Sleep Apnea, Obesity, and Readmissions: Real Risks or Residual Confounding?

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Obesity drives multiple adverse health impacts and presents a major public health concern (1). Among patients with chronic obstructive pulmonary disease (COPD), however, the implications of comorbid obesity may be more complex. On one end, obesity has confirmed deleterious effects. Individuals with COPD and obesity have augmented respiratory symptoms, including more severe dyspnea and exercise intolerance (2). In addition, obesity-related conditions like cardiovascular disease predispose many patients with COPD to adverse events, including recurrent hospitalizations and death (3). However, obesity is not associated with greater risk in all cases. Some COPD cohorts suggest an "obesity paradox," finding that individuals who are overweight or obese have lower mortality than those who are a normal weight or underweight (4). Although this "paradox" may simply reflect poor outcomes associated with cachexia rather than protection from obesity, the mechanisms are unclear. Untangling these risks is an important priority to the field and has particular relevance as up to 70% of patients with COPD meet criteria for obesity (2).

The obesity-related condition of obstructive sleep apnea (OSA) prompts particular attention and debate. Obesity explains 60% of OSA prevalence and severity, and the associations and interactions between OSA and COPD are well documented. First described in 1985 as the "overlap syndrome" (5), OSA is present in up to 65% of patients with COPD (6). This cooccurrence of OSA and COPD leads to augmented levels of sleep-related hypoxemia and sleep disruption (7). Among patients with COPD, OSA is associated with greater risks for exacerbations, recurrent hospitalization, and mortality (7). However, like obesity-related comorbidities more generally, the discrete risk posed by OSA is often difficult to disentangle from that posed by obesity and other obesity-related conditions (e.g., cardiovascular disease and diabetes).

In this issue of *AnnalsATS*, Channick and colleagues (pp. 462–468) sought to assess the independent associations of obesity and OSA with hospital readmissions among patients with COPD (8). Hospital readmissions have become a recent target because of penalties imposed by the U.S. Centers for Medicare and Medicaid Services to reduce costs. Coexisting conditions, including OSA and obesity, are associated with an increased risk of readmissions in the COPD population, but the nature of the relationship is unclear (9, 10). To conduct their analyses, the authors leveraged the Nationwide Readmissions Database (NRD). The NRD includes 18 million discharges across the United States and allows researchers to assess whether a patient was admitted and readmitted within a given calendar year. The authors used NRD data from 2010 to 2016 to identify discharges of patients with COPD admissions. Because of the nature of NRD, the authors could not uniquely identify patients across years and used hospital discharge as the unit of analysis. The authors defined the presence of the key exposures of interest, obesity and OSA, based on *International Classification of Disease, Ninth Revision* and *International Classification of Disease, Tenth Revision* (ICD 9/10) billing codes. The authors also used available NRD data to classify potential confounders at the patient (e.g., age, sex, Charlson comorbidity index) and health system level (e.g., hospital size, teaching hospital status).

In unadjusted analyses, the authors found small associations for readmission with both obesity and OSA diagnoses, with odds ratios (ORs) of 1.04 (95% confidence interval [CI], 1.03–1.05) and 1.11 (95% CI, 1.10–13) respectively. In a mediation analysis, the authors found the association between obesity diagnoses with readmissions was diminished after adjusting for OSA diagnosis. The analyses also addressed the role of other confounders, including patient demographics, comorbidities (Charlson comorbidity index score), and hospital characteristics. In fully adjusted models accounting for these confounders, OSA diagnosis remained associated with a small risk for readmissions, with an OR of 1.05 (95% CI, 1.03–1.06). In contrast, obesity diagnosis was associated with a lower risk of readmission in fully adjusted models. Altogether, the authors' results suggest that the small association of obesity diagnosis with readmissions in the NRD is mediated by patient and hospital characteristics as well as comorbid diagnoses such as OSA (8).

The authors' approach to modeling allowed them to adjust for the measured confounders present within the NRD. However, there are several limitations to the authors' approach that merit discussion. The most salient limitations are those inherent to administrative data sets in general and the NRD in

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particular. Administrative data sets reflect billable actions of a healthcare system, not a systematic assessment of patients' exposures of interest. As such, administrative data sets like NRD are subject to imprecision as well as random and nonrandom misclassification and missingness. This is the case for the two exposures of interest, obesity and OSA. The prevalence of having overweight or obese body mass indexes (BMIs) across the COPD population is as high as 70% (2), yet only 19% of patients in NRD were classified as obese by ICD 9/10 billing codes. This observation tracks with a recent investigation estimating that only 30–40% of patients with a BMI indicating obesity carry a formal ICD-9/10 diagnosis (11). Of relevance to this study, obesity diagnoses are not missing at random. Patients with obesity-related comorbidities like type 2 diabetes are more likely to have an ICD 9/10 code for obesity (11). In fact, some codes for obesity (e.g., Z68.X) cannot be used without the concomitant diagnosis of another obesity-related condition. The relationship between comorbid diagnoses and coding for obesity may at least partially explain why the authors found no association between obesity and readmissions after accounting for comorbidities. In addition, the data available in the NRD did not allow the authors to evaluate different levels of obesity. Therefore, the authors could not evaluate threshold or dose effects.

OSA presents similar barriers. Like obesity, OSA is frequently misclassified by ICD-9/10 codes and is markedly underdiagnosed (12). Also like obesity, the underdiagnosis of OSA is not at random. We have known for some time that those who identify as African American or Hispanic appear to have particularly high prevalence of undiagnosed OSA (13). Although the mechanism is not clear, patients identifying as African American and Hispanic also appear to have lower rates of COPD readmissions than patients identifying as White in some, but not all, cohorts (14, 15). Clearly, race and ethnicity are potential confounders in the relationship between OSA diagnoses and readmissions. Unfortunately, race and ethnicity are not included in the NRD and remain unaccounted for in the current analysis.

As the authors point out, NRD's large sample size offsets some of its limitations. However, a large sample size cannot overcome differential misclassification and bias (e.g., obesity is less likely to be missing among those with obesity and comorbidities). Given the small effect sizes observed for the risks of OSA and obesity, it is distinctly possible that some, or all, of the observed effects could stem from residual confounding.

Nevertheless, the findings of Channick and colleagues reinforce that the association between obesity and COPD readmissions is mediated at least in part by comorbid conditions. The authors' findings also support prior findings that OSA may have a small but independent role in hospital readmissions. However, it is important that we do not rush to judgment. Similar to associations between OSA and other adverse outcomes (e.g., cardiovascular disease) (16), the specter of residual confounding looms large. Therefore, we cannot yet conclude causality and assume a deleterious effect of OSA or a protective effect of OSA management. It is incumbent on us as a field to directly test whether the management of OSA leads to improved outcomes among patients with COPD. Similarly, it is important that we test the role of weight loss services in mitigating adverse outcomes from obesity and other obesity-related conditions among patients with COPD. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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