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Random Errors and Misclassification Bias

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To the Editor

Turan et al.'s discussion and accompanying editorial^{1, 2} cogently discuss the limitations of their retrospective study design and are further complemented by the senior author's recent manuscript demonstrating the importance of prospective validation of retrospective findings.³ Nevertheless, I would like to offer an important factual correction to the stated limitations that continues to go unrecognized in many studies of this type.

Turan et al. state: "To the extent that outcomes occurred postoperatively or were missed through incomplete coding, reported frequencies will underestimate the true incidence. But unless outcome identification in our registry is biased (i.e., nonrandomly erroneous in patients given or not given N2O), reported odds ratios will remain accurate."¹

Alas, the idea that independent, random errors in the assessment of an outcome will not affect observed odds-ratios of that outcome is likely not true. An imperfect marker of an outcome when used to compare an actual outcome between two sample populations, will carry disparate positive and negative predictive values for the actual outcome that depend on the sensitivity and specificity of the imperfect marker and on the differences in the incidence of the true outcome between the two sample populations being compared. In the case of mortality, markers for this outcome are frequently quite accurate so that the observed odds ratio of the imperfect marker for mortality will likely be close to the corresponding odds ratio of actual mortality in the study samples. Although bias occurring as a result of random errors in ascertaining an outcome will certainly distort an observed odds ratio away from the actual odds ratio present between samples, the effect will only become large in cases where the odds ratio of actual outcome between samples departs dramatically from 1 and where the marker for the outcome is relatively inaccurate.

More concerning in the present study, however, may be the distortional effect stemming from imperfect comorbidity coding in the face of baseline systematic differences in disease prevalence between healthier patients receiving nitrous oxide and sicker patients not receiving it. Because of the relationship among comorbidity prevalence and the positive and negative predictive values of comorbidity coding, purely random errors in ascertaining comorbidity status likely distorted the observed odds ratios away from 1. I do not know whether the resulting differences were of the magnitude to have changed the conclusions of the manuscript, but this is a question that could no doubt be well handled by this superb group of investigators. As a demonstration of the relevance of this issue, my colleagues and I have recently modeled the effects of misclassification bias on Type 1 error when

comparisons of a systematically sicker and healthier population are made using imperfectly measured confounders.⁴ Whatever the actual effects of misclassification bias were in the Turan et al. study, the supposition that nonbiased, random errors in ascertaining outcomes will not affect observed odds ratios between sample populations is a common misperception that deserves correction.

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