
No OSA	13/395 (3.3)	1 [Reference]		1 [Reference]	
Postoperative delirium[l]					
Severe OSA	8/136 (5.9)	2.15 (0.87-5.36)	.10	1.87 (0.75-4.66)	.18
Moderate OSA	15/235 (6.4)	2.32 (1.07-5.05)	.03	2.09 (0.96-4.56)	.06
Mild OSA	20/452 (4.4)	1.60 (0.77-3.35)	.21	1.52 (0.73-3.18)	.27
No OSA	12/395 (3.0)	1 [Reference]		1 [Reference]	

Abbreviations: HR, hazard ratio; ICU, intensive care unit; OR, odds ratio; OSA, obstructive sleep apnea.

[a] Death due to a cardiovascular cause (eg, myocardial infarction, arrhythmias, pulmonary embolism) within 30 days of surgery.

[b] An increase of 65 ng/L or greater in postoperative high-sensitivity troponin T concentration or an absolute change of 5 ng/L or greater when troponin T concentration is in the range between 20 ng/L to less than 65 ng/L, irrespective of ischemic symptoms or electrocardiographic changes.

[c] Elevated jugular venous pressure, respiratory crackles, or presence of third heart sound and at least 1 radiographic feature (vascular redistribution, interstitial edema, or alveolar pulmonary edema).

[d] Included either pulmonary embolism (confirmed by ventilation-perfusion lung scan, helical computed tomography or pulmonary angiography) or deep venous thrombosis (confirmed by compression ultrasonography, computed tomography, or contrast venography).

[e] Electrocardiographic documentation of atrial fibrillation occurred after surgery with or without symptoms or treatment.

[f] New focal neurologic deficit thought to be vascular in origin, with signs or symptoms that last more than 24 hours.

[g] Unplanned ICU admission or readmission from ward because of perioperative events after surgery.

[h] Included unplanned invasive or noninvasive (continuous or bi-level positive airway pressure) lung ventilation within 30 days of surgery.

[i] Infiltrate, cavitation, consolidation, or effusion confirmed by chest radiography or computed tomography, in association with change in sputum production or positive microbial culture of blood or respiratory secretion.

[j] Purulent discharge from surgical wound with or without a positive microbial culture, or pathogenic organisms isolated from aseptically obtained microbial culture.

[k] Included those of the urinary tract, upper respiratory tract, and central nervous system.

[l] Assessed daily in the mornings after surgery using the confusion assessment method.

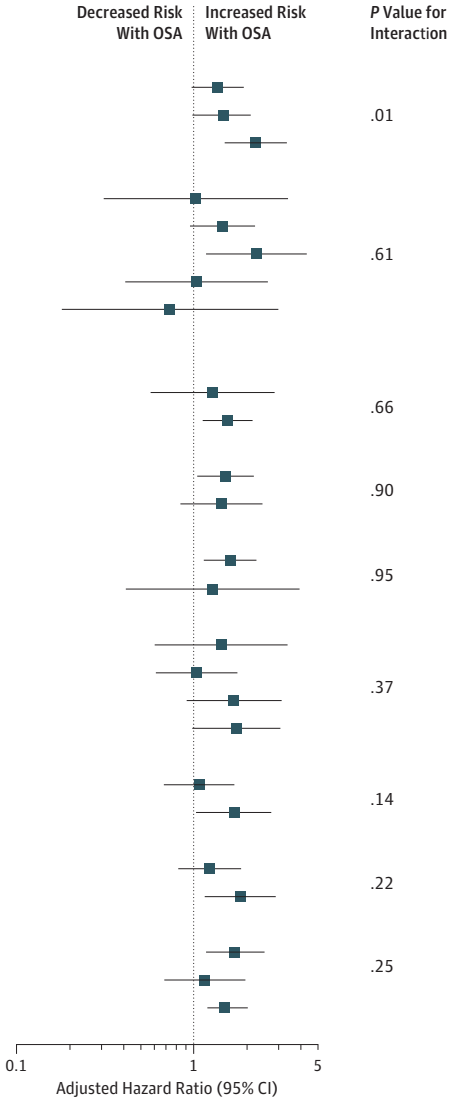
completed follow-up, and postoperative monitoring of troponin concentrations was used to detect myocardial injury.

