

Postoperative Outcomes in Obstructive Sleep Apnea: Matched Cohort Study

To the Editor:

The cohort study by Mutter *et al.*¹ is the first observational study with large polysomnography data allowing a comparison of clinically important outcomes of patients with undiagnosed obstructive sleep apnea (OSA) and diagnosed OSA (DOSA) *versus* controls (chosen from the general population) after a wide variety of surgical procedures. For the first time, large polysomnography data may allow answer the questions whether the severity of OSA is related to poor postoperative outcomes and whether the diagnosis of OSA before surgery affects postoperative outcomes.

The conclusions of this study seem to go much beyond what the data suggest and should be viewed in the light of following limitations:

1. First, it is not realistic to conclude that the diagnosis and presumed treatment of OSA in the DOSA group had any bearing on fewer cardiac complications compared with postoperative pulmonary complications in the first place. No details of treatment of OSA in the DOSA group are provided in the article, which, barring measures of adherence and compliance and the use of positive airway pressure therapy during the preoperative period, may be possible to obtain from their database. In the absence of that information, it is only presumptive that diagnosis and possible treatment of OSA were associated with the reduction of postoperative cardiovascular complications and not those of postoperative respiratory complications.
2. The investigators use data from a large polysomnography database (1990–2006) with more than 3,000 patients with polysomnographically confirmed OSA, and they may have been able to find non-OSA matches for a lot of these patients, some from within the polysomnography database (1990–2006) itself and others who tested negative in the general population. However, it is understandable that besides the advantage of having numerous general population controls who were never tested, it was also easier to use the general population as controls. As the authors themselves report as many as 90% of those afflicted by OSA are not yet diagnosed, this methodology introduces a bias of many such population controls having OSA particularly of the mild-to-moderate variety. This could be one of the reasons that the investigators found only

severe OSA associated with significant postoperative respiratory and cardiac complications, which has not been shown among most studies till date.^{2–4}

3. Given that the authors chose to use general population controls as they were numerous and easy to find, they did not seem to do a good job with matching and adjustment for comorbidities. Also given the total number of postoperative complications, it is quite possible that the regression models are overfitted.
4. Last, in studies reporting postoperative cardiac outcomes among patients with OSA, significant heterogeneity exists in the types of reported cardiac events and it then not surprisingly enough contributes to the difficulty of uncovering the relationship, if any, between OSA and postoperative cardiac events, which in general has been harder to prove even in this study in the DOSA group. By way of example, when used as an International Classification of Diseases-9 diagnosis, it is difficult to believe that acute respiratory distress syndrome has the same connotation as what is meant in the clinical sense where it is based on hemodynamic measurements. Similarly, in the case of this study, it is not clear what the International Classification of Diseases diagnosis of cardiac arrest and shock actually pertains to when reporting postoperative cardiac outcomes. Looking specifically at the results of this study, it is harder to believe that the outcomes of cardiac arrest and shock differ significantly between the OSA groups and controls, whereas those of acute coronary syndrome and atrial fibrillation/flutter, which on an average are more common (and often times, the basis for the more serious event of cardiac arrest and shock), not differ between the two groups. As much the authors do not have any way of explaining this difference, they should probably recognize this important limitation stemming from the use of outcomes based on administrative data in their article. If they believe that such an outcome does have biologic plausibility, then they should at least try to explain the possible mechanisms.

Competing Interests

The author declares no competing interests.

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In Reply:

We appreciate Dr. Kaw's interest in our article,¹ but we believe our interpretation of the data respected the study's limitations, offering valid new insight on postoperative outcomes in patients with obstructive sleep apnea (OSA). We will respond in turn to the four issues raised by Dr. Kaw.

1. Although the patients with undiagnosed OSA (UOSA) in our study definitely did not have access to perioperative continuous positive airway pressure (CPAP), Dr. Kaw has correctly noted that even if CPAP was prescribed, it is unknown whether each patient with diagnosed OSA (DOSA) in our study used it perioperatively. We chose not to substitute procedure codes for noninvasive ventilation as a surrogate for perioperative CPAP use in these patients because this code definition has poor sensitivity based on the exceedingly low rates in another administrative database study² and our own unpublished results (unpublished rate of procedure codes for noninvasive ventilation in surgical admissions for patients with OSA, from queries of our own database¹ by Thomas C. Mutter, M.D., F.R.C.P.C., M.Sc., Assistant Professor, Department of Anesthesia, University of Manitoba, Winnipeg, Manitoba, Canada, in 2012). Due to these and other limitations documented in the Discussion, we carefully interpreted our finding as an *association* between *polysomnography diagnosis of OSA with prescription of CPAP* and reduced risk of cardiovascular complications. Nowhere do we propose an absence of effect of CPAP on respiratory complications, and we devote the fifth last paragraph of the Discussion to hypothesizing why such a risk reduction was not detected in our study. Furthermore, in the last three paragraphs of the article, based on our results and others', we discussed how CPAP could have a causal role in reducing cardiovascular complications. However, consistent with the aforementioned limitations, we also indicated that large clinical studies are ultimately needed to test these hypotheses.
2. We did not attempt to find controls from within the polysomnography database as it represents a referral population distinct from the typical surgical patient, and there were only approximately 100 database patients without OSA or another sleep disorder; too few for matching on surgical risk, which was integral to our analysis (see

Materials and Methods). To be clear, the general population controls in our study were screened to be at low risk of having UOSA or DOSA (see Materials and Methods and Supplementary Digital Content 2), but Dr. Kaw has correctly noted that false negatives from this screening could result in a misclassification bias. As reviewed in the fourth paragraph of the Discussion, this misclassification would not affect relationships between the UOSA and DOSA groups but would bias estimates of risk for OSA *versus* non-OSA controls toward a nil effect. In a worst case scenario, if our control group had the prevalence of OSA in the general population (20 to 25%), the true risk estimates would be modestly higher than we estimated. It is uncertain whether the mild and moderate OSA estimates would become statistically or clinically significant.

Nevertheless, due to this potential bias and the wide CIs for risk estimates in less severe OSA, we did not conclude that only severe OSA is associated with increased risk. Instead, due to the significant relationships between risk and OSA severity, we suggested that patients with severe OSA are at *greatest risk*. Finally, the novel finding of a relationship between OSA severity and postoperative complications in this study is surely a matter of statistical power. The three studies cited by Dr. Kaw are at least 10 times smaller than our study and the largest (n = 1,547) only included low-risk ambulatory surgeries, whereas we included almost all surgeries.

3. Our matching strategy and justification for not matching on comorbidities (using propensity-based methods) are extensively documented in the Study Design and Analysis sections of the article. We chose instead to adjust for comorbidities at the analysis stage. This enabled us for the first time to estimate the importance of OSA relative to age, type of surgery, comorbidities, and other factors in predicting postoperative complications. These models were robust through multiple sensitivity analyses (see Supplemental Digital Content 8), and we believe that any unmeasured confounders are unlikely to significantly alter our interpretation of the data as presented in the article. It is also unlikely that the models were overfitted as (1) we did not observe large changes in regression coefficient estimates when adding or deleting predictor variables from the final models, (2) multiple sensitivity analyses did not change the results, (3) we arrived at the same models through backwards and forwards regression, and (4) whether OSA variables were added first or last. Nevertheless, due to the limitations of administrative data, we believe that even though the models can inform clinical practice, they should not be directly applied to it.
4. We agree with Dr. Kaw that caution is necessary in assigning clinical meaning to administrative data, and we accordingly recognized this methodologic challenge in the discussion. To enhance the construct validity of our outcomes, we chose International Classification Disease