8. Moll M, Peljto AL, Kim JS, Xu H, Debban CL, Chen X, *et al.* A polygenic risk score for idiopathic pulmonary fibrosis and interstitial lung abnormalities. *Am J Respir Crit Care Med* 2023;208: 791–801.
9. Hatabu H, Hunninghake GM, Richeldi L, Brown KK, Wells AU, Remy-Jardin M, *et al.* Interstitial lung abnormalities detected incidentally on CT: a Position Paper from the Fleischner Society. *Lancet Respir Med* 2020;8:726–737.
10. Grant-Orser A, Min B, Elmrayed S, Podolanczuk AJ, Johannson KA. Prevalence, risk factors, and outcomes of adult interstitial lung abnormalities: a systematic review and meta-analysis. *Am J Respir Crit Care Med* 2023;208:695–708.
11. Hunninghake GM, Hatabu H, Okajima Y, Gao W, Dupuis J, Latourelle JC, *et al.* MUC5B promoter polymorphism and interstitial lung abnormalities. *N Engl J Med* 2013;368:2192–2200.
12. Escott-Price V, Schmidt KM. Pitfalls of predicting age-related traits by polygenic risk scores. *Ann Hum Genet* 2023;87:203–209.
13. Novembre J, Stein C, Asgari S, Gonzaga-Jauregui C, Landstrom A, Lemke A, *et al.* Addressing the challenges of polygenic scores in human genetic research. *Am J Hum Genet* 2022;109:2095–2100.
14. Adam Y, Sadeeq S, Kumuthini J, Ajayi O, Wells G, Solomon R, *et al.* Polygenic risk score in African populations: progress and challenges. *F1000 Res* 2023;11:175.
15. Dressen A, Abbas AR, Cabanski C, Reeder J, Ramalingam TR, Neighbors M, *et al.* Analysis of protein-altering variants in telomerase genes and their association with MUC5B common variant status in patients with idiopathic pulmonary fibrosis: a candidate gene sequencing study. *Lancet Respir Med* 2018;6:603–614.

The Influence of Physiologic Burdens Related to Obstructive Sleep Apnea on Cardiovascular Outcomes

It is impossible to ignore the impact of cardiovascular disease (CVD), as it claims more than 800,000 lives each year and accounts for 32% of all deaths (1). Diving into the complex etiology of CVD, the increasing role of sleep disorders has become evident, thus shaping this nationwide health crisis and propelling the American Heart Association to include healthy sleep in its Life's Essential 8 guidelines (2).

Obstructive sleep apnea (OSA) is arguably foremost among sleep disorders augmenting cardiovascular risk, with its diagnosis and severity typically gleaned from the apnea–hypopnea index (AHI), measured on polysomnography (PSG) or home sleep apnea tests. Although patients with OSA are at increased cardiovascular risk, there is lingering obscurity regarding the AHI metric and questions as to its precision, how accurately it reflects the salient biologic aspects of OSA, and its utility as a defining metric potentially explaining negative clinical trials involving intervention with continuous positive airway pressure (3, 4).

Although there are other traditional metrics besides AHI in PSG reports, such as oxygen saturation (Sp_{O_2}) nadir and the percentage of sleep time spent under 90% Sp_{O_2}, these provide only a partial reflection of the true biophysiological sleep landscape. They fail, for instance, to delve into the depth and duration of physiological signal desaturations during events. This limitation of current standard reporting of metrics, combined with the richness of the data captured during the examination, serves as a major impetus for researchers to explore other ideas for PSG metrics, including those derived from event-based physiological burdens.

In this issue of the *Journal*, Labarca and colleagues (pp. 802–813) examine in depth the association of hypoxic burden (OSA-related total area under the desaturation curve) with incident CVD, coronary heart disease (CHD), and mortality compared with the ventilatory burden (the event-specific area under the ventilation signal identified by amplitude changes in the nasal pressure signal) and arousal burden (the total duration of all arousals divided by the total sleep time) (5). Their study provides information on the strength of predicting CVD-related outcomes even when accounting for confounding. Of note, some measures of sleep disturbance physiological burden, such as the sleep apnea–specific hypoxic burden in association with CVD, have been reported and in of itself does not represent a novel finding (6–8). Rather, the novelty of the present work resides in providing key insights into the interrelatedness of sleep-specific physiological burden metrics reflecting different pathophysiologic aspects.