This study demonstrated that severe OSA was associated with increased risk of postoperative cardiovascular events. Despite a substantial decrease in ODI with oxygen therapy in patients with OSA during the first 3 postoperative nights, supplemental oxygen did not modify the association between OSA and postoperative cardiovascular event. Given that these events were associated with longer duration of severe oxyhemoglobin desaturation (<80%), more aggressive interventions may be required. Currently, positive airway pressure and oral appliances have been shown to overcome the collapsed upper airway and to relieve severe desaturation in nonoperative settings.[29,30] However, high-level evidence demonstrating the effect of these measures on perioperative outcomes is lacking.[31,32] Further clinical trials are now required to test if additional monitoring or alternative interventions would reduce the risk.

In contrast to the current guideline recommendations,[33] regional analgesia or avoidance of postoperative opioids were

Figure 3. Subgroup Analyses of the Primary Composite Outcome (Death, Myocardial Injury, Congestive Heart Failure, Thromboembolism, New Atrial Fibrillation, and Stroke at 30 Days After Surgery)

	No. of Patients With Event/Total No. of Patients		Adjusted Hazard Ratio (95% CI)	P Value for Interaction
	No OSA	OSA		
Severity of OSA				
Mild	56/395	86/425	1.36 (0.97-1.91)	
Moderate	56/395	52/235	1.47 (0.98-2.09)	.01
Severe	56/395	41/136	2.23 (1.49-3.34)	
Body mass index[a]				
<18.5	5/20	6/21	1.02 (0.31-3.39)	
18.5-24.9	31/194	76/300	1.45 (0.95-2.21)	
25.0-29.9	11/119	62/298	2.25 (1.17-4.32)	.61
30.0-34.9	6/44	26/298	1.04 (0.41-2.61)	
≥35.0	3/18	9/69	0.73 (0.18-2.99)	
Type of anesthesia				
General				
No	8/11	26/186	1.27 (0.57-2.85)	.66
Yes	48/314	153/637	1.55 (1.12-2.14)	
Regional or neuraxial block				
No	38/248	121/502	1.51 (1.04-2.18)	.90
Yes	18/147	58/321	1.43 (0.84-2.43)	
Anesthetic agents				
Volatile-based	44/295	143/595	1.60 (1.14-2.25)	.95
Propofol infusion	4/34	13/84	1.28 (0.41-3.94)	
Oxygen administration after surgery				
None	8/107	17/185	1.42 (0.60-3.37)	
1 Night	19/128	53/279	1.03 (0.61-1.76)	.37
2 Nights	14/89	42/169	1.68 (0.91-3.12)	
3 Nights	15/71	67/190	1.73 (0.98-3.07)	
Postoperative opioid administration				
No	27/172	64/339	1.07 (0.68-1.69)	.14
Yes	29/223	115/484	1.70 (1.03-2.73)	
Postoperative patient-controlled analgesia administration				
No	33/207	85/411	1.23 (0.82-1.84)	.22
Yes	23/188	94/412	1.83 (1.15-2.89)	
Minimally invasive surgery				
No	35/274	133/599	1.70 (1.17-2.50)	.25
Yes	21/121	46/224	1.15 (0.68-1.95)	
Overall	56/395	179/823	1.49 (1.19-2.01)	



OSA indicates obstructive sleep apnea.

