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The Next 25 Years of Obstructive Sleep Apnea Epidemiology—Don't Keep Repeating Past Mistakes

To the Editor:

Peppard and Hagen recently published a Perspective on obstructive sleep apnea (OSA) epidemiology (1). The authors offer a thoughtful analysis of existing knowledge gaps and outline an ambitious research agenda. However, we believe a different, simpler approach will lead to more meaningful advances.

Everything starts with defining hypopneas. Consider, the apnea–hypopnea index (AHI) can triple simply by going from arousal to desaturation criteria (2–4). The number of hypopneas can increase eightfold (3). Because the definition, irrespective of patient factors, has such a large effect on the magnitude of the AHI, correlation with outcomes will always be inconsistent. For example, 38 studies were used as evidence to support OSA treatments in a 2013 guideline published by the American College of Physicians (5). Within those 38 studies were 13 separate definitions for hypopneas. Seven studies didn't provide a definition at all, 14 required desaturations, 9 included arousals, and 8 didn't require a desaturation or an arousal. Not surprisingly, the authors found poor evidence that the AHI predicts clinical outcomes (Table 4 from Reference 5).

To its credit, the American Academy of Sleep Medicine tried to standardize the definition for a hypopnea in the first iteration of its 2012 scoring guidelines (v2.0) (6). It picked a very liberal definition that dramatically increases OSA prevalence when compared with estimates from the Wisconsin Sleep Cohort (7) and an updated analysis by Peppard and colleagues (8). Unfortunately, it was unable to offer substantial evidence to support this definition or other changes recommended in this guideline. Subsequent iterations (v2.1–v2.4) included a second definition for scoring hypopneas, considered "acceptable," that is very conservative. Therefore, a consensus on defining hypopneas remains elusive, and the AHI will continue to be influenced by the chosen definition.

There are pros and cons to using a liberal (maximizing OSA prevalence) versus conservative (minimizing it) definition for hypopneas. There are advocates for each approach, and the debate spans across payers and tests (level I vs. level III polysomnography). That said, funding for elaborative and expensive research, as proposed by Peppard and Hagen, is unlikely to provide clarity if we can't define the disease. Without a definition, we'll end up repeating the mistakes of the past 25 years instead of advancing the field. ■

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Reply to Holley and Phillips

From the Authors:

In their letter commenting on our Perspective (1), Drs. Holley and Phillips point to the priority of "defining the disease" (obstructive sleep apnea [OSA]). They specifically note that the multiplicity of hypopnea definitions in use gives rise to large variations in OSA prevalence estimates and inconsistent correlations with outcomes of OSA.

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We agree that from a clinical perspective, standardization of a single, universally adopted, evidence-supported definition of a hypopnea event is an important goal. Many of the variations in the apnea–hypopnea index (AHI) that arise from different hypopnea definitions are, in effect, rescaled metrics of OSA disease severity. For example, in a comparison of recommended (AHI_{Rec}) and alternative (AHI_{Alt}) hypopnea definitions proposed by the American Academy of Sleep Medicine in 2007 (2), Ruehland and colleagues (3) found that although the more liberal AHI_{Alt} definition produced ~80% higher mean AHIs, the correlation between AHI_{Rec} and AHI_{Alt} was high (0.93). Similarly, when Dean and colleagues (4) compared AHIs that (all else being equal) varied with the desaturation cutoff point (4% vs. 3%) and according to whether or not arousals were incorporated into the hypopnea definition, they also found that although the mean values varied substantially, the AHIs were highly correlated (generally >0.9). This suggests that for many patients, AHIs that use various hypopnea definitions contain similar information presented on different scales. Given this, it is indeed bizarre that the same cutoff points (e.g., 5, 15, or 30 events/h) should be used to define OSA severity categories whatever the hypopnea definition. Thus, for OSA classification in a clinical context, we agree that either a single standardized definition of hypopnea is required or different absolute cutoff points for OSA classification should be used for varying hypopnea definitions, with the former being the more parsimonious approach.

From a research perspective, however, we believe standardization of a single hypopnea definition would be needlessly limiting, given the current state of knowledge. Even though AHIs using different hypopnea definitions are highly correlated, they are not perfectly so. Thus, it may be that some definitions are more predictive of some outcomes. For example, Dean and colleagues found that an AHI definition that classified hypopneas by an oxygen desaturation of at least 4% (without considering arousals) was most consistently predictive of systolic blood pressure (4). However, it may be that definitions that incorporate arousals or lesser desaturations are better predictors of, say, long-term cognitive decline. Thus, in a research context, the scoring of polysomnograms in a manner that allows multiple definitions of breathing events to be flexibly generated is of substantial value. We hope that the next 25 years will bring nonproprietary computer algorithms for polysomnography interpretation that can rapidly and ever more accurately and reliably generate multiple characterizations of OSA to permit further exploration of important unanswered questions. ■

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Early Chronic Obstructive Pulmonary Disease or Early Detection of Mild Disease?

To the Editor:

The Perspective article by Martinez and colleagues on differentiating early chronic obstructive pulmonary disease (COPD) from mild disease is an excellent and timely discourse on this important topic (1). Mild and early airflow obstruction are frequently conflated by both clinicians and researchers. Mild disease, when observed, is hard to differentiate from early disease, and the only differentiator is temporal information. The authors propose a number of criteria to attempt differentiation of early and mild disease. Although these suggestions are practical, there are some issues with adapting the "required" criteria for clinical or research purposes. The recommendation that persons younger than 50 years of age should be considered to have early disease does not have a temporal component and does not take into consideration that a majority of smokers start smoking in their teens and hence would have already accumulated a substantial number of pack-years of smoking burden by the time they are in their forties. We recently showed that the duration of smoking is more strongly associated with measures of COPD than the composite index of pack-years (2). It is easy to ascertain the onset of smoking, and so a temporal component can be easily included by terming those with airflow obstruction within a conservative 10 years of smoking onset as having early COPD. For non–smoking-related COPD, temporality is harder to establish, but a lower age threshold may help.

Furthermore, a few other suggestions need clarification. First, the authors recommend using post-bronchodilator values for the lower limit of normal (LLN). Unfortunately, available LLN values are prebronchodilator. This is not a trivial issue; Tilert and colleagues showed that using post-bronchodilator fixed ratio less than 0.70 and prebronchodilator ratio less than LLN provide similar population estimates of airflow obstruction, whereas applying prebronchodilator criteria to post-bronchodilator tests results in prevalence estimates that are two-thirds of those obtained using prebronchodilator tests (3). Thus, post-bronchodilator LLN is likely to be more specific, but this may result in missing early cases of airflow obstruction for which sensitivity may be more important. Second, computed tomography can identify alteration in the lung parenchyma and airways before detection of airflow obstruction, but most smokers are likely to have some structural changes, and

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