

The Last 25 Years of Obstructive Sleep Apnea Epidemiology—and the Next 25?

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Epidemiologic investigations of obstructive sleep apnea (OSA) in adults reach back more than a quarter century. However, beginning in and throughout the 1990s, early payoffs of substantial investments by the U.S. NIH in large-scale, population-based epidemiologic investigations of nonclinical samples—including the Cleveland Family Study (1), the Penn State sleep study (2, 3), and the Wisconsin Sleep Cohort (4)—began yielding evidence that OSA was far more common than had been previously supposed. These findings, in addition to a proliferating literature hinting at associations between OSA and a host of noxious outcomes, and the then-recent development of positive airway pressure therapy, propelled both a rapid expansion of epidemiologic investigations into objectively assessed OSA and outcomes in the United States and elsewhere around the world, as well as an exponential growth in the rate of clinical diagnoses of OSA (5, 6). A quarter century later, in broad terms, what have we learned from these population-based epidemiologic investigations?

First, we know OSA to be highly prevalent in adults—especially in its mild to moderate manifestation—and prevalence has increased throughout the 25-year period, in large part due to increasing prevalence of obesity in the developed world (7, 8). Prevalence estimates depend on populations examined, time periods of assessment, and how breathing events of OSA are defined, but can reach large minorities to majorities of specific population subgroups (e.g., older males) (8).

Second, the “big three” risk factors for OSA are male sex, higher body mass, and

greater age (8). This was known decades ago. However, associations of these risk factors, as well as interactions among them, have been better quantified in the last 25 years. For example: OSA has been identified as a not-at-all-rare condition in women; obesity is a relatively stronger risk factor for OSA in younger adults; and the relation of sex and OSA diminishes with older age—OSA prevalence in older women becomes closer to that of men (9, 10).

Third, there are, as there must be, genetic components to OSA. The condition is approximately one-third heritable, with some heritability mediated by excess body mass and, possibly, race-related factors, such as facial and upper-airway morphology (11, 12). However, elucidation of the roles of specific polymorphisms identified by candidate gene and genome-wide association studies (e.g., References 13 and 14) is in its early phases, and prior findings require further replication (15).

Fourth, there are modifiable risk factors for OSA other than obesity. However, the associations are weaker and less consistent. These factors include physical inactivity (independent of body weight) and excess alcohol use (7, 16).

Fifth, very generally, severe OSA, independent of age, sex, and obesity, is associated with a wide range of quality-of-life–diminishing and life-depriving afflictions—daytime sleepiness, car crashes, depression, cardiovascular and cerebrovascular morbidity, cognitive and metabolic dysfunction, and accelerated mortality—whereas estimated associations of these outcomes with mild-to-moderate OSA exhibit considerable inconsistency

(17–25). Although some of these outcomes have been targets of investigation since the 1980s, the last 25 years have brought objective measures of OSA and longitudinal study designs that, collectively, make stronger cases for causal associations than had been previously available. In addition, a potential role of severe OSA in cancer morbidity and mortality has been recently uncovered, opening—indeed, compelling—new avenues of research not widely contemplated even a decade ago (26, 27). The lack of clarity and consistency regarding the importance of milder OSA is unfortunate, given its high prevalence. We believe that this inconsistency is most likely due to limitations of observational methods used over the last 25 years, including relatively small study sample sizes due to the expense and burden of objective OSA assessment, few long-term longitudinal investigations, and overly simplistic characterizations (e.g., as a single parameter, such as the apnea–hypopnea index [AHI]) of varied complex phenotypes collectively lumped together as “OSA.”

Prescriptions for methodologic advancements to address limitations are readily enumerated, if not easily implemented, and include: 1) large-sample, long-running longitudinal investigations for identifying subtle, but important, associations—and differences among key subgroups—initiated at younger ages so that disease processes have not been underway for years; 2) multidimensional, in-depth characterization of OSA, as well as high-precision, objective assessments of important confounding factors; and 3) natural histories of OSA and outcomes unaffected by medical interventions. As it is not ethical to prevent medical treatments of

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OSA (or OSA outcomes), this last point (point 3) is an ever-increasing scientific challenge to the field. However, there are important opportunities for advancements in epidemiologic investigations beyond those of the last 25 years relating to points 1 and 2.

Some of the most promising opportunities address point 2, and will result from conceptual and technologic advancements. One key conceptual area is how we assess the time course of outcomes of OSA. Many outcomes of interest (e.g., cardiovascular, cognitive, and metabolic dysfunction) may have acute responses to “last night” exposure to OSA. Next-day blood pressure may be elevated, particularly in the morning; sleepiness may negatively affect next-day cognitive functioning. However, these same outcomes may also result from long-term “accretive” processes, due to years of exposure to OSA, via a host of mechanisms that promote vascular or neural injury (22). Thus far, epidemiologic investigations have made little effort to disentangle acute versus long-term cumulative effects, as traditional longitudinal studies have minimal ability to measure acute effects, and cross-sectional studies cannot distinguish acute from long-term effects. Alternative study designs based on frequently repeated assessments of OSA—or yet-to-be-discovered valid biomarkers of OSA (28)—and outcomes are required to disentangle acute and long-term effects, knowledge necessary for understanding the full value of prevention and long-term treatment of OSA.