[a] Calculated as weight in kilograms divided by height in meters squared.

not associated with better outcome. These data are consistent with a retrospective analysis of an administrative database of 30 294 patients with documented OSA undergoing hip or knee arthroplasties with neuraxial block, general anesthesia, or both.[34] The study showed no change in postoperative cardiac or respiratory complications with neuraxial or general anesthesia. However, blood transfusion, requirement for postoperative mechanical lung ventilation, and ICU admission were decreased with neuraxial block. In the current study, patients undergoing major noncardiac surgery were recruited, few received regional blocks, and the majority required larger doses of systemic opioids for postoperative analgesia. This may have limited the statistical power to detect important interactions between OSA, anesthetic techniques, and postoperative analgesia.

Limitations

This study has several limitations. First, electroencephalograms were not recorded in the preoperative sleep studies. Thus, it was not possible to track whether patients were asleep during measurement, and this may have underestimated the severity of OSA. Second, perioperative management was not controlled, but there was no difference in the administration of anesthesia and analgesics in patients with varying degrees of OSA. Although the surgical team was blinded to the results of the preoperative sleep study, recognition of minor

respiratory events, such as episodes of apnea and higher level of sedation in the postanesthetic care unit and surgical ward, may have influenced perioperative management. This may include reducing doses of opioids or prolonging supplemental oxygen therapy. It is unclear how these interventions may affect perioperative outcomes. Nevertheless, the event rates reported in this study would represent the expected perioperative outcomes associated with untreated OSA in contemporary anesthetic practice for major noncardiac surgery. Third, the results should not be extrapolated to ambulatory procedures or minor surgery, for which anesthetic and analgesic techniques may have a larger effect on perioperative adverse events. Fourth, 54.7% of patients in this study were Chinese. Although Chinese patients with OSA have a lower body mass index and distinct differences in craniofacial anatomy compared with white patients,[35,36] it remains unclear how these differences might influence outcomes.

Conclusions

Among at-risk adults undergoing major noncardiac surgery, unrecognized severe obstructive sleep apnea was significantly associated with increased risk of 30-day postoperative cardiovascular complications. Further research would be needed to assess whether interventions can modify this risk.

ARTICLE INFORMATION

Accepted for Publication: April 4, 2019.

Author Affiliations: Chinese University of Hong Kong, Hong Kong Special Administrative Region, China (Chan, Wu, Hui); University of Malaya, Kuala Lumpur, Malaysia (Wang, Lai); Khoo Teck Puat Hospital, Singapore (Seet); Scarborough Health Network, Ontario, Canada (Tam); Hospital Kuala Lumpur, Kuala Lumpur, Malaysia (Chew); Tuen Mun Hospital, Hong Kong Special Administrative Region, China (Cheng, Lam); Auckland City Hospital, Auckland, New Zealand (Short); Toronto Western Hospital, University Health Network, University of Toronto, Toronto, Ontario, Canada (Chung).

Author Contributions: Drs Chan and Chung had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Chan, Wang, Seet, and Chung contributed equally to this article.
Concept and design: Chan, Wang, Seet, Hui, Chung.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Chan.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Chan, Wu.
Obtained funding: Chan, Wang, Seet, Short, Chung.
Administrative, technical, or material support: Chan, Wang, Seet, Tam, Lai, Chew, Cheng, Lam, Short, Hui, Chung.
Supervision: Chan, Wang, Seet, Tam, Lai, Chew, Cheng, Lam, Short, Chung.

Conflict of Interest Disclosures: Dr Chung reported receiving grants from the Ontario Ministry of Health and Long-term Care, Acacia Pharma, and Medtronics and holding a patent pending for the STOP-Bang questionnaire. No other authors reported disclosures.

Funding/Support: The study was funded through grants from the Health and Medical Research Fund (09100351), Hong Kong, National Healthcare Group-Khoo Teck Puat Hospital, Small Innovative Grants (12019, 15201), University Health Network Foundation (Ontario, Canada), University of Malaya, High Impact Research Grant (UM.C/625/1/HIR/067) , Malaysian Society of Anaesthesiologists K Inbasegaran Research Grant and Auckland Medical Research Foundation, New Zealand. ResMed has supplied the ApneaLink devices and PULSOX-300i oximeter wristwatch in all sites as an unrestricted loan. These were returned at the end of the study.