To perform the study, Labarca and colleagues (5) analyzed PSGs from the community-based cohort of MESA (Multi-Ethnic Study of Atherosclerosis) ($n = 2{,}035$, 917 men) and the MrOS (Osteoporotic Fractures in Men) cohort ($n = 2{,}896$, all men). In MESA, outcomes were based on regular follow-up calls, and in MrOS, participants were contacted every 4 months after the sleep study. In both cohorts, medical records and death certificates were also evaluated. Fortunately, both cohorts are publicly available in the National Sleep Research Resource, a valuable, accessible, and extensive collection of deidentified physiological signals and clinical data elements.

In their primary analysis, the authors address the associations of hypoxic, arousal, and ventilatory burdens with longitudinal outcomes. They used Cox regression and four different models, each with an increasing number of covariates for adjustment from demographics to comorbidities. Also, for model 4, they added the variable desaturation sensitivity, defined as the ratio of hypoxic burden to ventilatory burden, aiming to adjust for the tendency toward desaturation of the individual. For the MESA dataset, every 1 SD increase in hypoxic burden was significantly associated with a 21% increase in the risk of all-cause mortality and a 33% increase in the risk of all CVD. The ventilatory burden was significantly associated with a 24% increased risk of all-cause mortality and a 32% increased risk of all CVD. The statistical significance of the results persisted even when attempting to more rigorously take into account visceral adiposity (i.e., replacing body mass index with waist

Originally Published in Press as DOI: 10.1164/rccm.202307-1243ED on August 23, 2023

circumference, hip circumference, waist-to-hip ratio, waist-to-height ratio, and total body fat). In the MrOS cohort, the hypoxic burden was associated with a 13% increased risk of incident CVD and a 22% increase of CVD death. The ventilatory burden was associated with a 12% increased risk of incident CVD and a 21% increased risk of cardiovascular death. Only in the MrOS cohort was arousal burden significantly associated with a major CVD outcome.

In their secondary analysis, using the MESA dataset, Labarca and colleagues (5) investigated the extent to which ventilatory burden captures the variability in hypoxic burden using five different types of models with an increasing number of covariates for adjustments. They found that ventilatory burden was strongly associated with hypoxic burden, accounting for 74% of its variability in the fully adjusted model. Findings were robust to model inclusion of FVC as a measure of restrictive pulmonary physiology exerted by obesity, which explained $<2\%$ of the hypoxic burden.

After carefully considering covariates with different models, the results support the importance of hypoxic and ventilatory burdens in predicting CVD, CHD, and mortality. Given the lack of existing clarity of physiological representativeness of these metrics (9), the authors conducted additional sensitivity analysis of proxy-related metrics to visceral adiposity instead of just body mass index. The authors show that the observation remained unchanged, reinforcing the hypothesis that hypoxic and ventilatory burdens at least partially influence CVD and appear to be independent of patients' adiposity. Also interesting is the predictability of hypoxic burden given its ventilatory counterpart. The authors conjecture that for any given AHI, there are individual variations on their respective physiological burdens, and this could be the reason for many of the null findings regarding AHI treatment with continuous positive airway pressure.

Of note, arousal burden did not emerge as a strong predictor of cardiovascular outcomes. Low arousal responses are potentially reflective of aberrancies in autonomic mechanisms, respiratory reflexes, or, as pointed out by the authors, adaptive responses over time. In the meantime, certain limitations of the study should be considered, such as the older age of the population in MESA (67 years old on average) and the exclusively male cohort of MrOS (76 years old on average), which can affect the generalization of the results to younger and middle-aged individuals with OSA.

Although these metrics are well described in text format, there are still particularities in their implementations (10). Thus, this is also an opportunity to consider reproducibility and the recent and significant movement by the NIH toward promoting rigorous and transparent research (11). In this case, Labarca and colleagues (5) share partially the code of the metrics they computed. They share a link for an application that computes hypoxic burden absent the source code, and they share the code for computing ventilatory burden, which relies on software licensing and author collaborative agreements.

As we turn toward the future, the potential avenues for enriching and improving what we extract from PSGs are evident. Particularly noteworthy are the recent advances in artificial intelligence in combining metrics for optimal all-cause mortality prediction (12) and automatically extracting clinically meaningful information from analyzing raw data from sleep studies (13).

