Sleep Apnea and COVID-19 Mortality and Hospitalization

To the Editor:

A report describing 5,700 patients with coronavirus disease (COVID-19) identified that common risk factors for poor outcomes are older age, minority ethnicity, obesity, hypertension, and diabetes (1). However, mortality and hospitalizations, estimated by the CDC COVID-19 Response Team to occur in 1.8–3.4% and 20.7–31.4% of COVID-19–positive individuals, respectively (2), are not fully explained by recognized risk factors. Sleep apnea—prevalent in older, obese, and minority individuals—increases risk for COVID-19 comorbidities and may contribute to poor outcomes by exacerbating or causing endothelial dysfunction, inflammation, oxidative stress, microaspiration, and lung injury (3–8). Although prior reports of COVID-19 risk factors have not identified sleep apnea as a prevalent risk factor, data were from healthcare systems where clinical recognition of sleep apnea is markedly underrecognized. Given its association with recognized COVID-19 comorbidities and physiological plausibility, we analyzed electronic health record (EHR) data (9) from a large New England healthcare system to ask whether sleep apnea is an unrecognized risk factor for COVID-19–related death, hospitalization, ventilator use, and ICU admission among patients with positive COVID-19 diagnostic testing.

Methods

The sample was adult nonemployee participants with positive COVID-19 RNA PCR diagnostic results who had available demographic data, a minimum of two clinical notes, two encounters, and three International Classification of Disease (ICD) diagnoses of any disease (to minimize the effect of minimal EHR documentation in participants with out-of-network care). Participants were further restricted to include those with either zero or two or more ICD-9 or ICD-10 diagnoses of sleep apnea or obstructive sleep apnea on different dates (to minimize the effect of rule-out diagnosis codes). Natural language processing (10) was used to obtain documentation of continuous positive airway pressure (CPAP) usage in the year before the first COVID-19 test.

Results

The sample of 4,668 patients included 55.6% females with a median age of 56.1 years (interquartile range, 40.5–71.1) and body mass index (BMI) of 28.8 (interquartile range, 25.4–33.1) and was composed of 48.3% European Americans, 14.8% African Americans, 14.0% Hispanic and Latino Americans, and 22.9% others. The mortality rate was 7.4% (median days from first test to May 24, 2020, or death = 31). The 443 participants (9.5%) with sleep apnea had an increased all-cause mortality rate (11.7%) compared with sleep apnea controls (6.9%) ($P < 0.001$; odds ratio [OR], 1.79; 95% confidence interval [CI], 1.31–2.45). A significant association between with sleep apnea and COVID-19 death persisted in analyses adjusted for demographics (Table 1). Associations were somewhat attenuated after adjusting for BMI class and diagnoses associated with sleep apnea. Similar but weaker associations were observed between sleep apnea and the composite outcome of ICU admission, mechanical ventilation, or death, or for hospitalization. In an exploratory analysis, participants with EHR CPAP documentation in the prior year displayed a nonsignificant trend for attenuated composite outcome results ($n = 310$; model 4 OR, 0.97 [95% CI, 0.73–1.30]; reference = no sleep apnea) compared with participants without evidence of CPAP documentation ($n = 133$; model 4 OR, 1.23 [95% CI, 0.82–1.84]; reference = no sleep apnea).

Table 1. Odds Ratios Associating Sleep Apnea with COVID-19 Mortality and Severe Morbidity

Outcome	Reference	Model 1 (Unadjusted)	Model 2 (Adjusted for Demographics)	Model 3 (Model 2 Plus WHO BMI Class)	Model 4 (Model 3 Plus Comorbidities)
Death	Alive	1.79 (1.31–2.45)*	1.53 (1.08–2.15)†	1.39 (0.97–1.98)‡	1.16 (0.8–1.68)
Death, mechanical ventilation, or ICU admission	All others	1.64 (1.32–2.04)*	1.29 (1.03–1.62)†	1.11 (0.87–1.40)	1.04 (0.81–1.34)
Inpatient admission	Outpatient	1.55 (1.27–1.89)*	1.18 (0.95–1.45)	1.01 (0.81–1.26)	0.91 (0.72–1.14)

Definition of abbreviations: BMI = body mass index; COVID-19 = coronavirus disease; WHO = World Health Organization.
Results are presented as odds ratios with 95% confidence intervals. Model 1 = unadjusted (base); model 2 = adjusted for race and ethnicity, age, sex (demographics); model 3 = model 2 plus BMI (demographics + BMI); model 4 = model 3 plus asthma, chronic bronchitis, emphysema, essential hypertension, BMI, and type 2 diabetes (fully adjusted).
*$P \leq 0.001$ (Wald's test).
†$P \leq 0.05$.
‡$P = 0.07$.

Supported by grants from the NIH (K01HL135405 to B.E.C., R35HL135818 to S.R., and U01HG008685 to E.W.K.).