Role of the Funder/Sponsor: The study funders/sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Group Information: The Postoperative Vascular Complications in Unrecognized Obstructive Sleep Apnea (POSA) Study Investigators: **Steering Committee:** Frances Chung (chair); Matthew Chan, Chew-Yin Wang, Edwin Seet. **Event Adjudication Committee:** Gordon Choi (chair), David Hui, Tony Gin. **Investigators: Canada:** *Scarborough Health Network—Central Campus:* Frances Chung, MBBS, Stanley Tam, MD, Sohail Iqbal, BSc; **Hong Kong:** *Prince of Wales Hospital:* Matthew Chan, MBBS, PhD, Gordon Choi, MBBS, David Hui, MD, Tony Gin, MD, Matthew Tsang, BSc, Beaker Fung, BSc, Angela Miu, BSc, Alex Lee, MSc; *Tuen Mun Hospital:* Benny Cheng, MBBS, Carmen Lam, MBBS, Sharon Tsang, MBChB, PhD, Chuen Ho Cheung, MBChB, Hoi Lam Pang, MBBS; **Malaysia:** *University of Malaya Medical Centre:* Chew Yin Wang, MBChB, Hou Yee Lai, MBBS, Carolyn C.W. Yim, MBBS, Alvin S.B. Tan, MBBS, Ching Yen Chong, BA, Jason H. Kueh, BSc, Xue Lin Chan, MBBS; *Hospital Kuala Lumpur:* Eleanor F.F. Chew, MBBS, Su Yin Loo, MBBS, Simon M.T. Hui, MBBS; **New Zealand:** *Middlemore Hospital:* Joyce Tai, MBChB, Stuart Walker, MBBS, Sue Olliff, BSc; *Auckland City Hospital:* Ivan Bergman, MBBS, Nicola Broadbent, MBBS, Maartje Tulp, MBBS, Timothy Short, MD, Davina McAllister, BSc; **Singapore:** *Khoo Teck Puat Hospital:* Edwin Seet, MBBS, Pei Fen Teoh, MBBS, Audris Chia, BSc.

Additional Contributions: We thank Andrew Forbes, PhD (Monash University, Australia), for his statistical advice and Ying Liu, MPH, Thomas Lo, MSc, and Beaker Fung, MSocSc (Chinese University of Hong Kong), who helped with figures preparation. None of these individuals received compensation for their contributions.

Study Coordination: This study was coordinated by the Chinese University of Hong Kong, Hong Kong Special Administrative region, China.

REFERENCES

1. Subramani Y, Singh M, Wong J, Kushida CA, Malhotra A, Chung F. Understanding phenotypes of obstructive sleep apnea: applications in anesthesia, surgery, and perioperative medicine. *Anesth Analg*. 2017;124(1):179-191. doi:10.1213/ANE.0000000000001546

2. Abboud F, Kumar R. Obstructive sleep apnea and insight into mechanisms of sympathetic overactivity. *J Clin Invest*. 2014;124(4):1454-1457. doi:10.1172/JCI70420

3. Heinzer R, Vat S, Marques-Vidal P, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. *Lancet Respir Med*. 2015;3(4):310-318. doi:10.1016/S2213-2600(15)00043-0

4. Marin JM, Agusti A, Villar I, et al. Association between treated and untreated obstructive sleep apnea and risk of hypertension. *JAMA*. 2012;307(20):2169-2176. doi:10.1001/jama.2012.3418

5. Gottlieb DJ, Yenokyan G, Newman AB, et al. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the Sleep Heart Health Study. *Circulation*. 2010;122(4):352-360. doi:10.1161/CIRCULATIONAHA.109.901801

6. Arzt M, Young T, Finn L, Skatrud JB, Bradley TD. Association of sleep-disordered breathing and the occurrence of stroke. *Am J Respir Crit Care Med*. 2005;172(11):1447-1451. doi:10.1164/rccm.200505-702OC