Labarca and colleagues (5) raise our attention to clinically relevant physiological burden metrics that are still not used in clinical practice but provide strong predictive information for CVD, CHD, and mortality, even after robust accounting of confounding variables. The findings are strengthened by external validation, including two independent cohorts that were well characterized, diverse, and publicly available. Consequently, these findings not only can be expeditiously used in secondary analyses of existing data from prior trials but also have a high potential to identify the individuals most likely to respond to OSA treatment and therefore contribute to the design of future OSA trials. ■

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

Matheus Araujo, Ph.D.
Neurological Institute
Cleveland Clinic Foundation
Cleveland, Ohio
and
Cleveland Clinic Lerner College of Medicine
Case Western Reserve University
Cleveland, Ohio

Reena Mehra, M.D., M.S.
Neurological Institute
Respiratory Institute

Heart and Vascular Institute
Cleveland Clinic Foundation
Cleveland, Ohio
and
Department of Cardiovascular and Metabolic Sciences
Cleveland Clinic Lerner Research Institute
Cleveland, Ohio

ORCID ID: 0000-0003-0979-3417 (M.A.).

References

1. Coronado F, Melvin SC, Bell RA, Zhao G. Global responses to prevent, manage, and control cardiovascular diseases. *Prev Chronic Dis* 2022; 19:E84.
2. Lloyd-Jones DM, Allen NB, Anderson CAM, Black T, Brewer LC, Foraker RE, *et al.*; American Heart Association. Life's Essential 8: updating and enhancing the American Heart Association's construct of cardiovascular health: a presidential advisory from the American Heart Association. *Circulation* 2022;146:e18–e43.
3. Balk EM, Adam GP, Cao W, Bhuma MR, Forbes S, Mehta S, *et al.* Long-term health outcomes in obstructive sleep apnea: a systematic review of comparative studies evaluating positive airway pressure and the validity of breathing measures as surrogate outcomes. Rockville, MD: Agency for Healthcare Research and Quality; 2022.
4. Malhotra A, Ayappa I, Ayas N, Collop N, Kirsch D, Mcardle N, *et al.* Metrics of sleep apnea severity: beyond the apnea-hypopnea index. *Sleep (Basel)* 2021;44:zsab030.
5. Labarca G, Vena D, Hu WH, Esmaeili N, Gell L, Yang HC, *et al.* Sleep apnea physiological burdens and cardiovascular morbidity and mortality. *Am J Respir Crit Care Med* 2023;208:802–813.
6. Trzepizur W, Blanchard M, Ganem T, Balusson F, Feuilloy M, Girault JM, *et al.* Sleep apnea-specific hypoxic burden, symptom subtypes, and risk of cardiovascular events and all-cause mortality. *Am J Respir Crit Care Med* 2022;205:108–117.
7. Azarbarzin A, Sands SA, Stone KL, Taranto-Montemurro L, Messineo L, Terrill PI, *et al.* The hypoxic burden of sleep apnoea predicts cardiovascular disease-related mortality: the Osteoporotic Fractures in

Men Study and the Sleep Heart Health Study. *Eur Heart J* 2019;40: 1149–1157.
8. Shahrbabaki SS, Linz D, Redline S, Stone K, Ensrud K, Baumert M. Sleep arousal-related ventricular repolarization lability is associated with cardiovascular mortality in older community-dwelling men. *Chest* 2023; 163:419–432.
9. Jun JC. Dying with OSA, or from it: a cautionary note about novel hypoxia metrics. *Am J Respir Crit Care Med* 2022;206:1563–1564.
10. Sutherland K, Sadr N, Bin YS, Cook K, Dissanayake HU, Cistulli PA, *et al.* Comparative associations of oximetry patterns in obstructive sleep apnea with incident cardiovascular disease. *Sleep (Basel)* 2022; 45:zsac179.
11. LaPolla FWZ, Bakker CJ, Exner N, Montnech T, Surkis A, Ye H. Rigor and reproducibility instruction in academic medical libraries. *J Med Libr Assoc* 2022;110:281–293.
12. Wickramaratne S, Kam K, Tolbert T, Varga A, Ayappa I, Rapoport D, *et al.* Combination of ventilatory, hypoxic, and arousal burden predicts short-and long-term consequences of OSA better than the apnea-hypopnea index. *Am J Respir Crit Care Med* 2023;207:A5968.
13. Bandyopadhyay A, Goldstein C. Clinical applications of artificial intelligence in sleep medicine: a sleep clinician's perspective. *Sleep Breath* 2023;27:39–55.