Another opportunity for advancing the field is to develop comprehensive ways to characterize OSA. Most epidemiology studies have measured OSA with a breathing event rate (e.g., the AHI). This degree of data reduction—from a full night of polysomnography to a single number—conceals a great degree of variation in disease experience that can occur between individuals with the same AHI. Alternative measures are sometimes used; however, all commonly used OSA metrics still do not capture many facets of even the blood oxygen saturation component of OSA events (e.g., depth, rapidity, and duration, clustering, sleep state, and within-night variability of desaturations) that may be important in understanding how disease outcomes are generated, and other potentially informative signals captured by polysomnography (e.g., from ECG) have not been widely applied to OSA characterization in epidemiology investigations. In addition, although logistically challenging in large

epidemiologic samples, the incorporation of “deeper” physiologic assessments (e.g., respiratory arousal thresholds, loop gain, airway critical closing pressures, etc.) would allow exploration of a range of “OSA phenotypes” that will have implications for more targeted treatment of OSA and a better understanding of individual-level variations in susceptibility to specific outcomes of OSA (29). Such advancements would likely be further informed, refined, and accelerated by parallel advancements in genomic and other “-omics” sciences as they relate to OSA.

Finally, with respect to point 1, larger, longer-running epidemiology studies of OSA are technically and ethically feasible. However, they are also expensive and require many years to come to fruition. Meanwhile, two alternative approaches that use existing data are taking on greater roles: aggregation of previously collected “research-grade” data from multiple cohorts—such as consortium collaborations or database consolidations—and an increasing use of electronic health records (EHRs) to investigate OSA–outcome associations. Having participated in both types of studies over the last several years, we believe there is promise and peril in each.

Investigations based on consortium collaborations or database consolidations are common for genome-wide association studies that require large samples to search for modest genetic signals. Large samples are usually not available from a single OSA cohort, and so data must be combined. As yet, there are limited examples of this approach for OSA (e.g., Reference 14), but more are likely to come in the near future, including consortium studies not solely focused on genetic exposures. Another promising approach is the creation of data repositories, such as the NIH NHLBI-funded NSRR (National Sleep Research Resource [30]) that includes a growing depth and breadth of data from NIH-funded studies of OSA and other sleep-related conditions. These data may be used by investigators interested in a wide range of questions, from traditional epidemiologic investigations to, for example, machine learning applications for extracting information from polysomnography to better characterize OSA. Working with aggregations of existing data has substantial practical challenges—including difficulties in “harmonizing” data from multiple sources in a way that allows the data to be validly combined. However, we expect that considerable new knowledge regarding

OSA will come from aggregations and further analyses of high-quality existing data.

The appeal of EHR-based investigations is straightforward: for costs that are a fraction of those of bespoke epidemiology cohorts, patients diagnosed with OSA (and “controls”) can be followed over time for development of conditions of interest. For this reason, we expect an increasing use of epidemiologic study designs (e.g., nested case–control, cohort) to be applied to EHR in OSA research. For some types of questions that can be circumscribed within clinical settings (e.g., research regarding health services practices *per se*), EHR-based observational studies of outcomes of OSA may be suitable. However, for epidemiologic research that probes for etiologic insight into pathophysiologic questions (does years of exposure to untreated mild OSA increase risk of cancer? dementia?, etc.), investigators will need to be wary of the limitations of EHR-based epidemiology, because the “usual suspects” threats to validity of epidemiologic studies—selection bias, measurement error, and confounding—can be amplified in the EHR setting. The likelihood of selection biases due to the use of clinical populations has been recognized for the better part of a century, and, for OSA, could readily arise if, for example, primary care clinicians (sensibly) use knowledge of a patient’s cardiovascular risk factors to decide whether to refer a patient to a sleep clinic for polysomnographic evaluation. In this case, one cannot validly use patient populations to examine associations between OSA and vascular disease. Furthermore, EHR data are typically not “research grade”; for example, the standardization of polysomnography equipment, procedures, and scoring algorithms present in epidemiology cohorts generally do not occur across myriad clinical encounters among varying care providers that generate EHR. Finally, confounding may be magnified using EHR. EHR rarely have high-quality data on important covariates, such as physical activity, diet, education, etc., and suffer from the lack of standardization for basic, but critical, measures, such as height and weight. Thus, although the use of EHR to address questions regarding associations between OSA and outcomes is attractive, without sufficient care, large EHR-based investigations may simply result in estimated associations characterized by tight confidence intervals around dubious point estimates.

Over the last 25 years, rigorous population-based epidemiologic investigations of adults have produced needed refinements and new insights regarding the role of severe OSA across a broad range of adverse sequelae. Over the coming decades, there will be many paths to achieving further clarifications on pressing questions regarding the role of years of exposure to less severe OSA in vascular, brain, and heart pathology, cancer risk, and suboptimal

functioning—broadly defined—in older adults, to name a few. A traditional path would be to produce bigger and better “next-generation” cohorts that systematically improve on methods of those that have gone before. Of course, we advocate for this approach. However, we also expect that many new insights will be gained from: deep explorations into the rich data already available to better characterize OSA; consideration of the

multiplicity of OSA phenotypes; identification of factors (genetic or otherwise) that predict individual-level variations in susceptibility to OSA; and the development of methods to validly aggregate data from multiple sources of rigorously collected OSA, covariates, and outcomes. ■

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

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