7. Gami AS, Howard DE, Olson EJ, Somers VK. Day-night pattern of sudden death in obstructive sleep apnea. *N Engl J Med*. 2005;352(12):1206-1214. doi:10.1056/NEJMoa041832

8. Fouladpour N, Jesudoss R, Bolden N, Shaman Z, Auckley D. Perioperative complications in obstructive sleep apnea patients undergoing surgery: a review of the legal literature. *Anesth Analg*. 2016;122(1):145-151. doi:10.1213/ANE.0000000000000841

9. D'Apuzzo MR, Browne JA. Obstructive sleep apnea as a risk factor for postoperative complications after revision joint arthroplasty. *J Arthroplasty*. 2012;27(8)(suppl):95-98. doi:10.1016/j.arth.2012.03.025

10. Mokhlesi B, Hovda MD, Vekhter B, Arora VM, Chung F, Meltzer DO. Sleep-disordered breathing and postoperative outcomes after bariatric surgery: analysis of the nationwide inpatient sample. *Obes Surg*. 2013;23(11):1842-1851. doi:10.1007/s11695-013-0991-2

11. Mokhlesi B, Hovda MD, Vekhter B, Arora VM, Chung F, Meltzer DO. Sleep-disordered breathing and postoperative outcomes after elective surgery: analysis of the nationwide inpatient sample. *Chest*. 2013;144(3):903-914. doi:10.1378/chest.12-2905

12. Memtsoudis SG, Stundner O, Rasul R, et al. The impact of sleep apnea on postoperative utilization of resources and adverse outcomes.

Anesth Analg. 2014;118(2):407-418. doi:10.1213/ANE.0000000000000051

13. Stundner O, Chiu YL, Sun X, et al. Sleep apnoea adversely affects the outcome in patients who undergo posterior lumbar fusion: a population-based study. *Bone Joint J*. 2014;96-B (2):242-248. doi:10.1302/0301-620X.96B2.31842

14. Mutter TC, Chateau D, Moffatt M, Ramsey C, Roos LL, Kryger M. A matched cohort study of postoperative outcomes in obstructive sleep apnea: could preoperative diagnosis and treatment prevent complications? *Anesthesiology*. 2014;121 (4):707-718. doi:10.1097/ALN.0000000000000407

15. Griffin JW, Novicoff WM, Browne JA, Brockmeier SF. Obstructive sleep apnea as a risk factor after shoulder arthroplasty. *J Shoulder Elbow Surg*. 2013;22(12):e6-e9. doi:10.1016/j.jse.2013.06.003

16. Chan MTV, Wang CY, Seet E, et al; POSA Investigators. Postoperative vascular complications in unrecognised Obstructive Sleep Apnoea (POSA) study protocol: an observational cohort study in moderate-to-high risk patients undergoing non-cardiac surgery. *BMJ Open*. 2014;4(1):e004097. doi:10.1136/bmjopen-2013-004097

17. Ng SSS, Chan TO, To KW, et al. Validation of a portable recording device (ApneaLink) for identifying patients with suspected obstructive sleep apnoea syndrome. *Intern Med J*. 2009;39(11): 757-762. doi:10.1111/j.1445-5994.2008.01827.x

18. Collop NA, Tracy SL, Kapur V, et al. Obstructive sleep apnea devices for out-of-center (OOC) testing: technology evaluation. *J Clin Sleep Med*. 2011;7(5):531-548.

19. Berry RB, Budhiraja R, Gottlieb DJ, et al; American Academy of Sleep Medicine. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events: deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med*. 2012;8(5):597-619.