Author Contributions: Conception and design: B.E.C., H.S.D., S.R., and E.W.K. Data acquisition: B.E.C., H.S.D., S.M.H., S.R., and E.W.K. Analysis: B.E.C. Interpretation, draft and review, and final approval: all authors. B.E.C. and E.W.K. had full access to the study data and take responsibility for the integrity of the data and accuracy of analyses.

Originally Published in Press as DOI: 10.1164/rccm.202006-2252LE on September 18, 2020

Discussion

The results of this U.S. healthcare system–based analysis of mortality and markers of severe morbidity identify sleep apnea as a risk factor for COVID-19 mortality, highlighting the need for close monitoring of patients with sleep apnea who become infected. Study strengths include analysis of a comprehensive electronic health data set and inclusion of a "data floor" to exclude participants with insufficient clinical data. Outcomes were based on a relatively long period of observation (median 31 d of follow-up) within a large healthcare system serving a diverse population and an area with high COVID-19 prevalence. Overall prevalence of sleep apnea, however, was lower than in community-based epidemiological studies, likely leading to some misclassification and attenuation of effect sizes. The CPAP analysis results are consistent with associations being driven by the untreated group; however, we caution that the analysis is limited by a lack of adherence data and should be replicated in a larger study. Although associations were somewhat reduced after adjusting for BMI, a common comorbidity of sleep apnea, the magnitude of effect and underlying biological plausibility of pathways linking sleep apnea to COVID-19–related morbidity highlight the importance of improved efforts to recognize sleep apnea in individuals presenting with COVID-19 infection. Given the urgent need to target mechanistic pathways underlying COVID-19 morbidity, research is warranted to understand whether sleep apnea–related hypoxemia, endothelial dysfunction, coagulopathy, inflammation, cardiac dysfunction, and other related pathologies contribute to the excessive COVID-19 morbidity and mortality observed in obese, minority, and other individuals at risk for sleep apnea. ■

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

Brian E. Cade, Ph.D.*
Brigham and Women's Hospital
Boston, Massachusetts
and
Harvard Medical School
Boston, Massachusetts

Hassan S. Dashti, Ph.D.
Harvard Medical School
Boston, Massachusetts
Massachusetts General Hospital
Boston, Massachusetts
and
Broad Institute
Cambridge, Massachusetts

Syed M. Hassan, M.D.
Brigham and Women's Hospital
Boston, Massachusetts
and
Harvard Medical School
Boston, Massachusetts

Susan Redline, M.D., M.P.H.
Brigham and Women's Hospital
Boston, Massachusetts
Harvard Medical School
Boston, Massachusetts
and
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Elizabeth W. Karlson, M.D.
Brigham and Women's Hospital
Boston, Massachusetts
Harvard Medical School
Boston, Massachusetts
and
Massachusetts General Hospital
Boston, Massachusetts

ORCID IDs: 0000-0003-1424-0673 (B.E.C.); 0000-0002-1650-679X (H.S.D.).

*Corresponding author (e-mail: bcade@bwh.harvard.edu).

References

1. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, *et al*.; the Northwell COVID-19 Research Consortium. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York city area. *JAMA* 2020;323:2052–2059.
2. CDC COVID-19 Response Team. Severe outcomes among patients with coronavirus disease 2019 (COVID-19) - United States, February 12-March 16, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69: 343–346.
3. Peppard PE, Hagen EW. The last 25 years of obstructive sleep apnea epidemiology-and the next 25? *Am J Respir Crit Care Med* 2018;197: 310–312.
4. Bironneau V, Tamisier R, Trzepizur W, Andriantsitohaina R, Berger M, Goupil F, *et al*. Sleep apnoea and endothelial dysfunction: an individual patient data meta-analysis. *Sleep Med Rev* 2020;52:101309.
5. Jelic S, Padeletti M, Kawut SM, Higgins C, Canfield SM, Onat D, *et al*. Inflammation, oxidative stress, and repair capacity of the vascular endothelium in obstructive sleep apnea. *Circulation* 2008;117:2270–2278.
6. Lavie L. Oxidative stress in obstructive sleep apnea and intermittent hypoxia--revisited--the bad ugly and good: implications to the heart and brain. *Sleep Med Rev* 2015;20:27–45.
7. Chiner E, Llombart M, Valls J, Pastor E, Sancho-Chust JN, Andreu AL, *et al*. Association between obstructive sleep apnea and community-acquired pneumonia. *PLoS One* 2016;11:e0152749.
8. Kim JS, Podolanczuk AJ, Borker P, Kawut SM, Raghu G, Kaufman JD, *et al*. Obstructive sleep apnea and subclinical interstitial lung disease in the Multi-Ethnic Study of Atherosclerosis (MESA). *Ann Am Thorac Soc* 2017;14:1786–1795.
9. Weiss ST, Shin MS. Infrastructure for personalized medicine at partners healthCare. *J Pers Med* 2016;6:13.
10. Savova GK, Masanz JJ, Ogren PV, Zheng J, Sohn S, Kipper-Schuler KC, *et al*. Mayo clinical Text Analysis and Knowledge Extraction System (cTAKES): architecture, component evaluation and applications. *J Am Med Inform Assoc* 2010;17: 507–513.