20. Chung F, Liao P, Elsaid H, Islam S, Shapiro CM, Sun Y. Oxygen desaturation index from nocturnal oximetry: a sensitive and specific tool to detect sleep-disordered breathing in surgical patients. *Anesth Analg*. 2012;114(5):993-1000. doi:10.1213/ANE.0b013e318248f4f5

21. Chung F, Subramanyam R, Liao P, Sasaki E, Shapiro C, Sun Y. High STOP-Bang score indicates a high probability of obstructive sleep apnoea. *Br J Anaesth*. 2012;108(5):768-775. doi:10.1093/bja/aes022

22. Devereaux PJ, Chan MTV, Alonso-Coello P, et al; Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) Study Investigators. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. *JAMA*. 2012;307(21):2295-2304. doi:10.1001/jama.2012.5502

23. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation*. 1999;100(10): 1043-1049. doi:10.1161/01.CIR.100.10.1043

24. O'Brien RM. A caution regarding rules of thumb for variance inflation factors. *Qual Quant*. 2007;41 (5):673-690. doi:10.1007/s11135-006-9018-6

25. Ha ID, Vaida F, Lee Y. Interval estimation of random effects in proportional hazards models with frailties. *Stat Methods Med Res*. 2016;25(2):936-953. doi:10.1177/0962280212474059

26. Thygesen K, Alpert JS, Jaffe AS, et al; ESC Scientific Document Group. Fourth universal definition of myocardial infarction (2018). *Eur Heart J*. 2019;40(3):237-269. doi:10.1093/eurheartj/ehy462

27. Kaw R, Chung F, Pasupuleti V, Mehta J, Gay PC, Hernandez AV. Meta-analysis of the association between obstructive sleep apnoea and postoperative outcome. *Br J Anaesth*. 2012;109(6): 897-906. doi:10.1093/bja/aes308

28. Opperer M, Cozowicz C, Bugada D, et al. Does obstructive sleep apnea influence perioperative outcome? a qualitative systematic review for the Society of Anesthesia and Sleep Medicine Task Force on preoperative preparation of patients with sleep-disordered breathing. *Anesth Analg*. 2016;122 (5):1321-1334. doi:10.1213/ANE.0000000000001178

29. Jonas DE, Amick HR, Feltner C, et al. Screening for obstructive sleep apnea in adults: evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2017;317(4):415-433. doi:10.1001/jama.2016.19635

30. Randerath WJ, Verbraecken J, Andreas S, et al; European Respiratory Society Task Force on Non-CPAP Therapies in Sleep Apnoea. Non-CPAP therapies in obstructive sleep apnoea. *Eur Respir J*. 2011;37(5):1000-1028. doi:10.1183/09031936.00099710

31. Chung F, Nagappa M, Singh M, Mokhlesi B. CPAP in the perioperative setting: evidence of support. *Chest*. 2016;149(2):586-597. doi:10.1378/chest.15-1777

32. Chung F, Memtsoudis SG, Ramachandran SK, et al. Society of Anesthesia and Sleep Medicine guidelines on preoperative screening and assessment of adult patients with obstructive sleep apnea. *Anesth Analg*. 2016;123(2):452-473. doi:10.1213/ANE.0000000000001416

33. Memtsoudis SG, Cozowicz C, Nagappa M, et al. Society of Anesthesia and Sleep Medicine guideline on intraoperative management of adult patients with obstructive sleep apnea. *Anesth Analg*. 2018; 127(4):967-987. doi:10.1213/ANE.0000000000003434

34. Memtsoudis SG, Stundner O, Rasul R, et al. Sleep apnea and total joint arthroplasty under various types of anesthesia: a population-based study of perioperative outcomes. *Reg Anesth Pain Med*. 2013;38(4):274-281. doi:10.1097/AAP.0b013e31828d0173

35. Lee RW, Vasudavan S, Hui DS, et al. Differences in craniofacial structures and obesity in Caucasian and Chinese patients with obstructive sleep apnea. *Sleep*. 2010;33(8):1075-1080.

36. Li KK, Kushida C, Powell NB, Riley RW, Guilleminault C. Obstructive sleep apnea syndrome: a comparison between Far-East Asian and white men. *Laryngoscope*. 2000;110(10, pt 1):1689-1693. doi:10.1097/00005537-200010000-00022